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Βιβλιογραφία: 1. Woodcock A, et al. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial. Lancet. 2017; 390: 2247-2255.

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Βιβλιογραφία:

1. Global initiative for chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of COPD-GOLD 2023 Report. Available at: https://goldcopd.org/goldreports.
2. Anoro Ellipta, Περίληψη Χαρακτηριστικών Προϊόντος Νοέμβριος 2022.

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1. Περίληψη Χαρακτηριστικών Προϊόντος Trelegy Ellipta, Φεβρουάριος 2023.
2. Lipson DA et al. Am J Respir Crit Care Med 2017; 196:438-446.
3. Lipson DA et al. N Engl J Med 2018;378:1671-1680.

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Table of Contents

Acknowledgement of manuscript reviewers 2023 12
Bridges of Pulmonology 2023 proceedings: Highlights in the field of interstitial lung diseases 14
Determinants of tobacco use patterns and predictors of quit among older women in India: Findings from the study on global aging and adult health 18
Lung cancer epidemiology based on bronchoscopic and imaging findings from newly diagnosed patients in Central Greece 28
Drug-overdose associated acute hypoxemic respiratory failure: A secondary analysis 38
Impact of COVID-19 pandemic and country of origin on TB treatment outcome in Greece 46
Factors of impaired health-related quality of life in patients with precapillary pulmonary hypertension 53
Clinical and polysomnographic characteristics of REM-related obstructive sleep apnea patients 61
Impact of non-invasive ventilation on exacerbation frequency in COPD patients 72
Effect of prone position in non-intubated COVID-19 patients 78
New therapies in small cell lung cancer: A narrative review 95
Pulmonary embolism and sarcopenia: The potential interplay 103
Tuberculosis of the temporomandibular joint: A rare case report and review of the literature 111
Spontaneous pneumothorax following COVID-19 infection in an adolescent: A case report and review of literature 116
A case report of late pleural effusion and hemoptysis as a result of pulmonary vein stenosis due to atrial fibrillation ablation 123
Instructions to authors 127

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Konstantinos Kostikas[1,2]

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Bridges of Pulmonology 2023 proceedings: Highlights in the field of interstitial lung diseases

Vasilina Sotiropoulou[1]*, Panagiota Tsiri[1]*, Athena Gogali[2], Vasileios Tzilas[3], Demosthenes Bouros[4], Argyris Tzouvelekis[1]

The first patient-centered scientific congress in the field of Greek respiratory medicine, Bridges of Pulmonology 2023, took place on June 2023, in Patras. The congress welcomed over 1000 participants on its hybrid platform 'bridging' specialized professionals from different medical fields and highlighting the importance of a modern holistic approach in the management of the respiratory patient. A wide spectrum of topics was discussed, some of which were focused on interstitial lung diseases (ILDs). We aim to summarize the scientific highlights of Bridges of Pulmonology 2023 in the field of ILDs, enriched with the latest literature review.

Despite their similar clinical presentation, fibrotic lung diseases of different cause may have different prognosis and management. Grouping ILDs with progressive fibrosing behavior remains challenging, given that the response to treatment and the risk of further progression may differ according to the underlying disease entity[1]. On the other hand, splitting pulmonary fibrosis in order to apply personalized medicine has been hampered by the lack of clinically applicable molecular biomarkers linking endotypes with clinical phenotypes. Shedding light on the cellular and molecular mechanisms that generate and regulate fibrosis would be of great importance[2]. Recently, single cell profiling data have revealed cellular changes and immune aberrations in the usual interstitial pneumonia (UIP) lung. Several cell populations, such as alveolar epithelial cells and endothelial capillary cells, are substantially reduced in the fibrotic lung parenchyma samples[3]. In contrast, aberrant basaloid cells, a previously unknown cell type co-expressing epithelial, basal, mesenchymal and senescence genes and highly expressing genes typically related to idiopathic pulmonary fibrosis (IPF), have been identified in the fibroblastic foci, but not in control donor lungs[3]. Ectopic bronchial vascular endothelial cells abound in the affected alveolar regions of remodeling in IPF, while these cells are limited to the normal airway circulation. This finding is consistent with the already described histological observation of 'proximalization' of the distal airways in IPF[3]. Moreover, peripheral blood and lung single-cell RNA data from patients with IPF demonstrated that the immune elements and the chemokine signaling pathways could differentiate progressors from non-progressors. Classical monocytes and regulatory T-cells are increased, while other lymphocytic populations are decreased in progressive IPF compared to stable. Combined evidence from lung and blood samples, associated specific cytokines receptors (CCR) and their ligands (CCL) with the accumulation of these cell types, such as CCR2/CCL7 for monocytes and CCR4/CCL17 and CCR8/CCL18 for regulatory T-cells, and a mechanism of lung-blood recruitment has been suggested[4]. Despite promising data, the future taxonomy of pulmonary fibrosis based on sequencing technology is still in its infancy.

The recently-introduced term 'progressive pulmonary fibrosis' (PPF) encompasses certain non-IPF ILDs that develop a progressive phenotype, as defined by clinical, functional and radiological criteria[5]. Both anti-fibrotic agents can decelerate disease progression, as measured by forced vital capacity (FVC) decline from baseline, but only nintedanib has received conditional recommendation for the treatment of PPF[6]. The identification of the predictors of disease progression, to integrate an individually tailored management approach

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in the context of personalized medicine is of paramount importance. UIP pattern is an independent predictor of acute exacerbations and disease progression in non-IPF ILDs[7]. In a cohort of 167 patients with rheumatoid arthritis-ILD (RA-ILD), the gradual decline of pulmonary function is worse in UIP pattern than nonspecific interstitial pneumonia[8]. Moreover, the extent of fibrotic features, the presence of honeycombing and traction bronchiectasis, as well as the elevated systolic pulmonary artery pressure >36.5 mmHg, are independent risk factors for mortality in IPF and other fibrosing ILDs[9,10]. A substantial minority of patients with scleroderma-related-ILD (SSc-ILD) may present with a rapid, continuous pattern of FVC decline with several consecutive episodes of deterioration. The phenotype of rapid progressors includes early-onset diffuse cutaneous SSc, with elevated acute-phase markers and topoisomerase I antibody positivity[11].

With regard to recent advances in non-IPF ILDs treatment, both mycophenolate mofetil (MMF) and cyclophosphamide presented favorable results in lung function, imaging, and clinical presentation in symptomatic/progressive SSc-ILD, while MMF had a better toxicity profile[12]. Additionally, improvement of skin thickening and FVC measurements were noticed in patients with SSc treated with rituximab[13]. Towards this direction, the RECITAL study showed non-superiority of rituximab compared to cyclophosphamide in progressive connective-tissue disease-ILDs (CTD-ILDs), and therefore, rituximab may be an alternative therapeutic choice in severe CTD-ILDs[14]; yet, the majority of these patients displayed an inflammatory imaging phenotype based on HRCT pattern. In the FOCUSSCED trial, tocilizumab stabilized lung function in a population of patients with early SSc-ILD with diffuse skin involvement, active disease and high inflammatory markers or platelet count[15]. Among anti-fibrotics, only nintedanib has been proved to reduce the annual rate of FVC decline in patients with SSc-ILD. Moreover, a subgroup analysis of SENSCIS trial suggests a possible benefit of nintedanib on top of MMF in SSc, along with a good safety profile[16]. Nintedanib's safety profile and efficacy were also assessed on SENSCIS-ON trial favoring its long-term use[17]. On the other hand, there is a pressing need for further research about pirfenidone, as the unclassifiable ILD and RELIEF trials were limited by their small sample size and the non-significance level of their primary endpoint[18,19]. These results may indicate pitfalls in current clinical practice, where treatment initiation occurs after FVC decline and thus, irreversible lung damage has already been installed.

Ongoing clinical trials could hopefully broaden the therapeutic horizons of ILDs by identifying potential molecular targets and novel effective agents. However, drug development can take years for a single asset, and therefore, acceleration of these processes could be a game-changer. Growing interest has been noted in enhanced methods to bring robust evidence particularly in heterogenous diseases requiring multiple concomitant therapies. A new approach to trial design, which is known as Randomized, Embedded, Multifactorial, Adaptive Platform (REMAP), will favor the assessment of multiple concurrent therapies. A flagship study designed before COVID-19 pandemic for the assessment of community acquired pneumonia (CAP), REMAP-CAP, successfully showed the effectiveness of various treatment options for COVID-19 patients as well. Towards this direction, the aim of REMAP-ILD, detailly presented in this congress, is to create an international platform for clinical trials that can accelerate the assessment of therapies for individuals with ILD[20]. The primary endpoint is the FVC trajectory incorporating data from baseline, 12-month follow-up and any time points in between, indicating it as a better marker due to its easiness and frequency of measurement. The numerous medications that could be assessed simultaneously, the lower risk of individuals receiving ineffective therapy and the spectrum of patients with different types and stages of the disease, including rare forms, highlight a promising global modular adaptive trial.

In the era of personalized medicine, genetic screening could be a strong asset. During the last decades, intense research has elucidated pulmonary fibrosis genetic predisposition by the detection of numerous gene variants related to sporadic or familial fibrotic lung diseases[21]. Fibrogenic variants may reflect disease clinical characteristics, natural history and prognosis and may provide timely therapeutic approaches. Mutations in telomerase reverse transcriptase (TERT) and telomerase RNA(TERC) have been associated with multisystemic clinical syndromes, the telomeropathies, with concurrent hepatic, cutaneous or hematological disorders. Moreover, carriers of TERT and TERC pathogenic variations present pulmonary fibrosis of early onset and rapidly progressive course, with worse prognosis and worse outcomes after lung transplantation compared to non-carriers[22,23]. Interestingly, the prognostic significance of the telomere related gene (TRG) variants is higher than the histopathological and clinical features[24]. Additionally, higher incidence of lung cancer, usually adenocarcinomas, has been noticed in patients carrying pathogenic surfactant-related gene (SRG) variants. In carriers of *SFTPA* mutations, lung cancer is diagnosed more frequently and in younger ages than expected and coexists with pulmonary fibrosis in two-thirds of cases. The possible underlying mechanisms include promotion of necroptosis without apoptosis and deficit surfactant protein-A-associated anti-neoplastic properties[25]. The mucin 5B promoter polymorphism has been associated with UIP pattern and may contribute to the early recognition of subclinical RA-ILD as part of a scoring system[26]. Regarding the therapeutic implications, recent data suggest that antifibrotic agents are beneficial for patients with pathogenic TRG alleles[27]. Clinical trials investigating the potential effect of the synthetic androgen Danazol in telomere related syndromes are currently in process[28]. Gene-based strategies of restoring surfactant function or telomere length are in the development pipeline with growing therapeutic potential, and may present favorable clinical outcomes in the future[29,30].

The recently published European Respiratory Society statement on familial pulmonary fibrosis (FPF), suggests that genetic testing and counselling may be beneficial for: 1) patients with FPF, defined as having more than one relative of first or second degree with pulmonary fibrosis; 2) asymptomatic individuals with a recognized disease-causing allele in their family; 3) patients aged under 50 years with pulmonary fibrosis of unknown cause; and 4) patients with clinical characteristics suggestive of telomeropathy[31]. In the appropriate setting, genetic testing could be an option for patients with interstitial lung abnormalities, pretransplant patients or members of families where pulmonary fibrosis or lung adenocarcinoma appear through generations[32,33]. The routinely analyzed gene panel includes SRGs and TRGs, while screening for single nucleotide polymorphisms is not currently suggested[31]. Considering the current lack of official guidelines, the implementation of genetic testing in clinical practice still presents major challenges. The availability of techniques, the funding requirements and the different legislation rules among countries comprise significant hurdles[33,34]. Expertise in the field, along with a multidisciplinary approach, are prerequisites for the accomplishment and evaluation of the genetic analysis, and therefore, it can only be performed in highly specialized and fully equipped institutions[33,34]. The psychosocial impact of ILD diagnosis or predisposition must be taken into consideration. Therefore, it is necessary that genetic testing be accompanied by genetic counselling and follow-up of the patients and relatives[33]. The discovery of more genetic culprits, the elucidation of possible clinical and therapeutic implications of pathogenic variants in asymptomatic individuals and the demarcation of the role of genetic screening in the personalized management of pulmonary fibrosis, are anticipated future perspectives.

A multidisciplinary team approach will improve the management of the ILD patient. Of note, ongoing efforts to promote personalized medicine will hopefully enrich this effort. The presented findings and proposals for further research may inspire both senior and young investigators to create 'bridges' in order to better understand the upcoming challenges, prolonging survival, and improving patients' quality of life.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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DISCLAIMER

A. Gogali and A. Tzouvelekis report that they are Editorial Board Members of Pneumon. They had no involvement in the peer-review or acceptance of this article, and had no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to a handling editor of the journal. The views and opinions expressed in this article are those of the authors.

REFERENCES

1. Rajan SK, Cottin V, Dhar R, et al. Progressive pulmonary fibrosis: an expert group consensus statement. Eur Respir J. 2023;61(3):2103187. doi:10.1183/13993003.03187-2021
2. Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ; IPF Consensus Working Group. What's in a name? That which we call IPF, by any other name would act the same. Eur Respir J. 2018;51(5):1800692. doi:10.1183/13993003.00692-2018
3. Adams TS, Schupp JC, Poli S, et al. Single-cell RNA-seq reveals ectopic and aberrant lung-resident cell populations in idiopathic pulmonary fibrosis. Sci Adv. 2020;6(28):eaba1983. doi:10.1126/sciadv.aba1983
4. Unterman A, Zhao AY, Neumark N, et al. Single-cell profiling reveals immune aberrations in progressive idiopathic pulmonary fibrosis. medRxiv. Preprint posted online April 29, 2023. doi:10.1101/2023.04.29.23289296
5. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022;205(9):e18-e47. doi:10.1164/rccm.202202-0399ST
6. Wongkarnjana A, Scallan C, Kolb MRJ. Progressive fibrosing interstitial lung disease: treatable traits and therapeutic strategies. Curr Opin Pulm Med. 2020;26(5):436-442. doi:10.1097/MCP.0000000000000712
7. Choe J, Chae EJ, Kim YJ, Do KH, Song JS, Song JW. Serial changes of CT findings in patients with chronic hypersensitivity pneumonitis: imaging trajectories and predictors of fibrotic progression and acute exacerbation. Eur Radiol. 2021;31(6):3993-4003. doi:10.1007/s00330-020-07469-2
8. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Progressive Decline of Lung Function in Rheumatoid Arthritis-Associated Interstitial Lung Disease. Arthritis Rheumatol. 2017;69(3):542-549. doi:10.1002/art.39971
9. Kolb M, Vašáková M. The natural history of progressive fibrosing interstitial lung diseases. Respir Res. 2019;20(1):57. doi:10.1186/s12931-019-1022-1
10. Chen X, Guo J, Yu D, Jie B, Zhou Y. Predictors of Mortality in

Progressive Fibrosing Interstitial Lung Diseases. Front Pharmacol. 2021;12:754851. doi:10.3389/fphar.2021.754851
11. Hoffmann-Vold AM, Allanore Y, Alves M, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. Ann Rheum Dis. 2021;80(2):219-227. doi:10.1136/annrheumdis-2020-217455
12. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4(9):708-719. doi:10.1016/S2213-2600(16)30152-7
13. Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. Semin Arthritis Rheum. 2017;46(5):625-631. doi:10.1016/j.semarthrit.2016.10.003
14. Maher TM, Tudor VA, Saunders P, et al. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. Lancet Respir Med. 2023;11(1):45-54. doi:10.1016/S2213-2600(22)00359-9
15. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2020;8(10):963-974. doi:10.1016/S2213-2600(20)30318-0
16. Highland KB, Distler O, Kuwana M, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. Lancet Respir Med. 2021;9(1):96-106. doi:10.1016/S2213-2600(20)30330-1
17. Allanore Y, Vonk MC, Distler O, et al. Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON. Ann Rheum Dis. 2022;81(12):1722-1729. doi:10.1136/ard-2022-222564
18. Behr J, Prasse A, Kreuter M, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med. 2021;9(5):476-486. doi:10.1016/S2213-2600(20)30554-3
19. Maher TM, Corte TJ, Fischer A, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med. 2020;8(2):147-157. doi:10.1016/S2213-2600(19)30341-8
20. REMAP-ILD: Randomised, embedded, multifactorial, adaptive platform trial for interstitial lung disease. Imperial College London. Accessed February 2, 2024. https://www.imperial.ac.uk/mtw-centre-fibrosing-lung-disease/research/remap-ild/
21. Borie R, Le Guen P, Ghanem M, et al. The genetics of interstitial lung diseases. Eur Respir Rev. 2019;28(153):190053. doi:10.1183/16000617.0053-2019
22. Borie R, Tabèze L, Thabut G, et al. Prevalence and characteristics of TERT and TERC mutations in suspected genetic pulmonary fibrosis. Eur Respir J. 2016;48(6):1721-1731. doi:10.1183/13993003.02115-2015
23. Choi B, Messika J, Courtwright A, et al. Airway complications in lung transplant recipients with telomere-related interstitial lung disease. Clin Transplant. 2022;36(3):e14552. doi:10.1111/ctr.14552
24. Newton CA, Batra K, Torrealba J, et al. Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive. Eur Respir J. 2016;48(6):1710-1720. doi:10.1183/13993003.00308-2016
25. van Moorsel CHM, van der Vis JJ, Grutters JC. Genetic disorders of the surfactant system: focus on adult disease. Eur Respir Rev. 2021;30(159):200085. doi:10.1183/16000617.0085-2020
26. Juge PA, Granger B, Debray MP, et al. A Risk Score to Detect Subclinical Rheumatoid Arthritis-Associated Interstitial Lung Disease. Arthritis Rheumatol. 2022;74(11):1755-1765. doi:10.1002/art.42162
27. Justet A, Klay D, Porcher R, et al. Safety and efficacy of pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis and carrying a telomere-related gene mutation. Eur Respir J. 2021;57(2):2003198. doi:10.1183/13993003.03198-2020
28. Mackintosh JA, Pietsch M, Lutzky V, et al. TELO-SCOPE study: a randomised, double-blind, placebo-controlled, phase 2 trial of danazol for short telomere related pulmonary fibrosis. BMJ Open Respir Res. 2021;8(1):e001127. doi:10.1136/bmjresp-2021-001127
29. Cooney AL, Wambach JA, Sinn PL, McCray PB. Gene Therapy Potential for Genetic Disorders of Surfactant Dysfunction. Front Genome Ed. 2022;3:785829. doi:10.3389/fgeed.2021.785829
30. Alder JK, Armanios M. Telomere-mediated lung disease. Physiol Rev. 2022;102(4):1703-1720. doi:10.1152/physrev.00046.2021
31. Borie R, Kannengiesser C, Antoniou K, et al. European Respiratory Society statement on familial pulmonary fibrosis. Eur Respir J. 2023;61(3):2201383. doi:10.1183/13993003.01383-2022
32. Newton CA, Oldham JM, Applegate C, et al. The Role of Genetic Testing in Pulmonary Fibrosis: A Perspective From the Pulmonary Fibrosis Foundation Genetic Testing Work Group. Chest. 2022;162(2):394-405. doi:10.1016/j.chest.2022.03.023
33. Papiris SA, Kannengiesser C, Borie R, et al. Genetics in Idiopathic Pulmonary Fibrosis: A Clinical Perspective. Diagnostics (Basel). 2022;12(12):2928. doi:10.3390/diagnostics12122928
34. Borie R, Kannengiesser C, Sicre de Fontbrune F, Gouya L, Nathan N, Crestani B. Management of suspected monogenic lung fibrosis in a specialised centre. Eur Respir Rev. 2017;26(144):160122. doi:10.1183/16000617.0122-2016

Determinants of tobacco use patterns and predictors of quit among older women in India: Findings from the study on global aging and adult health

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ABSTRACT

INTRODUCTION Despite low prevalence of tobacco smoking among women in India, smokeless tobacco (SLT) use constitutes a significantly higher burden. There is limited previous research in the field of tobacco use and quitting behavior particularly in older women in India. The study aims to ascertain the prevalence, patterns, and sociodemographic determinants of tobacco use and predictors of quit among older women in India.

METHODS Cross-sectional and nationally representative data from the first and second wave of WHO's Study on global Ageing and Adult Health (SAGE 2007 and 2015) were analyzed. Outcome variables included smoking and SLT use, with quit status assessed, while explanatory variables encompassed sociodemographic characteristics like age, education level, marital status, body mass index, religion, ethnicity, residence, wealth quintiles, and mother tongue.

RESULTS We observed a reduction in the prevalence of tobacco use in any form among women from 34.17% (SAGE-1) to 18.17% (SAGE-2). The prevalence of current tobacco use in any form was 9.89% (n=352; 95% CI: 8.74–11.17), tobacco smoking was 9.42% (n=331; 95% CI: 8.29–10.69), while the prevalence of current SLT use was 12.3% (n=454; 95% CI: 10.99–13.72). Muslim women had significantly higher odds of using SLT compared to Hindu women (AOR=1.86; 95% CI: 1.24–2.69). Successful quit after initiation to SLT use was reported in only 7.62% of the women. Women from scheduled caste ethnicity were less likely to achieve a successful quit (AOR=0.70; 95% CI: 0.09–5.81) compared to other caste groups.

CONCLUSIONS Approximately one in five older women used tobacco, with higher prevalence than GATS data, underscoring the need for continued surveillance and focused public health efforts. Furthermore, quit rates in female SLT users continue to be very low suggesting the need for strengthening access, availability, and affordability of tobacco cessation services to promote successful quitting behavior.

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INTRODUCTION

Tobacco use in either smoking or smokeless forms is a major public health challenge with 80% of users living in low- and middle-income countries (LMICs). Smokeless tobacco (SLT), defined as a tobacco containing product that is consumed through chewing in the mouth, sniffing, or as a dissolvable has over 356 million users globally with 232 million in India and Bangladesh[1,2]. SLT is a nicotine containing addicting substance with other carcinogenic chemicals that increases the risk of cancers of the head and neck, especially mouth and throat, and is independently associated with incidence of various cardiovascular diseases[3,4]. As per the Global Burden of Disease 2019 estimates, SLT is attributed to cause over 8.6 million DALYs and about 350000 deaths annually[5].

In LMICs, with most tobacco smokers being men and the prevalence of tobacco smoking being comparatively very low in women, there is a lack of policy attention and neglect of the impact of SLT use among women[6]. According to the Global Adult Tobacco Survey (GATS)-2 (2015–2016), India has 29.6% male and 12.1% female SLT users, signifying high prevalence in both genders compared to tobacco smoking in 19% men and only 2% women[7]. Women might have a higher risk of SLT addiction especially due to earlier initiation during adolescence and is also linked to a practice employed for suppression of hunger[8]. Furthermore, there is evidence to suggest that female SLT users have higher odds of developing oral cancer compared with males. SLT use during pregnancy is also linked to impairment of fetal lung and brain development, adverse maternal and infant nutritional outcomes, preterm delivery, low birth weight, and stillbirth[9-12].

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Evidence from the GATS is also indicative of a declining trend in smokeless tobacco use amongst women from 18.4% (2009–2010) to 12.8% (2016–2017). According to the National Family Health Survey-4 (2015–2016), a greater proportion of women in India have also reported an absence of intention to quit and also higher failure to quit SLT use compared to males[13]. Women in India are also less likely to notice health warnings related to tobacco including SLT use, suggestive of adverse social determinants such as reduced literacy contributing to higher risk of tobacco and SLT addiction compared to men. Consequently, three fifths of deaths attributable to SLT use occur in women[14]. In some cases, women may also lack confidence to access tobacco cessation services due to the perceived societal stigma linked to the phenomenon.

It is important to identify the prevalence and predictors of tobacco use through disaggregated data amongst women in India, particularly in the more vulnerable older population with prolonged addiction who, in the absence of interventions to promote cessation, have increased risk of developing cancer and heart disease due to the additive effect of multiple synergistic risk factors with tobacco[14]. However, there exists limited evidence on tobacco use characteristics by women in India. The evidence of tobacco use from demographic and health surveillance data is restricted to younger and middle-aged women who have comparatively improved educational parameters which limits generalizability of those findings to older women[13]. Consequently, the present study was conducted with the objective of ascertaining the prevalence and sociodemographic determinants of tobacco (smoking and SLT) use and the predictors of quit in SLT-using older women in India from analysis of nationally representative health survey data.

METHODS

Data source

The present study compares findings from two rounds of the WHO Study on Global Ageing and Adult Health (WHO SAGE) for India, a national survey that collected survey data from adults aged ≥50 years. Our work is based on the cross-sectional survey data collected in the SAGE Wave 1 (2007–2008) and the SAGE Wave 2 (2015), India, which were implemented in the six selected states of Assam, Karnataka, Maharashtra, Rajasthan, Uttar Pradesh and West Bengal. Both SAGE Wave 1 and SAGE Wave 2 focused on data collection in persons aged ≥50 years and another smaller comparative sample of adults aged 18–49 years. The same primary sampling units (PSUs) and households covered in the SAGE Wave 1 in 2007 comprised the follow-up sample for SAGE Wave 2 in 2015, although the extent of loss to follow-up and proportion of new recruitment is not reported. Both SAGE Wave 1 and 2, India, employed a multi-stage stratified cluster sample design. Based on the selection probability at each stage of selection, household, and individual weights for analysis at the household level and personal level, respectively, were determined. A total of 9116 completed household interviews were included in SAGE Wave 2, of which 1998 interviews were of persons aged 18–49 years (1165 women and 833 men) and 7118 interviews of persons aged ≥50 years (3781 women and 3337 men). Data were collected using a standardized questionnaire having country-specific adaptations[9,10].

Study population

The dataset consists of individuals aged 18–49 and ≥50 years. In households identified as 'older' for sampling purposes, all household members aged ≥50 years were invited to participate in the study. We included women aged ≥50 years in this analysis.

Outcome variables

The smoking status was assessed by the variable q3001: 'Have you ever smoked any tobacco products' and q3002, 'Do you currently use any tobacco products?'. The SLT use was assessed by the variable q3002a: 'Do you currently use smokeless tobacco?', wherein both daily and non-daily users were considered as having SLT usage. SLT quit was assessed using the questions: 'Used smokeless tobacco in the past?', and 'Do you currently use smokeless tobacco?'.

Explanatory variables

In our analysis, we considered a set of individual sociodemographic and lifestyle characteristics as controlling variables. These characteristics encompassed age, education level, marital status, body mass index (BMI), religion, ethnic group, place of residence, and wealth quintiles.

Education level had 4 categories ranging from 'Not educated/less than primary' to 'College and higher'. Principal Components Analysis was used to generate scores that were transformed into 'wealth quintiles', where quintile 1 represents the lowest wealth and quintile 5 the highest. For marital status, categories of currently married and cohabiting were combined to form three categories. Similarly, the religious denomination variable was classified into three broad categories: Hinduism, Islam, and Other. Ethnic groups were classified as scheduled tribes, scheduled castes, other backward classes, and other. The WHO's standard guidelines for BMI (kg/m^2) were used to divide into three categories: normal (18.5), underweight (18.5–24.9), and pre-obese/obese (≥25.0).

Statistical analysis

Univariate analysis was done to assess the distribution of the sample. The prevalence and frequency of SLT usage were calculated after applying sampling weights. For bivariate associations, a chi-squared test was performed. Binary logistic regression was used for multivariable regression analysis. Variables having a $p<0.20$ in the bivariate association were included in the binary logistic regression models for multivariable analysis. Both crude odds ratios

(ORs) and adjusted odds ratios (AOR) and their 95% CIs and p-values were calculated. A p<0.05 was considered significant in multivariable analysis. All assumptions were checked for the final logistic regression models. Data were analyzed using Stata version 15.1 (StataCorp, College Station, Texas).

Ethical considerations

The SAGE was approved by the World Health Organization's Ethical Review Board (reference number RPC149). Written informed consent was obtained from all study respondents. The de-identified datasets were obtained after a formal permission from the IIPS. Since the SAGE datasets are anonymous and publicly available with no identifiable information about the participants, no separate ethical approval is required for this secondary data analysis.

RESULTS

The SAGE-2 (2015) dataset consisted of 4946 females, with a mean age of 54.62 years (SD=14.42). The mean age of initiation of smoking in women aged ≥50 years was 27.57 years (SD=21.74) and for SLT it was 28.76 years (SD=24.28). Table 1 gives the sociodemographic characteristics in the study sample consisting of females aged ≥50 years (n=3781).

In Table 2, it can be seen that the prevalence of tobacco ever use, in any form, among women decreased from 34.17% (n=3254; 95% CI: 31.78–36.64) (SAGE-1; 2007) to 18.17% (n=3772; 95% CI: 16.63–19.82) (SAGE-2; 2015). The prevalence of current tobacco product use in any form was 9.89% (n=352; 95% CI: 8.74–11.17). Overall prevalence of current tobacco smoking was 9.42% (n=331; 95% CI: 8.29–10.69) and the mean duration of usage among current tobacco users was 18.67 years (SD=15.96). Overall prevalence of SLT usage among women aged ≥50 years was estimated as 12.3% (n=454; 95% CI: 10.99–13.72) and the mean duration of usage among current SLT users was 22.93 years (SD=16.83).

The prevalence of past SLT use in the women aged ≥50 years was 1.19% for daily but not current user (n=43; 95% CI: 0.84–1.69), while 98.67% women reported as never having initiated tobacco use (n=3731; 95% CI: 98.16–99.04) (Table 2). Among all women aged ≥50 years, 6.59% (n=267) were only SLT users, 3.72% (n=144) were only tobacco smokers, and 5.69% (n=187) were dual users. Within the tobacco users (n=598), 23.26% (n=144; 95% CI: 19.06–28.06) were only tobacco smokers, 41.17% (n=267; 95% CI: 36.11–46.42) were only SLT users, and 35.57% (n=187; 95% CI: 30.87–40.58) were dual users.

Table 3 gives the distribution of factors associated with smoking status among women aged ≥50 years. On adjusted analysis, increasing BMI and wealth quintiles were observed as having significantly lower odds of smoking in women. Furthermore, women belonging to 'Other' religions had significantly higher odds of smoking compared to Hindu

Table 1. Sociodemographic characteristics of the participants (SAGE Wave-2)

Characteristics	Women (N=3781)	
	n	%
Age (years)		
50–59	1734	45.57
60–69	1293	34.12
≥70	754	20.31
BMI (kg/m^2) (n=3450)		
Underweight	927	28.22
Normal weight	1784	49.65
Pre-obese/obese	739	22.13
Marital status		
Never married	26	0.45
Currently married/cohabiting	2358	62.94
Separated/widowed	1397	36.61
Education level		
Not educated/lower than primary	451	37.37
Up to secondary school	603	44.95
High school	111	10.09
College and higher	91	7.59
Religion		
Hinduism	3182	85.36
Islam	455	11.81
Other	142	2.83
Ethnic group		
Scheduled tribes	285	6.71
Scheduled castes	635	14.95
Other backward classes	1751	49.77
Other	1108	28.57
Quintiles of wealth score		
First	752	21.35
Second	699	17.88
Third	686	17.82
Fourth	792	21.42
Fifth	852	21.53
Residence		
Urban	833	28.78
Rural	2948	71.22
Mother tongue (n=3554)		
Hindi	1372	41.10
Bengali	828	19.70
Marathi	600	20.12
Other	981	19.08

Table 2. Distribution of tobacco use in women in India

Variable	SAGE Wave-2 (N=3781)		SAGE Wave-1 (N=3534)	
	n	% (95% CI)	n	% (95% CI)
Ever used any form of tobacco (either smoking or smokeless)	3772		3254	
Yes	687	18.17 (16.63–19.82)	1047	34.17 (31.78–36.64)
No	3085	81.83 (80.18–83.37)	2207	65.83 (63.36–68.22)
Ever used smokeless tobacco in the past				
Daily but not current user	43	1.19 (0.84–1.69)		
Non-daily but not current user	7	0.14 (0.06–0.29)		
Never initiated non-user	3731	98.67 (98.16–99.04)		
Current tobacco user				
Yes	352	9.89 (8.74–11.17)	985	29.14 (26.98–31.40)
No	3429	90.11 (88.83–91.26)	2549	70.86 (68.60–73.02)
Types of current tobacco user				
Smokeless only	267	6.59 (5.61–7.74)		
Smoking only	144	3.72 (2.99–4.63)		
Dual user	187	5.69 (4.85–6.69)		
Not using	3183	83.98 (82.39–85.46)		

Table 3. Distribution of factors associated with smoking status in women (SAGE Wave-2, N=3772)

Variable	Non-smoking (N=3085) n (weighted %)	Smoking (N=687) n (weighted %)	OR (95% CI)	p[a]	AOR (95% CI)	p[b]
Age (years)				**0.0067**		0.0705
50–59 (Ref.)	1450 (47.14)	282 (38.76)	1		1	
60–69	1042 (33.19)	249 (38.52)	1.41 (1.10–1.81)		1.34 (1.03–1.74)	
≥70	593 (19.67)	156 (22.72)	1.40 (1.08–1.82)		1.23 (0.92–1.65)	
BMI (kg/m^2) (n=3450)				**0.001**		**0.0003**
Underweight (Ref.)	696 (25.45)	231 (40.62)	1		1	
Normal weight	1460 (50.3)	324 (46.71)	0.58 (0.46–0.74)		0.67 (0.52–0.87)	
Pre-obese/obese	663 (24.25)	76 (12.67)	0.33 (0.22–0.49)		0.45 (0.29–0.68)	
Ethnic group (n=3771)				**0.001**		0.1087
Scheduled tribes (Ref.)	219 (6.383)	65 (8.13)	1		1	
Scheduled castes	481 (13.69)	153 (20.69)	1.19 (0.82–1.72)		1.14 (0.77–1.71)	
Other backward classes	1458 (50.48)	289 (46.6)	0.72 (0.51–1.03)		0.82 (0.56–1.20)	
Other	926 (29.45)	180 (24.57)	0.66 (0.46–0.94)		0.84 (0.56–1.24)	
Religion (n=3771)				**0.0005**		**0.0008**
Hinduism (Ref.)	2617 (86.71)	559 (79.47)	1		1	
Islam	354 (10.79)	99 (16.2)	1.64 (1.21–2.21)		1.72 (1.22–2.41)	

Continued

Table 3. Continued

Variable	Non-smoking (N=3085) n (weighted %)	Smoking (N=687) n (weighted %)	OR (95% CI)	p[a]	AOR (95% CI)	p[b]
Other	113 (2.506)	29 (4.335)	1.89 (1.16–3.08)		1.95 (1.11–3.44)	
Quintiles of wealth score				**0.001**		**0.0001**
First (Ref.)	560 (19.15)	191 (31.31)	1		1	
Second	550 (17.59)	147 (19.18)	0.67 (0.50–0.90)		0.68 (0.49–0.93)	
Third	546 (16.97)	137 (21.58)	0.78 (0.56–1.09)		0.88 (0.61–1.26)	
Fourth	657 (22.27)	135 (17.88)	0.49 (0.36–0.67)		0.55 (0.38–0.79)	
Fifth	772 (24.03)	77 (10.05)	0.26 (0.18–0.37)		0.37 (0.23–0.58)	
Residence				**0.0298**		0.9100
Urban (Ref.)	714 (30.17)	118 (22.86)	1		1	
Rural	2371 (69.83)	569 (77.14)	1.46 (1.04–2.05)		1.02 (0.69–1.51)	
Mother tongue				0.1788		
Hindi	1152 (41.38)	219 (40.1)	0.80 (0.62–1.03)			
Bengali	677 (19.67)	151 (20.06)	0.84 (0.65–1.10)			
Marathi	486 (20.59)	110 (17.62)	0.71 (0.49–1.02)			
Other (Ref.)	770 (18.36)	207 (22.22)	1			

AOR: adjusted odds ratio. **a** p<0.20 included in adjusted regression model (age, BMI, ethnic group, religious denomination, quintiles of wealth score, and residence). **b** p<0.05 considered significant. Goodness of fit, p=0.1552.

Table 4. Distribution of factors associated with current SLT use in women (SAGE Wave-2)

Variable	Not current SLT user (N=3327) n (weighted %)	Current SLT user (N=454) n (weighted %)*	OR (95 % CI)	p[a]	AOR (95% CI)	p[b]
Age (years)				**0.0057**		**0.0425**
50–59 (Ref.)	1548 (46.71)	186 (10.09)	1		1	
60–69	1135 (33.61)	158 (13.61)	1.40 (1.04–1.89)		1.33 (0.98–1.82)	
≥70	644 (19.68)	110 (15.01)	1.57 (1.17–2.21)		1.46 (1.05–2.03)	
BMI (kg/m^2) (n=3450)				**0.0005**		**0.0453**
Underweight (Ref.)	784 (26.78)	143 (16.89)	1		1	
Normal weight	1559 (49.84)	225 (12.09)	0.68 (0.51–0.90)		0.76 (0.56–1.03)	
Pre-obese/obese	686 (23.38)	53 (7.51)	0.40 (0.24–0.66)		0.53 (0.31–0.90)	
Ethnic group (n=3779)				**<0.001**		**0.008**
Scheduled tribes (Ref.)	240 (6.45)	45 (15.68)	1		1	
Scheduled castes	527 (13.90)	108 (18.49)	1.22 (0.80–1.86)		1.20 (0.77–1.86)	
Other backward classes	1561 (50.16)	190 (11.61)	0.71 (0.47–1.06)		0.74 (0.48–1.14)	
Other	997 (29.50)	111 (9.47)	0.56 (0.37–0.85)		0.66 (0.42–1.04)	

Continued

Table 4. Continued

Variable	Not current SLT user (N=3327) n (weighted %)	Current SLT user (N=454) n (weighted %)*	OR (95 % CI)	p[a]	AOR (95% CI)	p[b]
Religion (n=3779)				**0.0115**		**0.0057**
Hinduism (Ref.)	2817 (86.11)	365 (11.53)	1		1	
Islam	387 (11.28)	68 (16.23)	1.49 (1.06–2.08)		1.83 (1.24–2.69)	
Other	121 (2.61)	21 (19.07)	1.81 (1.05–3.12)		1.48 (0.80–2.73)	
Quintiles of wealth score				**0.001**		**0.0029**
First (Ref.)	637 (20.35)	115 (16.38)	1		1	
Second	615 (18.01)	84 (11.65)	0.67 (0.47–0.97)		0.67 (0.45–1.00)	
Third	579 (16.81)	107 (17.26)	1.06 (0.73–1.56)		1.11 (0.72–1.72)	
Fourth	696 (21.7)	96 (11.15)	0.64 (0.45–0.92)		0.69 (0.45–1.06)	
Fifth	800 (23.12)	52 (5.78)	0.31 (0.20–0.50)		0.45 (0.26–0.77)	
Residence				0.2977		
Urban (Ref.)	745 (29.4)	88 (10.42)	1			
Rural	2582 (70.6)	366 (13.05)	1.29 (0.88–1.90)			
Mother tongue				0.0710		0.0619
Hindi	1255 (42.02)	117 (10.33)	0.68 (0.50–0.91)		0.66 (0.48–0.91)	
Bengali	715 (19.44)	113 (13.44)	0.91 (0.67–1.23)		0.82 (0.59–1.15)	
Marathi	512 (19.95)	88 (13.04)	0.88 (0.58–1.34)		1.01 (0.65–1.56)	
Other (Ref.)	845 (18.6)	136 (14.54)	1		1	

AOR: adjusted odds ratio. **a** p<0.20 included in adjusted regression model (age, BMI, ethnic group, religious denomination, quintiles of wealth score, and mother tongue) **b** p<0.05 considered significant. *Row-wise percentages given. Goodness of fit, p=0.1861.

Table 5. Determinants of quitting behavior among women ever initiated on SLT (SAGE Wave-2, N=491)

Variable	Quit SLT (N=37) % (95% CI)	OR (95% CI)	p[a]	AOR (95% CI)	p[b]
Age (years)			0.664		
50–59 (Ref.)	42.7 (25.12–62.34)	1			
60–69	38.94 (22.49–58.35)	0.90 (0.36–2.29)			
≥70	18.36 (9.08–33.62)	0.65 (0.24–1.72)			
BMI (kg/m^2) (n=452)			0.3037		
Underweight (Ref.)	32.76 (17.36–53.05)	1			
Normal weight	40.13 (22.15–61.23)	0.97 (0.37–2.55)			
Pre-obese/obese	27.11 (11.81–50.82)	2.37 (0.70–7.98)			
Ethnic group			**0.041**		**0.05**
Scheduled tribes (Ref.)	4.35 (1.06–16.21)	1		1	
Scheduled castes	5.70 (1.75–17.02)	0.5 (0.08–3.16)		0.70 (0.09–5.81)	
Other backward classes	54.35 (35.64–71.92)	2.27 (0.49–10.63)		3.40 (0.51–22.54)	

Continued

Table 5. Continued

Variable	Quit SLT (N=37) % (95% CI)	OR (95% CI)	p[a]	AOR (95% CI)	p[b]
Other	35.59 (19.89–55.16)	3.18 (0.66–15.41)		4.37 (0.64–30)	
Religion			0.094		0.06
Hinduism (Ref.)	62.07 (40.57–79.68)	1		1	
Islam	23.69 (9.785–47.05)	1.96 (0.66–5.85)		1.35 (0.40–4.49)	
Other	14.24 (4.099–39.22)	4.18 (0.98–17.80)		4.77 (1.28–17.76)	
Quintiles of wealth score			0.737		
First (Ref.)	28.85 (14.39–49.44)	1			
Second	19.26 (9.20–35.96)	1.12 (0.37–3.39)			
Third	20.75 (9.29–40.11)	0.82 (0.25–2.67)			
Fourth	13.26 (5.85–27.34)	0.67 (0.21–2.12)			
Fifth	17.87 (6.26–41.50)	1.74 (0.42–7.17)			
Residence			0.409		
Urban (Ref.)	33.02 (16.19–55.70)	1			
Rural	66.98 (44.30–83.81)	0.65 (0.24–1.79)			
Mother tongue			0.295		
Hindi	26.74 (12.03–49.35)	1.10 (0.35–3.45)			
Bengali	37.12 (20.75–57.09)	2.45 (0.93–6.48)			
Marathi	20.27 (9.942–36.93)	1.35 (0.48–3.80)			
Other (Ref.)	15.87 (7.89–29.35)	1			
Type of past-use (n=50)			0.368		
Daily (Ref.)	87.77 (73.62–94.86)	1			
Non-daily	12.23 (5.14–26.38)	2.87 (0.28–29.40)			
Type of addiction (n=36)			0.859		
SLT only (Ref.)	81.60 (61.99–92.34)	1			
Dual user	18.40 (7.66–38.01)	1.18 (0.18–7.80)			

AOR: adjusted odds ratio. **a** p<0.20 included in the adjusted regression model (ethnic group and religious denomination). **b** p<0.05 considered significant. Goodness of fit, p=0.89.

women (AOR=1.95; 95% CI: 1.11– 3.44).

On bivariate analysis, age, BMI, ethnicity, religion, and quintiles of wealth score, were significantly associated (p<0.05) with SLT usage (Table 4). In the multivariate logistic regression analysis, increasing age, BMI, ethnic group, religion, and quintiles of wealth score, were significantly associated (p<0.05) with SLT usage. Elderly women (aged ≥70 years) had higher odds of using SLT (AOR=1.46; 95% CI: 1.05–2.03), while increasing BMI was negatively associated with SLT usage (AOR=0.53; 95% CI: 0.31–0.90). With reference to scheduled tribes, scheduled caste women had higher odds of using SLT (AOR=1.20; 95% CI: 0.77–1.86). Muslim women had higher odds of using SLT compared to the Hindu women (AOR=1.86; 95% CI: 1.24–2.69). There were 7.62% (n=37; 95% CI: 5.23–10.99) women who reported a successful quit after initiation with SLT (Table 5). The adjusted odds of quitting SLT in women belonging to the scheduled caste ethnicity were 0.70 times less (95% CI: 0.09–5.81) compared to the scheduled tribe ethnicity group.

DISCUSSION

The present study evaluated the prevalence and sociodemographic determinants of tobacco use patterns and predictors of quit among older women aged ≥50 years. Age, BMI, lower wealth quintiles, and ethnicity were found to be the determinants associated with tobacco smoking in

the study sample, in line with the results of prior studies[12,13]. However, the prevalence of tobacco smoking in women aged ≥50 years in this analysis from the SAGE survey (9.42%) was nearly two-fold higher compared to observations from the GATS survey data (5.14%), suggesting the need for repeated surveys to validate the extent of this public health problem in India, especially in women[12].

We found that the majority of tobacco users among females aged ≥60 years were SLT users, a finding similar to a study based on GATS I and II[15]. On bivariate analysis, age, BMI, ethnicity, quintiles of wealth index, and religious denomination were significantly associated with SLT usage. These findings agree with studies conducted in other LMICs such as Pakistan[16], Bangladesh[17] and Nepal[18]. SLT usage is often initiated at an early age when children are exposed and normalized to it and are frequently involved in its purchase for family members[19]. In this study, SLT use was found to have significantly declined among women, a finding which also corroborates the trend from GATS-1 and GATS-2[12]. Similar to previous studies, age was found to be directly associated with SLT use, whereas BMI was found to have an inverse relation in our analysis[15,20].

Furthermore, we observed that women belonging to the poorest section of society (first quintile) had higher odds of using SLT, a finding similar to that observed in the GATS 2 survey[21]. In this study, spoken language did not have a statistically significant association with SLT use unlike a previous study suggesting that the association was likely to have been coincidental[22].

Nevertheless, our study findings indicate that ethnicity is possibly linked with SLT use in India as the scheduled caste ethnicity women had significantly higher odds of consuming SLT compared to women from other caste groups. A study based on the second round of the Indian National Family Health Survey (NFHS-2; 1998–1999) had also reported that tobacco consumption was significantly more prevalent among scheduled caste populations, signifying their persistent vulnerability[13]. Prior evidence also suggests that women belonging to socioeconomically disadvantaged populations employed in hard labor activities often use tobacco to suppress hunger[8,23] and reduce perceived stress. Further, our finding suggests that Muslim women were more likely to use SLT, a finding consistent with evidence from NFHS-2[13] and Bangladesh[24].

The present study findings suggest that a very small proportion of older women who are SLT users in India successfully quit tobacco. Improving the awareness of the harmful effects of tobacco and especially SLT use among women is necessary to reduce its initiation and persistence[25]. Evidence from GATS 2 had shown that nearly half of the women in India (45.3%) fail to take notice of health warnings on SLT product packages[26]. Furthermore, the use of quitline/helpline/direct counselling is very low overall, due to difficult accessibility, lack of social support, and associated stigma[27].

Our study findings suggest the need for enhanced tobacco use surveillance and targeted interventions for promoting tobacco cessation, especially SLT, amongst older women users who experience the double impact of adverse social determinants such as lower SES, and belonging to marginalized communities that contribute to reduced access to tobacco quit services. Future research should also explore the evolving dynamics of determinants and cultural factors shaping tobacco use, since a nuanced understanding of the motivations for tobacco use in this vulnerable population can inform the design of tailored interventions which are effective in reducing tobacco consumption among women in India.

Strengths and limitations

The key strength of this study is that it used data from the SAGE survey which used standardized questionnaires, a robust sampling strategy, and validated data collection methods, with high representativeness for older populations. However, this study has a few limitations. First, the data in this study are mostly cross-sectional, and therefore causation cannot be assumed in any direction. Second, recall and social desirability bias may have led to the likely underestimation of the tobacco burden, especially due to social stigma related to tobacco use among women in India[28]. Third, data points on willingness to quit and frequency and type of quit attempts were not available in this survey.

CONCLUSIONS

Nearly one in five older women were found to use tobacco in some form. The higher prevalence of tobacco smoking and smokeless tobacco use compared to GATS data calls for continuous surveillance and focused public health efforts. Furthermore, quit rates in female SLT users continue to be very low (nearly one in ten) suggesting the need for strengthening access, availability, and affordability of tobacco cessation services to promote successful quitting behavior.

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CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this secondary analysis of the SAGE datasets which are anonymous and publicly available, with no identifiable information about the participants.

DATA AVAILABILITY

The SAGE-1 and SAGE-2 survey datasets are available free of charge on request from the International Institute of Population Sciences through the website: https://iipsindia.ac.in/content/SAGE-data.

PROVENANCE AND PEER REVIEW

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AUTHORS' CONTRIBUTIONS

VM and BS: concepts; literature search, data analysis, manuscript review and editing. RS: concepts; literature search, manuscript review and editing. SB: concepts, design, writing of first draft, manuscript review and editing.

REFERENCES

1. WHO report on the global tobacco epidemic 2021: addressing new and emerging products. World Health Organization. July 27, 2021. Accessed April 2, 2023. https://www.who.int/teams/health-promotion/tobacco-control/global-tobacco-report-2021
2. Radhika AG, Preetha GS, Neogi SB. Need for Gender Focused Policies Addressing Smokeless Tobacco Use among Women in India: A Review. Asian Pac J Cancer Prev. 2021;22(S2):7-12. doi:10.31557/APJCP.2021.22.S2.7
3. Liao CY, Chen YJ, Lee JF, Lu CL, Chen CH. Cigarettes and the developing brain: Picturing nicotine as a neuroteratogen using clinical and preclinical studies. Tzu Chi Med J. 2012;24(4):157-161. doi:10.1016/j.tcmj.2012.08.003
4. Rogers JM. Tobacco and pregnancy. Reprod Toxicol. 2009;28(2):152-160. doi:10.1016/j.reprotox.2009.03.012
5. Singh S, Jain P, Singh PK, Reddy KS, Bhargava B. White paper on smokeless tobacco & women's health in India. Indian J Med Res. 2020;151(6):513-521. doi:10.4103/ijmr.IJMR_537_20
6. Ashfaq M, Channa MA, Malik MA, Khan D. MORPHOLOGICAL CHANGES IN HUMAN PLACENTA OF WET SNUFF USERS. J Ayub Med Coll Abbottabad. 2008;20(2):110-113. Accessed November 5, 2023. https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=d7399038f5164ee00b9483d26b4a8d65747dbd65
7. Gupta PC, Subramoney S. Smokeless tobacco use, birth weight, and gestational age: population based, prospective cohort study of 1217 women in Mumbai, India. BMJ. 2004;328:1538. doi:10.1136/bmj.38113.687882.EB
8. Gupta PC, Subramoney S. Smokeless tobacco use and risk of stillbirth: a cohort study in Mumbai, India. Epidemiology. 2006;17(1):47-51. doi:10.1097/01.ede.0000190545.19168.c4
9. SAGE Wave-1. International Institute for Population Sciences. Accessed April 2, 2023. https://iipsindia.ac.in/content/SAGE-wave-1
10. SAGE Wave-2. International Institute for Population Sciences. Accessed April 2, 2023. https://iipsindia.ac.in/content/SAGE-wave-2
11. Gupta PC, Arora M, Sinha D, Asma S, Parascondola M, eds. Smokeless Tobacco and Public Health in India. Ministry of Health & Family Welfare, Government of India; 2016. Accessed November 5, 2023. https://portal-uat.who.int/fctcapps/sites/default/files/kh-media/Final-Version-of-SLT-Monograph.pdf
12. Singh A, Ladusingh L. Prevalence and determinants of tobacco use in India: evidence from recent Global Adult Tobacco Survey data. PLoS One. 2014;9(12):e114073. doi:10.1371/journal.pone.0114073
13. Rani M, Bonu S, Jha P, Nguyen SN, Jamjoum L. Tobacco use in India: prevalence and predictors of smoking and chewing in a national cross sectional household survey. Tob Control. 2003;12(4):e4. doi:10.1136/tc.12.4.e4
14. WHO Framework Convention on Tobacco Control: Overview. WHO Framework Convention on Tobacco Control. Accessed April 2, 2023. https://fctc.who.int/who-fctc/overview
15. Ghosal S, Sinha A, Kanungo S, Pati S. Declining trends in smokeless tobacco use among Indian women: findings from global adult tobacco survey I and II. BMC Public Health. 2021;21:2047. doi:10.1186/s12889-021-12089-6
16. Abbas SM, Alam AY, Usman M, Siddiqi K. Smokeless tobacco consumption in a multi-ethnic community in Pakistan: a cross-sectional study. East Mediterr Health J. 2014;20(6):385-390. Accessed November 5, 2023. https://applications.emro.who.int/EMHJ/V20/06/EMHJ_2014_20_6_385_390.pdf
17. Huque R, Zaman MM, Huq SM, Sinha DN. Smokeless tobacco and public health in Bangladesh. Indian J Public Health. 2017;61(suppl):S18-S24. doi:10.4103/ijph.IJPH_233_17
18. Sreeramareddy CT, Pradhan PMS, Mir IA, Sin S. Smoking and smokeless tobacco use in nine South and Southeast Asian countries: prevalence estimates and social determinants from Demographic and Health Surveys. Popul Health Metr. 2014;12:22. doi:10.1186/s12963-014-0022-0
19. Narain R, Sardana S, Gupta S, Sehgal A. Age at initiation & prevalence of tobacco use among school children in Noida, India: a cross-sectional questionnaire based survey. Indian J Med Res. 2011;133:300-307. Accessed November 5, 2023. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3103155/pdf/IJMR-133-300.pdf
20. Pednekar MS, Gupta PC, Shukla HC, Hebert JR. Association between tobacco use and body mass index in urban Indian population: implications for public health in India. BMC Public Health. 2006;6(70):1-8. doi:10.1186/1471-2458-6-70
21. Goyal LD, Verma M, Garg P, Bhatt G. Variations in the patterns of tobacco usage among indian females - findings from the global adult tobacco survey India. BMC Womens Health. 2022;22:442. doi:10.1186/s12905-022-02014-3
22. Mishra GA, Kulkarni SV, Gupta SD, Shastri SS. Smokeless tobacco use in Urban Indian women: Prevalence and predictors. Indian J Med Paediatr Oncol. 2015;36:176-182. doi:10.4103/0971-5851.166739
23. Aluckal E, Pulayath C, Chithra P, Balakrishna MS, Luke AM, Mathew S. Tobacco Cessation Behavior Among Smoking and Smokeless Form Tobacco Users in the Indigenous Population

of Ernakulam, India. J Pharm Bioallied Sci. 2020;12(Suppl 1):S194-S198. doi:10.4103/jpbs.JPBS_58_20
24. Hossain MS, Kypri K, Rahman B, Arslan I, Akter S, Milton AH. Prevalence and correlates of smokeless tobacco consumption among married women in rural Bangladesh. PLoS One. 2014;9(1):e84470. doi:10.1371/journal.pone.0084470
25. Nair S, Schensul JJ, Begum S, et al. Use of smokeless tobacco by Indian women aged 18-40 years during pregnancy and reproductive years. PLoS One. 2015;10(3):e0119814. doi:10.1371/journal.pone.0119814
26. Tata Institute of Social Sciences, Mumbai and Ministry of Health and Family Welfare, Government of India. Global Adult Tobacco Survey GATS 2 India 2016-17. Ministry of Health and Family Welfare, Government of India. Accessed April 2, 2023. https://main.mohfw.gov.in/sites/default/files/GlobaltobacoJune2018_0.pdf
27. Murthy P, Saddichha S. Tobacco cessation services in India: recent developments and the need for expansion. Indian J Cancer. 2010;47(Suppl 1):69-74. doi:10.4103/0019-509X.63873
28. Singh PK, Jain P, Singh N, et al. Social desirability and under-reporting of smokeless tobacco use among reproductive age women: Evidence from National Family Health Survey. SSM Popul Health. 2022;19:101257. doi:10.1016/j.ssmph.2022.101257

Lung cancer epidemiology based on bronchoscopic and imaging findings from newly diagnosed patients in Central Greece

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ABSTRACT

INTRODUCTION There is a current lack of epidemiological data regarding lung cancer in Greece. The aim of this study was to record and analyze pertinent data regarding demographic, clinical, radiological, bronchoscopic and histological findings in lung cancer cases over a ten-year period collected from a hospital in Central Greece, and to investigate potential specific features of lung cancer in Greek patients.

METHODS This was a retrospective cohort study. The data collected were obtained from newly diagnosed lung cancer patients with fiberoptic bronchoscopy during a ten-year period (2009–2018). From the database, we have extracted the demographic data, the tumor location based on the computed tomography (CT) scans, bronchoscopy report with associated images and the histopathology/cytology reports that yielded the diagnosis.

RESULTS A total number of 637 patients were diagnosed with primary lung cancer during the decade 2009–2018 from the authors in a major tertiary hospital in Athens, Greece. Most of the patients were aged 50–69 years (57.6%) and the majority were men (77.1%) and active smokers (74.1%). The most common histological type was adenocarcinoma (31.7%). In the majority of cases, the patients presented initially at advanced stages. At the time of diagnosis, the most common finding was a lung mass or nodule in computed tomography and an endobronchial mass in fiberoptic bronchoscopy. The patients' lesions were detected most frequently in the upper lobes.

CONCLUSIONS The results show a trend in ADLC histology, an increase in the proportion of women with lung cancer and highlight the significant percentage of patients diagnosed in advanced stages. This reflects the need for effective tobacco control strategies to reduce the incidence of lung cancer and a comprehensive national screening program for the purposes of early detection.

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INTRODUCTION

Lung cancer is currently the leading cause of death from neoplastic diseases worldwide. During the preceding decades, it was the most commonly occurring malignant disease, both in terms of impact and mortality. According to Globocan, it is estimated that for the year 2020 there were more than 2 million new cases and 1.7 million deaths from lung cancer, making lung cancer the most common and deadly malignant disease. In Greece, during 2020, almost 9000 new lung cancer cases were diagnosed[1]. Though lung cancer is the leading cause of death in most areas, the incidence rates vary significantly between countries, as they reflect the smoking habits, the socioeconomic status and cultural differences of each country as they evolve over time[2]. In Greece, in 13.8% of all newly diagnosed cancer cases during 2020, the primary location of the malignancy was the lung[2]; though, no further information on the specific features of the patients or their cancer characteristics was available. It is well known that available data for lung cancer epidemiology and specific features of lung cancer patients in Greece are scarce, as there is no official registry for lung cancer. It is unquestionable that epidemiology is the key to understanding the specific features of a disease in a local population, so every scientific information available is important to be collected in order to achieve an insightful perspective on the disease burden in the Greek population. The aim of the study was to record the epidemiological characteristics of patients newly diagnosed with lung cancer, from January 2009 to December 2018 at the Bronchoscopy Unit of a large tertiary Hospital of Greece and

Pneumon 2024;37(1):3
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to compare them with similar data from previous years from the international literature, in order to investigate potential differences in the features of the local population.

METHODS

This was a retrospective epidemiological cohort study. For this study we used data retrieved from the Bronchoscopy Unit database of the Pulmonology Department of the General Hospital 'Evangelismos', which is one of the largest tertiary hospitals in Greece. The Bronchoscopy Unit follows yearly a large number of patients which undergo bronchoscopy for diagnostic or therapeutic purposes.

The aforementioned database contained the retrospective data obtained from all patients diagnosed with neoplastic disease via fiberoptic bronchoscopy (FOB) from January 2009 to December 2018. From the database, we have extracted the demographic data (gender, age, smoking habit), the tumor location based on the computed tomography (CT) scans, bronchoscopy report with associated images, and the histopathology/cytology reports that yielded the diagnosis. The report from the CT performed before the initial bronchoscopy was studied, providing further information regarding staging. The diagnosis in each patient was established by the histopathological examination and/or assessment of the tissue biopsy of transbronchial needle biopsy (TBNB), from the cytology of bronchoalveolar lavage (BAL), washing fluid and brushing.

In this study we only included patients with primary lung cancer and we excluded patients that were diagnosed with a prior history of lung cancer, secondary lung cancer of extra-pulmonary origin, lymphoma or atypia without the confirmation of at least in situ carcinoma.

All the patients of the study had received an initial chest CT, and under the suspicion of a primary lung cancer, further investigation with FOB was scheduled. The results were stratified according to demographics, patient symptoms, CT imaging findings, FOB findings, and histology/cytology. The smoking status of the patients has been recorded based on the information they provided. The exposure has been measured as pack-years, meaning how many cigarettes they have smoked in their lifetime, with a pack equal to 20 cigarettes. A cut-off of 30 pack-years has been used to stratify heavy and light smokers. The current smoking status has been recorded as current smokers for those who continued smoking during the time of diagnosis, ex-smokers for those that had quit at least a year before diagnosis, and never smokers for those that have never been smokers.

All the patients consented to FOB (Olympus video bronchoscope) in our Bronchoscopy Unit. The findings of the bronchoscopy were reported right after the procedure and in most cases pictures of the endoscopic findings were taken.

The pathological types of the tumors had been classified according to the 2021 WHO classification for lung tumors[3] as: 1) Adenocarcinoma (ADLC), 2) Squamous cell carcinoma (SqCLC), and neuroendocrine tumors divided into: 3) Small cell lung cancer (SCLC), 4) Large cell neuroendocrine carcinoma (LCNEC), and 5) Adenosquamous carcinoma (combined type). Some non-small cell lung cancer types (NSCLC) that could not be further specified were classified as: 6) Not otherwise specified (NOS), and finally 7) Other, all the rare types found that cannot be classified in one of the previous categories.

Statistical analysis

Categorical variables are presented as mean and standard deviation (SD), and qualitative variables as absolute and relative frequencies. For comparisons of proportions, chi-squared and Fisher's exact tests were used. Student's t-tests were computed for comparison of mean values when the distribution was approximately symmetric. All p values reported are two-tailed. Statistical significance was set at 0.05 and analyses were conducted using SPSS 23.0 software.

RESULTS

A total of 637 patients were diagnosed with primary lung cancer between January 2009 and December 2018 at the Bronchoscopy Unit of the Pulmonary Department of the 'Evangelismos' Hospital. In all cases, the diagnosis was made through Fiberoptic Bronchoscopy, after the endoscopic acquisition of endobronchial sampling, transbronchial sampling, bronchial washing fluid, bronchial brushing and/or bronchoalveolar lavage (BAL), and the subsequent histopathological and/or cytological examinations.

Epidemiology

The patients' age ranged 36–91 years, but the majority (57.6%) of patients were aged 50–69 years at the time of diagnosis. Very few patients (3.3%) were aged <49 years. The mean age of the patients was 66 years and the median age of the patients was also 66 years. The majority of patients were men (77.1%) and only 22.9% were women (Table 1). In terms of smoking history, there is a significant percentage of missing data, but most of the patients were active smokers at the time of diagnosis (74.3%). Less than 10% had never been smokers and the majority had over 30 pack-years (Table 1).

At the time of diagnosis distant metastases were confirmed in 389 (61%) patients and 450 (70%) had enlarged lymph nodes in the mediastinum or other locations, as detected by the CT chest. Thirteen patients were classified as stage I or II, identified by CT scan and bronchoscopy, without further investigation. Even though the location of the primary tumor was the lungs for all patients, 48.7% had main symptoms from the respiratory system. The most common initial complaint of the patients was persistent cough (15.4%), symptoms from distant metastases (15.1%), and general symptoms (e.g. fatigue, fever, weight loss) (14%). A significant proportion of the patients (14.9%) had no symptoms at the time of diagnosis and the detection of the

Table 1. Demographic data, main symptom, computed tomography images and endobronchial findings from fiberoptic bronchoscopy of the patients at the time of diagnosis with primary lung cancer

	n (%)
Age (years)	
<40	2 (0.3)
40–49	19 (3.0)
50–59	128 (20.2)
60–69	238 (37.5)
70–79	184 (29.0)
≥80	64 (10.1)
Missing	2
Gender	
Male	491 (77.1)
Female	146 (22.9)
Smoking habit (pack-years)	
No	35 (8.2)
<29	17 (4.0)
≥30	376 (87.9)
Missing	209
Smoking status	
Never	35 (7.7)
Current smoker	338 (74.3)
Ex-smoker (quit >1 year)	82 (18.0)
Missing	181
Symptoms	
Cough	98 (15.4)
Distal metastases	96 (15.1)
Random finding	95 (14.9)
General symptoms	89 (14.0)
Hemoptysis	82 (12.9)
Dyspnea	71 (11.1)
Chest pain	56 (8.8)
Other/no data	50 (7.9)
Computed tomography findings	
Mass/nodule	368 (57.8)
Distal metastases	136 (21.4)
Pleural effusion	56 (8.8)
Mediastinal lymph node enlargement	32 (5.0)
Atelectasis	28 (4.4)
Consolidation–ground glass opacity	15 (2.4)
Other	2 (0.3)
Endobronchial findings (FOB)	
Endobronchial mass	235 (36.9)
Submucosal infiltration	215 (33.8)
No visible lesion	112 (17.6)
External pressure	73 (11.5)
Other	2 (0.3)

FOB: fiberoptic bronchoscopy.

malignancy was an incidental finding (Table 1).

In the initial CT scan performed before the FOB that set the diagnosis, the most common finding was one or more nodules or masses in the lungs. Although in most cases the chest CT scan showed findings located in the lung parenchyma or bronchi, about one-fourth of the patients had only findings outside of the lungs, most commonly from metastatic locations. In less than 10% of the cases, the main finding was a pleural effusion, atelectasis, ground glass opacities, consolidation or mediastinal lymph node enlargement (Table 1). A FOB has been performed in all patients and the histological/cytological examinations of collected specimens established the diagnosis. Though, 36.9% of the patients presented a visible endobronchial lesion, the remainder featured the presence of a submucosal lesion, external pressure at the bronchi, or no pathological

Table 2. Histopathological type of the tumor and location of the primary lung cancer lesion at the time of diagnosis

Diagnosis	n (%)
Histopathological type of tumor	
ADLC	202 (31.7)
SqCLC	169 (26.5)
SCLC	165 (25.9)
NSCLC NOS	67 (10.5)
LCNEC	9 (1.4)
Combined	5 (0.8)
Other	20 (3.1)
Location	
Right lung (RL)	252 (39.6)
Right upper lobe (RUL)	163 (25.9)
Right middle lobe (RML)	29 (4.6)
Right lower lobe (RLL)	60 (9.4)
Left lung (LL)	140 (22.0)
Left upper lobe (LUL)	82 (12.9)
Lingula	7 (1.1)
Left lower lobe (LLL)	51 (8.0)
>1 lobe ipsilateral	132 (27.0)
>1 lobe contralateral	40 (6.3)
Outside lung parenchyma/bronchi	29 (4.6)
Mediastinum	12 (1.9)
Trachea	17 (2.7)
Unidentified primary location	44 (6.9)

ADLC: adenocarcinoma. SqCLC: squamous cell carcinoma. SCLC: small cell lung cancer. NSCLC: non-small cell lung cancer. NOS: no otherwise specified. LCNEC: large cell neuroendocrine carcinoma.

Table 3. Correlation of the location of the primary lesions with the symptoms of the patients, the presence of lymphadenopathy, the endobronchial findings from fiberoptic bronchoscopy and computed tomography findings at the time of diagnosis

Factors	Location										
	RUL	RML	RLL	LUL	LLL	LG	MS	TR	>1 lesion ipsilateral	>1 lesion contralateral	UPL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Symptoms (p<0.001)											
Hemoptysis	20 (12.3)	7 (24.1)	9 (15.0)	11 (13.4)	9 (17.6)	1 (14.3)	0 (0)	2 (11.8)	16 (12.1)	7 (17.5)	0 (0)
Cough	36 (22.1)	5 (17.2)	9 (15.0)	9 (11.0)	6 (11.8)	0 (0)	0 (0)	2 (11.8)	21 (15.9)	7 (17.5)	1 (4.8)
Dyspnea	13 (8.0)	2 (6.9)	7 (11.7)	9 (11.0)	3 (5.9)	0 (0)	2 (16.7)	4 (23.5)	20 (15.2)	8 (20.0)	0 (0)
Chest pain	11 (6.7)	3 (10.3)	8 (13.3)	8 (9.8)	5 (9.8)	0 (0)	1 (8.3)	0 (0)	10 (7.6)	4 (10.0)	4 (19.0)
General symptoms	19 (11.7)	4 (13.8)	7 (11.7)	15 (18.3)	7 (13.7)	1 (14.3)	5 (41.7)	5 (29.4)	19 (14.4)	3 (7.5)	1 (4.8)
Secondary locations	26 (16.0)	4 (13.8)	10 (16.7)	10 (12.2)	8 (15.7)	1 (14.3)	0 (0)	2 (11.8)	16 (12.1)	6 (15.0)	8 (38.1)
Random finding	26 (15.9)	3 (10.3)	6 (10.0)	14 (17.1)	13 (25.5)	2 (28.6)	3 (25.0)	0 (0)	12 (10.3)	3 (7.5)	4 (19.0)
Other/No data	12 (7.4)	1 (3.4)	4 (6.7)	6 (8.3)	0 (0)	2 (28.6)	1 (8.3)	2 (11.8)	15 (11.4)	2 (5.0)	3 (14.3)
Lymphadenopathy (p<0.001)											
Yes	119 (73)	17 (58.6)	44 (73.3)	42 (51.2)	32 (62.7)	3 (42.9)	10 (83.3)	12 (70.6)	92 (69.7)	39 (97.5)	21 (100)
No	44 (27)	12 (41.4)	16 (26.7)	40 (48.8)	19 (37.3)	4 (57.1)	2 (16.7)	5 (29.4)	40 (30.3)	1 (2.5)	0 (0)
Endobronchial findings (FOB) (p<0.001)											
No visible lesion	16 (9.8)	2 (6.9)	14 (23.3)	11 (13.4)	12 (23.5)	3 (42.9)	7 (58.3)	0 (0)	5 (3.8)	3 (7.5)	19 (90.5)
Endobronchial mass	75 (46.1)	12 (42.4)	23 (38.4)	38 (46.3)	19 (37.2)	3 (42.9)	2 (16.6)	8 (47.1)	0 (0)	1 (2.5)	0 (0)
Submucosal infiltration	50 (30.7)	12 (41.4)	12 (20.0)	26 (31.7)	13 (25.5)	1 (14.3)	0 (0)	8 (47.1)	73 (55.3)	20 (50.0)	0 (0)
External pressure	22 (13.5)	3 (10.3)	11 (18.3)	7 (8.5)	6 (11.8)	0 (0)	3 (25.0)	1 (5.9)	13 (9.8)	3 (7.5)	1 (4.8)
Other	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.0)	0 (0)	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)
Computed tomography findings (p<0.001)											
Mass/nodule	101 (62)	14 (48.3)	33 (55.0)	52 (63.4)	38 (74.5)	5 (71.4)	5 (41.7)	9 (52.9)	73 (55.3)	17 (42.5)	5 (23.8)

Continued

Pneumon 2024;37(1):3
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Table 3. Continued

Factors	Location										
	RUL	RML	RLL	LUL	LLL	LG	MS	TR	>1 lesion ipsilateral	>1 lesion contralateral	UPL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Atelectasis	7 (4.3)	4 (13.8)	1 (1.7)	5 (6.1)	1 (2.0)	0 (0)	0 (0)	0 (0)	10 (7.6)	0 (0)	0 (0)
Pleural effusion	6 (3.7)	2 (6.9)	7 (11.7)	6 (7.3)	3 (5.9)	0 (0)	0 (0)	3 (17.6)	19 (14.4)	5 (12.5)	3 (14.3)
Consolidation-GGO	7 (4.3)	0 (0)	2 (3.3)	2 (2.4)	0 (0)	0 (0)	0 (0)	1 (5.9)	2 (1.5)	0 (0)	0 (0)
Lymph node enlargement	7 (4.3)	3 (10.3)	2 (3.3)	1 (1.2)	1 (2.0)	1 (14.3)	4 (33.3)	2 (11.8)	5 (3.8)	1 (2.5)	3 (14.3)
Metastatic lesions	35 (21.5)	6 (20.7)	14 (23.3)	16 (19.5)	8 (15.7)	0 (0)	3 (25.0)	2 (11.8)	23 (17.4)	17 (42.5)	10 (47.6)
Other	0 (0)	0 (0)	1 (1.7)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

RUL: right upper lobe. RML: right middle lobe. RLL: right lower lobe. LUL: left upper lobe. LLL: left lower lobe. LG: lingula. MS: mediastinum. TR: trachea. UPL: unidentified primary lesion. CT: computed tomography. GGO: ground glass opacity. FOB: fiberoptic bronchoscopy.

Pneumon 2024;37(1):3
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findings (Table 1).

As far as endoscopic inspection at the time of diagnosis, the most commonly observed finding was an endobronchial mass (36.9%), but in only 2.4% of the patients the endobronchial mass caused signs of bronchial obstruction. In a significant proportion (17.6%), no visible lesion had been detected during bronchoscopy and the diagnosis was made without direct visualization of the lesion under the guidance of CT images and endobronchial ultrasound (EBUS).

The most common histopathological diagnosis was adenocarcinoma (ADLC) (31.7%), followed by squamous cell carcinoma (SqCLC) and small cell carcinoma (SCLC) (26.5% and 25.9%, respectively). A less commonly observed diagnosis was non-small-cell-lung carcinoma non-otherwise-specified (NSCLC-NOS). Various not commonly observed histopathological diagnoses had appeared in a very small percentage and were grouped under the term 'Other', and 57.8% of the patients had a solitary lesion in the lungs and only in a small percentage the lesion was not identified inside the lung parenchyma or the bronchi. In the majority of patients, the lesion was located in the right lung (39.6%) and more specifically in the right upper lobe (RUL) (25.9%). The upper lobes in both lungs were generally a common location for a primary lesion (35.6%) (Table 2).

Correlation of the primary tumor location with other characteristics of the patients and tumor features

The location of the primary tumor correlated with statistical significance to specific characteristics of the patients' symptomatic presentation during the initial assessment ($p<0.001$); this p-value applies to the general category of symptoms, meaning that the symptoms of the patients were statistically significant related to the location of the tumor (Table 3). When the location of the primary tumor was in the right middle lobe (RML), they presented most frequently with hemoptysis (24.1%). The patients with a primary lesion in the RUL experienced cough more often (22.1%) and the patients with findings only in the mediastinum had mainly general systemic symptoms (41.7%).

The patients presented more often with lymph node enlargement, as detected at the initial CT assessment when their primary tumor was located in the RUL, right lower lobe (RLL), mediastinum or when they presented with multiple ipsilateral or contralateral lesions ($p<0.001$) (Table 3).

The patients smoking history showed no statistically significant correlation with the location of the tumor ($p=0.222$). Submucosal infiltration was the most commonly observed endoscopic sign for multiple lung lesions, as seen in 55.3% of cases with more than one ipsilateral lesion and 50% of cases with multiple contralateral lesions. When the lesion was located in the RUL or RML, it was most commonly visualized endobronchially ($p<0.001$), with exception in lesions located in the lingula and thus not easily accessible. Distant metastases were identified more often when the patients had multiple pulmonary contralateral lesions (42.5%) on their initial CT scan, and pleural effusions were present most commonly in patients who had multiple ipsilateral lesions (14.4%). When the main lesion was located in the left lung, the CT showed a mass or nodule in almost all cases but in the right lung we often had other findings, such as consolidations, ground glass opacities (GGOs), atelectasis or distant metastases ($p<0.001$) (Table 3).

Correlation of the primary tumor pathology with other characteristics of the patients and tumor features

The majority of patients were smokers, a finding independent of the histological type of the tumor (Table 4). Among the thirty-five non-smoker patients, seventeen of them had an ADLC, there was though a small number of five non-smokers with SCLC ($p=0.028$); this p-value and all relevant p-values apply to the general categories compared and not to an individual characteristic. Half of the patients with ADLC or neuroendocrine tumors had recognizable distant metastases at the time of diagnosis, but this percentage was significantly lower for patients with SqCLC (27.2%) ($p<0.001$) (Table 4). Comparing the histological type of the tumor with the CT findings, patients with neuroendocrine tumors had a higher rate of metastatic disease (27.3%) than other histological types, and patients with SqCLC had more often a solitary mass or nodule at initial imaging (65.1%) ($p<0.001$). The evidence of lymph node involvement from the CT was not correlated with statistical significance to the histologic diagnosis ($p=0.063$) (Table 4).

Correlation of the patients' symptoms with other characteristics of the patients and tumor features

Irrespective of the main presenting symptom, the most common radiological sign was a mass or nodule located in the lungs. Though, in patients who presented with symptoms attributable to distant metastases, the main radiological finding was evidence of metastatic disease (59.4%) (Table 5). Also, patients presenting with dyspnea had an associated pleural effusion (36.6%) and patients with disease located only in the mediastinum presented more often with generalized systemic symptoms (11.2%) ($p<0.001$); this p-value and all relevant p-values apply to the general categories compared and not to an individual characteristic.

Patients presenting with dyspnea, chest pain or generalized symptoms had an associated lymphadenopathy with a prevalence of approximately 70%, but when presenting with hemoptysis this percentage was lower (53.7%). Almost all the patients who presented with symptoms from distant metastases had pathologically enlarged lymph nodes at the CT scan at the time of diagnosis (92.7%) ($p<0.001$).

Finally, when comparing the endobronchial findings during the FOB that established the diagnosis with the existence of distant metastases, a lower rate of metastases was observed when the main finding was an endobronchial mass (30.2%)

Table 4. Correlation of histopathologic type of the cancer with the smoking habit of the patients, the existence of distal metastases and the computed tomography findings

Factors	Histopathological type						
	ADLC	SqCLC	SCLC	NSCLC NOS	Combined	LCNEC	Other
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Smoking habit (p=0.028)							
Yes	130 (88.4)	114 (94.2)	106 (95.5)	29 (93.5)	2 (100)	5 (100)	7 (63.6)
No	17 (11.6)	7 (5.5)	5 (4.5)	2 (6.5)	0 (0)	0 (0)	4 (36.4)
Distal metastases (p=0.007)							
Yes	91 (45.0)	46 (27.2)	71(43.0)	26 (38.8)	3 (60.0)	5 (55.6)	6 (30.0)
No	111 (55.0)	123 (72.8)	94 (57.0)	41 (61.2)	2 (40.0)	4 (44.4)	14 (70.0)
Computed tomography findings (p<0.001)							
Mass/nodule	114 (56.4)	110 (65.1)	84 (50.9)	37 (55.2)	4 (80.0)	5 (55.6)	14 (70.0)
Atelectasis	5 (2.5)	16 (9.5)	4 (2.4)	2 (3.0)	0 (0)	0 (0)	1 (5.0)
Pleural effusion	24 (11.9)	12 (7.1)	14 (8.5)	5 (7.5)	0 (0)	0 (0)	1 (5.0)
Consolidation-GGO	3 (1.5)	5 (3.0)	3 (1.8)	2 (3.0)	0 (0)	0 (0)	2 (10.0)
Lymph node enlargement	7 (3.5)	2 (1.2)	15 (9.1)	5 (7.5)	0 (0)	3 (33.3)	0 (0)
Metastatic lesions	49 (24.3)	23 (13.6)	45 (27.3)	15 (22.4)	1 (20.0)	1 (11.1)	2 (10.0)
Other	0 (0)	1 (0.6)	0 (0)	1 (1.5)	0 (0)	0 (0)	0 (0)

ADLC: adenocarcinoma. SqCLC: squamous cell carcinoma. SCLC: small cell lung cancer. NSCLC: non-small cell lung cancer. NOS: no otherwise specified. LCNEC: large cell neuroendocrine carcinoma. CT: computed tomography. GGO: ground glass opacity.

Table 5. Correlation of the symptoms of the patients with the computed tomography findings and the presence of lymphadenopathy

Factors	Symptoms							
	Hemoptysis	Cough	Dyspnea	Chest pain	General symptoms	Secondary locations	Random finding	Other/ no data
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Computed tomography findings (p<0.001)								
Mass/nodule	61 (74.4)	72 (73.5)	26 (36.6)	34 (60.7)	49 (55.1)	25 (26.0)	66 (78.6)	10 (71.4)
Atelectasis	5 (6.1)	6 (6.1)	2 (2.8)	2 (3.6)	5 (5.6)	2 (2.1)	1 (1.2)	0 (0)
Pleural effusion	4 (4.9)	5 (5.1)	26 (36.6)	6 (10.7)	4 (4.5)	3 (3.1)	2 (2.4)	1 (7.14)
Consolidation–GGO	0 (0)	2 (2.0)	1 (1.4)	2 (3.6)	5 (5.6)	4 (4.2)	1 (1.2)	0 (0)
Lymph node enlargement	3 (3.7)	1 (1.0)	4 (5.6)	1 (1.8)	10 (11.2)	5 (5.2)	3 (3.6)	2 (14.3)
Metastatic lesions	9 (11.0)	12 (12.2)	12 (16.9)	11 (19.6)	16 (18.0)	57 (59.4)	11 (13.1)	1 (7.14)
Lymphadenopathy (p<0.001)								
Yes	34 (53.7)	67 (68.4)	55 (77.5)	41 (73.2)	62 (69.7)	89 (92.7)	42 (62.2)	31 (62.0)
No	38 (46.3)	31 (31.6)	16 (22.5)	15 (26.8)	27 (30.3)	7 (7.3)	37 (37.8)	19 (38.0)

GGO: ground glass opacity.

or external pressure at the bronchi (38.4%). In the rest of the cases, this percentage was close to 50% (p<0.001) (Table 5).

DISCUSSION

Epidemiological data concerning the distribution and determinants of lung cancer in Greece are scarce, as there is no official registry for lung cancer. The objective of this study was to record and analyze basic epidemiological, clinical, radiological, bronchoscopic and histopathological/cytological data of lung cancer cases in Greece. During the aforementioned period, the diagnosis of primary lung cancer was established in 637 patients. As the exact number of lung cancer cases diagnosed in Greece during the same period is unknown, we cannot safely assume if the number of cases diagnosed in our Center is representative of the total cases in Central Greece. We can only compare our results with previous studies conducted in other Greek regions.

The mean age of the patients in our study was 66 years and the median age was 66 years, with a high proportion (57.6%) of patients aged 50–69 years. The majority of patients were men (77.1%) and active smokers at the time of diagnosis (74.3%). Two previous studies have also recorded lung cancer cases in larger populations, similarly to our study. Kontakiotis et al.[4] analyzed 9981 patients from northern Greece with bronchoscopic specimens positive for lung cancer over two decades (1986–2005). The mean age of all patients was 63.6 ± 9.3 years, while men represented the vast majority of the patients (92%). A second more recent study by Sifaki-Pistolla et al.[5] analyzed 5509 primary lung cancer cases diagnosed from 1992 to 2013 on the Greek island of Crete. Patients were mostly males (87.3%), aged >55 years (20.4% aged 55–64; and 35.2% aged 65–74). A positive smoking history was present in 75.1% of the cases[5]. One could hypothesize that in Greek populations the obvious predominance of males amongst lung cancer patients may be attributed, at least partly, to their smoking patterns[6,7]. Nevertheless, non-smoking related risk factors may also be important for the sex disparities in lung cancer incidence[8,9].

In our cohort study the most common radiological finding was the presence of one or more nodules or masses in the lungs. Less commonly (<10%), the initial radiological examination revealed pleural effusion, atelectasis, ground glass opacities, consolidation or mediastinal lymph node enlargement. Concerning patients with pulmonary lesions, two-thirds of them presented with a solitary lesion, most commonly located in one of the upper lobes and predominantly in RUL. This finding is in line with previous published results in Greek lung cancer patients by Kontakiotis et al.[4]. Other earlier studies have also reported a preference of lung cancer for the upper lobes[10,11]. This predilection of lung tumors to the upper lobes could be attributed to various anatomical and physiological factors that render the upper lobe vulnerable[12], including a more prolonged and intense contact with tobacco smoke inhalation[10]. It should be noted that in one-quarter of our cases, extrapulmonary metastatic lesions represented the only visible finding.

According to previous data, a substantial percentage of lung cancer cases in asymptomatic patients are detected upon radiological evaluation[13-15]. In our study, about 15% of our patients were asymptomatic at the time of diagnosis. Unfortunately, it is known that patients with lung cancer usually present late and around 80% of them have stage III or IV disease at presentation[16]. In accordance with this, most of our patients showed distant metastases or lymph node enlargement at the time of the diagnosis. Lymph node enlargement and distant metastases were more common in the presence of multiple pulmonary lesions. Thus, in our study the vast majority of patients were identified at stage III or higher by means of the initial CT scan and bronchoscopy. Similarly in the study of Sifaki-Pistolla et al.[5], most patients (61.6%) were diagnosed at stage IIIA or higher.

Lung cancer may present with non-specific systemic symptoms of fever, weakness, anorexia, and weight loss, or with a wide range of direct signs and symptoms, most commonly dyspnea, cough, hemoptysis, hoarseness, chest and shoulder pain[17,18]. Respiratory symptoms were present in about half of the patients of our study, while general symptoms were very common. Interestingly, our study showed that the frequency of certain symptoms seems to differ depending on the anatomic location of the malignant pathology. Hemoptysis was more frequent in lesions of the RML, while cough was more common in lesions of the RUL. Patients with isolated mediastinal pathology had mainly general symptoms. In patients complaining about dyspnea, the presence of a pleural effusion was more likely. Finally, lymph node enlargement was evident in chest CT scans with a higher frequency in the presence of dyspnea, chest pain, general symptoms or symptoms from distant metastases.

The fiberoptic bronchoscopy (FOB) represents a very valuable tool for the diagnosis and staging of lung cancer patients[19]. In our study, bronchoscopic findings included the presence of an endobronchial mass or submucosal pathology or external pressure at the bronchi. Endobronchial tumors were the most common finding as they were detected in 36.9% of the patients. Nonetheless, bronchial obstruction was rarely noticed. It should be noted that in about 18% of the cases, bronchoscopic examination did not reveal any visible lesion. This can be expected especially in peripheral lung cancers. Hence, the diagnosis was made without direct visualization of the lesion, but based on CT images and the use of EBUS. Submucosal infiltration was more common in the presence of multiple lung lesions, while visible endobronchial masses were more frequently located in RUL or RML. Finally, when the main bronchoscopic finding was an endobronchial mass or external pressure on the bronchial lumen, the presence of distant metastases was less frequent.

In our cohort of patients, ADLC was the most common histopathological type as it appeared in about one-third (31.7%) of cases. SqCLC and SCLC appeared almost equally in about one-quarter of the cases, respectively. This finding

is in line with previous studies reporting NSCLC as the predominant type accounting for 85% of all cases[20]. Other histopathological types appeared in very small percentages. The majority of our patients were smokers, independently of the histological type of the tumor. This seems to be in agreement with previous knowledge linking all histological subtypes with tobacco use[20]. Similarly to previous findings, our results showed a significant frequency of ADLC in non-smokers[21]. Our study provided interesting correlations of the histopathology of lung cancer with radiological characteristics. Recognizable distant metastases at the time of the diagnosis were more frequent when the histopathological diagnosis was ADLC compared with SqCLC. Moreover, when initial imaging revealed a solitary mass or nodule, SqCLC was the most commonly observed diagnosis. Radiologically evident lymph node involvement showed no correlation with any histological diagnosis.

Strengths and limitations

The most important strength of this study is that the data come from a significant number of lung cancer patients over a large period of time and a large amount of information regarding demographic data, tumor and patient features have been recorded. Even though 'Evangelismos' Hospital is one of the largest tertiary Hospitals in Greece, the number of cases diagnosed in our Bronchoscopic Unit is not representative of all Greek cases and this is a significant limitation of this study. Also, there is a significant number of missing data, mainly because we could not follow up the patients after diagnosis, for the information about the exact stage, the course of disease or the treatment followed.

Implications

The information that we have for newly diagnosed lung cancer cases in Greece is limited. The main problem is that there is not an accurate data collection method in every Center and the registry of cases is not mandatory. In the future, a national registry of lung cancer cases in Greece should be established. This includes the cooperation between large reference lung cancer centers and the establishment of a network of lung cancer specialists so a large database of primary lung cancer cases can be formed[22].

CONCLUSIONS

In Greece, the histological distribution of lung cancer has changed over the years showing a trend in increased ADLC percentage. Furthermore, the proportion of women presenting with lung cancer over the last decades has increased, which reflects on the increasing number of female smokers. Patients with lung cancer are diagnosed in more advanced stages, and, as a result, the chances for curative treatment are reduced. All of the above underline the need of more effective tobacco control strategies and for the establishment of official screening programs for the early detection of pulmonary malignancies.

CONFLICTS OF INTEREST

The authors have completed and submitted to ICMJE for Disclosure of Potential Conflicts of Interest and none was reported.

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There was no source of funding for this research.

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this retrospective study.

DATA AVAILABILITY

The data supporting this research are available from the authors upon reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer-reviewed.

REFERENCES

1. Cancer Today. Global Cancer Observatory. 2020. Accessed September 2023. https://gco.iarc.fr/today/home
2. Lung Cancer. World Health Organization. June 26, 2023. Accessed September 2023. https://www.who.int/news-room/fact-sheets/detail/lung-cancer
3. Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO Classification of Lung Tumors: Impact of Advances Since 2015. J Thorac Oncol. 2022;17(3):362-387. doi:10.1016/j.jtho.2021.11.003
4. Kontakiotis T, Manolakoglou N, Zoglopitis F, et al. Epidemiologic trends in lung cancer over two decades in Northern Greece: an analysis of bronchscopic data. Monaldi Arch Chest Dis. 2009;71(4):147-152. doi:10.4081/monaldi.2009.346
5. Sifaki-Pistolla D, Lionis C, Georgoulias V, et al. Lung cancer and tobacco smoking in Crete, Greece: reflections from a population-based cancer registry from 1992 to 2013. Tob Induc Dis. 2017;15:6. doi:10.1186/s12971-017-0114-2
6. Gikas A, Merkouris P, Skliros E, Sotiropoulos A. Urban-rural differences in smoking prevalence in Greece. Eur J Public Health. 2007;17(4):402. doi:10.1093/eurpub/ckm055
7. Filippidis FT, Vardavas CI, Loukopoulou A, Behrakis P, Connolly GN, Tountas Y. Prevalence and determinants of tobacco use among adults in Greece: 4 year trends. Eur J Public Health. 2013;23(5):772-776. doi:10.1093/eurpub/cks148
8. Hellyer JA, Patel MI. Sex disparities in lung cancer incidence: validation of a long-observed trend. Transl Lung Cancer Res. 2019;8(4):543-545. doi:10.21037/tlcr.2019.04.06
9. Stapelfeld C, Dammann C, Maser E. Sex-specificity in lung cancer risk. Int J Cancer. 2020;146(9):2376-2382. doi:10.1002/ijc.32716
10. Celikoğlu SI, Aykan TB, Karayel T, Demirci S, Göksel FM. Frequency of distribution according to histological types of lung cancer in the tracheobronchial tree. Respiration.

1986;49(2):152-156. doi:10.1159/000194873
11. Pavlovska I, Danilovski D, Orovchanec N, Stefanovski T, Taushanova B, Ivanovska-Zafirova B. An epidemiologic study of some characteristics of lung cancer. Folia Med (Plovdiv). 2004;46(3):23-31.
12. Casha AR, Manché A, Gauci M, Navarro A, Farrugia E. Common Pathophysiological Pathways for Apical and Upper Lobe Lung Disease. J Infect Dis Epidemiol. 2018;4:053. doi:10.23937/2474-3658/1510053
13. Jett JR, Midthun DE. Commentary: CT screening for lung cancer-Caveat Emptor. Oncologist. 2008;13(4):439-444. doi:10.1634/theoncologist.2008-0027
14. In KH, Kwon YS, Oh IJ, et al. Lung cancer patients who are asymptomatic at diagnosis show favorable prognosis: A Korean Lung Cancer Registry Study. Lung Cancer. 2009;64(2):232-237. doi:10.1016/j.lungcan.2008.08.005
15. Alanen V, Koivunen JP. Association of diagnostic delays to survival in lung cancer: single center experience. Acta Oncol. 2019;58(7):1056-1061. doi:10.1080/0284186X.2019.1590635
16. Pearson FG. Current status of surgical resection for lung cancer. Chest. 1994;106(6 Suppl):337S-339S. doi:10.1378/chest.106.6_supplement.337s
17. Hyde L, Hyde CI. Clinical manifestations of lung cancer. Chest. 1974;65(3):299-306. doi:10.1378/chest.65.3.299
18. Collins LG, Haines C, Perkel R, Enck RE. Lung cancer: diagnosis and management. Am Fam Physician. 2007;75(1):56-63. Accessed October 31, 2023. https://www.aafp.org/pubs/afp/issues/2007/0101/p56.pdf
19. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e142S-e165S. doi:10.1378/chest.12-2353
20. Belani CP, Marts S, Schiller J, Socinski MA. Women and lung cancer: epidemiology, tumor biology, and emerging trends in clinical research. Lung Cancer. 2007;55(1):15-23. doi:10.1016/j.lungcan.2006.09.008
21. Marquez-Garban DC, Mah V, Alavi M, et al. Progesterone and estrogen receptor expression and activity in human non-small cell lung cancer. Steroids. 2011;76(9):910-920. doi:10.1016/j.steroids.2011.04.015
22. Rich A, Baldwin D, Alfageme I, et al. Achieving Thoracic Oncology data collection in Europe: a precursor study in 35 Countries. BMC Cancer. 2018;18:1144. doi:10.1186/s12885-018-5009-y

Drug-overdose associated acute hypoxemic respiratory failure: A secondary analysis

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ABSTRACT

INTRODUCTION The majority of fatal drug overdose cases are due to acute hypoxemic respiratory failure (AHRF). We examined whether AHRF associated with drug overdose has distinct features from AHRF associated with other risk factors.

METHODS We performed a secondary analysis of patient-level data from the LOTUS FRUIT study, a multicenter, prospective, observational study conducted by the PETAL Network. We classified patients with AHRF into the 'drug-overdose associated AHRF' (when PETAL investigators listed drug overdose as a risk factor of AHRF) versus the 'non-drug-overdose associated AHRF' group. To assess the association between drug overdose and 28-day mortality, we used a Cox proportional hazards regression analysis, both unadjusted and adjusted, and a mediation analysis.

RESULTS Of the 1280 patients with AHRF, 48 (3.8%) had drug-overdose associated AHRF. They were younger (42.0 vs 60.0 years), more likely to develop rapidly improving AHRF (50.0% vs 24.5%) and had lower unadjusted mortality than patients with non-drug-overdose associated AHRF (16.7% vs 34.4.%) (hazard ratio, HR=0.450; 95% CI: 0.223–0.905). However, after adjustment, drug overdose was no longer associated with lower mortality (adjusted hazard ratio, AHR=0.584; 95% CI: 0.288–1.185). Also, in mediation analysis, lower unadjusted mortality among patients with drug-overdose AHRF was significantly mediated by the development of rapidly improving AHRF ($p<0.001$ for the average causal mediation effect).

CONCLUSIONS Patients with drug-overdose associated AHRF were younger and had lower unadjusted mortality than patients with non-drug-overdose associated AHRF. However, this difference in mortality seemed to be due to confounders, such as age, and to be mediated by the development of rapidly improving AHRF.

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INTRODUCTION

Drug overdose is a serious public health problem requiring increasing usage of intensive care resources globally[1]. In the United States, the number of patients with drug overdose requiring admission to the intensive care unit (ICU) significantly increased by 34% between 2009 and 2015[2]. Around one in four of those patients presented with acute hypoxemic respiratory failure (AHRF)[2]. Potential mechanisms of drug-related AHRF may include (but not limited to): 1) impairment of consciousness leading to aspiration and subsequent pneumonia, and 2) direct insult of the lung parenchyma leading to pulmonary capillary leak and subsequent non-cardiogenic pulmonary oedema. The latter appears after abuse of opioids (such as heroin), cocaine, and amphetamines[3]. No matter what the underlying mechanism is, AHRF may be present in about 95% of fatal drug overdose cases[4,5], which substantially increased during the pandemic of the new coronavirus disease[6].

Although drug overdose is a recognized risk factor of AHRF, accounting for almost 2% of AHRF cases according to the large multicenter epidemiological LUNG SAFE study[7], a direct comparison between drug overdose and other risk factors of AHRF seems lacking in the literature. It is not, therefore, well known whether AHRF associated with drug overdose has distinct features compared to AHRF associated with other risk factors. We hypothesized that drug-overdose associated AHRF may be associated with lower mortality compared to non-drug-overdose associated AHRF, probably due to confounders. For this reason, we endeavoured to compare the clinical characteristics and outcomes of patients with AHRF associated or not with drug overdose.

METHODS

Study design and patient population

We performed a secondary analysis of individual patient-level data from the LOTUS FRUIT study[8]. The LOTUS FRUIT study

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was a multicenter, prospective, observational cohort study conducted by the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network and enrolled consecutive adult patients with acute respiratory failure who were admitted to ICU and received invasive mechanical ventilation[8]. Up to 100 patients per participating hospital were enrolled during a 30-day period between 1 July and 1 October 2016, and were followed until hospital discharge or day 28. Patients receiving chronic invasive mechanical ventilation through a tracheostomy, patients admitted to the ICU after elective surgery, those presenting to the hospital after more than a day of invasive mechanical ventilation, or those extubated before being transferred to the ICU, were excluded.

For the present secondary analysis, we included patients with AHRF following a two-step process. Firstly, given that AHRF necessarily encompasses acute respiratory distress syndrome (ARDS, a severe form of AHRF)[9], we included in our analysis all patients determined by the LOTUS FRUIT investigators to have ARDS on the day of intubation (defined as the partial pressure of arterial oxygen to fraction of inspired oxygen ratio PaO_2:FiO_2 ≤300, not fully explained by cardiac failure or fluid overload, and bilateral infiltrates not fully explained by mass, collapse, or effusion on chest radiography as reviewed by site investigator)[8,10]. Secondly, we included in our analysis patients who did not meet all of the abovementioned criteria of ARDS, but they were intubated due to acute hypoxemia (defined as oxygen saturation SpO_2 <90% or PaO_2 <60 mmHg)[8].

We categorized patients with AHRF into the two compared groups of the present secondary analysis, namely, the 'drug-overdose associated AHRF' group (when drug overdose was mentioned as either the sole risk factor or one of the risk factors associated with AHRF in a given patient) and the 'non-drug-overdose associated AHRF' group (when drug overdose was not mentioned among the risk factors associated with AHRF in a given patient). The latter group of 'non-drug-overdose associated AHRF' also included cases when no risk factor of AHRF was identifiable (256 patients, 20% of the included population)[11,12]. As previously[13,14], the Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung, and Blood Institute provided us with the requested data in a de-identified form after submission of a prospective protocol. The protocol was approved by the Institutional Review Board (protocol number 398/9-11-2022), which also waived the need for informed consent (non-human subjects research).

Outcomes

The primary outcome of the present analysis was 28-day mortality, with patients discharged from the hospital with unassisted breathing prior to 28 days considered to be alive at 28 days. Secondary outcomes were differences in ventilator-free days, ICU-free days and prevalence of rapidly improving AHRF between compared groups through day 28 following intubation. As previously[15,16], ventilator-free days were defined as the number of days from the end of the last period of assisted breathing up to day 28. Hospitalized patients who died before day 28 were considered to have zero ventilator-free days. ICU-free days were defined as the number of days that the patient was alive and not in the ICU. Rapidly improving AHRF was defined as extubation or having a PaO_2 to the fraction of inspired oxygen (FiO_2) ratio greater than 300 on the first day following intubation[17-19].

Statistical analysis

We present continuous variables as median (interquartile range) and compare them using the Mann-Whitney U test. We present categorical variables as frequencies and percentages and compare them using the chi-squared or Fisher's exact test, as appropriate. We assess the association between drug overdose and 28-day mortality (primary outcome) using a Cox proportional hazards regression analysis, both unadjusted and adjusted. The adjusted analysis takes into consideration age and the concurrent (i.e. along with drug overdose) presence of sepsis or shock as risk factors of AHRF. To construct the Cox proportional hazards regression model, we used all available information on outcomes (such as mortality) and the included variables. There were no missing data on outcomes, except from ICU-free days (15.9% missing values).

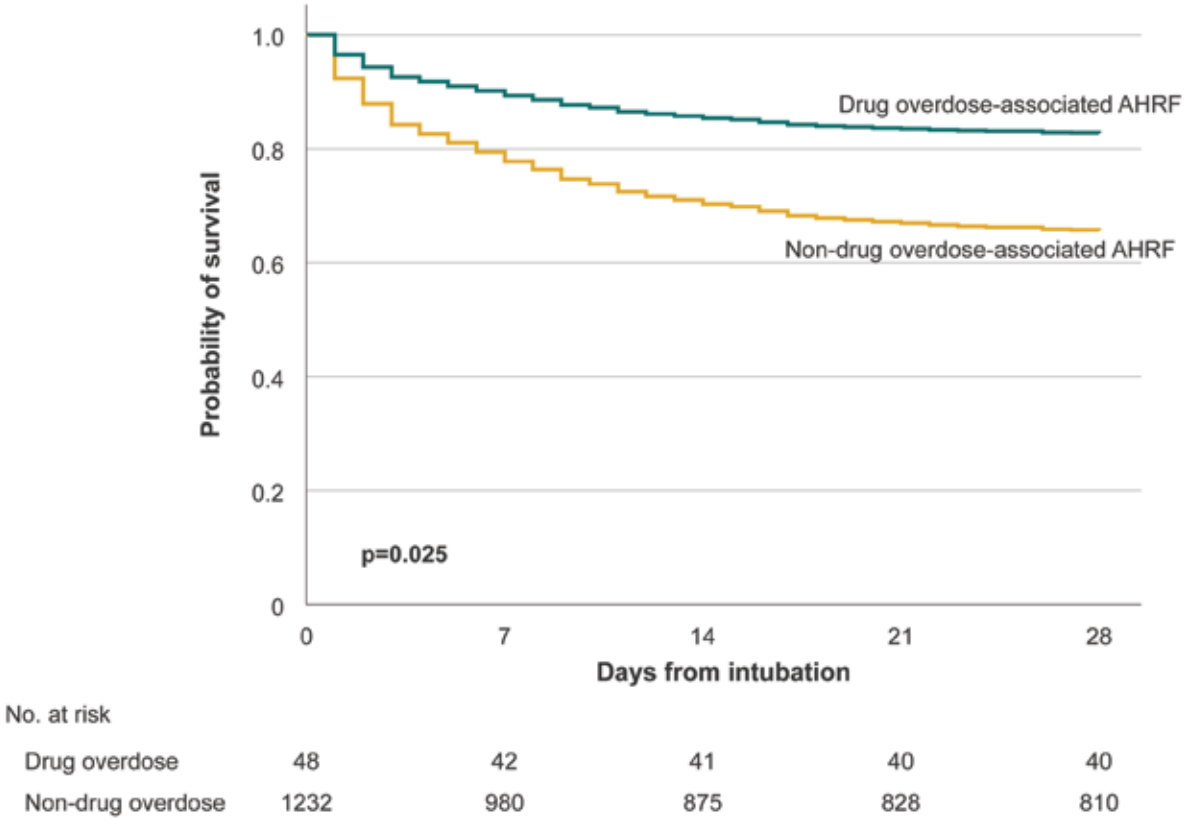
Also, we conducted a mediation analysis[20] by considering drug-overdose associated AHRF as the independent predictor of 28-day mortality and rapidly improving AHRF as the potential mediator. We examined whether variations in the mediator could explain the differential outcomes of patients with drug-overdose associated AHRF as opposed to patients with non-drug-overdose associated AHRF[21]. For the mediation analysis, we applied logistic regression of the generalized linear models to fit the binary mediator and outcome, and we utilized the nonparametric bootstrap for variance estimation. All p values were two-sided, and we considered statistical significance at an α level of 0.05. We conducted all statistical analyses using SPSS software version 28.0 (SPSS, Inc., Chicago, IL) and R software version 4.2.1, with the R Package for Causal Mediation Analysis for the mediation analysis (R Foundation for Statistical Computing).

RESULTS

Baseline characteristics

Supplementary file Figure 1 presents the flow diagram of patients included in the LOTUS FRUIT study. The present secondary analysis included 1280 patients with AHRF, of whom 684 (53.4%) met all definition criteria of ARDS, while the remaining 596 patients (46.6%) only met the acute hypoxemia criterion (Supplementary file Figure 1). Of the 1280 patients with AHRF, 48 (3.8%) had drug-overdose associated AHRF. Table 1 depicts the baseline characteristics of patients with AHRF in each of the compared groups. Patients with drug-overdose associated AHRF were younger

Figure 1. Survival curves of patients with drug-overdose associated acute hypoxemic respiratory failure (AHRF) and non-drug-overdose associated AHRF during a 30-day period between 1 July and 1 October 2016 (N=1280)



For time-to-event analysis from intubation to 28-day mortality, we used an unadjusted Cox proportional-hazards regression model, and we plotted the corresponding Cox-generated estimated survival curves.

(42.0 vs 60.0 years, p<0.001), and were less likely to have sepsis (12.5% vs 29.1%, p=0.012) or shock (6.3% vs 18.1%, p=0.035) as risk factors of AHRF than patients with non-drug-overdose associated AHRF. Compared groups did not differ substantially in terms of organ failures and respiratory variables on the day of intubation. This was also the case for the first day following intubation, i.e. there was no difference between compared groups in terms of PaO_2:FiO_2, tidal volume per predicted body weight, plateau pressure, and respiratory rate (Table 1).

Outcomes of patients

Table 2 depicts the outcomes of patients with AHRF in each of the compared groups. Patients with drug-overdose associated AHRF had lower unadjusted mortality (16.7% vs 34.4%, p=0.011) than patients with non-drug-overdose associated AHRF. In an unadjusted Cox proportional hazards-regression analysis, patients with drug-overdose associated AHRF had lower mortality by day 28 following intubation than patients with non-drug-overdose associated AHRF (hazard ratio, HR=0.450; 95% CI: 0.223–0.905, p=0.025) (Table 3). Figure 1 depicts the corresponding survival curves for each group.

With regard to secondary outcomes (Table 2), patients with drug-overdose associated AHRF, as opposed to non-drug-overdose associated AHRF, had more ventilator-free days (24.5 vs 18.0 days, p<0.001), more ICU-free days (24.0 vs 15.0 days, p<0.001) and were more likely to develop rapidly improving AHRF (50.0% vs 24.5%, p<0.001).

Table 3 depicts a Cox proportional-hazards regression analysis to isolate the contribution of drug overdose, age and the concurrent (i.e. along with drug overdose) presence of sepsis or shock as risk factors of AHRF (independent variables) to the 28-day mortality (dependent variable). In the adjusted analysis, drug overdose was no longer associated with lower mortality among patients with AHRF (adjusted hazards ratio, AHR=0.584; 95% CI: 0.288–1.185, p=0.136).

Given that patients with drug-overdose associated AHRF were more likely to develop rapidly improving AHRF than patients with non-drug-overdose associated AHRF, we conducted a mediation analysis by considering drug-overdose associated AHRF as the independent predictor of 28-day mortality, and rapidly improving AHRF as the potential mediator. The mediation analysis is depicted in

Table 1. Baseline characteristics of patients with AHRF in each of the compared groups during a 30-day period between 1 July and 1 October 2016 (N=1280)

Characteristics	All (N=1280) n (%)	Drug overdose (N=48)[a] n (%)	Non-drug overdose (N=1232) n (%)	p
Age (years), median (IQR)	60.0 (47.0–69.0)	42.0 (31.0–49.8)	60.0 (48.0–69.0)	<0.001
Females	522 (40.8)	16 (33.3)	506 (41.1)	0.284
Race				0.514
White	773 (66.8)	34 (75.6)	739 (66.5)	
Black	234 (20.2)	6 (13.3)	228 (20.5)	
Hispanic or Latino	105 (9.1)	3 (6.7)	102 (9.2)	
Asian	32 (2.8)	1 (2.2)	31 (2.8)	
American Indian or Alaskan Native	13 (1.1)	1 (2.2)	12 (1.1)	
Risk factors of AHRF				
Pneumonia	311 (24.3)	13 (27.1)	298 (24.2)	0.646
Aspiration	182 (14.2)	10 (20.8)	172 (14.0)	0.181
Sepsis	365 (28.5)	6 (12.5)	359 (29.1)	0.012
Trauma	125 (9.8)	1 (2.1)	124 (10.1)	0.080
Shock	226 (17.7)	3 (6.3)	223 (18.1)	0.035
Other[b]	111 (8.7)	0 (0.0)	111 (9.0)	0.018
On the day of intubation				
Renal failure	312 (29.0)	6 (12.8)	306 (29.8)	0.012
Liver failure	175 (16.3)	4 (8.5)	171 (16.6)	0.140
Coagulation failure	257 (23.9)	7 (14.9)	250 (24.3)	0.138
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	
PaO_2:FiO_2	146.5 (87.8–216.0)	157.0 (82.9–250.0)	146.3 (87.9–216.0)	0.518
Tidal volume per predicted body weight	7.0 (6.1–8.0)	6.5 (6.1–7.9)	7.0 (6.1–8.0)	0.251
Plateau pressure	21.0 (17.0–25.0)	18.0 (15.0–23.5)	21.0 (17.0–26.0)	0.051
Respiratory rate	20.0 (16.0–25.0)	20.0 (15.0–31.5)	20.0 (16.0–25.0)	0.666
On the first day following intubation				
PaO_2:FiO_2 among intubated patients[c]	169.0 (115.0–237.0)	165.0 (111.8–211.4)	170.0 (115.0–237.5)	0.667
Tidal volume per predicted body weight	6.7 (6.0–7.8)	6.3 (6.1–7.6)	6.7 (6.0–7.8)	0.472
Plateau pressure	20.0 (17.0–24.0)	19.0 (16.0–22.0)	21.0 (17.0–24.0)	0.369
Respiratory rate	20.0 (16.0–26.0)	21.5 (16.5–29.3)	20.0 (16.0–25.0)	0.336

IQR: interquartile range. AHRF: acute hypoxemic respiratory failure. PaO_2:FiO_2: partial pressure of arterial oxygen to fraction of inspired oxygen ratio. **a** Twenty-three (47.9%) out of the 48 patients with drug-overdose associated AHRF had at least one more risk factor of AHRF (other than drug overdose). **b** Other risk factors include blood transfusion, smoke inhalation, near drowning, pancreatitis and burn. **c** Twenty-two (45.8%) of the 48 patients with drug-overdose associated AHRF and 201 (16.3%) of the 1232 patients with non-drug-overdose associated AHRF were extubated at the first day following intubation.

Figure 2. Lower unadjusted mortality among patients with drug-overdose AHRF was significantly mediated by the development of rapidly improving AHRF (p<0.001 for the average causal mediation effect).

Table 2. Outcomes of patients with AHRF in each of the compared groups during a 30-day period between 1 July and 1 October 2016 (N=1280)

Outcome	All (N=1280)	Drug overdose (N=48)	Non-drug overdose (N=1232)	p
28-day mortality, n (%)	432 (33.8)	8 (16.7)	424 (34.4)	0.011
Ventilator-free days[a], median (IQR)	19.0 (0.0–26.0)	24.5 (17.3–27.0)	18.0 (0.0–26.0)	<0.001
ICU-free days[b], median (IQR)	16.0 (0.0–24.0)	24.0 (17.0–27.0)	15.0 (0.0–24.0)	<0.001
Rapidly improving[c] AHRF, n (%)	326 (25.5)	24 (50.0)	302 (24.5)	<0.001

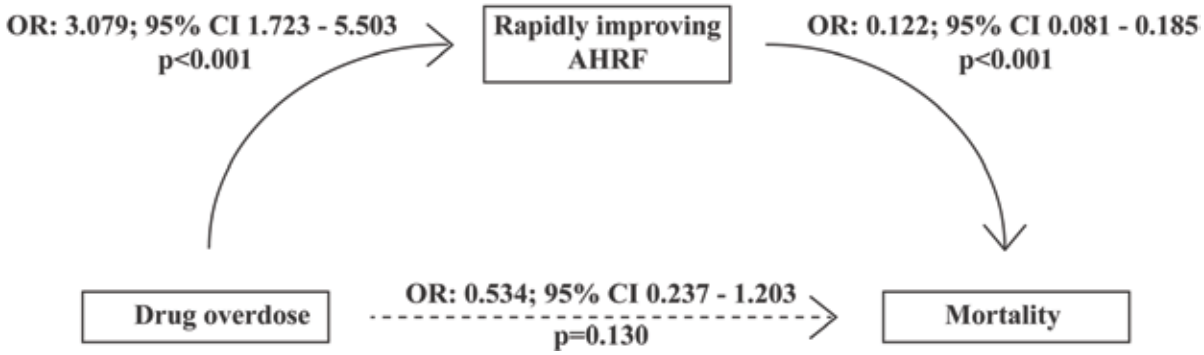
AHRF: acute hypoxemic respiratory failure. ICU: intensive care unit. **a** Ventilator-free days were defined as the number of days from the end of the last period of assisted breathing up to day 28. Hospitalized patients who died before day 28 were considered to have zero ventilator-free days. **b** ICU-free days were defined as the number of days that the patient was alive and not in the ICU. **c** Rapidly improving AHRF was defined as extubation or having a partial pressure of arterial oxygen to a fraction of inspired oxygen ratio greater than 300 on the first day following intubation. Extubation on the first day following intubation took place for 22 (45.8%) of the 48 patients with drug-overdose associated AHRF and 201 (16.3%) of the 1232 patients with non-drug-overdose associated AHRF.

Table 3. Cox proportional-hazards regression analyses to isolate the contribution of drug overdose, age and the concurrent (i.e. along with drug overdose) presence of sepsis or shock as risk factors of AHRF (independent variables) to the 28-day mortality (dependent variable)

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	p	AHR	95% CI	p
Drug overdose	0.45	0.22–0.91	0.025	0.58	0.29–1.19	0.136
Age	1.01	1.01–1.02	<0.001	1.01	1.00–1.02	<0.001
Concurrent presence of sepsis or shock as risk factors of AHRF	1.7	1.40–2.05	<0.001	1.61	1.33–1.94	<0.001

AHR: adjusted hazard ratio. AHRF: acute hypoxemic respiratory failure.

Figure 2. Mediation analysis by considering drug-overdose associated acute hypoxemic respiratory failure (AHRF) as the independent predictor of 28-day mortality and rapidly improving AHRF as the potential mediator



Lower unadjusted mortality among patients with drug-overdose AHRF was significantly mediated by development of rapidly improving AHRF.

DISCUSSION

By incorporating data from 1280 patients with AHRF enrolled in the LOTUS FRUIT prospective observational study[8], the present secondary analysis showed that patients with drug-overdose associated AHRF were younger and more likely to develop rapidly improving AHRF than those with non-drug-overdose associated AHRF. Also, patients with drug-overdose associated AHRF had lower unadjusted mortality compared to patients with non-drug-overdose associated AHRF. However, after adjustment, drug overdose was no longer associated with lower mortality and in a causal mediation analysis, lower unadjusted mortality among patients with drug-overdose AHRF was found to be significantly mediated by the development of rapidly improving AHRF.

Despite considerable recent evidence on the epidemiology of critically ill patients with drug overdose[2,22-26], there might

still be a lack of studies directly comparing AHRF associated with drug overdose as opposed to AHRF associated with other risk factors. This was revealed in a relevant systematic review which we performed in order to identify observational studies reporting on clinical characteristics and mortality of patients with drug-overdose associated AHRF. The protocol of the systematic review was registered with PROSPERO (CRD42022363770) and is available online[27]. Eligible studies reported that patients with drug-overdose associated AHRF were young and had short duration of mechanical ventilation (median duration up to 5.0 days)[28-30]. Some, but not all, patients with drug-overdose associated AHRF included in those studies also met the criteria of ARDS[28-30]. Moreover, previous studies reported that almost half of patients with drug-overdose associated AHRF got extubated the day after intubation; i.e. they had rapidly improved AHRF[28,31]. The above clinical features (young age and rapidly improving AHRF) were confirmed in our analysis. The originality of our analysis lies in that, contrary to the abovementioned studies[22-26,28-31], it directly compared patients with drug-overdose AHRF and patients with non-drug-overdose associated AHRF.

We found that patients with drug-overdose associated AHRF had lower (16.7% vs 34.4%) unadjusted mortality than patients with non-drug-overdose associated AHRF. This finding was in line with a recent study of ICU patients hospitalized with severe pneumonia, who reported that drug abuse was associated with decreased in-hospital mortality (OR=0.46; 95% CI 0.39–0.53) compared to no substance abuse[32]. Such findings (lower unadjusted mortality of patients with AHRF associated with drug overdose compared to other risk factors) should not lead to the misinterpretation that drug-overdose associated AHRF may be inconsequential. Indeed, after adjusting for confounders such as age, we found that mortality associated with drug overdose was comparable with mortality associated with other risk factors among patients with AHRF. Moreover, lower unadjusted mortality among patients with drug-overdose AHRF was significantly mediated by the development of rapidly improving AHRF. Taken together, the above findings may provide valuable insights into the association between drug overdose and mortality among patients with AHRF.

Limitations

The present analysis has limitations. Although there were available high-quality data from 1280 patients with AHRF, conducted by the PETAL Network, drug-overdose associated AHRF was present in 48 patients (i.e. the sample size of our analysis was not large). Even so, this analysis allowed us to perform the first study, to our knowledge, that directly compares AHRF associated with drug overdose and AHRF associated with other risk factors. Also, information was lacking regarding the type of drug used by the enrolled patients, which is an important limitation given that different drugs may have different clinical respiratory pictures and severity. However, this is not unusual for studies on ARDS[7]. Besides, given that the LOTUS FRUIT study took place in North America in 2016[8], one may assume that most drug-overdose cases were due to opioids.

CONCLUSIONS

This secondary analysis of the LOTUS FRUIT study showed that patients with drug-overdose associated AHRF were younger and had lower unadjusted mortality than patients with non-drug-overdose associated AHRF. However, this difference in mortality seemed to be due to confounders, such as age, and to be mediated by the development of rapidly improving AHRF. These results may provide insights into the association between drug overdose and mortality among patients with AHRF.

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CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval was obtained from Institutional Review Board of Evaggelismos Hospital (Approval number: 398/9-11-2022; Date: 9 November 2022), which also waived the need for informed consent (non-human subjects research).

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

AUTHORS' CONTRIBUTIONS

KG: contributed to study design and data interpretation, and

critically revised the manuscript for important intellectual content. EP: designed the study, contributed to data cleaning and data interpretation, undertook statistical analyses, and wrote the first draft of the manuscript. NA and SG: contributed to data interpretation and critically revised the manuscript for important intellectual content. IIS: conceived the study and contributed to study design and data interpretation, critically revised the manuscript for important intellectual content, and supervised the study. All authors read and approved the final manuscript.

REFERENCES

1. World Drug Report 2022. United Nations Office on Drugs and Crime. Accessed February 3, 2023. https://www.unodc.org/res/wdr2022/MS/WDR22_Special_Points.pdf
2. Stevens JP, Wall MJ, Novack L, Marshall J, Hsu DJ, Howell MD. The Critical Care Crisis of Opioid Overdoses in the United States. Ann Am Thorac Soc. 2017;14(12):1803-1809. doi:10.1513/AnnalsATS.201701-022OC
3. Wilson KC, Saukkonen JJ. Acute respiratory failure from abused substances. J Intensive Care Med. 2004;19(4):183-193. doi:10.1177/0885066604263918
4. Sterrett C, Brownfield J, Korn CS, Hollinger M, Henderson SO. Patterns of presentation in heroin overdose resulting in pulmonary edema. Am J Emerg Med. 2003;21(1):32-34. doi:10.1053/ajem.2003.50006
5. Pelletier DE, Andrew TA. Common Findings and Predictive Measures of Opioid Overdoses. Acad Forensic Pathol. 2017;7(1):91-98. doi:10.23907/2017.011
6. Friedman J, Akre S. COVID-19 and the Drug Overdose Crisis: Uncovering the Deadliest Months in the United States, January-July 2020. Am J Public Health. 2021;111(7):1284-1291. doi:10.2105/AJPH.2021.306256
7. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291
8. Lanspa MJ, Gong MN, Schoenfeld DA, et al. Prospective Assessment of the Feasibility of a Trial of Low-Tidal Volume Ventilation for Patients with Acute Respiratory Failure. Ann Am Thorac Soc. 2019;16(3):356-362. doi:10.1513/AnnalsATS.201807-459OC
9. Pham T, Pesenti A, Bellani G, et al. Outcome of acute hypoxaemic respiratory failure: insights from the LUNG SAFE Study. Eur Respir J. 2021;57(6):2003317. doi:10.1183/13993003.03317-2020
10. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669
11. Harrington JS, Schenck EJ, Oromendia C, Choi AMK, Siempos II. Acute respiratory distress syndrome without identifiable risk factors: A secondary analysis of the ARDS network trials. J Crit Care. 2018;47:49-54. doi:10.1016/j.jcrc.2018.06.002
12. Gibelin A, Parrot A, Maitre B, et al. Acute respiratory distress syndrome mimickers lacking common risk factors of the Berlin definition. Intensive Care Med. 2016;42(2):164-172. doi:10.1007/s00134-015-4064-y
13. Papoutsi E, Giannakoulis VG, Routsi C, Kotanidou A, Siempos II. Association between ventilatory ratio and mortality persists in patients with ARDS requiring prolonged mechanical ventilation. Intensive Care Med. 2023;49(7):876-877. doi:10.1007/s00134-023-07107-7
14. Papoutsi E, Routsi C, Kotanidou A, Vaporidi K, Siempos II. Association between driving pressure and mortality may depend on timing since onset of acute respiratory distress syndrome. Intensive Care Med. 2023;49(3):363-365. doi:10.1007/s00134-023-06996-y
15. Oromendia C, Siempos II. Reclassification of Acute Respiratory Distress Syndrome: A Secondary Analysis of the ARDS Network Trials. Ann Am Thorac Soc. 2018;15(8):998-1001. doi:10.1513/AnnalsATS.201803-192RL
16. Price DR, Hoffman KL, Sanchez E, Choi AMK, Siempos II. Temporal trends of outcomes of neutropenic patients with ARDS enrolled in therapeutic clinical trials. Intensive Care Med. 2021;47(1):122-123. doi:10.1007/s00134-020-06263-4
17. Schenck EJ, Oromendia C, Torres LK, Berlin DA, Choi AMK, Siempos II. Rapidly Improving ARDS in Therapeutic Randomized Controlled Trials. Chest. 2019;155(3):474-482. doi:10.1016/j.chest.2018.09.031
18. Gavrielatou E, Vaporidi K, Tsolaki V, et al. Rapidly improving acute respiratory distress syndrome in COVID-19: a multi-centre observational study. Respir Res. 2022;23(1):94. doi:10.1186/s12931-022-02015-8
19. Sathe NA, Zelnick LR, Mikacenic C, et al. Identification of persistent and resolving subphenotypes of acute hypoxemic respiratory failure in two independent cohorts. Crit Care. 2021;25(1):336. doi:10.1186/s13054-021-03755-7
20. Imai K, Keele L, Tingley D, Yamamoto T. Unpacking the Black Box of Causality: Learning about Causal Mechanisms from Experimental and Observational Studies. Am Polit Sci Rev. 2011;105(4):765-89. doi:10.1017/S0003055411000414
21. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. Annu Rev Psychol. 2007;58:593-614. doi:10.1146/annurev.psych.58.110405.085542
22. Mehta AB, Weinstein Z, Walkey AJ. The Untold Toll of the Opioid Crisis on Intensive Care Units in the United States. Ann Am Thorac Soc. 2017;14(12):1763-1765. doi:10.1513/AnnalsATS.201708-662ED
23. Burton BN, Lin TC, Said ET, Gabriel RA. National Trends and Factors Associated With Inpatient Mortality in Adult Patients With Opioid Overdose. Anesth Analg. 2019;128(1):152-160. doi:10.1213/ANE.0000000000003755
24. Nicol AL, Colquhoun DA, Brummett CM. The More You Know: Identifying Factors Associated With Inpatient Mortality Related to Opioid Overdose Can Drive Progress in the Opioid Health Crisis. Anesth Analg. 2019;128(1):16-18. doi:10.1213/ANE.0000000000003902

25. Goodwin AJ. Critical Care Outcomes Among Opioid Users: Hidden Sequelae of a Growing Crisis? Crit Care Med. 2018;46(6):1005-1006. doi:10.1097/CCM.0000000000003103
26. Munch T, Christiansen CF, Pedersen L, Sørensen HT. Impact of Preadmission Opioid Treatment on 1-Year Mortality Following Nonsurgical Intensive Care. Crit Care Med. 2018;46(6):860-868. doi:10.1097/CCM.0000000000003080
27. Papoutsi E, Gkirgkiris K, Siempos I. Clinical characteristics and outcomes of drug overdose-associated acute hypoxemic respiratory failure. PROSPERO. 2022. PROSPERO 2022 CRD42022363770. Accessed February 3, 2023. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022363770
28. Grigorakos L, Sakagianni K, Tsigou E, Apostolakos G, Nikolopoulos G, Veldekis D. Outcome of acute heroin overdose requiring intensive care unit admission. J Opioid Manag. 2010;6(3):227-231. doi:10.5055/jom.2010.0021
29. Kummer RL, Kempainen RR, Olives TD, Leatherman JW, Prekker ME. Naloxone-associated pulmonary edema following recreational opioid overdose. Am J Emerg Med. 2022;53:41-43. doi:10.1016/j.ajem.2021.12.030
30. Farkas A, Lynch MJ, Westover R, et al. Pulmonary Complications of Opioid Overdose Treated With Naloxone. Ann Emerg Med. 2020;75(1):39-48. doi:10.1016/j.annemergmed.2019.04.006
31. Sporer KA, Dorn E. Heroin-related noncardiogenic pulmonary edema : a case series. Chest. 2001;120(5):1628-1632. doi:10.1378/chest.120.5.1628
32. Reynolds PM, Afshar M, Wright GC, et al. Association between Substance Misuse and Outcomes in Critically Ill Patients with Pneumonia. Ann Am Thorac Soc. 2023;20(4):556-565. doi:10.1513/AnnalsATS.202206-532OC

Impact of COVID-19 pandemic and country of origin on TB treatment outcome in Greece

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ABSTRACT

INTRODUCTION Tuberculosis (TB) remains a cause of morbidity and mortality in Greece. The aim of this study was to assess TB treatment outcome (based on the new WHO definitions) according to date of diagnosis (before or during the COVID-19 pandemic) and country of origin. Positive outcome was defined as cure and completion of treatment, and negative outcome as lost to follow-up, failure or not evaluated. Death was assessed separately.

METHODS Patients registered at the Department of Pulmonary Medicine, Aristotle University of Thessaloniki, Greece, during the period 2018–2021, were retrospectively studied.

RESULTS A total of 102 patients (51 before and 51 during the pandemic), with mean age 44.8 ± 21.9 years, were included; 15 were women and 87 men, 45 were Greeks, 12 other Europeans, and 45 non-Europeans. Before the pandemic, 32 patients (62.8%) had positive outcome, 15 (29.4%) negative, and 4 (7.8%) died. During the pandemic, positive outcome was noted in 28 (54.9%), negative in 20 (39.2%), and 3 patients (5.9%) died (p=0.66). Greeks had a positive outcome rate of 66.7%, other Europeans 83.3%, and non-Europeans 44.4%. Negative outcome rate among patients was: 17.8% for Greeks, 16.7% for other Europeans, and 55.6% for non-Europeans (p<0.001). Greeks had the highest mortality rate (15.6%), with both other groups having zero deaths.

CONCLUSIONS The pandemic did not affect significantly treatment outcomes, as members of staff worked exclusively on TB. Country of origin significantly affected outcome, with non-European patients having the highest negative outcome rate. This observation can be attributed to the lack of social and/or familial support.

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INTRODUCTION

Tuberculosis (TB) remains one of the major causes of morbidity and mortality in the world, since, according to WHO, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS until the coronavirus (COVID-19) pandemic[1]. The progress noted in TB epidemiology at a global level was severely affected by the pandemic, which had a damaging impact on TB diagnosis, burden, and number of deaths. The most evident effect was a drop in the reported number of new TB notifications. From a peak of 7.1 million in 2019, it fell to 5.8 million in 2020 (-18%), which is back to the level of 2012. In 2021, there was a partial recovery to 6.4 million (the level of 2016–2017), according to WHO data, but, in total, the progress made in the years up until 2020 has been reversed, with global TB targets being off track much more ever since[2].

According to WHO's TB profile for Greece, 195 new cases were registered in 2021 (incidence rate: 4.1 per 100000 population)[3]. Underreporting is a serious problem for TB surveillance in Greece, while there is no TB treatment outcome registry. Up until 2011, Greek data were not provided to WHO, therefore Greece was not included in the study on TB treatment outcome in the European Union and the European Economic Area[4]. Furthermore, Greece is one of a few countries where TB treatment outcome is neither reported nor registered, according to the e-CDC (Bulgaria, France, Greece, Italy, Latvia, Poland in 2020)[5]. Recording treatment outcome, assessment of program performance, and the recording epidemiological trends provide the basis for programmatic and policy development; therefore, they are essential for identifying and assessing problems in treatment algorithms, as well as TB control in general, worldwide[6].

The present study aims to assess the outcome of tuberculosis treatment at the Department of Pulmonary Medicine, AUTH, at 'G. Papanikolaou' General Hospital of Thessaloniki, and to identify the factors potentially associated with a negative outcome. Specifically, TB treatment outcome was studied based on the time treatment was initiated (before or during the COVID-19 pandemic) and on the patients' country of origin, as about half of the study

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population is not Greek. This comes in accordance with Greek Public Health Organization data[7].

METHODS

This is a retrospective study of patients with TB disease, registered at the Department of Pulmonary Medicine, Aristotle University of Thessaloniki, between 1 January 2018 and 31 December 2021. The department functions as a TB reference center for the regions of West and Central Macedonia. TB outcome definitions suggested by WHO were used[1].

TB outcome definitions

Cured

Patients with pulmonary TB with bacteriologically confirmed TB at the beginning of treatment who completed treatment, as recommended by the national policy, with evidence of bacteriological response – conversion with at least two consecutive cultures – and no evidence of failure.

Treatment completed

Patients who completed treatment, as recommended by the national policy, whose outcome does not meet the definition for cure or treatment failure.

Treatment failed

Patients whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy.

Died

Patients who died before starting treatment or during the course of treatment.

Lost to follow-up

Patients who did not start treatment or whose treatment was interrupted for two consecutive months or more.

Not evaluated

Patients for whom no treatment outcome was assigned (e.g. patients transferred-out to another treatment unit).

In this study, TB treatment outcomes were also categorized in three different groups: positive, negative, or death. Positive outcome was defined as cure and completion of treatment while negative outcome was defined as loss to follow-up, failure, and no evaluation. Death was assessed separately. Although outcome definitions are the same for TB due to sensitive and resistant strains, patients with rifampicin-resistant or multidrug-resistant TB were excluded from the study since treatment for MDR-TB is longer and outcomes could not be assessed for the year 2021[8].

Apart from outcome, the following parameters were recorded for each patient: age, gender, country of origin, co-morbidities, and anatomical site of TB infection. Regarding co-morbidities, the Charlson index[9] was used as a tool to assess long-term mortality. Moreover, the diagnostic method (nucleic acid amplification test [NAATs] – Xpert® MTB/RIF Assay, Cepheid, California, US, acid-fast bacilli [AFB] smear, culture, histological), resistance profile, time to negative smear/cultures and duration of treatment, as well as outcome and possible adverse effects, were recorded.

Patients were divided into two groups based on time of diagnosis. The first group consisted of patients who started treatment before the beginning of COVID-19 pandemic, i.e. January 2018 – February 2020, and the second one during COVID-19, i.e. March 2020 – December 2021. Patients were also divided according to country of origin, i.e. Greece, born in Europe (apart from Greece), and born elsewhere. After March 2020, TB patients were tested for SARS-CoV-2 infection as part of the initial differential diagnosis. At follow-up, TB patients were tested only if an indication of viral infection was present. TB outcomes as well as demographic and microbiological parameters were compared between groups.

RESULTS

In total, 102 patients, 15 (14.7%) women and 87 (85.3%) men, with mean age 44.8 ± 21.9 years (range: 17–87) were included in the study. The characteristics of participants are presented in Table 1. Fifty-seven patients (55.9%) were of foreign origin: Pakistan (19), Somalia (6), Georgia (6), Afghanistan (4), Albania (3), Syria (3), Guinea (2), Iraq (2), Ukraine (2), Congo (2), Armenia (1), Iran (1), Cameroon (1), Mali (1), Bangladesh (1), Bali-Indonesia (1), Romania (1) and Senegal (1). Forty-five patients were born in Greece, representing 44.1% of all the sample. Pulmonary TB was diagnosed in 80 (78.4%) patients, with 12 having both pulmonary and extra-pulmonary disease, and two presenting with miliary TB. Extra-pulmonary TB alone was diagnosed in the remaining 22 patients (21.6%). Regarding the location of extra-pulmonary TB, most patients presented with TB lymphadenitis (9 cases, 40.9%), but involvement of pleura, kidney and testicle were also registered. Previous anti-TB treatment was reported in four of the cases, and HIV co-infection in one. Fifty-eight patients (56.9%) lived with comorbidities, including HCV or HBV infection, active malignancy or history of cancer, cardiovascular disease, diabetes, renal disease, autoimmune diseases, and inflammatory bowel disease, and four of them were also illicit drug users. None of the patients suffered from COVID-19 during their hospitalization.

Patients of Greek origin were significantly older with mean age 62.3 ± 15.5 versus 50.0 ± 16.9 in other Europeans, and 26.1 ± 10.5 in non-Europeans ($p<0.001$). They also had a higher rate of coexisting comorbidities, as indicated by a Charlson comorbidity index of 3.4 ± 2.7 vs 1.6 ± 1.8 in other Europeans, and 0.2 ± 0.7 in non-Europeans ($p<0.001$).

Out of 99 patients for whom the method of diagnosis was registered, microbiological confirmation was achieved in 86 patients (84.3%), and histological in 13 (12.7%). Patients with histological diagnosis of TB suffered mainly from extra-

pulmonary TB, or from both pulmonary and extra-pulmonary TB. Specifically, 9 patients had extra-pulmonary TB (3 patients had lymphadenitis, 4 patients had pleurisy, 1 patient had peritonitis, and 1 patient testicular TB). Of the other 4 patients, one had both pulmonary and extra-pulmonary TB (TB pleurisy), and was diagnosed with pleural biopsy, while the other 3 had only pulmonary TB, and were diagnosed with lung biopsy. In these cases, radiological findings were mainly pulmonary nodules. TB was diagnosed clinically in 3 cases (3%), all of them being before the pandemic outbreak.

Regarding outcome, out of 102 patients, 60 had a positive outcome, accounting for 58.8% of cases, while 35 (34.3%) had a negative outcome. Seven patients died, all of whom had comorbidities (heart conditions, underlying pulmonary disease, or cancer). Three of these deaths were attributed to causes other than tuberculosis disease, a car accident in one case, and metastatic lung cancer in the other two. Four of the patients who died had experienced side effects from TB treatment (such as drug-induced hepatitis, neuropathy, and psychosis). Out of these cases, only one (drug-induced hepatitis and hepatic failure in a woman aged 84 years with pulmonary fibrosis, diabetes, and hypertension) was associated with death, shortly after the beginning of treatment. In the three remaining patients with side effects, death took place after the side effects had been addressed and treatment had been accordingly modified. Three of the patients who died were diagnosed after the COVID-19 outbreak, but none of them tested positive for the virus.

Treatment outcome according to year of diagnosis (before and during the pandemic) is presented in Table 2. A statistically significant difference in treatment outcome between the pre-COVID-19 and the COVID-19 period was observed (p=0.02), with 43.1% vs 21.6% achieving cure before and during the pandemic, respectively. The percentage of patients who were lost to follow-up increased from 2% before COVID-19 to 15.7% during COVID-19. However, when outcomes were grouped (positive, negative, death) no difference between the periods was observed (Figure 1 A).

As shown in Table 3 and Figure 1 B, treatment outcome differed significantly according to origin, with positive outcome observed in 66.7%, 83.3% and 44.4% in Greeks, other Europeans, and non-Europeans, respectively (p<0.001). All patients who died were Greek. Treatment outcome did not differ according to gender, site of infection, method of diagnosis or presence of resistance. Age differed significantly among patients with positive outcome, negative outcome,

Table 1. Patients' characteristics

Characteristics	n/N (%)
Gender (male)	87/102 (85.3)
Age (years), mean ± SD	44.8 ± 21.9
Country of origin	
Greece	45/102 (44.1)
Other European	12/102 (11.8)
Non-European	45/102 (44.1)
Site of infection	
Pulmonary	80/102 (78.4)
Extrapulmonary	22/102 (21.6)
Comorbidity	
Yes	58/102 (56.9)
No	44/102 (43.1)
Charlson co-morbidity index	1.8 ± 2.5
Smear	
Positive	33/96 (34.4)
Negative	63/96 (65.6)
NAAT	
Positive	76/96 (79.2)
Negative	20/96 (20.8)
Culture	
Positive	71/95 (74.7)
Negative	24/95 (25.3)
Diagnosis	
Clinical	3/102 (2.9)
Microbiological	86/102 (84.3)
Histological	13/102 (12.7)
Resistance to isoniazid	9/76 (11.8)
Time to smear negative (days), mean ± SD	27.6 ± 33.8
Time to culture negative (days), mean ± SD	56.4 ± 46.0

NAAT: nucleic acid amplification test.

Table 2. Treatment outcome according to year of diagnosis

Outcome*	Pre-COVID-19 (N=51) n (%)	During COVID-19 (N=51) n (%)	Total (N=102) n (%)
Cured	22 (43.1)	11 (21.6)	33 (32.4)
Treatment completed	10 (19.6)	17 (33.3)	27 (26.5)
Treatment failed	0 (0.0)	1 (2.0)	1 (1.0)
Lost to follow-up	1 (2.0)	8 (15.7)	9 (8.8)
Not evaluated	14 (27.5)	11 (21.6)	25 (24.5)
Died	4 (7.8)	3 (5.9)	7 (6.9)

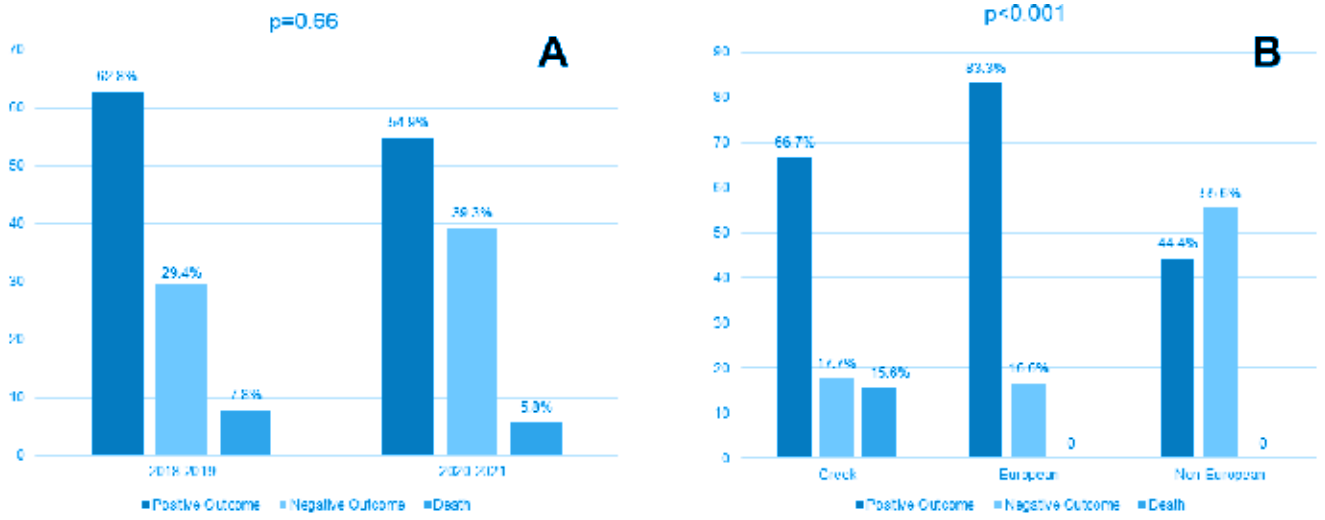
*Statistically different treatment outcome (p=0.02) between pre-COVID-19 and during COVID-19.

Table 3. Treatment outcome according to country of origin

Outcome*	Greece (N=45) n (%)	Other European (N=12) n (%)	Non-European (N=45) n (%)
Cured	18 (40.0)	5 (41.7)	10 (22.2)
Treatment completed	12 (26.7)	5 (41.7)	10 (22.2)
Treatment failed	1 (2.2)	0 (0.0)	0 (0.0)
Lost to follow-up	2 (4.4)	0 (0.0)	7 (15.6)
Not evaluated	5 (11.1)	2 (16.7)	18 (40.0)
Died	7 (15.6)	0 (0.0)	0 (0.0)

*Statistically different treatment outcome (p=0.002) between pre-COVID-19 and during COVID-19.

Figure 1. Treatment outcome according to: A) year of diagnosis; B) country of origin



or death (47.9 ± 20.0, 34.9 ± 19.9, and 68.0 ± 24.0, respectively, p<0.001). In addition, the Charlson co-morbidity index was significantly higher in patients who died (1.6 ± 1.7, 1.2 ± 2.2, and 6.9 ± 3.6, for patients with positive outcome, negative outcome, and death, respectively, p<0.001).

DISCUSSION

The main results of the present study are: 1) outcome groups (positive, negative or death) in the pandemic era did not differ from the pre-COVID-19 period, however, when all WHO groups were analyzed, a significant difference was observed; and 2) outcome was affected by country of origin, with patients of non-European origin presenting with the higher percentage of negative outcomes, and Greeks accounting for all the deaths.

The positive outcome rate post-pandemic (54.9%) had no statistically significant decrease in comparison to those of the period before (62.8%). At the same time negative outcome also appeared to be rather unaffected by the pandemic (39.2% vs 29.4%). In our view this fact reflects stability in TB management, which was mainly the result of the effort and engagement of staff members, some of whom were involved exclusively in TB. Indeed, one of the three doctors of the outpatient clinic, and the specialized TB nurse, did not participate in the treatment of COVID-19 patients. These members of staff were a crucial part of the operational efficiency of the outpatient clinic. Although not confirmed in our center, TB is considered to be a risk factor related to worse COVID-19 prognosis[10]. Tuberculosis and SARS-CoV-2 co-infection is not well-studied worldwide, and more data are needed to better understand them when they occur together.

Lockdown has favored the increased use of telemedicine, a means of health service that can easily be provided by TB programs. In TB centers surveyed in Australia, Russia, India, and the United Kingdom, telehealth service use increased in the first 4 months of 2020 according to the CDC[11]. An increased use of telehealth during the COVID-19 pandemic was observed in some TB centers worldwide[12]. As many of our patients come from remote parts of Northern Greece, telehealth has always been part of our clinic's work, and staff were well-familiar with it, and were thus able to immediately incorporate it into everyday routine for the

majority of patients. For example, laboratory exams were remotely performed and sent to the clinic's email. After that, scheduled telephone appointments were periodically held by doctors for stable patients, allowing them to have physical presence appointments every three months instead of every month. Telemedicine is probably the explanation for the low 'cure' but high 'treatment completed' rates post-COVID-19 versus the pre-pandemic era. This reflects that patients responding to treatment were managed from a distance without sputum results during the course of treatment. Sputum negativity is a perquisite for establishing 'cure' according to WHO definitions[13].

A significant rise in patients lost to follow-up was noted (8 during COVID-19 versus only one before COVID-19), marking the effect of the pandemic on TB control. An increase in the proportion of cases who are lost to follow-up is a worldwide phenomenon. According to a study in Northern Italy performed in 2020, the rate of patients lost to follow-up escalated from 2.6% to 10.8% due to the COVID-19 outbreak, respectively[14]. Patients canceled or postponed follow-up examinations, because of fear of infection with COVID-19 when visiting healthcare environments, objection of family members, or feeling lack of necessity[15]. In addition, tuberculosis patients diagnosed during the COVID-19 pandemic showed more extended pulmonary forms[16]. Regarding our center, our hospital has been a reference center for COVID-19 since March 2020, therefore the fear of stigma and of contamination at visits was unavoidable. It is also located away from the city center, and, as a result, transportation has always been a major inconvenience, even before the pandemic outbreak.

Reasons for the reduction in TB diagnosis may include decreased attention to TB by healthcare systems, difficulties in accessing health services, lockdown measures, and fear of stigma and contagion. During the pandemic, a significant amount of TB patients reported difficulty in transportation, particularly the lack of available vehicles and/or the high cost of travel. Receiving treatment from directly observed treatment programs from clinics was also highlighted as a barrier due to fear of contracting an infection[17].

Country of origin appears to be a major factor affecting outcome in our study, as patients from non-European countries showed the highest negative outcome rate. Lack of a support system (familial and/or social) was noted in most of the patients of non-European origin in our center, who are mainly immigrants and/or war refugees, and come to Greece unaccompanied by family members. Furthermore, such socially vulnerable groups are prone to other conditions associated with poor treatment outcomes, such as homelessness or illicit drug use, which, according to a Brazilian study by Chenciner et al.[18], are the two main factors leading to unfavorable results of TB treatment. In contrast, patients from European countries usually migrate in family groups, which provide support for patients. The lack of state-organized infrastructure for migrants with TB (such as a patient-centered approach with directly observed therapy, provision of food and residence, and social support) can probably explain the high lost to follow-up rate in non-European patients. The impact of social protection programs on adults with TB has been analyzed in several studies, which have demonstrated that they are associated with improvement in treatment, cure rates, treatment adherence, service provision, poverty, and TB control[19].

Another interesting finding of the present study was the number of deaths which accounted for 6.9% of patients. A systematic review of risk factors for death in adults during and after TB treatment reported that risk factors for death, in settings with high TB incidence and HIV prevalence, were co-infection with HIV, advanced immuno-compromised patients, smear-negative TB, and malnutrition. In regions of low TB incidence and HIV prevalence, like Greece, risk factors included non-infectious co-morbidities, sputum smear-positive TB, and alcohol and substance abuse[20]. Our study results come in accordance with these findings, as deaths occurred in Greeks, who were older, and with significantly more comorbidities in comparison to the other groups (although only 27.5% had sputum smear positivity). TB mortality is generally low in several studies, with most patients dying with comorbidities (malignancy, liver cirrhosis, etc.) and even because of them[21]. Migrants tend to be of younger age and previously healthy, therefore it comes as no surprise the zero deaths in this group.

Limitations

The main limitation of our study is that only one center, with a relatively small number of patients, is represented and therefore it is difficult to estimate whether our results can be extrapolated to the whole country. The circumstances especially regarding COVID-19 and the clinic's operating conditions may vary in other centers. Therefore, possibly the results regarding the effect of the pandemic on TB outcomes may be different in other centers, where the degree of involvement for the care of COVID-19 patients, as opposed to TB patients, was different to ours. On the other hand, the impact of country of origin on TB outcomes shown in the present study probably reflects the situation in Greece in general, as the social protection status is the same for the whole country.

CONCLUSIONS

The results of this single-center study show that the positive outcome rate of TB patients was in the most part not severely affected by the COVID-19 pandemic. On the other hand, the country of origin of the patients was a determining factor of outcome, with non-Europeans presenting with the higher rate of negative outcome. Since the reasons for that are mainly socioeconomic, development of a national anti-TB program providing financial and social support, especially for the Middle East and African immigrants in Greece, would optimize TB treatment outcome and raise the positive

outcome rate closer to the WHO global target. A multi-center study to assess all TB treatment outcome data from Greece would be of great importance to better understand Greek TB patients' profile, omissions on screening and diagnostic evaluation, and treatment underachievement. The need for a national anti-TB program to be scheduled and implemented is crucial, not only for the improvement of treatment outcomes, but also to establish alignment with WHO global targets and WHO's End TB Strategy.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported.

FUNDING

There was no source of funding for this research.

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this retrospective study.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

REFERENCES

1. Tuberculosis. World Health Organization. November 7, 2023. Accessed December 27, 2023. https://www.who.int/news-room/fact-sheets/detail/tuberculosis
2. Bagcchi S. WHO's Global Tuberculosis Report 2022. Lancet Microbe. 2023;4(1):e20. doi:10.1016/S2666-5247(22)00359-7
3. Tuberculosis Profile: Greece. worldhealthorg. Accessed December 27, 2023. https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&lan=%22EN%22&iso2=%22GR%22
4. Karo B, Hauer B, Hollo V, van der Werf MJ, Fiebig L, Haas W. Tuberculosis treatment outcome in the European Union and European Economic Area: an analysis of surveillance data from 2002-2011. Euro Surveill. 2015;20(49):pii=30087. doi:10.2807/1560-7917.ES.2015.20.49.30087
5. European Centre for Disease Prevention and Control. Tuberculosis surveillance and monitoring in Europe 2023 - 2021 data. European Centre for Disease Prevention and Control. Accessed December 27, 2023. https://www.ecdc.europa.eu/sites/default/files/documents/tuberculosis-surveillance-monitoring-2023.pdf
6. World Health Organization. Implementing the WHO Stop TB Strategy: A Handbook for National Tuberculosis Control Programmes. World Health Organization; 2008. Accessed December 27, 2023. https://iris.who.int/bitstream/handle/10665/43792/9789241546676_eng.pdf?sequence=1
7. Epidemiological tuberculosis data in Greece, 2004-2010. Ministry of Health and Social Solidarity, Hellenic Centre for Diseases Control and Prevention. Accessed December 27, 2023. https://eody.gov.gr/wp-content/uploads/2019/01/tuberculosis2004_2010.pdf
8. World Health Organization. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27-29 October 2020. World Health Organization; 2021:19-22. Accessed December 27, 2023. https://iris.who.int/bitstream/handle/10665/338776/9789240018662-eng.pdf?sequence=1
9. Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson Comorbidity Index: A Critical Review of Clinimetric Properties. Psychother Psychosom. 2022;91(1):8-35. doi:10.1159/000521288
10. TB/COVID-19 Global Study Group. Tuberculosis and COVID-19 co-infection: description of the global cohort. Eur Respir J. 2022;59(3):2102538. doi:10.1183/13993003.02538-2021
11. Migliori GB, Thong PM, Akkerman O, et al. Worldwide Effects of Coronavirus Disease Pandemic on Tuberculosis Services, January-April 2020. Emerg Infect Dis. 2020;26(11):2709-2712. doi:10.3201/eid2611.203163
12. Migliori GB, Thong PM, Alffenaar JW, et al. Gauging the impact of the COVID-19 pandemic on tuberculosis services: a global study. Eur Respir J. 2021;58(5):2101786. doi:10.1183/13993003.01786-2021
13. World Health Organization. Meeting report of the WHO expert consultation on drug-resistant tuberculosis treatment outcome definitions: 17-19 November 2020. World Health Organization; 2021. Accessed December 27, 2023. https://iris.who.int/bitstream/handle/10665/340284/9789240022195-eng.pdf?sequence=1
14. Magro P, Formenti B, Marchese V, et al. Impact of the SARS-CoV-2 epidemic on tuberculosis treatment outcome in Northern Italy. Eur Respir J. 2020;56(4):2002665. doi:10.1183/13993003.02665-2020
15. Xia Y, Huang F, Chen H, et al. The Impact of COVID-19 on Tuberculosis Patients' Behavior of Seeking Medical Care - China, 2020. China CDC Wkly. 2021;3(26):553-556. doi:10.46234/ccdcw2021.143
16. Aznar ML, Espinosa-Pereiro J, Saborit N, et al. Impact of the COVID-19 pandemic on tuberculosis management in Spain. Int J Infect Dis. 2021;108:300-305. doi:10.1016/j.ijid.2021.04.075
17. Mihika FA, Jubayer Biswas MAA, Khan MMH, et al. The Effect of the COVID-19 Pandemic on Pulmonary Tuberculosis Control in the Selected Upazila Health Complexes of Dhaka Division, Bangladesh. Trop Med Infect Dis. 2022;7(11):385. doi:10.3390/tropicalmed7110385
18. Chenciner L, Annerstedt KS, Pescarini JM, Wingfield T. Social and health factors associated with unfavourable treatment outcome in adolescents and young adults with tuberculosis

in Brazil: a national retrospective cohort study. Lancet Glob Health. 2021;9(10):e1380-e1390. doi:10.1016/S2214-109X(21)00300-4
19. Aragão FBA, Arcêncio RA, Fuentealba-Torres M, et al. Impact of social protection programs on adults diagnosed with Tuberculosis: systematic review. Rev Bras Enferm. 2021;74(3):e20190906. doi:10.1590/0034-7167-2019-0906
20. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. Int J Tuberc Lung Dis. 2011;15(7):871-885. doi:10.5588/ijtld.10.0352
21. Lin CH, Lin CJ, Kuo YW, et al. Tuberculosis mortality: patient characteristics and causes. BMC Infect Dis. 2014;14:5. doi:10.1186/1471-2334-14-5

Factors of impaired health-related quality of life in patients with precapillary pulmonary hypertension

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ABSTRACT

INTRODUCTION Pulmonary hypertension (PH) is related to a variety of symptoms like dyspnea at rest, fatigue and exercise intolerance, all of which have a detrimental influence on patients' quality of life (QOL). Disease-specific health-related QOL (HRQOL) questionnaires are useful tools to objectively estimate the functional and psychological status of PH patients. The purpose of this study was to identify potential factors affecting physical and mental HRQOL in patients with precapillary PH.

METHODS We conducted a prospective cross-sectional analysis of HRQOL questionnaires in individuals with precapillary PH (PH-Groups 1, 3, or 4) using the Short form 36-item health survey (SF-36) and the Minnesota living with pulmonary hypertension questionnaire (MLHF-PH). Between January and February 2019, 73 consecutive patients, being followed up in two Greek PH centers, being clinically stable at the last three months and receiving PH-specific therapies based on the European PH Guidelines, completed both questionnaires.

RESULTS Patients with PH due to lung disease (PH-Group 3) presented significantly worse scores on MLHF-PH and significantly reduced scores in SF-36 'physical functioning' and 'role physical' compared to the other PH-Groups. These patients were more frequently under oxygen therapy ($p<0.001$) and had a more advanced WHO FC ($p=0.01$). Oxygen treatment, WHO FC, 6MWD, and hemodynamic variables were also strongly associated with HRQOL. Patients receiving triple combination PH-therapy reported lower HRQOL scores.

CONCLUSIONS Patients with precapillary PH had impaired QOL. Those with PH due to lung disease reported the worst scores in HRQOL instruments. Several clinical, functional and hemodynamic factors were associated with reduced QOL.

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health-related quality of life, pulmonary hypertension, SF-36 survey, Minnesota living with pulmonary hypertension questionnaire

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INTRODUCTION

Precapillary pulmonary hypertension (PH) remains a rare entity, characterized by elevated pulmonary artery pressures which lead to an increase in right ventricular afterload and consequently to impairment of ventricular interdependence[1,2]. These hemodynamic alterations not only produce the debilitating symptoms of dyspnea and fatigue, but also result in cognitive impairment and peripheral muscle dysfunction[3-5]. Therefore, the negative influence of PH on patients' quality of life (QOL) is an anticipated consequence.

To monitor disease progression, guide therapeutic strategies and evaluate drug efficacy, hemodynamic, echocardiographic, biochemical and exercise testing parameters have been used according to existing guidelines[6,7]. Patient-reported outcomes such as health-related QOL (HRQOL) are now being established in chronic, medical conditions integrating the patient's perspective[8,9]. In this context, HRQOL questionnaires are useful tools that can be applied on an individual basis, providing a more holistic evaluation of patients' physical and mental health[10].

The purpose of this study was to investigate potential factors affecting physical and mental HRQOL in patients with precapillary PH (PH-Groups 1, 3, or 4) by utilizing the Minnesota living with pulmonary hypertension questionnaire (MLHF-PH) and the Short form 36-item health survey (SF-36).

METHODS

Study design, participants and data collection

We conducted a prospective cross-sectional analysis of HRQOL questionnaires in individuals with precapillary PH using the SF-

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36 and the MLHF-PH. Between January and February 2019, 73 consecutive patients, aged >18 years, with hemodynamically confirmed precapillary PH who were previously classified in PH-Groups (1, 3, or 4) and followed up in two Greek PH-referral centers, completed both questionnaires either on follow-up appointments or by telephone interview, and deemed eligible for this study. All included patients were clinically stable, evaluated in the PH outpatient clinic the last 3 months and received PH-specific therapies based on the European PH Guidelines[7]. Those with postcapillary PH due to left heart disease and individuals experiencing serious mobility problems, due to previous stroke or surgery, were excluded. Demographic, clinical and hemodynamic variables, six-minute walk distance (6MWD) values and World Health Organization Functional Class (WHO FC) were provided by a physician who was blinded to patients' responses.

The study was approved by the local ethics committee at both centers and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients.

HRQOL questionnaires

We administered the MLHF-PH, after legal permission, a validated modified version of the Minnesota living with heart failure questionnaire[11]. The MLHF-PH consists of 21 questions about the influence of PH on physical, emotional and social aspects of life, producing scores ranging 0–105 (MLHF-PH Total), with lower scores indicating better quality of life[11]. Two separate scores can also be calculated, one that is produced by 8 questions and refers to physical health (MLHF-PH Phys) and one that is produced by 5 questions and refers to emotional status (MLHF-PH Emot). Concurrently, we administered the SF-36, a widely used tool for self-assessment of physical and mental health status[12,13]. It consists of 36 questions yielding scores from 0 (worse) to 100 (best) in eight health-specific domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. From them, 'physical functioning' and 'role physical' are correlated most highly with physical status, while 'role emotional' and 'mental health' are correlated most highly with mental status[12].

Statistical analysis

Continuous variables are presented as mean ± standard deviation or as median (interquartile range) as appropriate, while categorical variables as frequencies (n) and percentages (%). Student's t-test was used to compare a continuous variable normally distributed between two independent groups, and the Mann-Whitney U-test was used as the non-parametric equivalent test. The Kruskal-Wallis method (with *post hoc* Dunn's test) was used to compare a continuous variable between more than two independent groups. Categorical variables were compared with the chi-squared test. Pearson's correlation coefficient was utilized to analyze the linear correlation between two quantitative and normally distributed variables, and Spearman's correlation coefficient was the non-parametric equivalent test. Cronbach's alpha was calculated for both questionnaires as an estimate of their reliability.

Univariable linear regression analyses were conducted to identify clinical, functional or hemodynamic predictors of physical (MLHF-PH Phys, SF-36 physical functioning and role physical) and mental (MLHF-PH Emot, SF-36 role emotional and mental health) HRQOL domains. A multivariable regression analysis model was then performed for each score, adjusted for the following covariates: age, gender, PH-Group, PH-specific therapies, mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), WHO FC, and oxygen treatment. Multicollinearity was assessed with the variance inflation factor (<5 suggested absence of multicollinearity). Two-tailed p-values <0.05 were considered significant. All data analyses were performed with the R version 4.3.2 (www.r-project.org).

RESULTS

Patients' characteristics

SF-36 and MLHF-PH were evaluated in 73 consecutive patients (mean age 60.6 years, 69% female). Demographic, clinical, functional and hemodynamic characteristics of the population are presented in Table 1. In all, 63% of patients were classified as PH Group 1, 18% as Group 3 due to lung disease, and 19% as Group 4. The median duration since PH diagnosis was 3 years. The majority of patients were under PH monotherapy, while 15% received a triple combination. The most common comorbidities were arterial hypertension, diabetes mellitus, and dyslipidemia. Active smoking was reported only in 6% of the total population. Most patients were classified as WHO FC II (52%) and WHO FC III (34%); half of the total population was under continuous oxygen treatment. The 6MWD values were available in 85% of patients and the median 6MWD was 409 m.

SF-36 and MLHF-PH scores

Analysis of the separate domains of the two questionnaires revealed that PH had a profoundly negative impact on patients' HRQOL. Specifically, the mean MLHF-PH Total score was almost 50 and the median SF-36 sub-scores were ≤50 in five out of the eight domains (Table 1). 'General health' was assessed as moderately impaired by most patients and clinical worsening was anticipated. More than half of patients reported impaired 'physical functioning', as they had limited everyday activities and difficulty in working. Their 'role physical' was also influenced. 'Vitality' was reduced, with fatigue being present in 38% of the population and complete lack of 'vitality' in 11%. 'Emotional health' varied more, with anxiety feelings in 34.2%, depression in 50%, happiness in 34.2% and calmness in 31.5%.

Factors associated with HRQOL scores

Women, compared to men, presented a trend towards better

Table 1. Demographic, clinical, functional and hemodynamic characteristics of the studied population (N=73)

Characteristics	n (%)
Total	73 (100)
Gender	
Male	23 (31.5)
Female	50 (68.5)
Age (years), mean ± SD	60.6 ± 11.3
BMI (kg/m^2), mean ± SD	27.4 ± 6.8
Marital status	
Married	50 (68.5)
Single	23 (31.5)
Education level	
Primary education	33 (45.2)
Secondary education	22 (30.1)
Graduate degree	18 (24.7)
Employment status	
Employed	7 (9.6)
Unemployed	14 (19.2)
Retired	52 (71.2)
Smoking status	
Non-smoker	30 (41.1)
Smoker	4 (5.5)
Ex-smoker	39 (53.4)
PH Group	
1	46 (63)
3	13 (17.8)
4	14 (19.2)
Time duration since PH diagnosis (years), median (IQR)	3 (4)
PH Group 1	
Idiopathic	14 (30.4)
Heritable	1 (2.2)
Drug-associated	1 (2.2)
Connective tissue disease	22 (47.8)
Congenital heart disease	8 (17.4)
PH Group 4	
Operable	5 (36)
Non-operable	9 (64)
PH-specific therapies	
Monotherapy	42 (57.5)
Double combination	20 (27.4)
Triple combination	11 (15.1)
WHO FC	
I	4 (5.5)
II	38 (52.1)
III	25 (34.2)
IV	6 (8.2)
Oxygen treatment	
No	40 (54.8)
Yes	33 (45.2)
MLHF-PH	
Total, mean ± SD	42.4 ± 22.8
Physical component, median (IQR)	20 (18)
Emotional component, median (IQR)	8 (11)
SF-36 survey	**Median (IQR)**
Physical functioning	45 (45)
Role physical	25 (100)
Bodily pain	80 (32)
General health	30 (30)
Vitality, mean ± SD	53.5 ± 22.3
Social functioning	50 (25)
Role emotional	100 (67)
Mental Health	64 (36)
Hemodynamic parameters	**Median (IQR)**
CO (L/min)	5.4 (2.5)
CI (L/min/m^2)	3 (1.1)
mPAP (mmHg)	37 (16)
PCWP (mmHg), mean ± SD	11.3 ± 3.2
PVR (WU)	4.3 (4.2)
SVO_2 (%)	71 (10)
Functional and neurohormonal parameters	
NT-proBNP (pg/mL) (N=40)	269 (958)
6MWD (m) (N=62)	409 (206)
Comorbidities	**n (%)**
Arterial hypertension	24 (32)
Diabetes mellitus	12 (16.5)
Dyslipidemia	13 (18)
Chronic lung disease	12 (16.5)
Coronary artery disease	8 (11)
Hypothyroidism	15 (20)

BMI: body mass index. PH: pulmonary hypertension. WHO FC: World Health Organization functional class. MLHF-PH: Minnesota living with pulmonary hypertension questionnaire. SF-36: Short form 36-item health survey. CO: cardiac output. CI: cardiac index. mPAP: mean pulmonary artery pressure. PCWP: pulmonary capillary wedge pressure. PVR: pulmonary vascular resistance. SVO_2: mixed venous blood saturation. WU: Wood units. NT-proBNP: N-terminal-pro brain natriuretic peptide. 6MWD: six-minute walk distance. IQR: interquartile range.

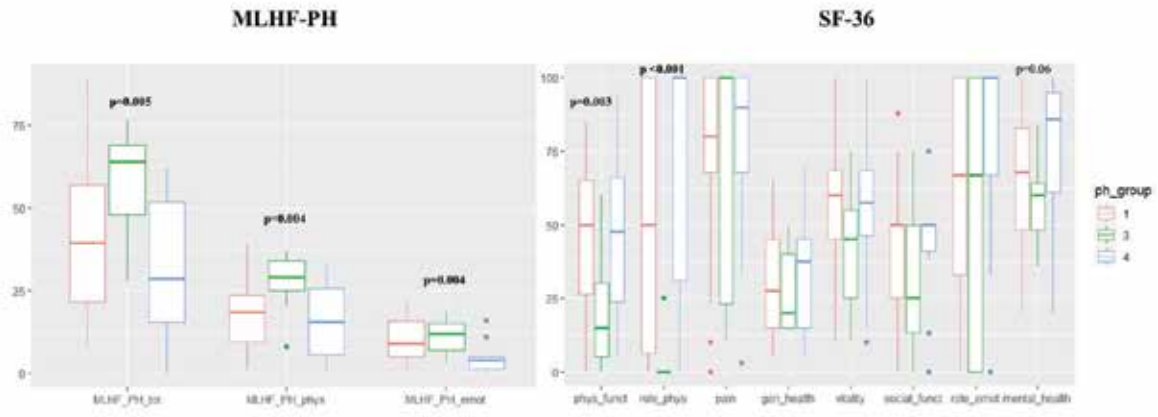
MLHF-PH Total score (median score 37 vs 53, respectively, p=0.057) and MLHF-PH Phys score (median score 17.5 vs 25, p=0.052); they also had a greater SF-36 'physical

Table 2. HRQOL in different PH-Groups

	Group 1 Median (IQR)	Group 3 Median (IQR)	Group 4 Median (IQR)	p
MLHF-PH				
Total	39.5 (35.5)	64.0 (21.0)	28.5 (36.3)	**0.005**
Physical component	18.5 (14.3)	29.0 (9.0)	15.5 (20.3)	**0.004**
Emotional component	9.0 (10.8)	12.0 (8.0)	4.0 (3.7)	**0.004**
SF-36				
Physical functioning	50.0 (38.8)	15.0 (25.0)	47.5 (42.4)	**0.003**
Role physical	50.0 (93.7)	0	100 (68.8)	**<0.001**
Bodily pain	80.0 (32.0)	100 (77.0)	90.0 (32.0)	0.808
General health	27.5 (30.0)	20.0 (25.0)	37.5 (30.0)	0.862
Vitality	60.0 (23.8)	45 (30.0)	57.5 (22.6)	0.208
Social functioning	50.0 (25.0)	25.0 (37.0)	50.0 (9.0)	0.265
Role emotional	67.0 (67.0)	67.0 (100)	100 (33.0)	0.426
Mental health	68.0 (35.0)	60.0 (16.0)	86.0 (34.0)	0.06*

Bold values denote statistical significance. *Trend towards statistical significance. HRQOL: health-related quality of life. PH: pulmonary hypertension. MLHF-PH: Minnesota living with pulmonary hypertension questionnaire. SF-36: Short form 36-item health survey.

Figure 1. Box-and-whisker plots demonstrating the sub-scores of the Minnesota living with pulmonary hypertension questionnaire (MLHF-PH) and the Short form 36-item health survey (SF-36) for the different PH-Groups



functioning' score (median score 45 vs 25, p=0.02). However, their mental status was not significantly different compared to the male sub-population (MLHF-PH Emot, p=0.59; SF-36 role emotional, p=0.71; SF-36 mental health, p=0.27). Age, marital status and level of education were not associated with HRQOL.

Patients with PH due to lung disease (Group 3) presented significantly worse scores on MLHF-PH compared to the other PH-Groups (Table 2). Furthermore, they had significantly reduced scores in SF-36 'physical functioning' and 'role physical' (Table 2). These patients were more frequently under oxygen therapy (p<0.001) and had a more advanced WHO FC (p=0.01). However, differences in hemodynamic parameters between PH-Groups were not evident (Supplementary file Table S1). Graphical presentations of MLHF-PH and SF-36 scores for the different PH-Groups are given in Figure 1. Patients under triple combination PH-therapy had also significantly worse HRQOL scores, both in the physical and mental domains (Supplementary file Table S2).

A significant correlation of all scores of MLHF-PH with mPAP, PVR and mixed venous blood saturation (SVO_2) was observed (Table 3). Moreover, increased mPAP and PVR were correlated with deterioration in SF-36 'physical

Table 3. Correlations† between HRQOL and hemodynamic parameters

	mPAP (mmHg)		PVR (WU)		SVO_2 (%)	
MLHF-PH	**r-coeff**	**p**	**r-coeff**	**p**	**r-coeff**	**p**
Total	0.33	**0.004**	0.26	**0.02**	-0.33	**0.004**
Physical component	0.31	**0.007**	0.26	**0.02**	-0.26	**0.03**
Emotional component	0.34	**0.003**	0.24	**0.04**	-0.31	**0.007**
SF-36						
Physical functioning	-0.28	**0.01**	-0.24	**0.04**	0.31	**0.008**
General health	-0.24	**0.04**	-0.2	0.08	0.19	0.107
Vitality	-0.24	**0.04**	-0.26	**0.02**	0.18	0.126

† r-correlation coefficients and p-values were produced using Pearson's or Spearman's correlation test, as appropriate. Bold values denote statistical significance. HRQOL: health-related quality of life. mPAP: mean pulmonary artery pressure. PVR: pulmonary vascular resistance. SVO_2: mixed venous blood saturation. WU: Wood units. MLHF-PH: Minnesota living with pulmonary hypertension questionnaire. SF-36: Short form 36-item health survey.

Table 4. Correlations† between HRQOL, functional and neurohormonal parameters

	6MWD (m) (N=62)		Borg scale (N=59)		NT-proBNP (pg/mL) (N=40)	
MLHF-PH	**r-coeff**	**p**	**r-coeff**	**p**	**r-coeff**	**p**
Total	-0.59	**<0.001**	0.6	**<0.001**	0.26	0.11
Physical component	-0.58	**<0.001**	0.67	**<0.001**	0.24	0.132
Emotional component	-0.47	**<0.001**	0.36	**0.005**	0.20	0.216
SF-36						
Physical functioning	0.65	**<0.001**	-0.63	**<0.001**	-0.32	**0.04**
Role physical	0.32	**0.01**	-0.40	**0.001**	-0.20	0.213
Bodily pain	0.04	0.740	-0.17	0.192	0.13	0.425
General health	0.36	**0.004**	-0.27	**0.03**	-0.1	0.528
Vitality	0.46	**<0.001**	-0.38	**0.003**	-0.29	0.06*
Social functioning	0.40	**0.001**	-0.38	**0.003**	-0.004	0.981
Role emotional	0.09	0.483	0.02	0.897	-0.04	0.804
Mental Health	0.54	**<0.001**	-0.24	0.06*	-0.08	0.602

† r-correlation coefficients and p-values were produced using Pearson's or Spearman's correlation test, as appropriate. Bold values denote statistical significance. *Trend towards statistical significance. HRQOL: health-related quality of life. 6MWD: six-minute walk distance. NT-proBNP: N-terminal-pro brain natriuretic peptide. MLHF-PH: Minnesota living with pulmonary hypertension questionnaire. SF-36: Short form 36-item health survey.

functioning' (mPAP: r= -0.28, p=0.01; PVR: r= -0.24, p=0.04) and in SF-36 'general health' (mPAP: r= -0.24, p=0.04) (Table 3).

Oxygen treatment was related to worse HRQOL in terms of physical (MLHF-PH Phys, SF-36 physical functioning, SF-36 role physical; all p<0.001) and emotional (MLHF-PH Emot, SF-36 role emotional, SF-36 mental health; all p<0.001) status. Regarding functional indices, 6MWD and Borg scale presented strong correlations with MLHF-PH scores as well as SF-36 physical domain scores (physical functioning, role physical, general health) and SF-36 'mental health' (Table 4). Patients, categorized in advanced WHO FC, reported poor HRQOL scores.

Predictors of HRQOL

Univariable regression analyses of physical (MLHF-PH Phys, SF-36 physical functioning, SF-36 role physical) and mental (MLHF-PH Emot, SF-36 role emotional, SF-36 mental health) HRQOL domains are presented in Supplementary file Tables S4 and S5. After multivariable adjustment, the use of PH-specific therapies, advanced WHO FC and use of oxygen treatment, were associated with worse HRQOL physical status (higher MLHF-PH Phys score, lower SF-36 physical functioning score) (Figure 2). Regarding HRQOL mental status, PH-specific therapies and advanced WHO FC but no oxygen treatment, were related to worse scores (higher MLHF-PH Emot score, lower SF-36 role emotional

Figure 2. Forest plots of the multivariable regression analyses for the Minnesota living with pulmonary hypertension physical component (MLHF-PH Phys) and the Short form 36-item health survey (SF-36) 'physical functioning' and 'role physical' domains

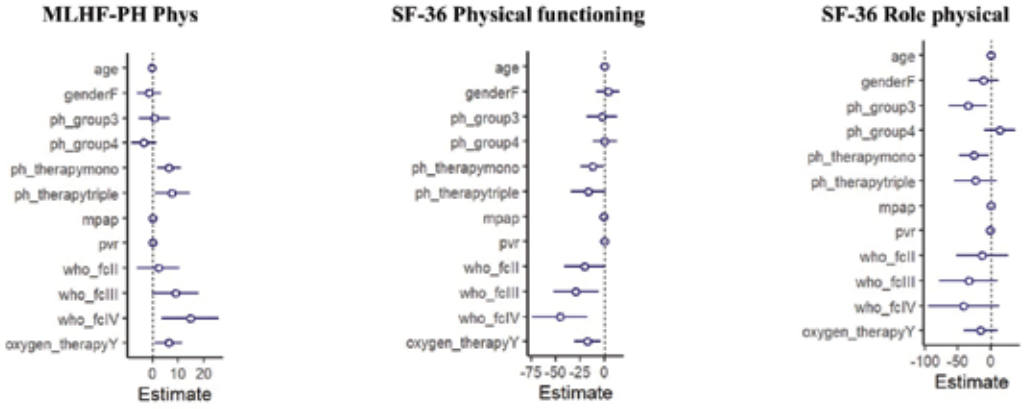
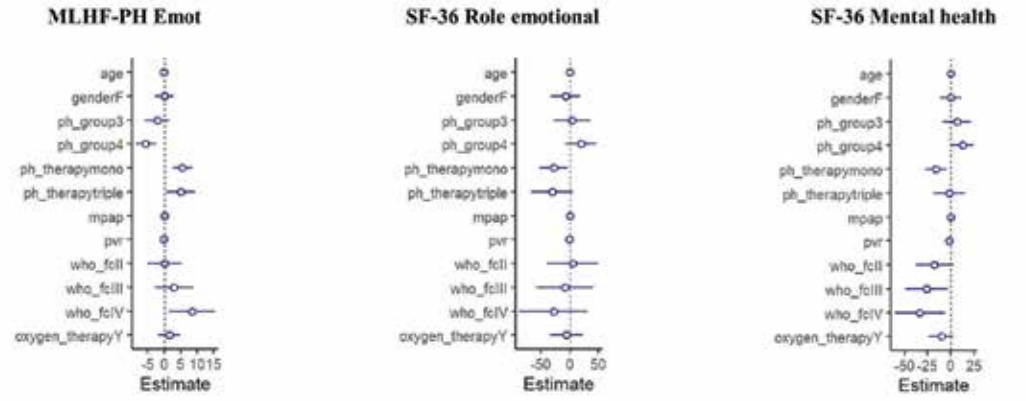


Figure 3. Forest plots of the multivariable regression analyses for the Minnesota living with pulmonary hypertension emotional component (MLHF-PH Emot) and the Short form 36-item health survey (SF-36) 'role physical' and 'mental health' domains



and mental health scores) (Figure 3). PH-Group 3 was independently associated with SF-36 'role physical' (β= -34.3; 95% CI: -63.6 – -5.1, p=0.02), whereas PH-Group 4 was independently associated with MLHF-PH Emot (β= -5.6; 95% CI: -8.7 – -2.6, p<0.001), after adjustment for all other covariates in the model.

DISCUSSION

This prospective cross-sectional study aimed to investigate HRQOL in patients with precapillary PH, and explore the relation of HRQOL questionnaires with clinical, hemodynamic, and functional parameters. The MLHF-PH and SF-36 instruments were used, since they have been previously established in the assessment of QOL in PH[11,14]. Our analysis demonstrated that QOL was impaired in PH patients. Participants had a score near or lower than 50 (0=worse, 100=best) in several domains of the SF-36, emphasizing the disease burden on both physical and mental status of this peculiar population[15].

Patients with PH due to lung disease (PH-Group 3) reported worse QOL, indicated by the significantly worse scores in MLHF-PH compared to the other groups. Physical domains of the SF-36 also presented significant impairment. We found that this group of patients was more frequently treated with oxygen therapy and had a more affected functional status, as reflected by the advanced WHO FC, but without hemodynamic differences compared to PH-Groups 1 and 4. After adjustment, PH-Group 3 emerged as an independent predictor of one of the physical domains in SF-36 (SF-36 role physical). These findings are in line with the study by Brewis et al.[16] which compared 188 patients with severe PH due to lung disease with 74 patients with idiopathic PH (PH-Group 1), and showed that patients with pulmonary disorders were more hypoxemic, had worse FC, and achieved lower 6MWD[16]. Our study possibly reflects that a poorer QOL might be anticipated in this population.

In our study, there was also a strong association between oxygen treatment and worse physical and mental aspects of

both questionnaires. After adjustment, oxygen use emerged as an independent predictor of worse physical scores (higher MLHF-PH Phys score, lower SF-36 physical functioning score) but not for mental scores. Previous studies have also indicated oxygen to be related to reduced HRQOL in PH patients[17,18]. These associations could be attributed to embarrassment feelings in public, along with reduced mobility and carrying issues that oxygen users tend to face[19,20]. Therefore, they may confine themselves indoors, something that inevitably leads to reduced QOL.

Another noteworthy finding was that HRQOL instruments, used in the current study, were also associated with hemodynamic indices (mPAP, PVR, SVO_2). Positive correlations of MLHF-PH scores with mPAP and PVR [higher hemodynamic values – higher (worse) score] and negative correlations with physical domains of SF-36 [higher hemodynamic values – lower (worse) score] emphasize the relation of QOL with PH severity. Our group had previously[21] demonstrated the significant correlation of hemodynamics in precapillary PH with emPHasis-10, which is another well-developed and easy to use HRQOL measure in PH[22]. Functional impairment as a consequence of the disease tended to have an evident impact on patients' HRQOL, shown by the correlations of WHO FC and 6MWD with the majority of questionnaire scores. WHO FC, a known determinant of HRQOL[17,21], was also a multivariable independent predictor in the current study. Furthermore, the strong correlation of MLHF-PH Emot score with hemodynamics in the studied population, highlights the potentially emotional impact of disease severity apart from functional limitations.

Triple combination PH-therapy, which includes the use of prostanoids, as add-on treatment to previously concomitant administration of endothelin receptor antagonists and phosphodiesterase type 5 inhibitors, was strongly associated with diminished state of health. The complexity of administration of these medications (mainly by intravenous or subcutaneous infusion) along with the frequently experienced adverse effects, may be responsible for the impact on patients' QOL. In a recent British study, researchers explored the differences in QOL between various administration modes of prostanoids and found that intravenous administration was related to the most affected health state (assessed with the EQ-5D-5L instrument)[23].

Limitations

The current study has several limitations, since it was an observational design study, conducted on a short-term basis. Therefore, only associations between HRQOL scores and independent variables can be established. Another important limitation is the small number of included patients, which is evident in between-group analyses as well. However, the limited number of participants is probably related to the limited population of northern Greece. Moreover, it is worth mentioning that there was a significant proportion of PH-Group 3 and operable PH-Group 4 patients in outpatient clinics, who were not offered medical treatment and thus were excluded from the study. Regarding hemodynamic variables, they were included from a right heart catheterization having been performed within 12 months before or after the questionnaire completion. The mean time was calculated at 7 months. Finally, HRQOL assessment was not available at the time of PH diagnosis, before the initiation of PH-specific therapies so that comparisons between and after treatment initiation could be conducted.

CONCLUSIONS

Patients with precapillary PH had impaired QOL. Those with PH due to lung disease reported the worst scores in HRQOL instruments (in both physical and mental domains). Several clinical, functional and hemodynamic factors were associated with reduced QOL. Oxygen use and WHO functional class were independent predictors of patients' physical and mental HRQOL status.

CONFLICTS OF INTEREST

The authors have each completed and submitted an ICMJE form for Disclosure of Potential Conflicts of Interest. The authors declare that they have no competing interests, financial or otherwise, related to the current work. G. Giannakoulas reports receiving consultancy fees from Janssen Pharmaceuticals, GlaxoSmithKline, MSD, Bayer, Pfizer, United Therapeutics, ELPEN Pharmaceuticals, Gossammer Bio, and Lilly. A. Boutou declares having received honoraria for lectures from CHIESI, ELPEN, MENARINI and ASTRA-ZENECA. H. Karvounis reports receiving honoraria and consultancy fees from Janssen Pharmaceuticals, Pfizer, GlaxoSmithKline, Bayer and MSD. I. Stanopoulos reports receiving consultancy fees from Janssen Pharmaceuticals. G. Pitsiou reports receiving honoraria and consultancy fees from Janssen Pharmaceuticals, GlaxoSmithKline, Bayer, and MSD.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval was obtained from the Administrative Committee of The University General Hospital of Thessaloniki 'AHEPA' (Approval number: 56079/10.12.2018; Date: 31 January 2019), and from the Scientific Committee of the General Hospital of Thessaloniki 'G. Papanikolaou' (Approval number: 112/25.1.2019; Date: 30 January 2019). Written informed consent was obtained from all patients.

DATA AVAILABILITY AND SHARING

The data supporting this research are available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

REFERENCES

1. Hoeper MM, Ghofrani HA, Grünig E, Klose H, Olschewski H, Rosenkranz S. Pulmonary Hypertension. Dtsch Arztebl Int. 2017;114(5):73-84. doi:10.3238/arztebl.2017.0073
2. Vonk Noordegraaf A, Galiè N. The role of the right ventricle in pulmonary arterial hypertension. Eur Respir Rev. 2011;20(122):243-253. doi:10.1183/09059180.00006511
3. Mainguy V, Maltais F, Saey D, et al. Peripheral muscle dysfunction in idiopathic pulmonary arterial hypertension. Thorax. 2010;65(2):113-117. doi:10.1136/thx.2009.117168
4. White J, Hopkins RO, Glissmeyer EW, Kitterman N, Elliott CG. Cognitive, emotional, and quality of life outcomes in patients with pulmonary arterial hypertension. Respir Res. 2006;7(1):55. doi:10.1186/1465-9921-7-55
5. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation. 2010;122(2):164-172. doi:10.1161/CIRCULATIONAHA.109.898122
6. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119. doi:10.1093/eurheartj/ehv317
7. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618-3731. doi:10.1093/eurheartj/ehac237
8. Fernandes CJSC, Martins BCS, Jardim CVP, et al. Quality of life as a prognostic marker in pulmonary arterial hypertension. Health Qual Life Outcomes. 2014;12:130. doi:10.1186/s12955-014-0130-3
9. Van Bulck L, Kovacs AH, Goossens E, et al. Rationale, design and methodology of APPROACH-IS II: International study of patient-reported outcomes and frailty phenotyping in adults with congenital heart disease. Int J Cardiol. 2022;363:30-39. doi:10.1016/j.ijcard.2022.06.064
10. Haraldstad K, Wahl A, Andenæs R, et al. A systematic review of quality of life research in medicine and health sciences. Qual Life Res. 2019;28(10):2641-2650. doi:10.1007/s11136-019-02214-9
11. Bonner N, Abetz L, Meunier J, Sikirica M, Mathai SC. Development and validation of the living with pulmonary hypertension questionnaire in pulmonary arterial hypertension patients. Health Qual Life Outcomes. 2013;11:161. doi:10.1186/1477-7525-11-161
12. Ware JE. SF-36 health survey update. Spine. 2000;25(24):3130-3139. doi:10.1097/00007632-200012150-00008
13. Anagnostopoulos F, Niakas D, Pappa E. Construct validation of the Greek SF-36 Health Survey. Qual Life Res. 2005;14(8):1959-1965. doi:10.1007/s11136-005-3866-8
14. Chua R, Keogh AM, Byth K, O'Loughlin A. Comparison and validation of three measures of quality of life in patients with pulmonary hypertension. Intern Med J. 2006;36(11):705-710. doi:10.1111/j.1445-5994.2006.01169.x
15. Shafazand S, Goldstein MK, Doyle RL, Hlatky MA, Gould MK. Health-related quality of life in patients with pulmonary arterial hypertension. Chest. 2004;126(5):1452-1459. doi:10.1378/chest.126.5.1452
16. Brewis MJ, Church AC, Johnson MK, Peacock AJ. Severe pulmonary hypertension in lung disease: phenotypes and response to treatment. Eur Respir J. 2015;46(5):1378-1389. doi:10.1183/13993003.02307-2014
17. Yorke J, Deaton C, Campbell M, et al. Symptom severity and its effect on health-related quality of life over time in patients with pulmonary hypertension: a multisite longitudinal cohort study. BMJ Open Respir Res. 2018;5(1):e000263. doi:10.1136/bmjresp-2017-000263
18. Taichman DB, Shin J, Hud L, et al. Health-related quality of life in patients with pulmonary arterial hypertension. Respir Res. 2005;6(1):92. doi:10.1186/1465-9921-6-92
19. Arnold E, Bruton A, Donovan-Hall M, Fenwick A, Dibb B, Walker E. Ambulatory oxygen: why do COPD patients not use their portable systems as prescribed? A qualitative study. BMC Pulm Med. 2011;11:9. doi:10.1186/1471-2466-11-9
20. Khor YH, Goh NSL, McDonald CF, Holland AE. Oxygen Therapy for Interstitial Lung Disease. A Mismatch between Patient Expectations and Experiences. Ann Am Thorac Soc. 2017;14(6):888-895. doi:10.1513/AnnalsATS.201611-934OC
21. Arvanitaki A, Mouratoglou SA, Evangeliou A, et al. Quality of Life is Related to Haemodynamics in Precapillary Pulmonary Hypertension. Heart Lung Circ. 2020;29(1):142-148. doi:10.1016/j.hlc.2018.12.005
22. Yorke J, Corris P, Gaine S, et al. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. Eur Respir J. 2014;43(4):1106-1113. doi:10.1183/09031936.00127113
23. Davies EW, Llewellyn S, Beaudet A, Kosmas CE, Gin-Sing W, Doll HA. Elicitation of health state utilities associated with the mode of administration of drugs acting on the prostacyclin pathway in pulmonary arterial hypertension. Patient Prefer Adherence. 2018;12:1079-1088. doi:10.2147/PPA.S16066

Clinical and polysomnographic characteristics of REM-related obstructive sleep apnea patients

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ABSTRACT

INTRODUCTION The clinical importance of obstructive sleep apnea (OPSA), which can be prevalent during rapid eye movement (REM) sleep, is unclear. This study aimed to explore possible differences between patients with REM-related OSA and non-REM-related OSA.

METHODS This retrospective study consisted of two groups of OSA patients, matched in age, gender and body mass index, who were examined at a Greek tertiary hospital; 147 patients with REM-related OSA were compared with 147 patients with non-REM-related OSA.

RESULTS Respiratory events occurred predominantly during REM sleep in REM-related OSA patients (p<0.001) and during non-rapid eye movement sleep (NREM) in the control group (p<0.001). The majority of REM-related OSA patients had mild OSA, while the majority of the control group had severe OSA. REM-related OSA patients had lower Arousal Index (p<0.001), lower Oxygen Desaturation Index (p<0.001), lower percent of recording time, spent at oxyhemoglobin saturation below 90% (p<0.001) and shorter mean event duration (p<0.001). The average $SatO_2$% and the minimum $SatO_2$% oxyhemoglobin saturation during sleep, were significantly higher, compared to the control group (p=0.002 and p=0.005, respectively). When comparing the anthropometric characteristics, the majority of the clinical features and the reported comorbidities, no significant differences were found between the two groups. However, REM-related OSA patients reported less frequently, excessive daytime sleepiness (p<0.001). Also, a positive correlation was found between reported insomnia and the minimum $SatO_2$% in them.

CONCLUSIONS Our results show that REM-related OSA patients, despite their milder polysomnographic phenotype, they do not carry a lighter comorbidity load, when compared to non-REM-related OSA patients.

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KEYWORDS

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INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by recurrent upper airway obstructive events, leading to intermittent hypoxemia, cortical arousals, sleep fragmentation, increased inflammation, and oxidative stress[1]. Phenotyping OSA, besides of improving understanding of disease mechanisms, has prognostic and therapeutic utility[2]. REM-related OSA is a distinct polysomnographic phenotype with an estimated prevalence ranging from as little as 10% to as much as 45%[3,4]. This wide range of prevalence could be attributed to inconsistent definitions of REM-related OSA and to differences in studies' methodology, sample size, and composition[3,5].

A broadly used definition requires an overall apnea-hypopnea index (AHI), measured during total sleep time (AHI_{TST}), of at least 5 obstructive respiratory events/h (AHI_{TST} ≥5) and AHI in REM sleep (AHI_{REM}) that is at least twice the AHI in NREM sleep (AHI_{NREM}), (AHI_{REM}/AHI_{NREM} ≥2)[5-7]. Subsequently stricter definitions have emerged, that include various degrees of cut-off levels of AHI_{NREM}[8-12] or both of AHI_{NREM} and AHI_{REM}[7,13,14]. Furthermore, a minimum duration of REM sleep has been an additional criterion in some of the previous definitions[7,12-14]. The stricter definitions, include the aforementioned criterion of a sufficient REM sleep duration, aiming to estimate more precisely the REM sleep disordered breathing[7,12-14]. It is notable that the proposed definition of Mokhlesi and Punjabi[13] does not include the AHI_{REM}/AHI_{NREM} ratio, since its nominator and denominator are correlated values, and by using their ratio, it could be difficult to separate out the NREM sleep component in REM-related OSA patients[13]. However, to date, comparative studies failed to demonstrate significant differences in the most of their major endpoints, when stricter and broader definitions were applied and compared at the same sample[5,7,15-18]. The broader definition, besides the fact that it is easier to apply in daytime practice, it seems that it is not affected by changes in hypopnea scoring rules and as a result its employment augments the conduction of less biased retrospective

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studies[19].

In the current literature, despite the numerous studies conducted in other Caucasian ethnicities, there are no published data about REM-related OSA in the Greek population. In this study, we aim to record demographic, anthropometric and clinical characteristics, polysomnographic findings and comorbidities of REM-related OSA patients, and to evaluate possible differences with non-REM-related OSA patients. Also, we explore possible correlations of excessive daytime sleepiness (EDS) and insomnia, in REM-related OSA and non-REM-related OSA compared groups.

METHODS

Study population

In the present retrospective observational study, a total of 2561 medical files of patients with suspected sleep-related breathing disorders, who underwent polysomnography (PSG) at the Sleep Laboratory of the University General Hospital of Alexandroupolis from 2007 to 2019, were reviewed. A total of 1495 patients had been diagnosed with OSA, and approximately 16% of them (239 patients) were classified as REM-related OSA patients, while the rest (1256 patients) were classified as non-REM-related OSA patients.

The broad REM-related OSA definition was used. According to it, an overall apnea-hypopnea index of at least 5 obstructive respiratory events/h (AHI_{TST} ≥5) and AHI_{REM} that is at least twice the AHI_{NREM} (AHI_{REM}/AHI_{NREM} ≥2) are required. Eventually 147 patients were included from each group and each case (REM-related OSA patient) was matched to one control (non-REM-related OSA patient) by age, gender, and body mass index (BMI).

Ethical approval

All procedures were performed in accordance with the ethical standards of the institutional review board of Alexandroupolis University Hospital, which approved the protocol of the study (approval number:7/07-04-2022).

Data collection

The demographic and anthropometric data that were recorded between two groups include: age, gender, BMI, neck circumference, waist-to-hip ratio (WHR), and tobacco smoking history. Clinical symptoms (snoring, witnessed apneas, EDS, insomnia) and comorbidities (chronic diseases under current treatment or not) were also recorded.

The validated Greek version of the Epworth Sleepiness Scale (ESS) was applied for the assessment of EDS[20]. ESS score >10 was the cut-off value used to define EDS. Assessment of insomnia was performed with a self-report questionnaire that includes the essential criteria of the International Classification of Sleep Disorders for chronic insomnia. Patients with insomnia were further classified in subtype groups of onset or maintenance insomnia, or combination of the above, according to the documented answers in the previous questionnaire.

Furthermore, Comorbidities Index (CoSA Index) was applied and compared in both groups. This evaluates the mortality risk of sleep apnea patients, based on their comorbidity burden (hypertension, COPD, diabetes mellitus, ischemic stroke, malignancy, heart failure, dementia, atrial fibrillation, end stage renal disease, aortic aneurysm, and age ≥65 years). Points, ranging 1–6, are assigned to each selected comorbidity and they are proportional to its mortality hazard ratio. The final CoSA Index score is stratified in four severity levels (0, 1–3, 4–6, >6) with different crude mortalities (0.57%, 1.71%, 6.79%, 15.88%, respectively)[21]. Polysomnograms were scored according to the updated for each period AASM criteria, AASM 2007 and AASM 2012, since data are retrospectively analyzed, including archives of patients who were referred for sleep evaluation from 2007 to 2019.

Based on severity grading of OSA, by using the AHI system OSA, subjects with (5≤ AHI_{TST} <15), (15≤ AHI_{TST} <30) and (AHI_{TST} ≥30) were classified as mild, moderate, and severe OSA, respectively.

Besides AHI_{TST}, AHI_{REM} and AHI_{NREM}, the following polysomnographic measurements were recorded: Total Sleep Time (TST), Sleep Efficiency (SE)(%), Sleep Latency (SL), sleep stages duration presented as percent of TST (N1/TST%, N2/TST%, N3/TST%, REM/TST%), REM Latency, Mean event duration, Average and minimum oxyhemoglobin saturation during sleep (Average $SatO_2$%, Minimum $SatO_2$%), cumulative percentage of time spent at oxyhemoglobin saturation below 90%, presented as percent of total recording time [CT90%/TRT(%)], Oxygen Desaturation Index (ODI), and Arousal Index (ArI).

Statistical analysis

All analyses were carried out using IBM Statistical Package for Social Sciences (SPSS Inc. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc). Throughout the study, categorical variables are described as frequencies and percentages, and chi-squared test was used for their comparison, except for the cases of very small samples where Fisher's exact test was applied.

Quantitative variables were tested for normality of distribution by the Shapiro-Wilk test. Because distributions of all quantitative variables were skewed, the non-parametric Mann–Whitney test was used for their comparison and they are presented as median and interquartile range (IQR).

Binary logistic regression analysis was used to estimate the association between EDS and insomnia (defined as primary dependent variables) and AHI_{TST}, AHI_{REM}, AHI_{NREM}, Average $SatO_2$, Minimum $SatO_2$, ODI, ArI, BMI (defined as primary independent variables), in the REM-related OSA and the non-REM-related OSA group. Odds ratios are presented, along with 95% confidence intervals. All comparisons were two-tailed, and a $p<0.05$ was considered statistically significant.

RESULTS

Patients' general characteristics

The demographic and anthropometric characteristics of the REM-related OSA and the matched non-REM-related OSA group are presented in Table 1. REM-related OSA participants were predominantly males (57.8%), middle or older aged, with high BMI. Their median neck circumference and waist-to-hip ratio was 42 cm (IQR: 39–44) and 0.82 cm (IQR: 0.76–0.90), respectively, and no significant differences were found compared to the control group. Also, no significant differences were found in both groups regarding their smoking status.

Polysomnographic characteristics

Table 2 displays the comparison of polysomnographic findings between the REM-related OSA and the non-REM-related OSA group. The two groups were similar in terms of the total sleep time (TST), Sleep Efficiency (SE), Sleep Latency (SL) and the percentage of sleep time spent in N1 stage ($p>0.05$, respectively). REM-related OSA patients had higher amounts of slow wave sleep (SWS) ($p=0.003$) and REM sleep ($p<0.001$), and lower amounts of N2 stage sleep ($p=0.001$). REM latency was shorter in the REM-related OSA group ($p=0.016$). Comparison of the nocturnal oximetry findings among the two groups showed that REM-related OSA patients had significantly higher Average $SatO_2$% ($p=0.002$) and higher Minimum $SatO_2$% ($p=0.005$), but lower CT90%/TRT(%) ($p<0.001$) and ODI ($p<0.001$). Furthermore, REM-related OSA patients had significantly shorter mean duration of respiratory events during TST ($p<0.001$), and lower ArI ($p<0.001$).

Analysis of respiratory disturbances revealed that REM-related OSA patients had lower AHI_{TST} ($p<0.001$) and AHI_{NREM} ($p<0.001$), while their AHI_{REM} index was significantly higher ($p<0.001$). These findings were expected, given the criteria of the broad REM-related OSA definition that was applied in our study's subjects.

In agreement with the aforementioned data, significant differences have been documented across all OSA severity levels between the two groups. In REM-related OSA patients there is a significant prevalence of mild ($p<0.001$) or moderate OSA syndrome ($p=0.006$), compared to the non-REM-related OSA group, while in the latter group, severe OSA is predominant ($p<0.001$). Indeed, the majority of REM-related OSA patients have mild OSA (about 60%), while 34% have moderate OSA, and only about 6% has severe OSA. In contrast, the majority of the OSA patients suffer from severe OSA (51.7%), while 28.6% and 19.7% have mild and moderate OSA, respectively (Figure 1).

Clinical features and comorbidities

Table 3 shows the frequency of the specific sleep related complaints and the CoSA Index values of both groups, and the results of their comparison. Subjective sleepiness, as evaluated by ESS score, revealed a significant difference between the two groups of patients. REM-related OSA patients had lower ESS score ($p<0.001$) and lower EDS prevalence ($p=0.003$). However, there were no significant differences in frequency of habitual snoring, witnessed apneas, chronic insomnia, and insomnia subtypes ($p>0.05$, respectively).

Figures 2 and 3 depict the frequency distribution of insomnia subtypes of both groups. It is clearly observed that the middle insomnia (difficulty in maintaining sleep) and the combination of initial (difficulty in initiating sleep) with middle insomnia are the most frequent subtypes. As regards

Table 1. Participants' demographic and anthropometric characteristics

Characteristics	REM-related OSA (N=147)	non-REM-related OSA (N=147)	p
Gender*	**n**	**n**	1
Male	85	85	
Female	62	62	
	Median (IQR)	**Median (IQR)**	
Age (years)*	58 (49–64)	57 (50–65)	0.891
BMI (kg/m^2)*	33.8 (29.7–38.9)	33.7 (29.5–38.9)	0.854
Neck circumference (cm)	42 (39–44)	42 (40–44.5)	0.097
WHR	0.82 (0.76–0.90)	0.81 (0.75–0.89)	0.660
Smoking status	**n (%)**	**n (%)**	
Non-smoker	71 (47.5)	60 (40.8)	0.197
Current smoker	37 (25.6)	43 (29.3)	0.432
Former smoker	39 (26.9)	44 (29.9)	0.517

BMI: body mass index. WHR: waist-to-hip ratio. *Matched characteristics in REM-related OSA and non-REM-related OSA group. IQR: interquartile range.

Table 2. Comparison of polysomnographic characteristics between REM-related OSA and non-REM-related OSA patients

Characteristics	REM-related OSA (N=147) Median (IQR)	non-REM-related OSA (N=147) Median (IQR)	p
TST (min)	315.5 (277–345.5)	318 (271.5–348.5)	0.816
N1/TST (%)	10.2 (6.2–8.4)	10.7 (5.4–20.1)	0.983
N2/TST (%)	61.3 (52.3–71.6)	68.1 (55.4–86.3)	**0.001**
N3/TST (%)	11 (5.2–19.7)	7 (2– 5.2)	**0.003**
REM/TST (%)	12.1 (6.7–16.2)	7.3 (2–12.7)	**<0.001**
REM Latency (min)	125 (85.3–185)	148 (99.6–225.1)	**0.016**
SE (%)	84.3 (73.1–90.4)	86.4 (76.3–91.1)	0.073
SL (min)	17.00 (9.50–30.50)	15.50 (8.00–27.00)	0.192
Mean event duration (sec)	16.20 (14.80–18.70)	17.70 (15.60–21.90)	**<0.001**
ArI (events/h)	14.2 (6–22)	20.3 (7.3–35.5)	**<0.001**
AHI_{TST} (events/h)	13.1 (8.7–18.5)	30.8 (12.9–60.7)	**<0.001**
AHI_{REM} (events/h)	38.4 (25.6–51.8)	12 (0–52)	**<0.001**
$AHIN_{REM}$ (events/h)	9.2 (5.5–15.2)	33.2 (12.4–62.1)	**<0.001**
Average $SatO_2$ (%)	93 (91.9–94.6)	92 (90–94)	**0.002**
Minimum $SatO_2$ (%)	80 (74–84)	77 (67–83)	**0.005**
$CT_{90\%}$ /TRT (%)	2.9 (0.8–9.8)	9.4 (2–35.1)	**<0.001**
ODI (events/h)	18.9 (12.1–28.8)	38.1 (18.9–69.1)	**<0.001**
OSA severity	**n (%)**	**n (%)**	
Mild	88 (59.9)	42 (28.6)	**<0.001**
Moderate	50 (34)	29 (19.7)	**0.006**
Severe	9 (6.1)	76 (51.7)	**<0.001**

AHI: apnoea hypopnea index. ArI: arousal index. $SatO_2$: oxyhemoglobin saturation. $CT_{90\%}$: cumulative percentage of time spent at oxyhemoglobin saturation below 90%. EDS: excessive daytime sleepiness. ESS: Epworth Sleepiness Scale. N1: sleep stage 1. N2: sleep stage 2. N3: sleep stage 3. ODI: oxygen desaturation index. OSA: obstructive sleep apnoea. REM: rapid eye movement. SE: sleep efficiency. SL: sleep latency. TRT: total recording time. TST: total sleep time. IQR: interquartile range.

Figure 1. OSA severity in REM-related OSA and non-REM-related OSA patients

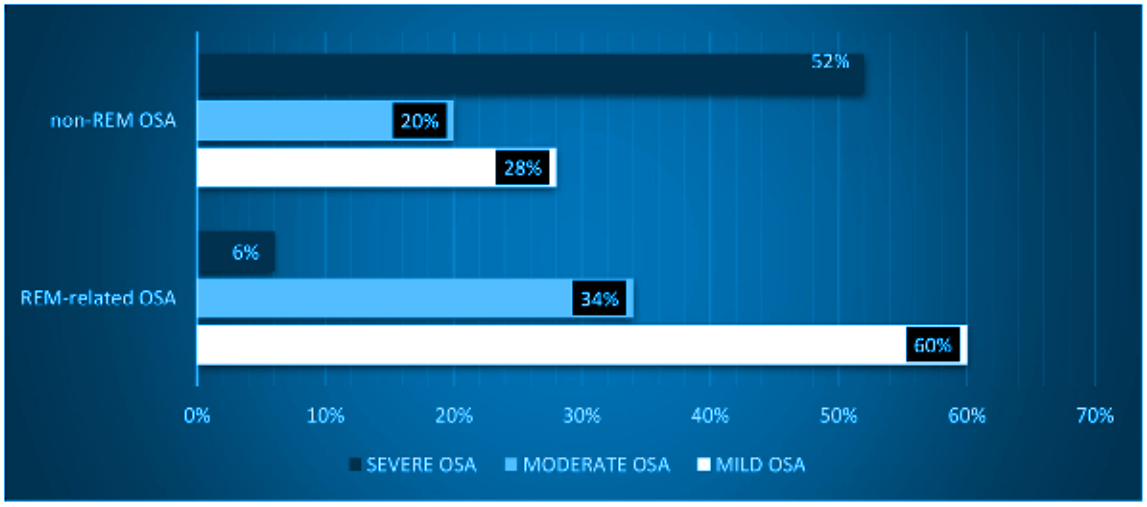
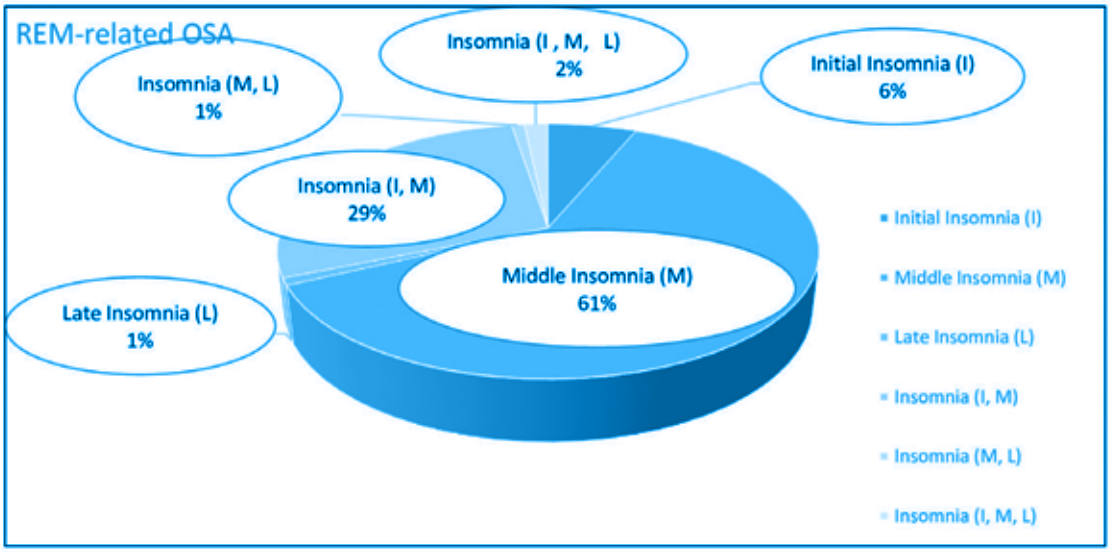


Table 3. Comparison of clinical characteristics and CoSA Index between REM-related OSA and non-REM-related OSA patients

Characteristics	REM-related OSA (N=147) n (%)	non-REM-related OSA (N=147) n (%)	p
ESS score, median (IQR)	7 (4–11)	9 (7–13)	**<0.001**
EDS	45 (30.6)	69 (47.6)	**0.003**
Snoring	142 (96.6)	145 (98.6)	0.251
Witnessed apneas	83 (56.5)	74 (50.3)	0.293
Insomnia	112 (76.2)	97 (66)	0.110
Initial	7 (6.3)[a]	4 (4.1)[b]	0.492
Middle	69 (61.6)[a]	60 (61.9)[b]	0.971
Late	1 (0.9)[a]	3 (3.1)[b]	0.185*
Initial/Middle	32 (28.6)[a]	27 (2.8)[b]	0.776
Middle/Late	1 (0.9)[a]	3 (3.1)[b]	0.339
Initial/Middle/Late	2 (1.7)[a]	0 (0)b	0.500
CoSA Index, median (IQR)	2 (0–4)	2 (0–4)	0.590
CoSA Index level			
0	59 (40.1)	45 (30.6)	0.088
1–3	49 (33.3)	65 (44.2)	0.055
4–6	30 (20.4)	29 (19.7)	0.884
>6	9 (6.1)	8 (5.4)	0.803

EDS: excessive daytime sleepiness. ESS: Epworth Sleepiness Scale. CoSA Index: comorbidity sleep apnea index. **a** N=112 patients with insomnia and REM-related OSA. **b** N=97 patients with insomnia and non-REM-related OSA. *Exact Fisher value.

Figure 2. Insomnia subtypes in REM-related OSA patients



comorbidities' load, comparisons across all CoSA Index severity levels showed no significant differences between REM-related OSA and non-REM-related OSA patients.

Comorbidities' distribution in both groups is illustrated in Figure 4. Arterial hypertension and metabolic diseases, specifically diabetes mellitus and dyslipidemia, are the most

Figure 3. Insomnia subtypes in OSA patients

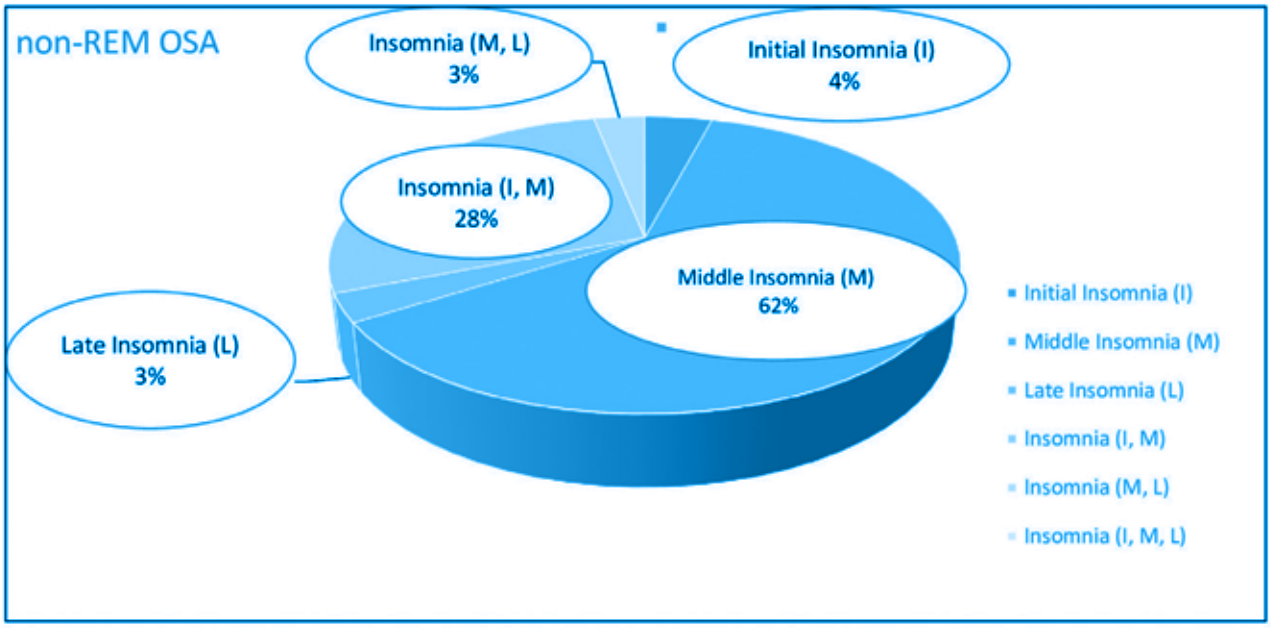
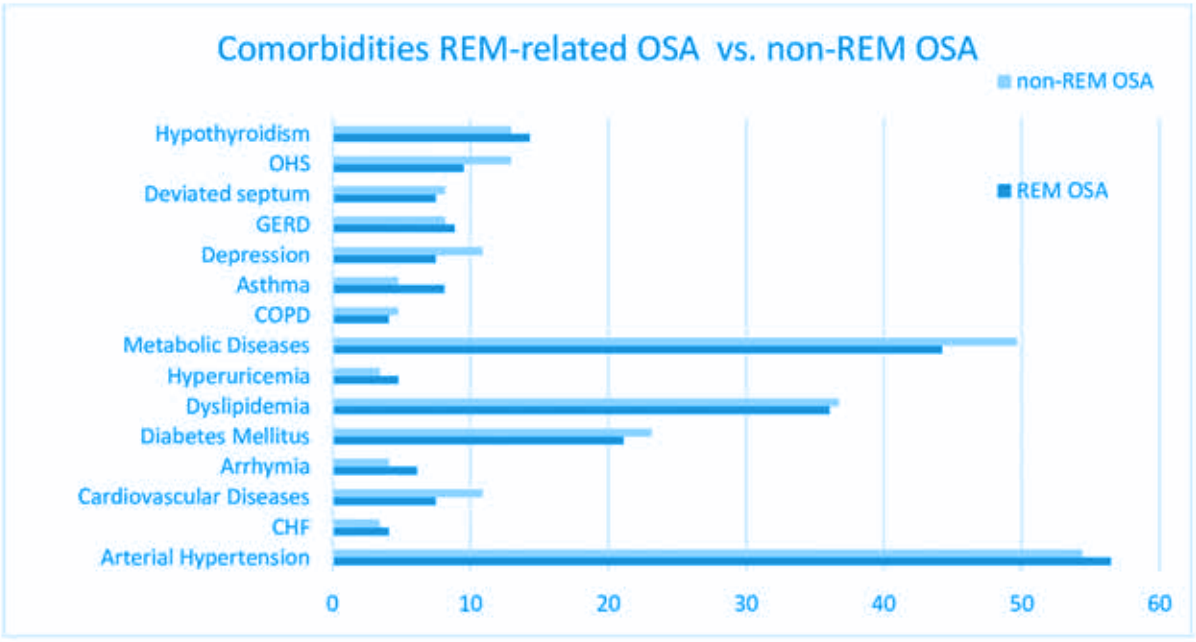


Figure 4. Comorbidities' distribution in REM-related OSA and non-REM-related OSA patients



frequently reported comorbidities in both groups, followed by hypothyroidism, cardiovascular diseases, e.g. coronary artery disease, ischemic strokes, and chronic respiratory diseases, e.g. COPD, asthma etc.

Table 4 shows the frequency of the recorded comorbidities and their comparison between REM-related and non-REM-related OSA patients. No significant differences in comorbidities were noted between the two groups.

Association between polysomnographic parameters and clinical features in REM-related OSA and control group

We analyzed the association of insomnia with polysomnographic findings mainly in REM-related OSA and non-REM-related OSA group, using binary logistic regression model, with insomnia defined as the dependent binary variable. The included independent variables were:

Table 4. Comparison of comorbidities between REM-related OSA and non-REM-related OSA patients

Comorbidities	REM-related OSA (N=147) n (%)	non-REM-related OSA (N=147) n (%)	p
AH	83 (56.46)	80 (54.42)	0.725
CHF	6 (4.08)	4 (2.72)	0.520
CVD	11 (7.48)	16 (10.88)	0.313
Arrhythmias	9 (6.12)	6 (4.08)	0.427
Metabolic disorders	65 (44.22)	73 (49.66)	0.35
Diabetes mellitus	31 (21.38)	34 (23.13)	0.719
Dyslipidemia	53 (36.05)	54 (36.73)	0.904
Hyperuricemia	7 (4.76)	5 (3.40)	0.556
Respiratory diseases	18 (12.24)	14 (9.52)	0.454
Asthma	12 (8.16)	7 (4.76)	0.236
COPD	6 (4.08)	7 (4.76)	0.777
Depression	11 (7.48)	16 (10.88)	0.313
GERD	13 (8.84)	12 (8.16)	0.834
Deviated septum	11 (7.48)	12 (8.16)	0.828
OHS	14 (9.52)	19 (12.93)	0.356
Hypothyroidism	21 (14.29)	19 (12.93)	0.734

AH: arterial hypertension. CHF: congestive heart failure. COPD: chronic obstructive sleep apnea. CVD: cardiovascular disease. GERD: gastroesophageal reflux disease. OHS: obesity hypoventilation syndrome.

AHI_{TST}, AHI_{REM}, $AHI_{NREM,}$ Average $SatO_2$%, Minimum $SatO_2$%, ODI, ArI, and BMI. In the REM-related OSA group, a weak positive correlation was found between insomnia and the Minimum $SatO_2$% (β=0.083, p=0.041, RR=1.086; 95% CI: 1.003–1.176), whereas no significant association was found regarding insomnia in non-REM-related OSA patients.

Similarly, we analyzed the association of EDS with the same parameters, separately in the REM-related OSA and non-REM-related OSA group, using the binary logistic regression model, with the EDS defined as the dependent variable. No significant association was found, regarding EDS, in both groups.

DISCUSSION

In this retrospective study, no differences were found regarding the anthropometric characteristics of the compared groups. To our knowledge, two studies have performed anthropometric comparisons among REM-related OSA and non-REM-related OSA subjects and found that they did not differ significantly in terms of age, gender and BMI, simultaneously[22,23]. The study of Sattaratpaijit et al.[23] found that REM-related OSA patients tend to have thinner necks, while the study of Liu et al.[22] documented no differences, as we did.

Looking at the polysomnographic features of REM-related OSA patients, the studies either document higher TST[16,24,25] and SE[12,22,24] or – as our study did – they report no differences in them[6,16,26]. The current study also showed that REM-related OSA patients had significantly higher amounts of SWS and REM sleep. These results agree with other studies, where time spent in N3[5,6,12,16,24,27] and in REM sleep[5,6,12,15,16,24-26] stage, was significantly higher in REM-related OSA subjects, although there are a few studies that do not report differences in REM sleep duration[22,26,27]. The possible underestimation of REM sleep duration, due to the first night effect that is encountered in hospital-conducted studies[28], as ours, should be reasonably considered when assessing the severity of breathing disorders, confined mainly at this sleep stage, i.e. in the REM-related OSA patients, and even more when deciding to offer or not, treatment to these patients.

SL was not significantly different between our two groups, a finding that is in agreement with the results of the study by Sakao et al.[16]. In that study, the previous finding did not change when different definitions of REM-related OSA were used[16]. However, other studies have reported significantly longer[15] or shorter[22] SL in REM-related OSA patients. Moreover, REM latency had a significantly shorter duration in our study, in agreement with the study of Liu et al.[22].

The data about the duration of N1 and N2 sleep stages are limited and inconsistent. Our study did not report significant differences in the duration of N1 stage. On the

contrary, according to some studies, REM-related OSA patients have shorter N1 sleep stage[6,12,15,16]. Regarding the duration of N2 stage in REM-related OSA patients, some studies report longer N2 sleep stage[15,16] while our study reported shorter N2 stage. These results are similar to the Bahammam et al.[12] and Haba-Rubio et al.[6] studies, though there was no statistical significance in the latter study.

REM-related OSA patients had lower ArI in our study, in agreement with the results of other published studies[5,7,12,15,16,24,26]. More specifically, in the studies of Conwell et al.[5] and Hoshino et al.[15], this difference was significant, even after the application of the stricter REM-related OSA definition.

The comparison of the nocturnal oximetry data between the two groups showed that REM-related OSA patients presented milder nocturnal hypoxia. Also, the majority of previously published studies reported significant higher Minimum $SatO_2$% values[6,7,12,15,22,24] and lower $CT_{90\%}$/TRT (%)[7,12,15,24] and ODI[6,12,16,24]. In contrast to Liu et al.[22], our study reported higher Average $SatO_2$%. Two comparative studies[6,22] demonstrated shorter mean duration of the obstructive events in REM-related OSA, a finding confirmed by our study.

REM-related OSA patients have lower AHI_{TST} values and milder syndrome compared to the non-REM-related OSA patients in all published studies[6,12,22,24-27], including ours. Our results indicated that the majority of REM-related OSA patients present more frequently mild or moderate syndrome, while non-REM-related OSA patients present more often severe OSA. These findings are comparable to those recorded by other studies[5,7,12,25,27]. It has long been suggested that REM-related OSA could be a part in the spectrum of sleep disordered breathing that appears in younger ages, pertains and progresses over time to non-REM-related OSA[13]. This hypothesis, though not still verified, could offer an explanation for the fact that younger age is an independent, strong correlate of REM-related OSA[8,9,12] and for the previously mentioned differences in disease severity among REM-related OSA and non-REM-related OSA.

It is plausible that the kind of REM-related OSA definition could affect the distribution of the recorded events across REM and NREM sleep, as stated in some studies[5,15,16]. This is clearly observed in the study of Hoshino et al.[15] where the majority of the events either clustered in REM sleep or in NREM sleep, when the broad – as ours – or stricter definitions were applied, respectively.

No significant differences were reported between the REM-related OSA and the control group, regarding witnessed apneas and disturbing snoring. Our findings agree with those of Sakao et al.[16] and Liu et al.[22], who also obtained such information during clinical interview of patients and their bed partners. Other studies describe lower percentages of witnessed apneas[6,12] or loud snoring[5,12] in REM-related OSA. However, the previous findings should be interpreted cautiously, since the majority of REM-related OSA patients were females and no gender matching has been performed between groups.

In the current study, the prevalence rates of EDS that were reported in REM-related OSA and control group were up to approximately 31% and 48%, respectively. These rates are in agreement with the described percentages of many studies where EDS, measured by ESS score, with range 20–68% in REM-related OSA, and 30–67% in non-REM-related OSA patients[5,8,14,16,22,25].

In contrast to already published studies, which use the ESS and do not reveal any significant differences in EDS between REM-related OSA and non-REM-related OSA patients[5-7,15,16,22,24-27,29], our study and a recent prospective study of Bahammam et al.[12] showed that EDS is less frequently encountered in REM-related OSA patients. It is recognized that many factors can induce EDS in OSA population such male gender, increased age, and BMI[30,31]. Since such matching is lacking in the majority of published studies, comparing REM-related OSA and non-REM-related OSA patients, it could be difficult to come to safe conclusions about possible EDS differences between them. To our knowledge, only one comparative study[22] has matched included subjects by age, gender and BMI simultaneously, as in the present study, and according to it, no differences in EDS were recorded between the two groups of patients. However, it is noteworthy that the REM OSA definition that was used in the previous study has not been used or evaluated in other studies.

In the literature, there are scarce and conflicting data about the association of EDS – quantified by ESS – with OSA severity indices, in REM-related OSA and non-REM-related OSA. No correlation of EDS with either apnea-hypopnea indices ($AHI_{TST,}$ AHI_{NREM}, AHI_{REM}) or nocturnal oximetry parameters (Average $SatO_2$%, Minimum $SatO_2$%, $CT_{90\%}$/TRT (%), ODI) or ArI, was noted in our study. Indeed REM-related OSA patients in our study presented better sleep quality (increased N3, decreased ArI). Similarly, in the study of Gabryelska and Białasiewicz[26], no association was found between ESS score and AHI. Additionally, in the study of Khan et al.[32] which included old-aged males suffering from REM-related OSA, no association was presented between AHI_{REM} severity levels and ESS score[32]. Interestingly, the majority of published studies do not reveal any correlation between AHI_{REM} and EDS[24,29,33].

However, according to Chami et al.[33], AHI_{NREM} was associated with EDS, evaluated with ESS, in both REM-related OSA and non-REM-related OSA subjects, while Pamidi et al.[24] reported AHI_{NREM} association only in non-REM-related OSA patients. Notably, in the last study, a positive correlation between BMI and ESS score was documented in REM-related OSA patients, a finding that was not confirmed by our study.

In our study both groups presented high percentages of reported insomnia (76% and 66%, in REM-related OSA and in non- REM OSA group, respectively). Given the fact that older age, the female sex, the comorbidity of OSA[34] and the

smoking habit[35] are related to higher prevalence of insomnia, high percentages of insomnia are expected in our study, since our participants with OSA were predominantly middle or older aged, females in a considerable proportion (about 42%) of the whole sample, and often smokers (current or former).

Despite the significant differences in the severity of underlying OSA and in the sleep quality between groups, no differences in the perceived insomnia were demonstrated among them. It is possible that the amount of the reported insomnia could be influenced by other factors that were not included and controlled. For instance, given the retrospective characteristics of the current study, patient records about their daily consumption of caffeine or theine, or the consumption of insomnia-related medication or other psychoactive substances, were difficult to find consistently[36]. Furthermore, even sleep misperception disorders, that are frequently encountered in insomniacs, could be a confounding factor that is also difficult to be identified and adjusted in retrospective studies as ours[37].

Very limited data are available on this topic, and mainly Pittsburgh Sleep Quality Index (PSQI) was applied for evaluating insomnia-related sleep disturbances. In the study by Khan et al.[32], no association was described between distinct REM-related OSA severity groups and insomnia. On the other hand, according to the study by Hoshino et al.[15], REM-related OSA was associated with increased PSQI score and this association was found to be stronger for definitions stricter than ours. More specifically, when the broad definition – used also in our study – was applied, this association was confined in the females only. In a recent study by Bahammam et al.[12] who used a stricter REM-related OSA definition, comorbidity insomnia was more common in REM predominant patients, although there was no matching among groups in terms of sex.

Up to now, to our knowledge, no data regarding insomnia subtypes or associations of insomnia with polysomnographic parameters in both groups have been published. According to our findings, middle insomnia, and combination of initial and middle insomnia, are the most frequently reported subtypes. Furthermore, a positive correlation between Minimum $SatO_2$% and insomnia was identified in our study, indicating a possible weak relation between insomnia and mild REM-related OSA syndrome.

Systemic hypertension is the most frequently recorded comorbidity in both groups of our study and no significant difference between them was demonstrated, a finding that was confirmed in other studies too[24,27]. However, some other studies showed less frequently hypertension in REM-related OSA, but it seems that there was no matching in the recruited subjects for confounding factors such as age and BMI[5,12,25].

Several studies[6,16,22] reported no differences in the prevalence of cardiovascular diseases, arrhythmias and heart failure, similarly to our study, ever after employing stricter and broader REM-related OSA definitions[16]. However, according to the prospective study of Bahammam et al.[12], REM-related OSA patients had less frequently coronary disease, though there were no differences in compensated heart failure or strokes.

Regarding metabolic diseases and hypothyroidism, a considerable number of studies, including ours, suggest no significant differences between the two groups[6,12,22,24], although one study described lower prevalence of diabetes mellitus in REM-related OSA patients[5].

Additionally, our study suggests no differences in respiratory diseases, in agreement with other results[5,6,16,22] with the exception of one recent study, which describes higher prevalence of bronchial asthma in REM-related OSA group[12].

No differences were also found in reported depression among the two groups. Literature findings are variable and conflicting, since some studies that have used the Beck Depression Inventory[22] or just the medical history information[6], identified no difference in depression rates, whereas two studies that applied the CES-D (Center for Epidemiologic Research Depression Scale) questionnaire found more depression in REM-related OSA group[5,24]. However, female predominance in REM-related OSA participants in the latter studies, should be underlined.

Moreover, in our study, no differences in comorbidity burden were recorded between the two groups and the majority of patients were clustered in the lower two grades of the CoSA index.

The similar comorbidities rates should be taken into consideration from sleep physicians, when deciding to suggest or not treatment in REM-related OSA patients, even when they are minimally symptomatic, and especially when they carry a notable comorbidity load, as the patients of our study, since therapy must be tailored to individual patient's needs, not only by controlling their symptoms, but by preventing comorbidities, ameliorating the impact of existing comorbidities, and improving their life expectancy too.

Limitations

The reported results should be interpreted within the limitations of our study. First, this is a single-center retrospective study, with all the biases related to such clinical recruitment and referral recording patterns. Secondly, it has a relatively small sample size of patients, being examined at a tertiary hospital, where usually more symptomatic or complicated patients are admitted, and as a result possible referral biases could not be eliminated. In addition to the abovementioned features, the male preponderance in our study sample, could impair the representativeness of our findings. since female sex is an independent correlate of REM-related OSA[7]. Furthermore, it must be stated that clinical assessment was subjective, based mainly on medical history, obtained during clinical interview of patients and of their bed-partners when this was feasible. In particular, the

questionnaire that was used for the evaluation of insomnia and its subclassifications, though updated, was not validated. According to the ICSD-3 Classification[38], a minimum frequency of 3 times per week was added to diagnostic criteria of chronic insomnia. This additional criterion, established since 2014, was a confounding factor that we could not eliminate, given the retrospective characteristics of our study.

CONCLUSIONS

According to the polysomnographic features of the patients in both groups, we conclude that the REM-related OSA patients have more often mild to moderate OSA and demonstrate a better nocturnal oximetry profile with less sleep fragmentation, in comparison to the non-REM-related OSA patients. No differences were reported regarding anthropometric characteristics (neck circumference, waist-to-hip ratio), the majority of the compared clinical features (witnessed apneas, snoring, and insomnia) and comorbidities. However, REM-related OSA patients reported less frequently EDS, as measured by ESS score. Furthermore, a positive correlation was found between insomnia and Minimum $SatO_2$% in the REM-related OSA group. Despite their differences in polysomnography, REM-related OSA patients do not report overall milder symptoms and do not carry a lighter comorbidity burden, which may imply that they possibly do not comprise a milder, distinct clinical phenotype. More extended and prospective studies have to be conducted in order to draw definite conclusions about the impact of REM-related OSA to quality and expectancy of living, and the possible beneficial effect of implementing treatment modalities to all REM-related OSA patients.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported.

FUNDING

There was no source of funding for this research.

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval was obtained from the Institutional Review Board of Alexandroupolis University Hospital (Approval number:7/07-04-2022; Date: 7 April 2022). Patient informed consent was not required as this was a confidential retrospective observational study.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

REFERENCES

1. White DP. Sleep-related breathing disorder.2. Pathophysiology of obstructive sleep apnoea. Thorax. 1995;50(7):797-804. doi:10.1136/thx.50.7.797
2. Zinchuk AV, Gentry MJ, Concato J, Yaggi HK. Phenotypes in obstructive sleep apnea: A definition, examples and evolution of approaches. Sleep Med Rev. 2017;35:113-123. doi:10.1016/j.smrv.2016.10.002
3. Rishi AR, Rishi MA. Rapid eye movement related obstructive sleep apnea: Where do we stand? Respir Investig. 2021;59(5):589-595. doi:10.1016/j.resinv.2021.06.006
4. Joosten SA, Hamza K, Sands S, Turton A, Berger P, Hamilton G. Phenotypes of patients with mild to moderate obstructive sleep apnoea as confirmed by cluster analysis. Respirology. 2012;17(1):99-107. doi:10.1111/j.1440-1843.2011.02037.x
5. Conwell W, Patel B, Doeing D, et al. Prevalence, clinical features, and CPAP adherence in REM-related sleep-disordered breathing: a cross-sectional analysis of a large clinical population. Sleep Breath. 2012;16(2):519-526. doi:10.1007/s11325-011-0537-6
6. Haba-Rubio J, Janssens JP, Rochat T, Sforza E. Rapid eye movement-related disordered breathing: clinical and polysomnographic features. Chest. 2005;128(5):3350-3357. doi:10.1378/chest.128.5.3350
7. Al Oweidat K, AlRyalat SA, Al-Essa M, Obeidat N. Comparing REM- and NREM -Related Obstructive Sleep Apnea in Jordan: A Cross-Sectional Study. Can Respir J. 2018;2018:9270329. doi:10.1155/2018/9270329
8. Koo BB, Dostal J, Ioachimescu O, Budur K. The effects of gender and age on REM-related sleep-disordered breathing. Sleep Breath. 2008;12(3):259-64. doi:10.1007/s11325-007-0161-7
9. Koo BB, Patel SR, Strohl K, Hoffstein V. Rapid eye movement-related sleep-disordered breathing: influence of age and gender. Chest. 2008;134(6):1156-1161. doi:10.1378/chest.08-1311
10. Resta O, Carpanano GE, Lacedonia D, et al. Gender difference in sleep profile of severely obese patients with obstructive sleep apnea (OSA). Respir Med. 2005;99(1):91-96. doi:10.1016/j.rmed.2004.05.014
11. O'Connor C, Thornley KS, Hanly PJ. Gender differences in the polysomnographic features of obstructive sleep apnea. Am J Respir Crit Care Med. 2000;161(5):1465-1472. doi:10.1164/ajrccm.161.5.9904121
12. Bahammam RA, Al-Qahtani KM, Aleissi SA, Olaish AH, Almeneessier AS, Bahammam AS. The Associations of Gender, Menopause, Age, and Asthma with REM-Predominant Obstructive Sleep Apnea: A Prospective Observational Study. Nat Sci Sleep. 2020;12:721-735. doi:10.2147/NSS.S275051
13. Mokhlesi B, Punjabi NM. "REM-related" obstructive sleep apnea: an epiphenomenon or a clinically important entity? Sleep. 2012;35(1):5-7. doi:10.5665/sleep.1570
14. Mokhlesi B, Finn LA, Hagen EW, et al. Obstructive sleep

apnea during REM sleep and hypertension. results of the Wisconsin Sleep Cohort. Am J Respir Crit Care Med. 2014;190(10):1158-1167. doi:10.1164/rccm.201406-1136OC
15. Hoshino T, Sasanabe R, Murotani K, et al. Insomnia as a Symptom of Rapid Eye Movement-Related Obstructive Sleep Apnea. J Clin Med. 2020;9(6):1821. doi:10.3390/jcm9061821
16. Sakao S, Sakurai T, Yahaba M, et al. Features of REM-related Sleep Disordered Breathing in the Japanese Population. Intern Med. 2015;54(12):1481-1487. doi:10.2169/internalmedicine.54.4248
17. Hoshino T, Sasanabe R, Mano M, et al. Prevalence of Rapid Eye Movement-related Obstructive Sleep Apnea in Adult Narcolepsy. Intern Med. 2019;58(15):2151-2157. doi:10.2169/internalmedicine.2601-18
18. Mano M, Hoshino T, Sasanabe R, et al. Impact of Gender and Age on Rapid Eye Movement-Related Obstructive Sleep Apnea: A Clinical Study of 3234 Japanese OSA Patients. Int J Environ Res Public Health. 2019;16(6):1068. doi:10.3390/ijerph16061068
19. Duce B, Kulkas A, Langton C, Töyräs J, Hukins C. The prevalence of REM-related obstructive sleep apnoea is reduced by the AASM 2012 hypopnoea criteria. Sleep Breath. 2018;22(1):57-64. doi:10.1007/s11325-017-1526-1
20. Tsara V, Serasli E, Amfilochiou A, Constantinidis T, Christaki P. Greek version of the Epworth Sleepiness Scale. Sleep Breath. 2004;8(2):91-95. doi:10.1007/s11325-004-0091-6
21. Chiang CL, Chen YT, Wang KL, et al. Comorbidities and risk of mortality in patients with sleep apnea. Ann Med. 2017;49(5):377-383. doi:10.1080/07853890.2017.1282167
22. Liu Y, Su C, Liu R, et al. NREM-AHI greater than REM-AHI versus REM-AHI greater than NREM-AHI in patients with obstructive sleep apnea: clinical and polysomnographic features. Sleep Breath. 2011;15(3):463-470. doi:10.1007/s11325-010-0358-z
23. Sattaratpaijit N, Kulalert P, Wongpradit W. Characteristics of rapid eye movement-related obstructive sleep apnea in Thai patients. Sci Rep. 2022;12(1):11360. doi:10.1038/s41598-022-13382-z
24. Pamidi S, Knutson KL, Ghods F, Mokhlesi B. Depressive symptoms and obesity as predictors of sleepiness and quality of life in patients with REM-related obstructive sleep apnea: cross-sectional analysis of a large clinical population. Sleep Med. 2011;12(9):827-831. doi:10.1016/j.sleep.2011.08.003
25. Lee SA, Paek JH, Han SH. REM-related sleep-disordered breathing is associated with depressive symptoms in men but not in women. Sleep Breath. 2016;20(3):995-1002. doi:10.1007/s11325-016-1323-2
26. Gabryelska A, Białasiewicz P. Association between excessive daytime sleepiness, REM phenotype and severity of obstructive sleep apnea. Sci Rep. 2020;10(1):34. doi:10.1038/s41598-019-56478-9
27. Oksenberg A, Arons E, Nasser K, Vander T, Radwan H. REM-related obstructive sleep apnea: the effect of body position. J Clin Sleep Med. 2010;6(4):343-348. Accessed December 31, 2023. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2919664/pdf/jcsm.6.4.343.pdf
28. Agnew HW, Webb WB, Williams RL. The first night effect: an EEG study of sleep. Psychophysiology. 1966;2(3):263-266. doi:10.1111/j.1469-8986.1966.tb02650.x
29. Kutbay Özçelik H, Akkoyunlu ME, Bostanlı P, et al. Hafif obstrüktif uyku apneli hastalarda REM ile ilişkili obstrüktif uyku apne sıklığı ve özellikleri. Tuberk Toraks. 2013;61(4):283-287. doi:10.5578/tt.6208
30. Koutsourelakis I, Perraki E, Bonakis A, Vagiakis E, Roussos C, Zakynthinos S. Determinants of subjective sleepiness in suspected obstructive sleep apnoea. J Sleep Res. 2008;17(4):437-443. doi:10.1111/j.1365-2869.2008.00663.x
31. Bixler EO, Vgontzas AN, Lin HM, Calhoun SL, Vela-Bueno A, Kales A. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. J Clin Endocrinol Metab. 2005;90(8):4510-4515. doi:10.1210/jc.2005-0035
32. Khan A, Harrison SL, Kezirian EJ, et al. Obstructive sleep apnea during rapid eye movement sleep, daytime sleepiness, and quality of life in older men in Osteoporotic Fractures in Men (MrOS) Sleep Study. J Clin Sleep Med. 2013;9(3):191-198. doi:10.5664/jcsm.2474
33. Chami HA, Baldwin CM, Silverman A, et al. Sleepiness, quality of life, and sleep maintenance in REM versus non-REM sleep-disordered breathin. Am J Respir Crit Care Med. 2010;181(9):997-1002. doi:10.1164/rccm.200908-1304OC
34. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev. 2002;6(2):97-111. doi:10.1053/smrv.2002.0186
35. Leger D, Andler R, Richard JB, et al. Sleep, substance misuse and addictions: a nationwide observational survey on smoking, alcohol, cannabis and sleep in 12,637 adults. J Sleep Res. 2022;31(5):e13553. doi:10.1111/jsr.13553
36. Ohayon MM. Epidemiological Overview of sleep Disorders in the General Population. Sleep Med Res. 2011;2(1):1-9. doi:10.17241/smr.2011.2.1.1
37. Harvey AG, Tang NKY. (Mis)perception of sleep in insomnia: a puzzle and a resolution. Psychol Bull. 2012;138(1):77-101. doi:10.1037/a0025730
38. The International Classification of Sleep Disorders – Third Edition (ICSD-3). 3rd ed. American Academy of Sleep Medicine; 2014.

Impact of non-invasive ventilation on exacerbation frequency in COPD patients

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ABSTRACT

INTRODUCTION Acute exacerbations of COPD are key events in the natural course of the patient's illness, as they significantly impair the health condition, accelerate the deterioration of lung function, worsen the prognosis for the patient and account for the majority of the COPD-related healthcare costs. Particularly in patients with a pre-existing non-invasive ventilation (NIV) therapy, a reduction of exacerbation frequency is crucial, as they are at high risk for a lasting morbidity and increased mortality.

METHODS A prospective cohort study was conducted. Data from adult patients with COPD diagnosis and existing High-Intensity NIV (HINIV) therapy from August 2021 to September 2023, were used. Exacerbation history of moderate and severe exacerbations of the past 12 months and blood gases at initiation and during HINIV therapy, were analyzed.

RESULTS A total of 20 patients were included in the study (mean age 69.2 ± 9.0 years; 70% female). After initiation of HINIV therapy the frequency of exacerbation showed a significant reduction from 1.5 ± 0.9 to 0.5 ± 0.5 per year ($p<0.001$). In addition, improvements in pCO_2 (73.0 ± 22.0 mmHg vs 44.0 ± 4.8 mmHg, $p<0.001$), the pH (7.33 ± 0.1 vs 7.42 ± 0.0, $p<0.001$) and HCO_{3-} (33.0 ± 4.9 mmol/L vs 27.9 ± 3.2 mmol/L, $p<0.001$), were successfully demonstrated.

CONCLUSIONS The present study demonstrates the positive effects of high-intensity NIV on COPD exacerbation rate, measured by the number of moderate and severe exacerbations in one year. Most significant effects were observed when patients had a high number of exacerbations before the initiation of NIV therapy.

ABBREVIATIONS CHRF: chronic hypercapnic respiratory failure, EPAP: expiratory positive airway pressure, HINIV: high-intensity NIV therapy, IPAP: inspiratory positive airway pressure, NIV: non-invasive ventilation

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INTRODUCTION

COPD is currently the fourth leading cause of death with approximately 3.2 million deaths in 2019[1,2]. In the course of the disease, chronic hypercapnic respiratory failure (CHRF) can occur due to the failure of the respiratory pump[3]. COPD patients with CHRF have higher rates of unplanned hospital admissions and rapid clinical deterioration after hospitalization due to a severe exacerbation. Additionally, chronic hypercapnia is a decisive factor contributing to mortality[4,5]. Therefore, reducing factors, influencing mortality, such as exacerbation rate, is an essential therapeutic goal. Non-invasive ventilation (NIV) with a facemask is the preferred choice of treatment to reduce mortality and hospitalization rate after acute exacerbation with persistent hypercapnia[6,7]. However, these positive effects are evident only when NIV is used with the target of maximal possible pCO_2 reduction[8,9]. This ventilatory strategy, based on maximal relief of the respiratory pump is referred to as high-intensity NIV therapy (HINIV). The required inspiratory positive airway pressures (IPAP) vary individually, as they depend on side effects of the NIV therapy, patient tolerance and adherence to therapy.

Despite the central therapeutic goal of reducing the exacerbation rate in the treatment of COPD patients, given its significant impact on the health condition, acceleration of lung function deterioration, worsening prognosis of the patient and responsibility for the majority of COPD-associated healthcare costs, scientific data on the effects of a HINIV therapy on the exacerbation rate are insufficient. A large German study by Koehnlein et al.[7] was the first to observe reduction in mortality with the use of HINIV in COPD patients, but no conclusion could be drawn regarding the influence of HINIV on exacerbation frequency, as it was not part of the study. In a large British study investigating

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the effect of HINIV on hospitalization-free survival after acute exacerbation of COPD and acute respiratory failure, only severe exacerbations leading to hospitalization were recorded[6]. The impact of HINIV on moderate exacerbation, however, is scientifically insufficiently documented[10].

The present analysis has addressed the lack of scientific evidence by initiating a study, evaluating the course of exacerbation retrospectively as well as prospectively, which compares the exacerbation frequency before initiation of HINIV and the exacerbation frequency after at least 12 months of HINIV therapy.

METHODS

The study protocol was approved by the Ethics Committee of Witten/Herdecke University and was conducted in accordance to the ethical guidelines of the declaration of Helsinki (last revised in October 2013). Written informed consent was obtained from all patients.

Patients

The data presented in this study are a preliminary analysis, which was registered at the German register for studies (DRKS00029273) and investigates supplementary telemonitoring of COPD patients after experiencing a severe exacerbation. Adult patients with the diagnosis of COPD receiving HINIV due to hypercapnic respiratory failure (PrismaVent Type 30 (n=16) and type 40 (n=4), Löwenstein medical SE & Co. KG Bad Ems, Germany) between August 2021 and September 2023, were enrolled in the study. Patients with mental retardation or those receiving invasive mechanical ventilation were not included in the study. The existing dataset of the main study was analyzed to determine availability of datasets regarding history of exacerbation as well as blood gases at the time of initiation or under existing HINIV therapy. The history of exacerbations is based on data from the clinical information system as well as from the anamnestic information provided by the patient, thus including exacerbations without hospitalization. Exacerbations that could be classified as moderate or severe according to the recommendations of the recent GOLD report were assessed[10]. Therefore, exacerbations requiring treatment with a fast-acting bronchodilator and oral corticosteroid (with/without antibiotics) or requiring hospitalization, were included. The anamnestic exacerbations were recorded using a predefined checklist as well as existing patient data records. The exacerbations were evaluated over the past 12 months in relation to the date of the consultation.

Ventilation setting

NIV was applied using either assisted pressure-controlled ventilation (aPCV) or pressure-supported ventilation (PSV). NIV was delivered via nasal or full-face masks. The treatment indication was based on the German guideline for treatment of chronic respiratory insufficiency, which recommends the initiation of NIV therapy in chronic hypercapnia or persistent hypercapnia after acute respiratory insufficiency[3]. In this case, ventilation should be performed as HINIV. HINIV refers to a specific ventilation setting in which NIV settings are aimed at achieving the lowest $PaCO_2$ values. In HINIV, the ventilator settings are gradually increased, either up to an individually tolerated maximum value or up to the values required to achieve normocapnia[8,9]. If feasible, these targets should already be aimed during initiation of NIV.

Study design and measurements

Demographic data (age, sex, exacerbation history) were evaluated for all patients. Additionally, laboratory parameters (pH, pCO_2, pO_2, HCO_3^-) were documented pre-therapeutically and after a minimum of 12 months after initiation of NIV therapy. If the data were collected during acute respiratory insufficiency, the ABG values were documented immediately after admission. There was no analysis of possible consultations between these two times, as the control intervals were different for all patients and this would not allow the interim results to be compared.

Statistical analysis

The data analysis was descriptive. Group comparison was conducted using Student's t-test for normally distributed data and the Mann-Whitney-U test for data with non-normally distributed data. Due to the small number of participants, the results are primarily intended to provide a descriptive analysis. Values of $p<0.05$ were therefore considered significant, although they do not provide statistical significance.

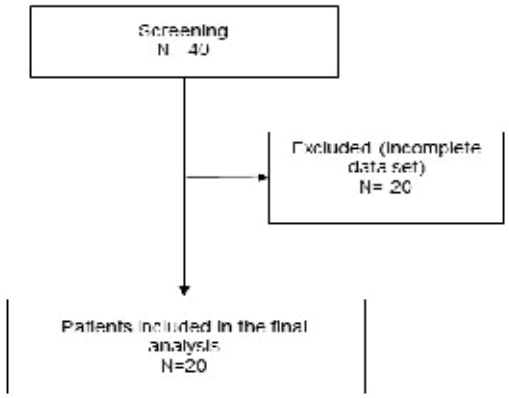
RESULTS

A total of 20 patients were included in the study (Figure 1). From those, 14 patients were female (70%). Average age of the patients was 69.2 ± 9.0 years. In the cohort analyzed, 15 patients had cardiac comorbidities, 7 of them suffering from coronary heart disease. Two patients had a sleep-related breathing disorder, one patient had chronic kidney failure, and 4 patients suffered from diabetes mellitus type II. The included patients had been treated with NIV therapy for 4.9 ± 3.5 years. Long-term NIV therapy was initiated for 9 patients, as a result of acute NIV therapy with respiratory acidosis. Patients were using the HINIV therapy 8.9 ± 4.5 h/day. The demographic data and the ventilation parameters from the time of blood gas analysis during therapy are listed in Table 1. Significant improvements in blood gas analysis were observed during therapy, compared to the results before HINV initiation. Results of the blood gas analyses are detailed in Table 2.

A separate analysis was conducted for patients who were initiated on NIV therapy under stable conditions without acute respiratory insufficiency. The results of this subgroup of 11 patients are presented in Table 3.

Prior to the start of HINIV therapy, patients reported an exacerbation frequency of 1.5 ± 0.9 exacerbations per

Figure 1. Diagram for patient inclusion



year. With HINIV therapy, this frequency was successfully reduced to 0.5 ± 0.5 per year (p<0.001). In patients who had ≥2 exacerbations prior to initiation of HINIV, there was a greater mean difference in the number of exacerbations before and after therapy. Patients who had less than 2 exacerbations per year before initiation of HINIV therapy showed a mean difference in the number of exacerbations before compared to the time after initiation of therapy of 0.5 exacerbations/year versus 2 exacerbations/year in patients with ≥2 exacerbations prior HINIV. Individual differences were observed, as shown in Figure 2.

Table 1. Demographic data and ventilation settings during HINIV of all patients (N=20)

Characteristics	Mean ± SD
Female, n (%)	14 (70)
Age (years)	69.2 ± 9.0
Body mass index (kg/m^2)	27.1 ± 6.1
Smoking status, n (active : prior)	6 : 14
Smoking index (pack-years)	45.9 ± 16.4
Time under NIV (years)	4.9 ± 3.5
NIV initiation	
Following acute NIV, n (%)	9 (45)
Chronic elective NIV, n (%)	11 (55)
Ventilator settings	
IPAP (mbar)	24.4 ± 3.1
EPAP (mbar)	6.7 ± 1.4
Rise time - inspiratory (s) Rise time - expiratory (s)	1.6 ± 0.8 2.9 ± 0.7
Adherence (h/day)	8.9 ± 4.5

NIV: non-invasive ventilation. IPAP: inspiratory positive airway pressure. EPAP: expiratory positive airway pressure.

Table 2. Comparison of blood gas values before and after initiation of HINIV therapy of the total population (N=20)

	Pre-therapeutic Mean ± SD	HINIV Mean ± SD	p
pH	7.33 ± 0.1	7.42 ± 0.0	<0.001
pCO_2 (mmHg)	73.0 ± 22.0	44.0 ± 4.8	<0.001
pO_2 (mmHg)	79.0 ± 27.0	69.8 ± 17.3	0.2
HCO_3^- (mmol/L)	33.0 ± 4.9	27.9 ± 3.2	<0.001

Figure 2. Illustration of individual differences in exacerbation frequency before and after established HINIV therapy (N=20)

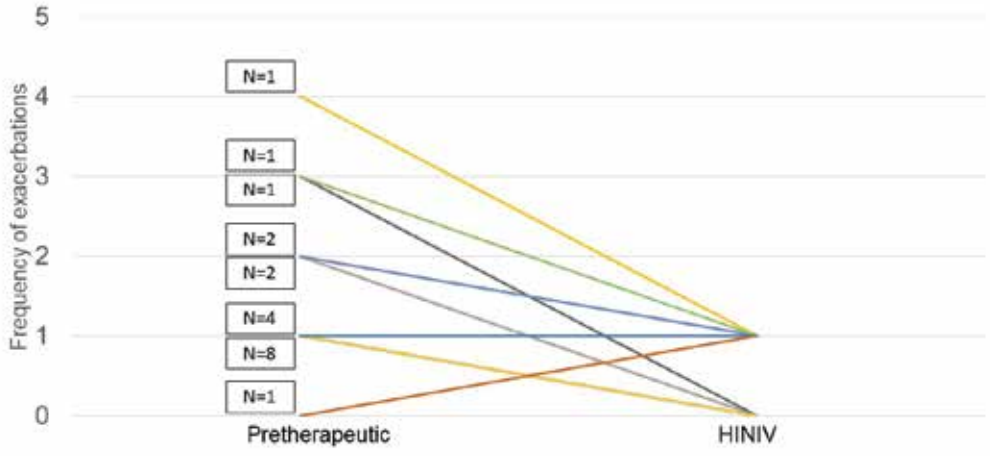


Table 3. Comparison of blood gas values before and after initiation of HINIV therapy in patients who had no acute respiratory insufficiency at the time of initiation (N=11)

	Pre-therapeutic Mean ± SD	HINIV Mean ± SD	p
pH	7.4 ± 0	7.4 ± 0	0.03
pCO_2 (mmHg)	61.4 ± 10.6	45.7 ± 5.3	<0.001
pO_2 (mmHg)	84.6 ± 23.1	66.3 ± 15.4	0.08
HCO_3^- (mmol/L)	32.9 ± 3.6	28.5 ± 3.9	0.01

DISCUSSION

This study provides further information on reducing the frequency of moderate and severe exacerbations with established HINIV therapy. The following are the main findings, which will be discussed further.

Firstly, a significant reduction in the number of exacerbations was demonstrated with HINIV. Secondly, it has been shown that a significant reduction of hypercapnia is observed during HINIV therapy, both in the setting of acute respiratory failure and chronic respiratory failure. Thirdly, further blood gas analysis parameters showed a significant improvement under the established HINIV therapy. Fourthly, there was a strong reduction in the frequency of exacerbations, especially in patients with a high frequency of exacerbations before the HINIV therapy was initiated.

The significant reduction in exacerbation frequency under HINIV therapy differs meaningfully from previous studies that examined exacerbation frequency in hypercapnic COPD patients on NIV, but used significantly lower pressures and therefore could not reduce pCO_2 (low intensity NIV)[11,12]. This suggests that the impact of the NIV therapy on the exacerbation frequency can only be achieved with a sufficient augmentation of ventilation and thereby a significant reduction of hypercapnia. In patients with persistent hypercapnic respiratory insufficiency, a reduction in re-admissions or mortality, following acute respiratory insufficiency, could be demonstrated after initiation of HINIV[6].

Furthermore, a recently published study by Hedsund et al.[13] demonstrated that the time to re-admission with an acute respiratory insufficiency, due to an exacerbation within 12 months, could be reduced by HINIV, although, a statistical significance could not be shown due to insufficient recruitment[13]. Nevertheless, a significant reduction in the number of exacerbations was observed, particularly in patients with frequent acute respiratory insufficiency. The lesser effects in comparison to the present study could be attributed to the fact that normocapnic patients were included as well and no re-evaluation according to current recommendations was performed[14]. All these studies only recorded the number of severe exacerbations that were hospitalized and did not include exacerbations that were treated in the outpatient setting.

The underlying pathophysiological mechanism of these reduced exacerbation rates resulting from HINIV therapy remains unknown. Besides the decrease in pCO_2 levels, mechanical bronchial dilatation itself may alter the microbiological milieu. This has already been demonstrated with pharmacological bronchodilation[15-17]. It has been shown that cytokines of the airways, which are elevated in patients with COPD, can be influenced by an effective treatment with bronchodilators[18]. Whether these biomarkers can also be influenced by HINV therapy is the subject of ongoing research.

Limitations

The present study has several limitations that should be taken into account. The data on exacerbations were mainly based on anamnestic information from the patient. Therefore, a higher incidence of exacerbations cannot be excluded. In addition, mild exacerbations were not recorded, so it is not possible to make any statements about the effect of HINIV on these exacerbations. The data were supplemented with information from the clinical information system. In addition, the number of participants is limited, resulting in a descriptive nature of data analysis, requiring larger subsequent studies to validate the findings presented here.

CONCLUSIONS

This study shows significant positive effects of HINIV on COPD exacerbation rate, measured by frequency of moderate and severe exacerbations in patients with severe COPD. Greatest effects are observed when patients present with a high number of exacerbations prior to initiation of NIV therapy. To verify these effects in a larger cohort, further studies are needed.

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This work has already been published as a pre-print under medrxiv.org (https://www.medrxiv.org/content/10.1101/2023.11.13.23298441v1).

CONFLICTS OF INTEREST

The authors have each completed and submitted an ICMJE

form for Disclosure of Potential Conflicts of Interest. The authors declare that they have no competing interests, financial or otherwise, related to the current work. M. Zimmerman, M. Wollsching, D. Kroppen, D.S. Majorski and S.B. Stanzel received travel grants from companies dealing with mechanical ventilation products. D.S. Majorski reports open research grant from Philips Respironics/USA. M. Zimmerman and W. Windisch received lecturing fees from companies dealing with mechanical ventilation products. The study group received open research grants from Löwenstein Medical/Germany since the initial planning of the work, and in the past from Löwenstein Medical/Germany, Weinmann/Germany, Vivisol/Germany, VitalAire/Germany, and Philips Respironics/USA.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval was obtained from the Ethics Committee of Witten/Herdecke University (Approval number: 255/2021; Date: 29 November 2021). Patients provided informed consent.

DATA AVAILABILITY

The authors intend to share individual deidentified participant data with any other unfunded or funded research-related purpose under appropriate circumstances. Please contact the corresponding author for more information.

AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

PROVENANCE AND PEER REVIEW

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REFERENCES

1. World Health Organization. World health statistics 2019: monitoring health for the SDGs, sustainable development goals. World Health Organization; 2019. Accessed January 10, 2024. https://iris.who.int/bitstream/handle/10665/324835/9789241565707-eng.pdf?sequence=9
2. 2023 GOLD REPORT: GLOBAL STRATEGY FOR PREVENTION, DIAGNOSIS AND MANAGEMENT OF COPD: 2023 Report. Global Initiative for Chronic Obstructive Lung Disease – GOLD. Accessed November 8, 2023. https://goldcopd.org/2023-gold-report-2/
3. Windisch W, Geiseler J, Simon K, Walterspacher S, Dreher M; on behalf of the Guideline Commission. German National Guideline for Treating Chronic Respiratory Failure with Invasive and Non-Invasive Ventilation: Revised Edition 2017 - Part 1. Respiration. 2018;96(1):66-97. doi:10.1159/000488001
4. Ahmadi Z, Bornefalk-Hermansson A, Franklin KA, Midgren B, Ekström MP. Hypo- and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: a population-based prospective study. Respir Res. 2014;15(1):30. doi:10.1186/1465-9921-15-30
5. Saraiva C, Abreu T, Neves D, Rodrigues F. Mortality Predictive Factors in Subjects With COPD After a Pulmonary Rehabilitation Program: A 3-Year Study. Respir Care. 2016;61(9):1179-1185. doi:10.4187/respcare.04477
6. Murphy PB, Rehal S, Arbane G, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. JAMA. 2017;317(21):2177-2186. doi:10.1001/jama.2017.4451
7. Köhnlein T, Windisch W, Köhler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med. 2014;2(9):698-705. doi:10.1016/S2213-2600(14)70153-5
8. Dreher M, Storre JH, Schmoor C, Windisch W. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax. 2010;65(4):303-308. doi:10.1136/thx.2009.124263
9. Schwarz SB, Magnet FS, Windisch W. Why High-Intensity NPPV is Favourable to Low-Intensity NPPV: Clinical and Physiological Reasons. COPD. 2017;14(4):389-395. doi:10.1080/15412555.2017.1318843
10. Agustí A, Celli BR, Criner GJ, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. Eur Respir J. 2023;61(4):2300239. doi:10.1183/13993003.00239-2023
11. Raveling T, Vonk J, Struik FM, et al. Chronic non-invasive ventilation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2021;8(8):CD002878. doi:10.1002/14651858.CD002878.pub3
12. Clini E, Sturani C, Rossi A, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J. 2002;20(3):529-538. doi:10.1183/09031936.02.02162001
13. Hedsund C, Linde Ankjærgaard K, Peick Sonne T, et al. Long-term non-invasive ventilation for COPD patients following an exacerbation with acute hypercapnic respiratory failure: a randomized controlled trial. Eur Clin Respir J. 2023;10(1):2257993. doi:10.1080/20018525.2023.2257993

14. Ergan B, Oczkowski S, Rochwerg B, et al. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. Eur Respir J. 2019;54(3):1901003. doi:10.1183/13993003.01003-2019
15. Noble PB, Pascoe CD, Lan B, et al. Airway smooth muscle in asthma: linking contraction and mechanotransduction to disease pathogenesis and remodelling. Pulm Pharmacol Ther. 2014;29(2):96-107. doi:10.1016/j.pupt.2014.07.005
16. Gosens R, Grainge C. Bronchoconstriction and airway biology: potential impact and therapeutic opportunities. Chest. 2015;147(3):798-803. doi:10.1378/chest.14-1142
17. Grainge CL, Lau LCK, Ward JA, et al. Effect of bronchoconstriction on airway remodeling in asthma. N Engl J Med. 2011;364(21):2006-2015. doi:10.1056/NEJMoa1014350
18. Chung KF. Cytokines in chronic obstructive pulmonary disease. Eur Respir J. 2001;18(suppl 34):50s-59s. doi:10.1183/09031936.01.00229701

Effect of prone position in non-intubated COVID-19 patients

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ABSTRACT

INTRODUCTION COVID-19 is an inflammatory disease with variable symptoms. Critical cases with ARDS on invasive mechanical ventilation benefit from prone positioning. The aim of the review is to determine the effect of prone position in spontaneously breathing patients with COVID-19.

METHODS The PubMed database was used for article research using the following search string: (prone position) AND (COVID-19). After the evaluation of eligibility of the initial number of articles, 31 studies were used for the current review.

RESULTS The population of the patients, methods of oxygenation, inclusion and exclusion criteria for participating in each study, outcomes and results of the studies are examined and presented.

CONCLUSIONS The majority of evidence showed beneficial effect of prone positioning in hypoxemia in non-intubated spontaneously breathing patients with COVID-19, although the heterogeneity of study designs limits the safe conduct of conclusions, indicating the need for large scale randomized control studies to ensure the credibility of the results.

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KEYWORDS

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INTRODUCTION

COVID-19 is an infectious disease declared as pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as was designated by the World Health Organization in February 2020[1]. The first cluster of cases was reported in the city of Wuhan, in China on the 31 December 2019 as 'pneumonia of unknown cause', later identifying the novel virus responsible for the disease. COVID-19 is a multisystem inflammatory syndrome with a rather wide variety of symptoms, the most common of which are fever, cough, fatigue, myalgia, headache, nasal obstruction/rhinorrhea, sore throat and loss of smell[2], along with up to 32% of asymptomatic cases[3]. According to WHO, the disease severity classification includes 3 categories of patients, those with non-severe, severe, and critical disease. The last regards patients with acute respiratory distress syndrome (ARDS) and other life-threatening situations[4].

ARDS is an acute, diffuse, inflammatory lung injury with acute hypoxemia, decreasing lung compliance and bilateral opacities. The damage to the alveolar-capillary membrane leads to increased permeability and subsequent interstitial and alveolar oedema, resulting in severe hypoxemia due to intrapulmonary shunting and V/Q mismatch[5]. Primary goal in treating ARDS is to improve patient ventilation. The improvement of ventilation during prone position is multifactorial; while in supine position, ventral transpulmonary pressure is greater than dorsal, resulting in overinflation of ventral alveoli and atelectasis of dorsal ones. On the other hand, prone position reduces ventral and dorsal transpulmonary pressure, making ventilation more homogeneous[6]. The application of positive end-expiratory pressure (PEEP) leads to more uniform pressure distribution, lung expansion and alveolar recruitment. In patients with ARDS in supine position, the heart and diaphragm compress the posterior lung parenchyma. Lung compression by both the heart and the diaphragm can be favorably affected by prone positioning, allowing previously non-ventilated lung regions to participate in the gas exchange[7]. At the same time, pulmonary perfusion remains distributed mainly to the dorsal lung regions. In other words, the gravitational distribution of pulmonary blood flow may be only minimally altered by prone position and the observed changes in gas exchange are primary due to changes in regional ventilation, thus improving overall alveolar ventilation/perfusion relationships[8]. Moreover, the reduction of hypoxic vasoconstriction in prone position decreases right heart afterload, resulting in a decrease in pulmonary resistance. Additionally, secretion drainage seems to be improved due to gravitational effect. Prone positioning combined with mechanical ventilation has shown significant improvement in oxygenation and ventilation[9].

In order to avoid the progression of COVID-19 pneumonia

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to ARDS and in an attempt to improve outcomes at times of limited resources, even in the most advanced healthcare systems, many centers have applied prone position as a therapeutic supportive measure in non-intubated patients with COVID-19 and respiratory failure.

The aim of the current review is to summarize the evidence of the effect of prone positioning in patients with COVID-19 pneumonia not on invasive mechanical ventilation, based on published literature.

METHODS

In this review, a search was conducted in PubMed for eligible studies. The key search terms were: (prone position) AND (COVID-19). Only observational studies and controlled trials in English were included. Two authors screened article titles and abstracts for inclusion/exclusion criteria. Detailed inclusion and exclusion criteria are displayed in Table 1. Full text of the remained articles was assessed and all studies without control group comparisons were excluded. This research was conducted on April 2023.

Regarding the exclusion criteria of each study, patients were not analyzed if they needed immediate intubation at admission or were already under mechanical ventilation, were hemodynamically unstable, were pregnant, had recent (in the last 30 days) abdominal surgery, were overweight with a body mass index over 30 kg/m^2, were unable to prone because of discomfort, were contraindicated to prone or had a do-not-intubate or do-not-resuscitate order. Additional exclusion criteria, were patients who were voluntarily discharged or referred to another hospital, were previously intubated due to COVID-19 AHRF, were unable to provide a consent form or to understand oral or written study information, subjects with incomplete clinical records, and specific conditions such as unstable fractures, intracranial hypertension, hypercapnia and terminal illness (less than 1 year life expectancy). The screening and selection process is displayed in Figure 1.

RESULTS

After inclusion/exclusion criteria were evaluated, a total of 31 studies were included in this review[10-40]. The main characteristics of the included studies are listed in Table 2.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Articles written in English language • Patients with SARS-CoV-2 infection • Adult patient population • Non-intubated patient population	• Reviews, meta-analyses, editorials, case reports, letters to the editor • Articles in pediatric population • Articles in special populations (e.g. pregnancy) • Articles in ARDS patients without SARS-CoV-2 infection • Articles with outcomes unrelated to respiratory status • Articles without control group comparisons

All the studies included patients with confirmed COVID-19 disease either with positive molecular swab test (RT-PCR) of nasopharyngeal or oropharyngeal sample (28 studies) and/or compatible imaging findings in combination with symptoms indicating infection with SARS-CoV-2 (8 studies, 3 studies, respectively).

Patients with acute hypoxemic respiratory failure (AHRF) were included in 25 studies, with 5 of them setting a condition of PaO_2/FiO_2 <300 mmHg, another 2 of PaO_2/FiO_2 >150 mmHg and 2 of them with a condition of PaO_2/FiO_2 <150 mmHg. Ten studies analyzed 0–50 patients, 10 analyzed 50–100 patients, 9 analyzed 100–500 patients, and 3 analyzed over 500 patients.

In the majority of the studies included in our review, the method of oxygenation was not defined with several types being used, more specifically low-flow nasal cannula (LFNC), simple face mask (SFM), non-rebreather mask (NRBM), high-flow nasal cannula (HFNC), and non-invasive mechanical ventilation either with continuous or bilevel positive airway pressure (NIV). Four studies analyzed patients on HFNC[15,20,30,33], 2 studies used NIV[16,36], 3 studies used LFNO[21,22,34], while Altinay et al.[28] included only patients under NRBM. Ates et al.[14] subsumed patients with mild COVID-19 with oxygen saturation over 94% therefore not in need of supplementary oxygen therapy.

The duration and initiation time of prone positioning

In 6 studies the duration of PP was determined in daily hours, sessions per day, and total days. In the Musso et al.[36] study, the median daily hours of PP were 12.2 (10.1–13.8) with a median of 2 sessions per day (1.3) and total days of PP 6 (5.8) in a period of 28 days. The median PP hours in Koike et al.[35] study was 3 (2–3) and the number of practice days of PP therapy was a median of 13 days (7–16). Liu et al.[22] noted 12.6 daily hours of PP in both early and late PP groups of patients and a total time of PP of 14.3 days. Patients in Rosen et al. study[25] were proned for 9 (4.4–10.6) hours daily with 4.2 (1.7–5.7) days in total. Jayakumar et al.[17] defined the adherence to protocol as >6 hours of PP daily which was among 13 (43%) patients of PP group, 4 patients tolerated PP for 5–6 hours, 5 patients for 4–5 hours, 4 patients for 1–4 hours and 2 patients for less than an hour, while 2 patients did not comply with PP. The maximum duration was 2 hours per session. The centers that participated in Ehrmann et al.[15] study recorded a range of median duration of PP from 1.6 to 8.6 hours per day.

The initiation time of PP was not determined in most of the studies. Barker et al.[29], Jha et al.[34], Fazzini et al.[31] and Vianello et al.[29] assigned all of the enrolled patients to undergo prone position. Those who could not tolerate PP or were contraindicated to prone, formed the control groups. In the study of Sryma et al.[26], patients were proned if they had a P/F ratio <100 mmHg using NIV or HFNO, or altered

mental status. Pierucci et al.[23] started prone positioning after achieving an SpO_2 >96% using supplemental oxygen in patients. In the Koike et al.[35] study, prone positioning was initiated when the FiO_2 reached ≥40%. Ates et al.[14] used six positions (prone, left/right lateral decubitus, left/right swimmer's, and supine). They determined the two positions with the best oxygen saturation by measuring SpO_2 after 5 min in each one and afterwards patients were instructed to maintain those two positions. Patients in the Musso et al.[36] study were proned 24 h after admission. Lastly, Kharat et al.[21] instructed patients to self-prone and report their PP duration in a diary.

We collected and recorded the following outcomes: 1) mortality rate (WHO ordinal scale, ISARIC mortality score); 2) intubation rate; 3) ventilator-free days; 4) oxygenation parameters (ROX index, SpO_2/FiO_2 or PaO_2/FiO_2 ratio, ABGs); 5) length of hospital or ICU stay; 6) upgrade or weaning in oxygen therapy; 7) patients' vitals and use of vasopressors to stabilize arterial blood pressure; and 8) prone positioning adverse events.

Mortality

Mortality rate was examined in 21 studies. Twelve studies showed no difference between prone and supine patients, while the rest (9 studies) noted a statistically significant decrease in mortality rate in prone patients. Specifically, Musso et al.[36] recorded 36% mortality in the control group (162 patients) versus 12% in PP (81 patients) (p<0.001), and Altinay et al.[28] found 16% in the control group (23 patients) versus 9% in PP (25 patients) (p=0.02). In the studies of Ates et al.[14] and Jagan et al.[10], none of the patients in prone position died compared to the control group (mortality rate 24.6% out of 65 patients, p<0.004; and 8.5% out of 47 patients, p<0.001; respectively). Kaur et al.[20] showed significantly higher mortality in late APP (APP initiated >24 h of starting HFNC therapy) group (45% of 33 patients) versus early APP (APP initiated within 24 h of starting HFNC therapy) (26% of 92 patients) (p=0.039). In Esperatti et al.[30] and Perez-Nieto et al.[33] studies, the adjusted OR of mortality decreased in PP group (0.38 and 0.40, respectively). Four studies examined the WHO ordinal scale and 1 study the ISARIC mortality score. Padrão et al.[12], Koike et al.[35] and Rosen et al.[25] noted no significant differences in WHO ordinal scale, while Qian et al.[39] observed a worse outcome rank in the intervention group from day 2 to 5 (p=0.03). Barker et al.[29] proved lower ISARIC mortality score in prone position (p=0.04).

Figure 1. Flow diagram of screening and selection process

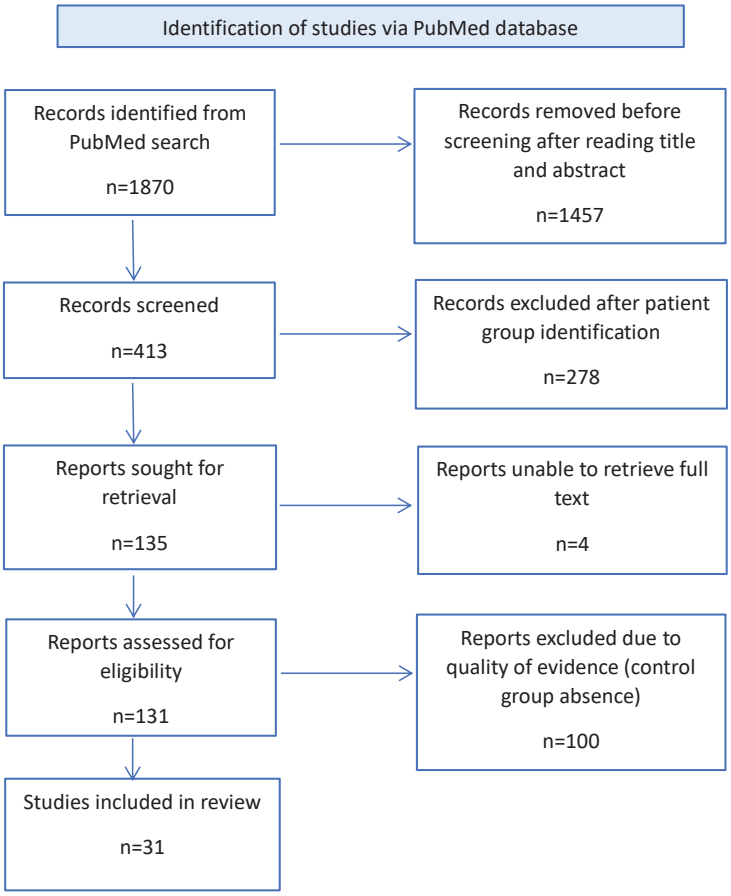

Table 2. Study characteristics

Authors Year	Location	Design	Enrollment period	Study population	Oxygen therapy	Prone protocol	COVID-19 category according to WHO of patients at enrollment	Outcomes	Results
Ehrmann et al.[15] 2021	Canada France Ireland Mexico USA Spain	Prospective collaborative meta-trial of 6 randomized controlled open-label superiority trials	2 April 2020 to 26 January 2021	1121 patients with COVID-19 AHRF (564 PP vs 557 SC)	HFNO	PP for as long as tolerated	Severe and Critical COVID-19 except for hemodynamically unstable P/F <300 mmHg	Treatment failure within 28 days of enrolment, defined as intubation or death	Lower incidence of intubation at day 28 in the intervention group (RR=0.86; 95% CI: 0.75–0.98), but same 28-day mortality rate (RR=0.87; 95% CI: 0.71–1.07)
Padrão et al.[12] 2020	Sao Paolo, Brazil	Retrospective cohort study	1 March to 30 April 2020	166 patients admitted to the ED as suspected COVID-19 case (57 PP vs 109 SC)	Supplemental oxygen with a flow rate ≥3 L/min	Prone position for at least 4 h in the first session	Severe and Critical COVID-19 except for hemodynamically unstable	Intubation rate up to 15 days after PP initiation	Not statistically significant difference between PP and control group (HR= 1.21; 95% CI: 0.78–1.88, p=0.39)
Jagan et al.[10] 2020	Nebraska, USA	Retrospective study	24 March to 5 May 2020	105 COVID-19 patients (40 PP vs 65 SC)	Not defined	Self-proning ≥1 h on ≥5 occasions/ day and ≥1 h overnight	Category not standardized	Need of ETI during hospital stay	Risk of ETI was lower in PP after adjustment for SOFA score (AHR=0.30; 95% CI: 0.09–0.96; p=0.043) or APACHE II scores (AHR=0.30; 95% CI: 0.10–0.91, p=0.034). No prone patient died compared with 24.6% of patients who were not prone (p<0.001; number needed to treat =5; 95% CI: 3–8)
Ni et al.[11] 2020	Wuhan, China	Prospective observational cohort study	31 January to 15 February 2020	52 patients with severe COVID-19 (17 PP vs 35 SC)	Not defined	Prone position for at least 4 h/day for 10 days	Severe COVID-19 P/F ≤300 mmHg RR ≥30 breaths/ min	Efficacy of early PP intervention on oxygenation improvement	PP resulted in improvement in SpO_2/FiO_2 (409; 95% CI: 86–733) and ROX index (26; 95% CI: 9–43) and decreased Borg scale (-9; 95% CI: -15 to -3)

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Pneumon 2024;37(1):12
https://doi.org/10.18332/pne/183167

Table 2. Continued

Authors Year	Location	Design	Enrollment period	Study population	Oxygen therapy	Prone protocol	COVID-19 category according to WHO of patients at enrollment	Outcomes	Results
Zang et al.[13] 2020	Beijing, China	Prospective single-center cohort study	1 February to 30 April 2020	60 COVID-19 patients with severe hypoxia (23 PP vs 37 SC)	Not defined	PP for 10 min and 30 min	Severe COVID-19	Improvement of hypoxia, CT imaging and survival	During PP, SpO_2 increased from 91.09 ± 1.54% to 95.30 ± 1.72% (p<0.01) after 10 min, 95.48 ± 1.73% after 30 min (p<0.01), but no significant difference after 30 min compared with 10 min (p=0.58)
Jouffroy et al.[19] 2021	Paris, France	Retrospective observational study	20 February to 24 April 2020	379 COVID-19 patients admitted in ICU (40 PP vs 339 SC)	LFNO, HFNO, NIV	Prone position for 3–6 h twice/day	Critical COVID-19	PaO_2/FiO_2 ratio, ABGs, survival and intubation rate at 28 days	Increase PaO_2/FiO_2 (p=0.004) and $PaCO_2$ (p=0.005) in the intervention group while NS difference in survival (p=0.419) and intubation (p=0.178) rate
Barker et al.[29] 2022	London, UK	Retrospective study	26 March to 26 June 2020	20 COVID-19 patients (10 PP vs 10 SC)	Not defined	Prone position for as long as possible	Severe COVID-19 $PaCO_2$ <45 mmHg	SpO_2/FiO_2 ratio recorded after each PP session	Only after the first PP episode, increase in SpO_2/FiO_2 ratio was observed (before, PP=152, IQR:135–185; after, PP=192, IQR: 156–234, p=0.04)

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Pneumon 2024;37(1):12
https://doi.org/10.18332/pne/183167

Table 2. Continued

Authors Year	Location	Design	Enrollment period	Study population	Oxygen therapy	Prone protocol	COVID-19 category according to WHO of patients at enrollment	Outcomes	Results
Ates et al.[14] 2021	Ankara, Türkiye	Retrospective study	15 August to 1 December 2020	124 patients (97 PP compliant vs 47 PP incompliant)	Oxygen therapy not needed	Six different positions were used in total (prone, left/right lateral decubitus, left/right swimmer's, supine). SpO_2 was assessed after 5 min in each position. Patients maintained the 2 positions with the better SpO_2, switching in 6-h to 8-h intervals, with breaks according tolerance	Mild COVID-19	Positioning duration, rate of ICU admission, anti-inflammatory treatment and length of hospital stay were assessed in compliant and incompliant with PP patients	Positioning duration was median 12 (3–20) vs 5 (2–16) in compliant and incompliant patients, while rates of ICU admission (7.2% vs 25.5%, p<0.001), anti-inflammatory treatment initiation (68% vs 97.9%, p<0.001) and length of hospital stay [5 (2–16] days vs 12 (3–20)] days, p<0.001) were significantly reduced in compliant with PP patients
Liu et al.[22] 2021	Wuhan, China	Retrospective observational study	22 January to 13 March 2020	29 patients (13 early PP vs 16 later PP), later defined as PP therapy after 3 days	LFNO	PP for ≥2 h in the morning, ≥2h in the afternoon and ≥6 h at night, total PP 10–14 h/day	Non-severe (mild) COVID-19	PP duration and length of hospitalization	Early PP group showed significantly shorter total PP time (HR= -5.8; 95% CI: -9.45 to -2.14, p=0.006) and total length of hospitalization (HR= -11.03 95% CI: -14.62 to -7.45), p=0.000)
Kaur et al.[20] 2021	USA	Collaborative meta-trial of six randomized controlled trials	2 April 2020 to 26 January 2021	125 COVID-19 patients [92 early PP (PP initiated within 24 h of starting HNFC therapy) vs 33 late PP]	HFNO	Early PP (within 24 h of starting HFNC therapy) PP ≥1 h	Severe and Critical COVID-19 S/F <240	28-day mortality and intubation rate among patients that received early vs late APP	Lower mortality rate in early APP group (45% vs 26%, p=0.039), while NS difference in intubation rate p=0.58

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Pneumon 2024;37(1):12
https://doi.org/10.18332/pne/183167

Table 2. Continued

Authors Year	Location	Design	Enrollment period	Study population	Oxygen therapy	Prone protocol	COVID-19 category according to WHO of patients at enrollment	Outcomes	Results
Jayakumar et al.[17] 2021	Chennai, India	Multicenter feasibility randomized controlled trial	Not defined	60 patients (30 PP vs 30 SC)	Not defined	PP ≥6 h/day	Severe and Critical COVID-19 P/F: 100–300 mmHg, $PaCO_2$ <45 mmHg ≥4 L/min supplemental oxygen to maintain SpO_2 ≥92%	Adherence to the protocol (PP for at least 6 h) in each group	43% protocol compliance
Hashemian et al.[16] 2021	Tehran, Iran	Prospective study	26 February to 25 April 2020	75 COVID-19 patients under NIV admitted in ICU (45 PP vs 30 SC)	NIV	PP of 30 min every 4 h, additional 30 min PP session if SpO2 <82%	Severe and Critical COVID-19	Effect of PP in SpO_2, PaO_2/FiO_2 and need for ETI	NIV combined with PP resulted in a significantly shorter length of ICU admission (8.6 vs 14.4, p=0.046)
Kharat et al.[21] 2021	Geneva, Switzerland	Cluster randomized control trial	April to May 2020	27 COVID-19 patients (10 PP vs 17 SC) with LFOT	LFNO	PP for 12 h/day	Non-severe and Severe COVID-19 S/F >225 with LFNO	Effect of PP in oxygen needs	No statistically significant difference between two groups
Prud'homme et al.[24] 2021	Marseille, France	Exposed/ non-exposed bicentric retrospective matched cohort study	20 March to 20 April 2020	96 COVID-19 patients (48 PP vs 48 SC)	LFNO, HFNO	PP for at least 3 h/day for 3 days	Category not standardized	Upgrade in oxygen delivery method at day 14, defined as doubling of the initial oxygen supply	31.2% of PP patients had an upgrading of oxygenation method vs 52.1% of the control group (p=0.038)
Vianello et al.[27] 2021	Padua, Italy	Prospective cohort study	1 November 2020 to 28 February 2021	93 COVID-19 patients under HFNC (50 PP vs 43 SC)	HFNO, NIV	PP ≥2 h twice/day	Severe COVID-19	Effect of PP in ETI	PP was associated with clinical benefit and survival without escalation of therapy in 80% of subjects of PP group

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Pneumon 2024;37(1):12
https://doi.org/10.18332/pne/183167

Table 2. Continued

Authors Year	Location	Design	Enrollment period	Study population	Oxygen therapy	Prone protocol	COVID-19 category according to WHO of patients at enrollment	Outcomes	Results
Johnson et al.[18] 2021	Utah, USA	Nonblinded pragmatic randomized controlled trial	29 April to 5 August 2020	30 COVID-19 patients (15 PP vs 15 SC)	Not defined	3 positions (prone, left/right lateral) for 1–2 h every 4 h	Category not standardized	Change in PaO_2/FiO_2 ratio at 72 h after admission	No difference between 2 groups (p=0.077)
Pierucci et al.[23] 2021	Bari, Italy	Observational prospective single-center study	11 March to 30 April 2020	32 COVID-19 patients with PaO_2/FiO_2 >150 (16 PP vs 16 SC)	Not defined	PP for as long as tolerated	Non-severe and Severe COVID-19	Feasibility and effects of prolonged PP	After 72 h, 62.5% of PP patients improved oxygenation [PaO_2/FiO_2: from 194.6 (42.1) to 304.7 (79.3.2), p<0.001]
Rosén et al.[25] 2021	Helsinki, Sweden	Prospective multicenter open label parallel arm randomized clinical superiority trial	7 October 2020 to 7 February 2021 with 30-day follow-up till 9 March 2021	75 COVID-19 patients (36 PP protocol vs 39 control group)	HFNO, NIV	PP for at least 16 h/day	Critical COVID-19 P/F ≤150 mmHg for more than 1h using HFNO or NIV	Effect of PP protocol in need for ETI	Longer prone in PP vs control group 9.0 h per day (IQR: 4.4–10.6) vs 3.4 h (IQR: 1.8–8.4) (p=0.014), but there was no difference in ETI
Sryma et al.[26] 2021	Delhi, India	Prospective interventional study	Not defined	45 COVID-19 patients (33 PP vs 15 SC)	LFNO, HFNO, NIV	PP ≥2 h/session, total PP ≥8 h per day	Severe COVID-19 SpO_2 <94% FiO_2=21% $PaCO_2$ <45 mmHg	Effect of PP in need for ETI and oxygenation	PP showed improvement in the mean (SD) ROX index [10.7 (3.8) vs 6.7 (2.6), p<0.001]. The need for ETI was higher in the control group (33.3% vs 6.7%, p=0.02)
Fralick et al.[32] 2022	Canada USA	Unblinded pragmatic randomized clinical trial	May 2020 to May 2021	248 patients (126 PP vs 122 SC)	Not defined	PP ≥2 h/session for 4 times day for ≥7 days	Severe and Critical COVID-19	Composite of in-hospital death, mechanical ventilation (intubation or BPAP) or worsening RF (FiO2 >60% for >24 h)	Same incidence in both groups (OR= 0.92; 95% CI: 0.44–1.92)

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Pneumon 2024;37(1):12
https://doi.org/10.18332/pne/183167

Table 2. Continued

Authors Year	Location	Design	Enrollment period	Study population	Oxygen therapy	Prone protocol	COVID-19 category according to WHO of patients at enrollment	Outcomes	Results
Perez-Nieto et al.[38] 2022	Mexico Ecuador	Retrospective multicenter observational study	1 May to 12 June 2020	827 COVID-19 patients (505 PP vs 322 SC)	Not defined	PP ≥2 h	Severe COVID-19 SpO_2 <94% FiO_2=21%	Successful orotracheal intubation for invasive mechanical ventilation	PP protective factor for orotracheal intubation (OR=0.35, 95% CI: 0.24–0.52, p<0.0002)
Ibarra-Estrada et al.[33] 2022	Guadalajara, Mexico	Multicenter randomized controlled trial	2 May 2020 to 26 January 2021	414 COVID-19 patients (216 PP vs 198 SC)	HFNO	PP ≥1 h/day	Severe and Critical COVID-19 except for hemodynamically unstable	Intubation rate within 28 days of enrollment	Significantly lower intubation incidence in PP group (RR=0.70; 95% CI: 0.54–0.90, p=0.006)
Altinay et al.[28] 2022	Istanbul, Türkiye	Retrospective observational cohort study	15 March to 15 June 2020	48 COVID-19 patients (25 PP vs 23 SC)	NRBM	PP 12–18 h/day	Severe COVID-19 P/F <300 mmHg using NRBM	Differences in PaO_2/FiO_2 ratio, length of ICU stay and ventilator-free days, mortality and intubation rate in PP vs SC	Lower mortality and intubation incidence in the intervention group (p=0.020, p=0.001), NS difference in other outcomes
Musso et al.[36] 2022	Turin, Italy	Controlled non randomized trial	16 December 2020 to 30 May 2021 follow-up till 30 June 2021	243 COVID-19 patients under NIV (81 PP vs 162 non-PP)	NIV	PP ≥8 h/one session/day	Severe and Critical COVID-19 except for hemodynamically unstable	Occurrence of NIV failure within 28 days of enrollment, defined as intubation of death	Significantly lower incidence of NIV failure in PP group (p<0.001)
Koike et al.[35] 2022	Sagamihara, Japan	Retrospective cohort study	1 October 2020 to 31 March 2021	58 COVID-19 patients (27 PP vs 31 SC)	Not defined	PP ≥30 min at least twice/day	Severe and Critical COVID-19	Effects of PP on the improvement of oxygenation over 3 weeks	PP for patients with FiO_2 ≥0.4 was associated with the improvement of short-term SpO_2/FiO_2 reduction and ROX index and was significantly associated with a lower rate of tracheal intubation (p=0.003)

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Pneumon 2024;37(1):12
https://doi.org/10.18332/pne/183167

Authors Year	Location	Design	Enrollment period	Study population	Oxygen therapy	Prone protocol	COVID-19 category according to WHO of patients at enrollment	Outcomes	Results
Jha et al.[34] 2022	Cambridge, UK	Prospective single-center study	3 September 2020 to 23 February 2021	25 COVID-19 patients and 10 healthy volunteers under hypoxic challenge	LFNO	Cycle of position changes: supine for 15 min, lateral for 15 min, prone for ≥30 min	Non-severe COVID-19	Change in peripheral oxygenation in PP vs SP	Increase in SpO_2 in PP vs SP (difference +1.62%, p=0.003) within 10 min of proning. Increase in subjective discomfort (p=0.003) in PP, with no difference in breathlessness
Esperatti et al.[30] 2022	Argentina	Prospective multicenter cohort study	June 2020 to January 2021	335 COVID-19 patients (187 PP >6 h vs 148 SC) treated with HFNC	HFNO	PP ≥6 h per day	Critical COVID-19 P/F <200 mmHg after receiving 4 h of HFNO	Effect of PP on the risk of ETI and in-hospital mortality	The OR (95% CI) for ETI in the PP group was 0.36 (0.2–0.7), with a progressive reduction in OR as the exposure increased. The AOR (95% CI) for hospital mortality in the PP group was 0.47 (0.19–1.31). PP ≥8 h/d resulted in reduction in OR [0.37 (0.17–0.8)]
Fazzini et al.[31] 2022	London, UK	Prospective single-center cohort study	1 March to 30 April 2020	46 COVID-19 patients (12 <1 h vs 34 >1 h)	LFNO, HFNO CPAP	PP for as long as tolerated	Severe and Critical COVID-19	Outcomes of PP vs SC	Oxygenation improvement in PP: P/F ratio (pre, 115 ± 43 mmHg vs post, 148 ± 70 mmHg, p=0.025) and S/F ratio (pre, 141 ± 37 vs post, 188 ± 49, p<0.001), lower RR (pre, 34 ± 7 vs post, 25 ± 7 breaths per min, p<0.001), lower WOB (pre, 43 vs post, 16) and improvements in reported shortness of breath after PP (pre, 45 vs post, 19; p<0.001). PP >1 h had lower ICU admissions (PP ≤1h, 83% vs PP > 1 h, 41%, p=0.011), required less invasive ventilation (PP ≤1 h, 83% vs PP >1 h, 29%, p=0.001) and had shorter median ICU length of stay (LOS) [PP ≤1 h, 13 (5–26) vs PP >1 h, 5 (3–18) days, p=0.016]

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Pneumon 2024;37(1):12
https://doi.org/10.18332/pne/183167

Authors Year	Location	Design	Enrollment period	Study population	Oxygen therapy	Prone protocol	COVID-19 category according to WHO of patients at enrollment	Outcomes	Results
Tonelli et al.[40] 2022	Italy	Retrospective multicenter observational cohort study	1 March to 1 June 2020	114 COVID-19 patients (38 PP vs 76 SC)	Not defined	PP ≥3 h/day, 1–4 sessions/day	Severe and Critical COVID-19 P/F <300 mmHg or SpO2 ≤93% breathing room air RR ≥30 breaths/min	Clinical benefit of PP vs SC of patients with non-invasive respiratory support	Greater effect of PP compared to SC on ETI rate after adjustment for confounders (HR=0.59; 95% CI: 0.3–0.94, p=0.03). PP showed greater significant benefit for those on HFNC (HR= 0.34; 95% CI: 0.12–0.84, p=0.04)
Qian et al.[39] 2022	USA	Non-randomized controlled trial	13 May to 11 December 2020	501 COVID-19 patients with hypoxemia	LFNO, HFNO, NIV	PP ≥3 h for 4 times/day	Severe and Critical COVID-19	Outcomes of PP vs SC	On day 5 the Bayesian posterior probability of PP group having worse outcomes was 0.998 (posterior median AOR=1.63; 95% credibility interval CrI: 1.16–2.31). On days 14 and 28, the posterior probabilities of harm were 0.874 (AOR= 1.29; 95% CrI: 0.84–1.99) and 0.673 (AOR=1.12; 95% CrI: 0.67–1.86), respectively
Othman et al.[37] 2022	Damanhour City, Egypt	Randomized controlled trial	20 February to 20 April 2021	82 COVID-19 patients (41 PP vs 41 SC) with PaO_2/FiO_2 ratio ≤150 mmHg	NRBM, CPAP	PP ≥1 h/day	Severe and Critical COVID-19 P/F ≤150 mm/Hg RR ≥30 breaths/min	Effects of awake PP on oxygenation and physiological outcomes in non-intubated patients	PP showed improvements in SpO_2, PaO_2/FiO_2, ROX index, PaO_2, and SaO_2, at the three study time points (p<0.001, 0.007; p<0.001, 0.011; and p<0.001, respectively)

PP: prone position. SC: standard care. ETI: endotracheal intubation. AHR: adjusted hazard ratio. HFNC: high-flow nasal cannula.

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Intubation rate

Ten out of 18 studies showed a statistically significant decrease in intubation rate. Koike et al.[35] recorded an intubation rate of 7% in PP group (2 out of 27 patients) vs 42% in SC group (13 out of 42 patients) (p=0.003). Endotracheal intubation was needed in 4 patients (8%) in prone position and in 12 patients (28%) who failed in PP in the Vianello et al.[27] study (p=0.014). Sryma et al.[26] also noted higher rates of intubation and mechanical ventilation in the control group (33.3%; 5/15 patients) vs prone group (6.7%; 2/30 patients) with p=0.02. In the study of Esperatti et al.[30] 23% of the PP group (44/187 patients) and 53% of the standard care group (79/148 patients) were intubated (p<0.0001). The rate of intubation in Musso et al.[36] was 10% of 81 patients in the intervention group and 32% of 162 patients in the control group (p=0.0012). In the Ibarra-Estrada et al.[15] study, 25% of the PP group (29/117 patients) and 41% of the non-PP group (128/313 patients) were intubated (p=0.004). Jagan et al.[10] showed as well a lower intubation rate in prone-positioned patients (10% vs 27.7%, p=0.031). According to Perez-Nieto et al.[33], 24.8% (77/505) and 39.5% (123/322) of patients were intubated in prone and supine group, respectively (p<0.0001). In the study of Altinay et al.[28], 32% of the patients required intubation in the prone position group (8/25 patients) and 82.6% in the supine position group (19/23 patients) with p=0.001. Jouffroy et al.[19] reported that at day 10, 40% (16/40) of the PP group and 71% (241/339) of the non-PP group were intubated (p<0.01).

In 3 studies the statistical significance of the difference in intubation rate between the intervention and the control group was not determined[15,18,32].

Ventilator-free days

Ventilator-free days were examined in 4 studies and none showed a statistically significant difference between prone and supine patients. Specifically, in the Padrão et al.[12] study, ventilator-free days were 8 (2–12) and 6 (0–11) in prone (57 patients) and supine (109 patients) positioned patients, respectively (p=0.4). In Johnson et al.[18], the patients in PP were off the ventilator for 24.3 (18.8–29.7) days while in the standard care group for 27 (24.8–29.2) days (p=0.332). Rosen et al.[25] recorded 30 (11–30) days without mechanical ventilation in both groups (p=0.69). In contrast, Altinay et al.[28] recorded 3.5 (3.0–6.5) days for PP group (25 patients) and 2 (2–3) days for non-PP group (23 patients) (p=0.004).

Oxygenation parameters: SpO_2/FiO_2 or PaO_2/FiO_2 ratio, ROX index and ABGs

Oxygenation parameters and ABGs were assessed in 18 studies; 13 studies examined the SpO_2/FiO_2 or PaO_2/FiO_2 ratio, with only 3 of them[17,18,29] not finding a statistically significant difference between the intervention and the control group. Respiratory rate oxygenation (ROX) index (combination of peripheral oxygen saturation to the fraction of inspired oxygen and RR [SpO_2/FiO_2]/RR) was evaluated in 5 studies, all of them showing a significant increase in the intervention group[11,13,26,35,37].

Another parameter that was assessed in the included studies were ABGs and/or SpO_2. In the Othman et al.[37] study a significant increase in SpO_2 (5.85%, p<0.001), PaO_2 (22.59%, p=0.011) and in SaO_2 (5.26%, p<0.001) was noted after proning, but without significant difference in pH and $PaCO_2$ (p=0.94 and p=0.83, respectively). In the Zang et al. study[13], SpO_2 increased from 91.09 ± 1.54% to 95.30 ± 1.72% (p<0.01) after 10 min, 95.48 ± 1.73% after 30 min (p<0.01), but no significant difference after 30 min compared with 10 min (p=0.58). Jouffroy et al.[19] showed no difference in SpO_2 (92% to 93%, p=0.34) and PaO_2 (59 to 62 mmHg, p=0.08) after PP; however, $PaCO_2$ slightly improved (35 to 38 mmHg, p=0.005). Jha et al.[34] reported that a lower SpO_2 value at admission was predictive of greater improvement in SpO_2 with proning (p=0.003) and smaller improvement for older patients (p=0.013). Changes in pH, PaO_2, $PaCO_2$ and SpO_2 in Altinay et al.[28] were 0 (p=0.002), 16 mmHg (p<0.001), -1 mmHg (p=0.007) and 5% (p=0.016), respectively, for proned patients. Finally, Liu et al.[22] noted no significant difference in pH and $PaCO_2$ after 24 h (p=0.86 and p=0.40, respectively).

Length of hospital or ICU stay

Duration of hospital stay was assessed in 7 studies, ICU stay in 5 studies, and both parameters in 5 studies. Vianello et al.[27] patients were hospitalized for a median time of 17 (6–46) days in PP and 21 (7–75) days in supine position (p<0.001). The median hospital days for PP group were 12.2 and for control group 23.2 in Liu et al.[22] (p=0). In the Ates et al. study[14], median length of hospital stay was 5 (2–16) vs 2 (3–20) days in PP vs SC group (p<0.001). Less days of hospitalization in proned patients or equal days to standard care group, but not statistically significant, were recorded in 3 studies[11,15,18,35].

Altinay et al.[28] recorded a median ICU stay of 5 (4–11) vs 8 (4–12) days in the PP vs SC group (Cohen's d=0.3). Hashemian et al.[16] estimated an ICU stay of 8.6 ± 3 days for PP group (NIV + PP) and 14.4 ± 3.9 days for SC group (NIV), with p=0.046. However, in Jayakumar et al.[17] and in Barker et al.[29], patients in the intervention group were hospitalized in ICU for more days comparing to the control.

Three out of 5 studies showed the beneficial effect of prone position in both hospital and ICU length of stay. Rosen et al.[25] recorded a median hospital stay of 16 (11–22) days for the PP group and 18 (11–30) days for the SC (p=0.44), and median ICU stay of 5 (4–13) days for PP and 11 (3–22) for SC (p=0.25). Median hospital and ICU length of stay for PP and SC groups were 12 (7–20) and 9 (6–14) days (p=0.0012) in the Esperatti et al.[30] study. In Tonelli et al.[40], median hospital stay was 20 (3–41) for PP and 24 (3–45) days for SC (p=0.03), and ICU stay duration of 10 (3–21) for PP and 15 (3–26) days for SC (p=0.02).

Upgrade or weaning in oxygen therapy

In the Prud'homme et al.[24] study, 25 (52.1%) patients in SC group (48 patients) and 15 (31.2%) patients in PP group (48 patients) needed upgrade in oxygenation (p=0.038). Vianello et al.[27] escalated the respiratory support in 7 (16%) patients in SC group (43 patients) and 2 (4%) in PP group (50 patients) (p=0.047).

Two studies recorded a not statistically significant decrease in supplemental oxygen in proned patients[17,21], while Sryma et al.[26] noted no difference in time to resolution of hypoxia between the intervention and control group.

Patients' vitals and use of vasopressors to stabilize arterial blood pressure

Liu et al.[22] recorded a decrease in both respiratory and heart rate equal to 3.62 breaths/min and 2.51 beats/min (p=0.005 and p=0.71, respectively). Respiratory rate was assessed in the Ibarra-Estrada et al.[15] study with a decrease from 25 to 22 breaths/min after the first PP session (p<0.001). The same parameter was examined in Fazzini et al. study[31] where patients had lower respiratory rate after proning (pre, 34 ± 7 vs post, 25 ± 7 breaths/min; p<0.001). After 12 h of PP respiratory rate was significantly different in the intervention group compared to controls in the Sryma et al.[26] study (23.8 ± 3.4 breaths/min among cases vs 27.5 ± 4.6 among controls, p=0.004).

Two studies showed an improvement of patients' vitals (blood pressure, respiratory rate) in prone position, but not statistically significant[13,19].

The need for vasopressor use in order to stabilize blood pressure was greater, but not statistically significant, in controls rather than proned patients in the Rosen et al.[25] study (44% controls vs 37% PP, p=0.57). In contrast, in the Padrão et al. study[12], more patients in PP were administered vasoactive drugs (47% PP vs 39% controls, p=0.32).

Prone positioning adverse events

The reported adverse events in the prone groups were accidental removal of peripheral intravenous lines, back/musculoskeletal pain (limiting prone positioning)[12], pressure sores, nausea and vomiting, cardiac arrest within 30 days[25], and general discomfort[21,35]. Musso et al.[36] observed that there was no statistically significant difference between the prone and supine group regarding the previously presented adverse events and additional ones which were barotrauma, pneumomediastinum, subcutaneous emphysema, nasal skin ulceration due to nasal cannula, facial edema, thoraco-abdominal wall hematoma, and venous thrombosis. In 2 studies no adverse events occurred[11,17].

DISCUSSION

As was previously stated, the aim of the current review was to summarize the evidence of the effect of prone positioning in patients with COVID-19 pneumonia, not on invasive mechanical ventilation, based on published literature.

The most interesting finding of the current review is that most studies showed a beneficial effect of prone positioning in hypoxemia in non-intubated COVID-19 patients, although the intubation rate and mortality varied among the studies.

The benefit of prone positioning on oxygenation in intubated patients with ARDS is well documented[41,42] and there is enough evidence that this benefit is sustained also in ARDS due to SARS-CoV-2 infection[43]. Although prone positioning was not extensively utilized in non-intubated patients before the COVID-19 outbreak, it was a widely used intervention from the beginning of the pandemic due to disease pathophysiology, but also due to the urgent necessity of finding non-invasive therapeutic interventions as a result of the large influx of patients in ICUs worldwide[44,45]. Before the COVID-19 outbreak, however, a number of studies regarding awake prone position in ARDS patients were published, therefore offering the rationale for the wide use of prone position during the COVID-19 pandemic[46,47].

Despite the evidence of beneficial effect of prone position in non-intubated patients with COVID-19, the results of the studies should be carefully evaluated, since a large heterogeneity is detected among researched populations and study designs alike.

There are notable differences among the studies regarding ventilation and oxygenation strategies in non-intubated COVID-19 patients. As previously mentioned, several types of oxygenation and ventilation have been utilized, while the exact type of respiratory support is not defined in the vast majority of the included studies.

According to the results of recent meta-analyses, there are insufficient data to determine differences in mortality reduction between patients who were treated with HFNC or NIV in prone position[48,49]. In comparison with LFNC, ventilatory support with HFNC or NIV in ICU settings appears to reduce intubation rates; however, these results may reflect differences in disease severity[49]. Specifically, a reduced need for intubation was shown among patients who received advanced respiratory support (HFNO or NIV) at enrollment (RR=0.83; 95% CI: 0.71–0.97) and in ICU settings (RR=0.83; 95% CI: 0.71–0.97), but not in patients receiving conventional oxygen therapy (RR=0.87; 95% CI: 0.45–1.69) or in non-ICU settings (RR=0.88; 95% CI: 0.44–1.76)49.

An additional factor that varies among the included studies is the prone positioning technique. Whereas the included patients are not sedated, patient cooperation for prone positioning and patient compliance to maintain position are prerequisites for successful intervention. It is interesting that in all studies not showing improvement in oxygenation and/or mortality[12,18,21,32,34,39], the patients were verbally instructed to assume and maintain prone position as long as possible, hence the prone position tolerance was poor. Nursing-directed protocols might increase adherence, leading to possible different results[18]. Several strategies including light sedation have been proposed in order to achieve adherence for long prone position sessions[50,51]. An

important issue is whether the effect of better oxygenation in prone position in patients with COVID-19 is indeed associated with a reduced intubation rate, even in an ICU setting, where the compliance and monitoring are better than in the ward. The study of Barker et al.[29] failed to show such a benefit. Nevertheless, in a recent meta-analysis, treatment in ICU setting seemed to be advantageous[52].

Another contributing factor that affects prone position outcomes is the exposure time. Prolonged prone position is known to decrease mortality in patients with severe ARDS and also in mechanically ventilated patients with ARDS due to COVID-19[53]. Similar results were found in our review. The hours in prone position among the studies vary and were not included in the statistical analysis in the majority of the aforementioned studies. Mostly due to patient discomfort, the duration of prone position sessions in most of the studies is relatively small in comparison with invasively ventilated patients, and lack of adherence may be an indicator of disease severity[27]. Whereas prone position seems to have a time-dependent effect, the optimal exposure time for non-intubated patients is yet to be established.

An important point is that patients with severe COVID-19 disease seem to benefit more from the prone position compared to those with less severe disease. In a recent meta-analysis, of the 1172 patients in the APP group, 281 were intubated, while 329 of the 1122 patients in the control group were intubated. Dividing patients into 2 subgroups (defined as 1: PaO_2/FiO_2 ≤200 mmHg, and 2: SpO_2/FiO_2 >200 mmHg), showed that patients with PaO_2/FiO_2 ≤200 mmHg had a lower intubation rate when compared with the control group (four trials, RR=0.80; 95% CI: 0.71–0.90). Intubation rate in patients with less severe disease (subgroup 2) was decreased although this finding was not statistically significant (four trials, RR=0.93, 95% CI: 0.40–2.19). Regarding mortality rate, the meta-analysis showed no difference between the intervention and the control group (RR=0.93; 95% CI: 0.77–1.11). Although, statistically significant decrease in survival was observed in patients in the APP group with severe disease, defined as PaO_2/FiO_2 <150 mmHg, highlighting the need for further research in order to establish the association between mortality and prone position[54].

Limitations

This review has several limitations. There is a wide heterogeneity regarding patient populations, oxygenation and ventilation methods, disease severity and outcomes, thus the comparison of the results was not feasible for all of the studies. Furthermore, the included studies were conducted during different phases of COVID-19 pandemic and the evolution of other therapeutic interventions was not taken into consideration.

CONCLUSIONS

Prone positioning seems to be an effective intervention for non-intubated COVID-19 patients. Due to the lack of comprehensive protocols, large scale randomized control studies with carefully selected population and thoroughly described interventions should be conducted to confirm the aforementioned effect not only in patients with COVID-19 but also with other causes of pneumonia.

CONFLICTS OF INTEREST

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DISCLAIMER

N. Rovina, A. Koutsoukou and P. Steiropoulos report that they are Editorial Board Members of Pneumon. They had no involvement in the peer-review or acceptance of this article, and had no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to a handling editor of the journal.

REFERENCES

1. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020;91(1):157-160. doi:10.23750/abm.v91i1.9397
2. Long B, Carius BM, Chavez S, et al. Clinical update on COVID-19 for the emergency clinician: Presentation and evaluation. Am J Emerg Med. 2022;54:46-57. doi:10.1016/j.ajem.2022.01.028
3. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott

HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;324(8):782-793. doi:10.1001/jama.2020.12839
4. Agarwal A, Hunt BJ, Stegemann M, et al. A living WHO guideline on drugs for covid-19. BMJ. 2020;370:m3379. doi:10.1136/bmj.m3379
5. Spiro SG, Silvestri GA, Agusti A. Clinical Respiratory Medicine. 4th ed. Elsevier Inc; 2012.
6. Pelosi P, Brazzi L, Gattinoni L. Prone position in acute respiratory distress syndrome. Eur Respir J. 2002;20(4):1017-1028. doi:10.1183/09031936.02.00401702
7. Hadaya J, Benharash P. Prone Positioning for Acute Respiratory Distress Syndrome (ARDS). JAMA. 2020;324(13):1361. doi:10.1001/jama.2020.14901
8. Kallet RH. A Comprehensive Review of Prone Position in ARDS. Respir Care. 2015;60(11):1660-1687. doi:10.4187/respcare.04271
9. Guérin C, Albert RK, Beitler J, et al. Prone position in ARDS patients: why, when, how and for whom. Intensive Care Med. 2020;46(12):2385-2396. doi:10.1007/s00134-020-06306-w
10. Jagan N, Morrow LE, Walters RW, et al. The POSITIONED Study: Prone Positioning in Nonventilated Coronavirus Disease 2019 Patients-A Retrospective Analysis. Crit Care Explor. 2020;2(10):e0229. doi:10.1097/CCE.0000000000000229
11. Ni Z, Wang K, Wang T, et al. Efficacy of early prone or lateral positioning in patients with severe COVID-19: a single-center prospective cohort. Precis Clin Med. 2020;3(4):260-271. doi:10.1093/pcmedi/pbaa034
12. Padrão EMH, Valente FS, Besen BAMP, et al. Awake Prone Positioning in COVID-19 Hypoxemic Respiratory Failure: Exploratory Findings in a Single-center Retrospective Cohort Study. Acad Emerg Med. 2020;27(12):1249-1259. doi:10.1111/acem.14160
13. Zang X, Wang Q, Zhou H, Liu S, Xue X; COVID-19 Early Prone Position Study Group. Efficacy of early prone position for COVID-19 patients with severe hypoxia: a single-center prospective cohort study. Intensive Care Med. 2020;46(10):1927-1929. doi:10.1007/s00134-020-06182-4
14. Ateş İ, Erden A, Gürler EK, et al. Compliance to not only prone but also lateral and supine positioning improves outcome in hospitalised COVID-19 patients. Int J Clin Pract. 2021;75(11):e14673. doi:10.1111/ijcp.14673
15. Ehrmann S, Li J, Ibarra-Estrada M, et al. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. Lancet Respir Med. 2021;9(12):1387-1395. doi:10.1016/S2213-2600(21)00356-8
16. Hashemian SM, Jamaati H, Malekmohammad M, Tabarsi P, Khoundabi B, Shafigh N. Efficacy of Early Prone Positioning Combined with Noninvasive Ventilation in COVID-19. Tanaffos. 2021;20(2):82-85.
17. Jayakumar D, Ramachandran P, Rabindrarajan E, Vijayaraghavan BKT, Ramakrishnan N, Venkataraman R. Standard Care Versus Awake Prone Position in Adult Nonintubated Patients With Acute Hypoxemic Respiratory Failure Secondary to COVID-19 Infection-A Multicenter Feasibility Randomized Controlled Trial. J Intensive Care Med. 2021;36(8):918-924. doi:10.1177/08850666211014480
18. Johnson SA, Horton DJ, Fuller MJ, et al. Patient-directed Prone Positioning in Awake Patients with COVID-19 Requiring Hospitalization (PAPR). Ann Am Thorac Soc. 2021;18(8):1424-1426. doi:10.1513/AnnalsATS.202011-1466RL
19. Jouffroy R, Darmon M, Isnard F, et al. Impact of prone position in non-intubated spontaneously breathing patients admitted to the ICU for severe acute respiratory failure due to COVID-19. J Crit Care. 2021;64:199-204. doi:10.1016/j.jcrc.2021.04.014
20. Kaur R, Vines DL, Mirza S, et al. Early versus late awake prone positioning in non-intubated patients with COVID-19. Crit Care. 2021;25(1):340. doi:10.1186/s13054-021-03761-9
21. Kharat A, Dupuis-Lozeron E, Cantero C, et al. Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomised controlled trial. ERJ Open Res. 2021;7(1):00692-2020. doi:10.1183/23120541.00692-2020
22. Liu X, Liu H, Lan Q, Zheng X, Duan J, Zeng F. Early prone positioning therapy for patients with mild COVID-19 disease. Med Clin (Barc). 2021;156(8):386-389. doi:10.1016/j.medcli.2020.11.036
23. Pierucci P, Ambrosino N, Di Lecce V, et al. Prolonged Active Prone Positioning in Spontaneously Breathing Non-intubated Patients With COVID-19-Associated Hypoxemic Acute Respiratory Failure With PaO2/FiO2 >150. Front Med (Lausanne). 2021;8:626321. doi:10.3389/fmed.2021.626321
24. Prud'homme E, Trigui Y, Elharrar X, et al. Effect of Prone Positioning on the Respiratory Support of Nonintubated Patients With COVID-19 and Acute Hypoxemic Respiratory Failure: A Retrospective Matching Cohort Study. Chest. 2021;160(1):85-88. doi:10.1016/j.chest.2021.01.048
25. Rosén J, von Oelreich E, Fors D, et al. Awake prone positioning in patients with hypoxemic respiratory failure due to COVID-19: the PROFLO multicenter randomized clinical trial. Crit Care. 2021;25(1):209. doi:10.1186/s13054-021-03602-9
26. Sryma PB, Mittal S, Mohan A, et al. Effect of proning in patients with COVID-19 acute hypoxemic respiratory failure receiving noninvasive oxygen therapy. Lung India. 2021;38(Supplement):S6-S10. doi:10.4103/lungindia.lungindia_794_20
27. Vianello A, Turrin M, Guarnieri G, et al. Prone Positioning Is Safe and May Reduce the Rate of Intubation in Selected COVID-19 Patients Receiving High-Flow Nasal Oxygen Therapy. J Clin Med. 2021;10(15):3404. doi:10.3390/jcm10153404
28. Altinay M, Sayan I, Turk HS, et al. Effect of early awake prone positioning application on prognosis in patients with acute respiratory failure due to COVID-19 pneumonia: a retrospective observational study. Braz J Anesthesiol.

2022;72(2):194-199. doi:10.1016/j.bjane.2021.07.029
29. Barker J, Pan D, Koeckerling D, Baldwin AJ, West R. Effect of serial awake prone positioning on oxygenation in patients admitted to intensive care with COVID-19. Postgrad Med J. 2022;98(1159):360-364. doi:10.1136/postgradmedj-2020-139631
30. Esperatti M, Busico M, Fuentes NA, et al. Impact of exposure time in awake prone positioning on clinical outcomes of patients with COVID-19-related acute respiratory failure treated with high-flow nasal oxygen: a multicenter cohort study. Crit Care. 2022;26(1):16. doi:10.1186/s13054-021-03881-2
31. Fazzini B, Fowler AJ, Zolfaghari P. Effectiveness of prone position in spontaneously breathing patients with COVID-19: A prospective cohort study. J Intensive Care Soc. 2022;23(3):362-365. doi:10.1177/1751143721996542
32. Fralick M, Colacci M, Munshi L, et al. Prone positioning of patients with moderate hypoxaemia due to covid-19: multicentre pragmatic randomised trial (COVID-PRONE). BMJ. 2022;376:e068585. doi:10.1136/bmj-2021-068585
33. Ibarra-Estrada M, Li J, Pavlov I, et al. Factors for success of awake prone positioning in patients with COVID-19-induced acute hypoxemic respiratory failure: analysis of a randomized controlled trial. Crit Care. 2022;26(1):84. doi:10.1186/s13054-022-03950-0
34. Jha A, Chen F, Mann S, et al. Physiological effects and subjective tolerability of prone positioning in COVID-19 and healthy hypoxic challenge. ERJ Open Res. 2022;8(1):00524-2021. doi:10.1183/23120541.00524-2021
35. Koike T, Hamazaki N, Kuroiwa M, et al. Detailed Changes in Oxygenation following Awake Prone Positioning for Non-Intubated Patients with COVID-19 and Hypoxemic Respiratory Failure-A Historical Cohort Study. Healthcare (Basel). 2022;10(6):1006. doi:10.3390/healthcare10061006
36. Musso G, Taliano C, Molinaro F, et al. Early prolonged prone position in noninvasively ventilated patients with SARS-CoV-2-related moderate-to-severe hypoxemic respiratory failure: clinical outcomes and mechanisms for treatment response in the PRO-NIV study. Crit Care. 2022;26(1):118. doi:10.1186/s13054-022-03937-x
37. Othman SY, El-Menshawy AM, Mohamed AM. Effects of awake-prone positioning on oxygenation and physiological outcomes in non-intubated patients with COVID-19: A randomized controlled trial. Nurs Crit Care. 2022;1-9. doi:10.1111/nicc.12833
38. Perez-Nieto OR, Escarraman-Martinez D, Guerrero-Gutierrez MA, et al. Awake prone positioning and oxygen therapy in patients with COVID-19: the APRONOX study. Eur Respir J. 2022;59(2):2100265. doi:10.1183/13993003.00265-2021
39. Qian ET, Gatto CL, Amusina O, et al. Assessment of Awake Prone Positioning in Hospitalized Adults With COVID-19: A Nonrandomized Controlled Trial. JAMA Intern Med. 2022;182(6):612-621. doi:10.1001/jamainternmed.2022.1070
40. Tonelli R, Pisani L, Tabbì L, et al. Early awake proning in critical and severe COVID-19 patients undergoing noninvasive respiratory support: A retrospective multicenter cohort study. Pulmonology. 2022;28(3):181-192. doi:10.1016/j.pulmoe.2021.03.002
41. Munshi L, Del Sorbo L, Adhikari NKJ, et al. Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2017;14(suppl 4):S280-S288. doi:10.1513/AnnalsATS.201704-343OT
42. Scholten EL, Beitler JR, Prisk GK, Malhotra A. Treatment of ARDS With Prone Positioning. Chest. 2017;151(1):215-224. doi:10.1016/j.chest.2016.06.032
43. Chua EX, Wong ZZ, Hasan MS, et al. Prone ventilation in intubated COVID-19 patients: a systematic review and meta-analysis. Braz J Anesthesiol. 2022;72(6):780-789. doi:10.1016/j.bjane.2022.06.007
44. McNicholas B, Cosgrave D, Giacomini C, Brennan A, Laffey JG. Prone positioning in COVID-19 acute respiratory failure: just do it? Br J Anaesth. 2020;125(4):440-443. doi:10.1016/j.bja.2020.06.003
45. Touchon F, Trigui Y, Prud'homme E, et al. Awake prone positioning for hypoxaemic respiratory failure: past, COVID-19 and perspectives. Eur Respir Rev. 2021;30(160):210022. doi:10.1183/16000617.0022-2021
46. Valter C, Christensen AM, Tollund C, Schønemann NK. Response to the prone position in spontaneously breathing patients with hypoxemic respiratory failure. Acta Anaesthesiol Scand. 2003;47(4):416-418. doi:10.1034/j.1399-6576.2003.00088.x
47. Tulleken JE, van der Werf TS, Ligtenberg JJM, Fijen JW, Zijlstra JG. Prone position in a spontaneously breathing near-drowning patient. Intensive Care Med. 1999;25(12):1469-1470. doi:10.1007/s001340051101
48. Schmid B, Griesel M, Fischer AL, et al. Awake Prone Positioning, High-Flow Nasal Oxygen and Non-Invasive Ventilation as Non-Invasive Respiratory Strategies in COVID-19 Acute Respiratory Failure: A Systematic Review and Meta-Analysis. J Clin Med. 2022;11(2):391. doi:10.3390/jcm11020391
49. Li J, Luo J, Pavlov I, et al. Awake prone positioning for non-intubated patients with COVID-19-related acute hypoxaemic respiratory failure: a systematic review and meta-analysis. Lancet Respir Med. 2022;10(6):573-583. doi:10.1016/S2213-2600(22)00043-1
50. Kang H, Gu X, Tong Z. Effect of Awake Prone Positioning in non-Intubated COVID-19 Patients with Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-Analysis. J Intensive Care Med. 2022;37(11):1493-1503. doi:10.1177/08850666221121593
51. Busico M, Laiz MM, Urrutia JG, et al. Strategies to achieve adherence to prone positioning in awake COVID-19 patients with high-flow nasal oxygen. A case series. Can J Respir Ther. 2022;58:151-154. doi:10.29390/cjrt-2022-035
52. Taboada M, Baluja A, Santos LD, et al. Effectiveness of dexmedetomidine combined with high flow nasal oxygen and long periods of awake prone positioning in moderate or severe

COVID-19 pneumonia. J Clin Anesth. 2021;72:110261. doi:10.1016/j.jclinane.2021.110261
53. Cheema HA, Siddiqui A, Ochani S, et al. Awake Prone Positioning for Non-Intubated COVID-19 Patients with Acute Respiratory Failure: A Meta-Analysis of Randomised Controlled Trials. J Clin Med. 2023;12(3):926. doi:10.3390/jcm12030926
54. Wang J, Chen D, Deng P, et al. Efficacy and safety of awake prone positioning in the treatment of non-intubated spontaneously breathing patients with COVID-19-related acute respiratory failure: A systematic review and meta-analysis. J Intensive Med. 2023;3(4):65-372. doi:10.1016/j.jointm.2023.02.001

New therapies in small cell lung cancer: A narrative review

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ABSTRACT

Lung cancer overall is the second most common malignancy in both men and women in the United States and remains the leading cause of cancer death. Small cell lung cancer (SCLC) accounts for approximately 10–15% of all cases. Chemotherapy with a platinum agent and etoposide remains the standard of care for limited-stage patients. In the past few years, several clinical trials have evaluated the efficacy of immunotherapy, when added to conventional chemotherapy, in extensive-stage patients, and two anti-PD-L1 monoclonal antibodies, atezolizumab and durvalumab, have already been approved by the USA Food and Drug Administration (FDA) for use in this setting. Moreover, numerous other new agents are currently being investigated while new molecular features of SCLC subtypes come to light. Further analysis of predictive biomarkers needs to be done as well as evaluation of immune checkpoint inhibitors in early-stage disease.

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INTRODUCTION

Lung cancer is the second most prevalent cancer in both men and women in the United States, maintaining its position as the primary cause of cancer-related deaths[1]. Small cell lung cancer (SCLC) represents around 10–15% of the total cases. SCLC is a poorly differentiated neuroendocrine carcinoma, strongly correlated with tobacco use, which is differentiated from non-small cell lung cancer (NSCLC) by its rapid doubling time, elevated growth fraction, and the prompt onset of metastases. At the time of SCLC diagnosis, the disease is usually disseminated and treatment strategies are mostly based on systemic therapy. According to the American Veterans Administration Lung Study Group (VALG) proposal in 1957, SCLC is divided into limited and extensive stages based on whether all known tumors can be treated within a single radiotherapy field. Limited-stage SCLC (LS-SCLC) is characterized by disease confined to the ipsilateral hemithorax and regional lymph nodes, amenable to safe coverage within a radiotherapy field. Extensive-stage SCLC (ES-SCLC) denotes disease that has extended beyond these boundaries and may involve distant metastases, malignant pericardial or pleural effusions, as well as the inclusion of contralateral supraclavicular and contralateral hilar lymph node involvement. Despite the ES/LS classification's usefulness in clinical decision-making and treatment recommendations, the AJCC 8th edition for lung cancer staging suggested the use of the TNM system which is far more accurate.

DEVELOPMENTS

Limited-Stage SCLC

According to the guidelines announced by the European Society for Medical Oncology (ESMO), the American College of Chest Physicians, and the National Comprehensive Cancer Network (NCCN), the first-line chemotherapy regimen for SCLC consists of the combination of a platinum agent (cisplatin or carboplatin) with etoposide[2]. The treatment efficacy of cisplatin- versus carboplatin-based chemotherapy was evaluated in the COCIS meta-analysis which suggested no differences in efficacy between the two agents for both ES and LS patients. However, carboplatin was associated with an increased frequency of high-grade hematological toxicity while cisplatin caused more severe neurological and renal toxicities as well as nausea and vomiting[3].

In conjunction with chemotherapy, radiation therapy (RT) plays a significant role in the management of limited-stage small cell lung cancer (LS-SCLC). The substantial reduction in high local recurrence rates is achieved by incorporating thoracic RT. Moreover, the combination of thoracic RT with chemotherapy results in improved survival compared to chemotherapy alone, as evidenced by a comprehensive meta-analysis involving 2140 patients from 13 trials. This analysis revealed a noteworthy enhancement in the 3-year overall survival, with rates rising from 8.9% for those treated with chemotherapy alone to 14.3% for those undergoing chemoradiotherapy (hazard ratio, HR=0.86; 95% CI: 0.78–

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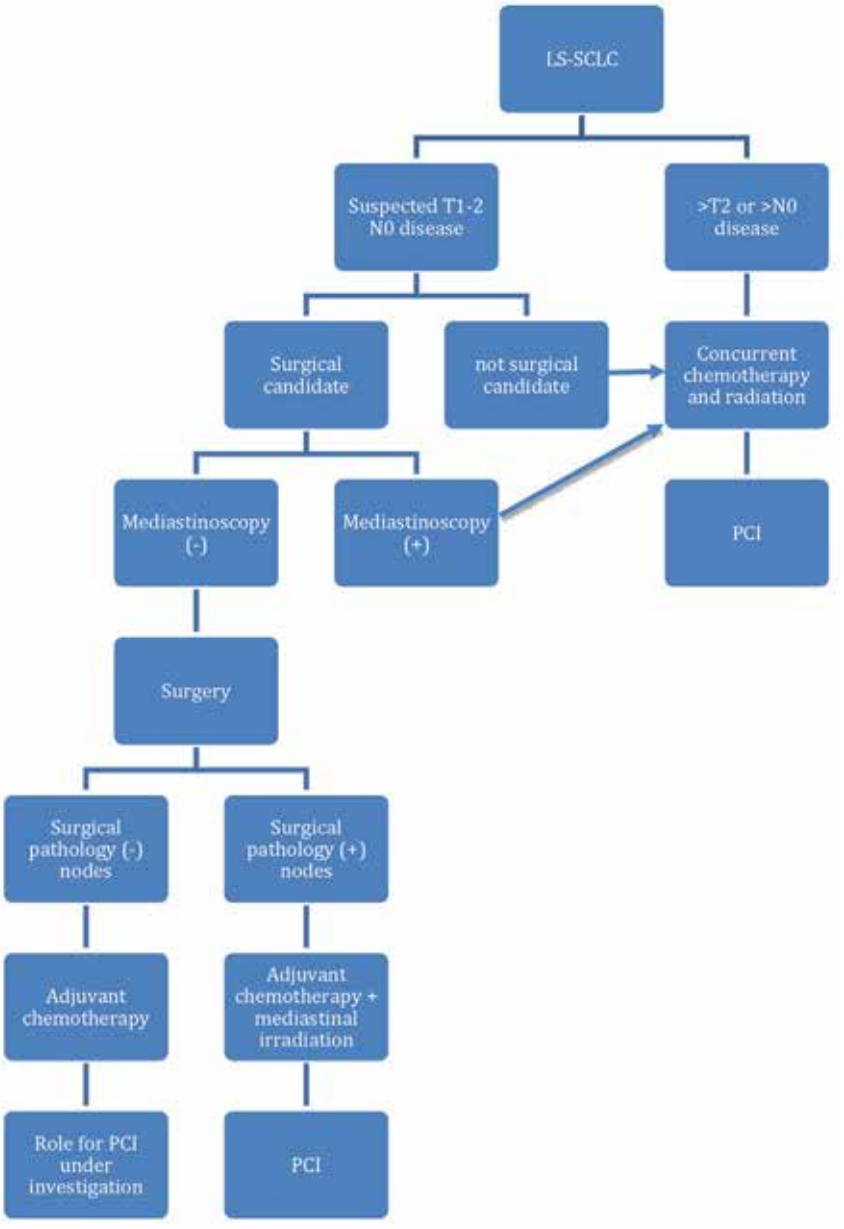
0.94; p=0.001)[4].

The ideal timing for thoracic RT was examined in a phase-III trial conducted by the Japan Clinical Oncology Group (JCOG). This study compared the concurrent administration versus sequential delivery of radiotherapy in conjunction with cisplatin and etoposide for patients with limited-stage small cell lung cancer (LS-SCLC). The results showed that the median survival in the sequential arm was 19.7 months (95% CI: 15.8–23.3) and 27.2 months (95% CI: 18.4– 31.0) in the concurrent arm, thus suggesting that the concurrent chemo-radiotherapy regimen is more effective[5]. The standard of care for patients with LS-SCLC involves incorporating thoracic RT alongside etoposide plus cisplatin (EP) chemotherapy, initiated during either the first or second cycle. The advantages of administering thoracic RT at an early stage for individuals with LS-SCLC were reinforced by a meta-analysis involving 1524 participants from seven studies. This analysis revealed that the likelihood of survival at the two-year mark was greater for those receiving early thoracic radiation, defined as treatment initiation before the third cycle of chemotherapy, compared to those receiving late radiation (RR=1.17; 95% CI: 1.02–1.35; p=0.03)[6]. A randomized phase-III trial by Turrisi et al.[7] compared once and twice-daily thoracic RT schedules in combination with

Figure 1. Suggested treatment algorithm for limited-stage small cell lung cancer (LS-SCLC)



PCI: prophylactic cranial irradiation.

cisplatin and etoposide in LS-SCLC patients, resulting in a significantly improved survival with the latter.

Moreover, recent data have suggested that surgical intervention may play a role in multimodality therapy for a subset of patients (5%) with early T stage, without nodal involvement (T1-T2N0M0) disease, confirmed by pathological mediastinal lymph node staging. The most effective additional treatment strategy for surgical patients has not been well defined but typically involves chemotherapy or chemoradiation. Generally, these patients exhibit a more favorable overall prognosis. An analysis of 29994 patients with clinical stages I to III small cell lung cancer (SCLC) from the National Cancer Database, revealed that among 2089 patients who underwent surgery and were matched with those who did not, those treated with surgery showed a 38-month median overall survival (OS) compared to 22 months for N0 patients. All patients with surgically resected SCLC should receive adjuvant chemotherapy with four cycles of EP, but when nodal involvement is found at the time of surgery, chemoradiation alone is recommended[8] (Figure 1).

Extensive-Stage SCLC

Since the 1980s, the established treatment approach for ES-SCLC patients has involved utilizing a platinum agent in combination with etoposide. Despite various studies exploring alternative first-line chemotherapy regimens, the majority have not succeeded in modifying the established standard of care. The substitution of etoposide to irinotecan in combination with cisplatin has been evaluated in a phase-III study by the JCOG with a limited patient size (n=154), which reported encouraging results for the irinotecan-cisplatin combination with the median survival being 12.8 and 9.4 months for the irinotecan and the etoposide-containing regimens, respectively[9]. Nevertheless, a more extensive North American phase-III trial, with a sample size of 651, was unable to validate the previously observed advantages of irinotecan plus cisplatin (IP) as documented in Japanese patients. The median overall survival (OS) for the IP group was 9.9 months versus 9.1 months for the etoposide-cisplatin (EP) group. Intense diarrhea occurred more frequently in the case of irinotecan plus cisplatin (IP) compared to a lower incidence in the alternative regimen (19% vs 3%). Conversely, severe neutropenia and thrombocytopenia were more prevalent with etoposide plus cisplatin (EP) compared to irinotecan plus cisplatin (68% vs 33% and 15% vs 4%, respectively)[10].

The great success of immune-checkpoint inhibitors (ICIs) in the treatment of non-small cell lung cancer (NSCLC) in addition to the hypothesis that SCLC is a highly immunogenic disease supported by its high mutation rate[11],

Table 1. Efficacy of immune checkpoint inhibitors in addition to chemotherapy in the first-line treatment of patients with extensive stage-small cell lung cancer as demonstrated in the three major immunotherapy phase 3 trials

Trial	Patients n	Patient population	Treatment Arm(s)	Control Arm	Overall RR	OS (months)	PFS (months)
IMpower 133 (2018) Double-blind	403	ES-SCLC, PS=0–1 Not previously treated No medical history of autoimmune disease	Carboplatin + etoposide + atezolizumab (A)	Carboplatin + etoposide (C)	60.1% (A) vs 64.3% (C)	12.3 (A) vs 10.3 (C) (HR=0.70; 95% CI: 0.54– 0.91; p=0.007)	5.2 (A) vs 4.3 (C) (HR=0.77; 95% CI: 0.62–0.96; p=0.02)
CASPIAN (2019) Open-label	805	ES-SCLC, PS=0–1 Not previously treated No medical history of autoimmune disease	Platinum + etoposide + durvalumab (D) +/- tremelimumab (T)	Platinum + etoposide (C)	68% (D) vs 58% (T) vs 58% (C)	12.9 (D) vs 10.4 (T) vs 10.5 (C) (HR=0.75; 95% CI: 0.62–0.91; p=0.0032)	5.1 (D) vs 4.9 (T) vs 5.4 (C) (HR=0.80; 95% CI: 0.66–0.96)
KEYNOTE-604 (2020) Double-blind	453	ES-SCLC, PS=0–1 Not previously treated	EP + pembrolizumab (P)	EP + placebo (C)	70.6% (P) vs 61.8% (C)	10.8 (P) vs 9.7 (C) (HR=0.80; 95% CI: 0.64–0.98; p=0.0164)	4.5 (P) vs 4.3 (C) (HR=0.75; 95% CI: 0.61–0.91)

HR: hazard ratio. OS: overall survival. PFS: progression-free survival. RR: response rate. PS: performance status. ES-SCLC: extensive stage-small cell lung cancer.

has led to the evaluation of ICIs' efficacy in several clinical trials.

In 2018, the IMpower 133 trial, a substantial randomized phase-III study evaluating carboplatin plus etoposide with or without the PD-L1 immune checkpoint inhibitor atezolizumab, demonstrated an OS advantage for the group receiving immunotherapy. This double-blind, placebo-controlled phase 3 trial enrolled 403 previously untreated patients with ES-SCLC and employed a 1:1 randomization. Participants received carboplatin plus etoposide for four cycles with either atezolizumab or a placebo, followed by atezolizumab or placebo maintenance, without any requirements concerning PD-L1 expression. The median overall survival was 12.3 months in the atezolizumab group and 10.3 months in the placebo group (HR=0.70; 95% CI: 0.54–0.91; p=0.007) (Table 1). The safety characteristics of the atezolizumab group aligned with the safety profile previously documented for the individual agents. There was an equivalent occurrence of all-cause adverse events (including grade 3–4 events) between the two treatment arms. Immune-mediated AEs in the atezolizumab and the placebo group occurred in a frequency of 40% and 24%, respectively. Rash and hypothyroidism were the most common[12]. Exploratory subgroup analyses assessing the efficacy according to (blood-based) tumor mutational burden, were not predictive of any benefit in the atezolizumab group at either cut-off (10 or 16 mutations per megabase).

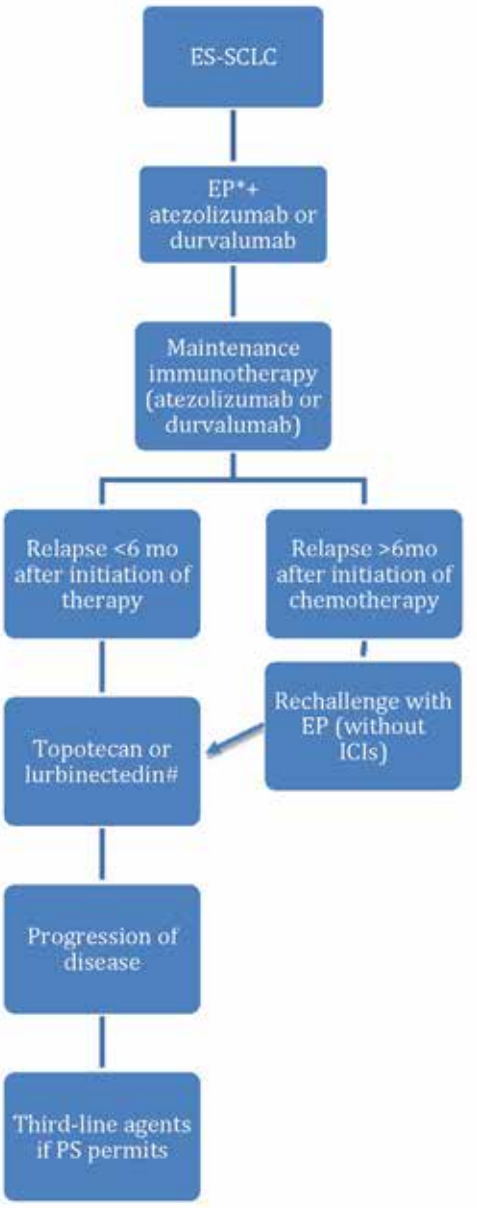
CASPIAN, another randomized, phase-III trial, randomly assigned 805 treatment-naive ES-SCLC patients (1:1:1) to receive durvalumab (a PD-L1 inhibitor) plus tremelimumab (an anti-CTLA-4 antibody) plus platinum-etoposide (PE) or durvalumab plus PE or PE alone, regardless of PD-L1 expression status. Durvalumab plus tremelimumab failed to significantly improve the OS versus PE alone (HR=0.82; 95% CI: 0.68–1.00; p=0.045) with the median OS being to 10.4 months (95% CI: 9.6–12.0) versus 10.5 months (95% CI: 9.3–11.2), respectively. Durvalumab plus PE provided a continuous enhancement in overall survival versus PE alone (HR=0.75; 95% CI: 0.62–0.91; nominal p=0.0032); median overall survival was 12.9 months (95% CI: 11.3–14.7) versus 10.5 months (95% CI: 9.3–11.2) (Table 1). The most common high-grade (≥3) adverse events were neutropenia and anemia with higher frequency in the PE group (33% vs 24% in the durvalumab plus PE group)[13].

Results from the studies mentioned above have led to the approval of PD-L1 inhibitors in the first-line treatment of patients with ES-SCLC, as shown in the treatment algorithm in Figure 2.

KEYNOTE-604, a randomized, double-blind, phase-III study, evaluated the efficacy of pembrolizumab, an anti-PD-1 antibody, with etoposide and platinum (EP) versus EP with placebo, in patients with previously untreated ES-SCLC. While pembrolizumab significantly improved the progression-free survival (PFS) with 13.6% (HR=0.75; 95% CI: 0.61–0.91; p=0.0023) vs 3.1% for the EP group, it did not meet the prespecified threshold of 0.0128 for the OS (HR=0.80; 95% CI: 0.64–0.98; p=0.0164). The 24-month OS estimates were 22.5% and 11.2%, respectively, and no unexpected toxicities were observed with pembrolizumab plus EP[14] (Table 1). Retrospective analyses of PD-L1 expression using the combined positive score (CPS) demonstrated similar HRs for OS and PFS in CPS>1 and CPS≤1 tumors.

In another phase-III randomized trial, Reck et al.[15] evaluated the efficacy of ipilimumab, an anti-CTLA-4 antibody, plus EP versus placebo plus EP in newly diagnosed

Figure 2. Suggested treatment algorithm for extensive-stage small cell lung cancer (ES-SCLC)



*EP: etoposide + cistplatin or carboplatin (carboplatin preferred due to its more favorable side effect profile). #Lurbinectedin is approved only by the USA FDA.

patients with ES-SCLC. The research did not yield a statistically significant enhancement in OS (HR=0.94; 95% CI: 0.81–1.09; p=0.3775), as the median OS was 11.0 months for the ipilimumab group and 10.9 months for the control group[15]. Maintenance therapy with nivolumab, an anti-PD-1 antibody, or nivolumab plus ipilimumab in ES-SCLC patients after 4 cycles of chemotherapy, failed to show a statistically significant enhancement in overall survival (OS). In CheckMate 451834 patients were randomly assigned (1:1:1) in three groups to receive nivolumab plus ipilimumab or nivolumab alone or placebo and the OS as 9.2 months for the nivolumab plus ipilimumab group versus 9.6 months for the placebo group (HR=0.92; 95% CI: 0.75–1.12; p=0.37). Median OS for nivolumab was 10.4 months (HR=0.84; 95% CI: 0.69–1.02)[16].

Prophylactic cranial irradiation (PCI)

PCI has shown efficacy in reducing the occurrence of symptomatic brain metastases and improving overall survival in patients who have initially responded to systemic therapy. The PCI Overview Collaborative Group meta-analysis of seven randomized trials evaluating the efficacy of PCI versus no PCI in 987 patients in complete remission, demonstrated a significant reduction in the risk of developing brain disease, but also improved overall and disease-free survival. Around 85% of patients in both groups were enrolled with limited disease. The addition of PCI resulted in a 5.4% enhancement in the 3-year survival rate[17]. Nevertheless, findings from a Japanese randomized trial indicated that for patients without baseline brain metastases detected on MRI, PCI did not confer a survival advantage compared to a strategy involving routine surveillance MRI and subsequent treatment upon identification of asymptomatic brain metastases[18].

Refractory and Relapsed SCLC

Although response rates to initial treatments are robust, responses lack durability and the majority of patients experience relapse with disease that is relatively resistant. The median survival of these patients when treated with subsequent systemic therapy is approximately 4–5 months. The time interval until disease progression influences the likelihood of response to subsequent treatment. If the disease-free interval was <3 months (resistant relapse) or there was no initial response (refractory disease), the majority of agents or treatment protocols exhibit low response rates (<10%). However, if the time to relapse was ≥3 months (sensitive relapse), anticipated response rates are higher (25%)[19].

According to the NCCN guidelines, patients who relapsed more than six months after the initial treatment should be treated with the original regimen. However, patients who relapse after six months while on maintenance therapy with atezolizumab, should receive carboplatin plus etoposide (without atezolizumab)[20]. For patients experiencing a relapse within six months of primary therapy, the preferred regimens for use include lurbinectedin or a campothecin (most commonly topotecan) monotherapy. Numerous other agents such as irinotecan, paclitaxel, docetaxel, temozolomide, nivolumab with or without ipilimumab, pembrolizumab, vinorelbine, oral etoposide, gemcitabine, CAV (cyclophosphamide, doxorubicin and vinorelbine) and bendamustine, constitute reasonable alternatives based on phase-II trials.

Lurbinectedin is an alkylating agent approved by the FDA for use in metastatic SCLC patients on disease progression on or after a platinum-based regimen. In a single-arm, phase-II, basket trial of 105 pre-treated patients with one chemotherapy regimen, the overall response was 35.2% (95% CI: 26.2–45.2)[21].

A randomized, phase-III trial compared the efficacy and safety of topotecan versus CAV in patients who had relapsed at least 60 days after completion of the initial therapy. Response rates were 24.3% for topotecan and 18.3% for the CAV group (p=0.285). Median survival was 25.0 and 24.7 weeks, respectively. Therefore, intravenous topotecan demonstrated efficacy comparable to that of the CAV regimen in the recurrent setting and it showed improved control of dyspnea, anorexia, hoarseness, and fatigue[22]. Another phase-III trial resulted in prolonged survival and quality of life benefit with topotecan compared with best supportive care (median survival of 25.9 vs 13.9 weeks, respectively)[23]. Oral compared with intravenous topotecan, in a phase-III study, demonstrated similar activity and safety and offered an alternative to IV therapy[24].

Irinotecan (CPT-11) was assessed in a small phase-II trial in sixteen patients with refractory or relapsed SCLC, showing a 47% (7/15) overall response (47%; 95% CI: 21.4–71.9) with myelosuppression, diarrhea, and pulmonary toxicity being reported[25].

In a phase-II study of 24 patients, paclitaxel showed a 29% (7/24) response rate (29%; 95% CI: 12–51)[26]. Docetaxel had similar response rates (25%; 7/28 patients) in another phase-II trial[27]. Temozolomide was evaluated in a phase-II trial for its safety profile showing no treatment-limiting prolonged cytopenia with the 5-day schedule, with the overall partial response being at 12% (3/25) (95% CI: 3–31). Also, temozolomide may be efficacious in patients with brain metastases, despite no noted responses in the specific trial[28].

ICIs have been evaluated in several studies in patients with relapsed SCLC and could be a reasonable alternative in this setting for patients who did not receive a prior immunotherapy-containing regimen. Phase-I/II data (CheckMate 032) showed durable responses with the use of nivolumab and nivolumab plus ipilimumab in recurrent SCLC[29] and led to their inclusion to the NCCN guidelines for the recurrent, platinum-refractory disease. Pembrolizumab has also been evaluated in recurrent SCLC treatment in the phase-Ib study KEYNOTE-028 and the phase-II study KEYNOTE-158. In the two studies, 83 patients were included,

reporting a response rate of 19.3% (95% CI: 11.4–29.4) with the median OS being 7.7 months (95% CI: 5.2–10.1). Tumors expressing PD-L1 exhibited elevated response rates and OS[30].

Sacituzumab govitecan, an antibody-drug conjugate (ADC), composed of the active metabolite of irinotecan (SN-38) linked to a humanized antibody targeting trophoblastic cell-surface antigen 2 (Trop-2), was evaluated in metastatic SCLC (mSCLC) patients in a phase I/II trial. In this study, previously pretreated mSCLC patients received 8 or 10 mg/kg of intravenous sacituzumab on days 1 and 8 of 21-day cycles. The overall response rate (ORR) was 14% and the median response duration was 5.7 months, demonstrating a safe and effective therapeutic profile[31]. Additional studies are required.

Another promising ADC molecule, rovalpituzumab terisine (Rova-T), has been tested in phase I and II studies. Rova-T is composed of SC16, a humanized IgG1 antibody against delta-like 3 protein (DLL3), conjugated to the cytotoxic pyrrolobenzodiazepine (PBD) by a protease-cleavable linker. In two phase I studies aiming to evaluate the safety and efficacy of Rova-T in advanced SCLC patients, findings indicated a manageable safety profile and activity supporting further exploration. However, results from the phase-II TRINITY study were not as promising as phase-I studies mentioned above. Rova-T used as 3rd line therapy and beyond in relapsed SCLC patients resulted in an ORR of 12.3% in 339 patients enrolled and 13.2% in DLL3-positive tumors by rabbit IHC[32].

Recently, a phase II study evaluating the safety and efficacy of tarlatamab, a bispecific T-cell engager immunotherapy targeting delta-like ligand 3 and CD3, among individuals with previously treated SCLC, a sustained objective response rate was observed in 40% of patients, and the median overall survival reached 14.3 months. The most common adverse events included pyrexia, decreased appetite and cytokine-release syndrome[33].

Molecular features

SCLC exhibits distinct genomic alterations compared to pulmonary NETs of intermediate and low grades. Nearly all SCLC patients experience loss of function alterations in the tumor suppressor genes TP53 and RB1(at 13q14). Haploinsufficiency, resulting from allele loss in various regions on chromosome 3p (including 3p21.3, 3p12, 3p14.2, and 3p24.4), leads to the absence or reduced expression of multiple tumor suppressor genes in over 90% of SCLCs, marking an early event in tumorigenesis. Genomic profiling of SCLC tumors, in addition to widespread TP53 and RB1 inactivation, reveals frequent (25%) inactivating mutations in NOTCH family genes. Mutually exclusive alterations are also common among histone acetyltransferase genes, such as CREB-binding protein (CREBBP) and E1A binding protein P300 (EP300), as well as various genes associated with TP53 and RB1. Amplification of MYC family members is detected in 20% of SCLCs. Although loss of phosphatase and tensin homolog (PTEN) is observed in 2–4% of tumors, alterations in the phosphoinositide 3-kinase (PI3K) pathway are overall more prevalent and contribute to SCLC tumorigenesis in preclinical models[34].

Even with the addition of immunotherapy to frontline platinum-based chemotherapy, the enhancements in PFS and OS are relatively modest. Clinical studies involving SCLC patients have predominantly concentrated on unselected populations and have produced unsatisfactory outcomes. There is a crucial requirement for a more precise understanding of the specific characteristics of SCLC that influence its response to targeted therapies and immunotherapy. In the past few years, the categorization of SCLC subtypes has transformed from classic/variant distinctions to subsets defined by transcription factors. Gay et al.[35] categorized SCLC into four subtypes primarily based on varying levels of expression of the transcription factors ASCL1, NEUROD1, and POU2F3, or by the presence of low expression in all three transcription factor signatures, along with the presence of an Inflamed gene signature. These subtypes are denoted as SCLC-A, N, P, and I, respectively[35]. Also, gene expression analyses in long-term survivors (LTS) of the IMpower 133 trial, identified that more LTS were treated with atezolizumab + chemotherapy than placebo + chemotherapy, and LTS in both treatment groups exhibited increased immune-related signaling. Atezolizumab and placebo showed a similar distribution of GE-defined subtypes, hinting at the possibility that the association of subtypes with treatment outcomes may have prognostic implications[36].

CONCLUSION

After more than thirty years of unsuccessful clinical trials and treatment strategies in the context of SCLC, immunotherapy emerges as the most encouraging therapeutic avenue. Since immune checkpoint inhibitors and chemotherapy agents target distinct cells and pathways, combining these drugs in synergistic treatments may enhance efficacy while maintaining comparable side effects. Being still in a non-curative setting, data from the latest trials demonstrate an improvement in OS and quality of life (QoL) in SCLC patients. Moreover, the role of immunotherapy in SCLC patients with brain metastases needs to be investigated in a larger number of patients in future trials. Several trials are looking at the role of ICIs in LS-SCLC as well. Finally, recent progress in the molecular profiling of SCLC subtypes can lead the way for tailored treatment approaches.

CONFLICTS OF INTEREST

The authors have each completed and submitted an ICMJE form for Disclosure of Potential Conflicts of Interest. The authors declare that they have no competing interests, financial or otherwise, related to the current work. A. Charpidou reports receiving consulting fees from ASTRA ZENECA, BMS and JANSSEN, also payments for

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ETHICAL APPROVAL AND INFORMED CONSENT

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DATA AVAILABILITY

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33. doi:10.3322/caac.21708
2. Stahel R, Thatcher N, Früh M, et al. 1st ESMO Consensus Conference in lung cancer; Lugano 2010: small-cell lung cancer. Ann Oncol. 2011;22(9):1973-1980. doi:10.1093/annonc/mdr313
3. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol. 2012;30(14):1692-1698. doi:10.1200/JCO.2011.40.4905
4. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med. 1992;327(23):1618-1624. doi:10.1056/NEJM199212033272302
5. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol. 2002;20(14):3054-3060. doi:10.1200/JCO.2002.12.071
6. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol. 2004;22(23):4837-4845. doi:10.1200/JCO.2004.01.178
7. Turrisi AT, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med. 1999;340(4):265-271. doi:10.1056/NEJM199901283400403
8. Wakeam E, Acuna SA, Leighl NB, et al. Surgery Versus Chemotherapy and Radiotherapy For Early and Locally Advanced Small Cell Lung Cancer: A Propensity-Matched Analysis of Survival. Lung Cancer. 2017;109:78-88. doi:10.1016/j.lungcan.2017.04.021
9. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med. 2002;346(2):85-91. doi:10.1056/NEJMoa003034
10. Lara PN, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol. 2009;27(15):2530-2535. doi:10.1200/JCO.2008.20.1061
11. Peifer M, Fernández-Cuesta L, Sos ML, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet. 2012;44(10):1104-1110. doi:10.1038/ng.2396
12. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018;379(23):2220-2229. doi:10.1056/NEJMoa1809064
13. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2021;22(1):51-65. doi:10.1016/S1470-2045(20)30539-8
14. Rudin CM, Awad MM, Navarro A, et al. Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study. J Clin Oncol. 2020;38(21):2369-2379. doi:10.1200/JCO.20.00793
15. Reck M, Luft A, Szczesna A, et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol. 2016;34(31):3740-3748. doi:10.1200/JCO.2016.67.6601
16. Owonikoko TK, Park K, Govindan R, et al. Nivolumab and Ipilimumab as Maintenance Therapy in Extensive-Disease Small-Cell Lung Cancer: CheckMate 451. J Clin Oncol. 2021;39(12):1349-1359. doi:10.1200/JCO.20.02212
17. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med. 1999;341(7):476-484.

doi:10.1056/NEJM199908123410703
18. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(5):663-671. doi:10.1016/S1470-2045(17)30230-9
19. Owonikoko TK, Behera M, Chen Z, et al. A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small-cell lung cancer. J Thorac Oncol. 2012;7(5):866-872. doi:10.1097/JTO.0b013e31824c7f4b
20. Postmus PE, Smit EF. Treatment of relapsed small cell lung cancer. Semin Oncol. 2001;28(2 Suppl 4):48-52. doi:10.1016/s0093-7754(01)90079-x
21. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol. 2020;21(5):645-654. doi:10.1016/S1470-2045(20)30068-1
22. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol. 1999;17(2):658-667. doi:10.1200/JCO.1999.17.2.658
23. O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006;24(34):5441-5447. doi:10.1200/JCO.2006.06.5821
24. Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol. 2007;25(15):2086-2092. doi:10.1200/JCO.2006.08.3998
25. Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol. 1992;10(8):1225-1229. doi:10.1200/JCO.1992.10.8.1225
26. Smit EF, Fokkema E, Biesma B, Groen HJ, Snoek W, Postmus PE. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. Br J Cancer. 1998;77(2):347-351. doi:10.1038/bjc.1998.54
27. Smyth JF, Smith IE, Sessa C, et al. Activity of docetaxel (Taxotere) in small cell lung cancer. The Early Clinical Trials Group of the EORTC. Eur J Cancer. 1994;30A(8):1058-1060. doi:10.1016/0959-8049(94)90455-3
28. Zauderer MG, Drilon A, Kadota K, et al. Trial of a 5-day dosing regimen of temozolomide in patients with relapsed small cell lung cancers with assessment of methylguanine-DNA methyltransferase. Lung Cancer. 2014;86(2):237-240. doi:10.1016/j.lungcan.2014.08.007
29. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016;17(7):883-895. doi:10.1016/S1470-2045(16)30098-5
30. Chung HC, Piha-Paul SA, Lopez-Martin J, et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies. J Thorac Oncol. 2020;15(4):618-627. doi:10.1016/j.jtho.2019.12.109
31. Gray JE, Heist RS, Starodub AN, et al. Therapy of Small Cell Lung Cancer (SCLC) with a Topoisomerase-I-inhibiting Antibody-Drug Conjugate (ADC) Targeting Trop-2, Sacituzumab Govitecan. Clin Cancer Res. 2017;23(19):5711-5719. doi:10.1158/1078-0432.CCR-17-0933
32. Morgensztern D, Besse B, Greillier L, et al. Efficacy and Safety of Rovalpituzumab Tesirine in Third-Line and Beyond Patients with DLL3-Expressing, Relapsed/Refractory Small-Cell Lung Cancer: Results From the Phase II TRINITY Study. Clin Cancer Res. 2019;25(23):6958-6966. doi:10.1158/1078-0432.CCR-19-1133
33. Ahn MJ, Cho BC, Felip E, et al. Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer. N Engl J Med. 2023;389(22):2063-2075. doi:10.1056/NEJMoa2307980
34. D'Angelo SP, Pietanza MC. The molecular pathogenesis of small cell lung cancer. Cancer Biol Ther. 2010;10(1):1-10. doi:10.4161/cbt.10.1.12045
35. Gay CM, Stewart CA, Park EM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell. 2021;39(3):346-360.e7. doi:10.1016/j.ccell.2020.12.014
36. Liu SV, Mok TSK, Mansfield AS, et al. VP5-2021: IMpower133: Gene expression (GE) analysis in long-term survivors (LTS) with ES-SCLC treated with first-line carboplatin and etoposide (CE) ± atezolizumab (atezo). Ann Oncol. 2021;32(8):1063-1065. doi:10.1016/j.annonc.2021.05.799

Pulmonary embolism and sarcopenia: The potential interplay

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ABSTRACT

INTRODUCTION Sarcopenia is a medical condition associated with skeletal muscle mass disorder. It might be related to poor and adverse outcomes including disability, hospitalization, increased mortality and morbidity. Pulmonary embolism (PE) is considered as the third most usual cause of cardiovascular death globally, after other adverse clinical conditions such as stroke and heart attack.

METHODS This study investigated the upcoming association between sarcopenia and pulmonary embolism via a non-systematic review.

RESULTS It is demonstrated by the existing literature that sarcopenia might be related to 30 days mortality in subjects with acute PE and additionally with in-hospital mortality. Sarcopenic subjects seem to be at increased risk for a deep vein thrombus (DVT) or PE, while rates of cardiorespiratory complications, among them PE, in sarcopenic colon cancer subjects were higher than cardiorespiratory complication rates in non-sarcopenic. Nevertheless, one study demonstrated that if skeletal muscle index (SMI) is increased by five points, the odds of PE are also increased.

CONCLUSIONS More studies are necessary to validate these outcomes and provide us with specific information about the upcoming intriguing interplay between these two potentially life-threatening conditions.

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KEYWORDS

pulmonary embolism, sarcopenia, low muscle mass, deep vein thrombosis, venus thromboembolism

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INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) compose venous thromboembolism (VTE)[1,2]. PE is recorded as the third most frequent cause of cardiovascular death globally, after stroke and heart attack[3]. It is already recorded that most PE cases derive from DVT of the lower extremities, and almost 50% of DVT cases may cause silent PE[3]. Moreover, it has been demonstrated that PE is responsible for death in nearly 5% to 10% of hospitalized subjects[3]. Entities that could obstruct the pulmonary arteries might be tumors, clots, fat, or air, and everything that leads to this obstruction could be considered as PE[3].

It is well-established that VTE and atherothrombosis may have common risk factors and pathophysiology profile, including inflammation, endothelial injury and hypercoagulability[1]. In addition, VTE is a clinical condition that could reinforce a pan-vascular syndrome that might consist of coronary artery disease, cerebrovascular disease, and peripheral arterial disease, while risk factors for VTE, including hypertension, diabetes mellitus (DM), cigarette smoking, and obesity, may often overlap with risk factors for atherosclerosis[1,4].

Concerning PE, risk factors might be old age (>65 years), long-haul travel, associated with thrombophilia (factor V Leiden or prothrombin gene mutation), hypertension, metabolic syndrome, cigarette smoking, air pollution, obesity, postoperative, immobilization, oral contraceptives, trauma, postmenopausal, hormonal replacement, pregnancy, malignancy, and acute disease such as congestive heart failure and pneumonia[1,5].

Diagnosis and clinical probability assessment of PE consist of tools such as the 'Wells scoring system', the D-dimer test, computed tomography pulmonary angiography (CTPA), and the VQ (ventilation perfusion) scan, are commonly utilized by clinical practitioners and other healthcare professionals to diagnose PE and VTE[1,6,7].

Concerning the management of PE and treatment implementation, primary reperfusion treatment, which usually includes systemic thrombolysis, is the therapy of choice for subjects with increased risk for PE, while surgical pulmonary embolectomy or percutaneous catheter-directed therapy are other reperfusion techniques and choices in subjects who cannot sustain thrombolysis[8,9]. In addition, following reperfusion therapy and hemodynamic stabilization of the patient, subjects recovering from high-risk PE can be redirected from parenteral to oral anticoagulation[8]. In cases of intermediate-risk and low-risk PE, anticoagulant treatment is appropriate[8].

Sarcopenia is a skeletal muscle mass condition that might be progressive and can be related to both skeletal muscle mass and muscle function, associated with many adverse clinical results, such as falls, disability, hospitalizations,

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increased hospital length of stay, and eventually higher mortality and morbidity[10,11]. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) recorded an initial sarcopenia definition, while in early 2018, the Working Group (EWGSOP2) tried to update the first definition to express evidence that has been demonstrated the last years concerning this clinical condition[12,13]. They ended up with specific criteria that tried to depict the operational definition of sarcopenia, including: 1) low muscle strength, 2) low muscle quality or quantity, and 3) low physical performance[12]. Utilizing these criteria they have concluded that probable sarcopenia is validated by criterion 1, diagnosis is validated by additional documentation of criterion 2, while if criteria 1–3 are all present, sarcopenia is considered severe[12].

The SARC-F questionnaire which is used to find sarcopenia cases has a low-to-moderate sensitivity and a very high specificity to forecast low muscle strength and, as a result will mainly demonstrate and record severe cases, while it can be widely used by everyday physicians[12]. The measurement of skeletal muscle strength might be conducted by the assessment of hand grip strength utilizing a hand grip dynamometer, while skeletal muscle quality or skeletal muscle mass might be evaluated by Dual-energy X-ray Absorptiometry (DXA), which is a commonly available method to assess muscle quantity in a non-invasive manner and Bioelectrical Impedance Analysis (BIA)[12,14,15]. Muscle quantity might be recorded as Appendicular Skeletal Muscle Mass (ASM), as total body Skeletal Muscle Mass (SMM), or as muscle cross-sectional area of specific muscle groups or body locations, while magnetic resonance imaging (MRI) and computed tomography (CT) are considered as gold standards for non-invasive muscle quantity/mass assessment[12].

Concerning interventions that could be considered, there are no pharmacological agents for managing and treating sarcopenia[16]. The management of this clinical condition mainly concerns physical therapy for gait training and muscle strengthening, and training programs[16]. Exercise programs, especially resistance training, have been identified as promising to enhance strength and muscle mass[17]. In addition, specific dietary approaches and interventions, including adequate protein intake, antioxidant nutrients, vitamin D, and long-chain polyunsaturated fatty acid, have demonstrated a positive impact on sarcopenia, but more studies are needed to support these claims[18]. Interventions concerning exercise and combination of dietary and exercise interventions, resulted in improvement concerning decreased body muscle strength but it seems to have less consistent outcomes concerning hand grip strength and walking speed[19].

In this literature review, we tried to investigate whether there is any link and interplay between the entities of sarcopenia and PE, which can both have detrimental effects and can be life-threatening medical conditions. It is already recorded that bed rest, or acute inactivity related to hospitalization or disease state, might be a potential risk to muscle tissue, muscle mass and functional capacity[20,21]. In addition, it is already well established that immobility is related to decreased venous blood flow, especially in the pockets of the venous valves, causing hypercoagulability, inflammation and increasing the possibility of thrombosis especially due to hospitalization or minor injuries[22]. As it seems, both sarcopenia and PE might be present at the abovementioned conditions, so it is imperative to study their interplay.

METHODS

A thorough investigation was carried out among the databases of EMBASE, Google Scholar and PubMed, for the period 1976 to November 2023, utilizing the following search string: ['sarcopenia' OR 'low muscle mass' OR 'muscle mass'] AND ['pulmonary embolism']. Only original studies in English were analyzed in this non-systematic review. In addition, all the references of the included studies were also exhaustively examined. Articles related to animal studies were not included in this review. The organization of the literature review is encapsulated in the flowchart diagram (Figure 1).

RESULTS

The impact of sarcopenia on PE and PE mortality

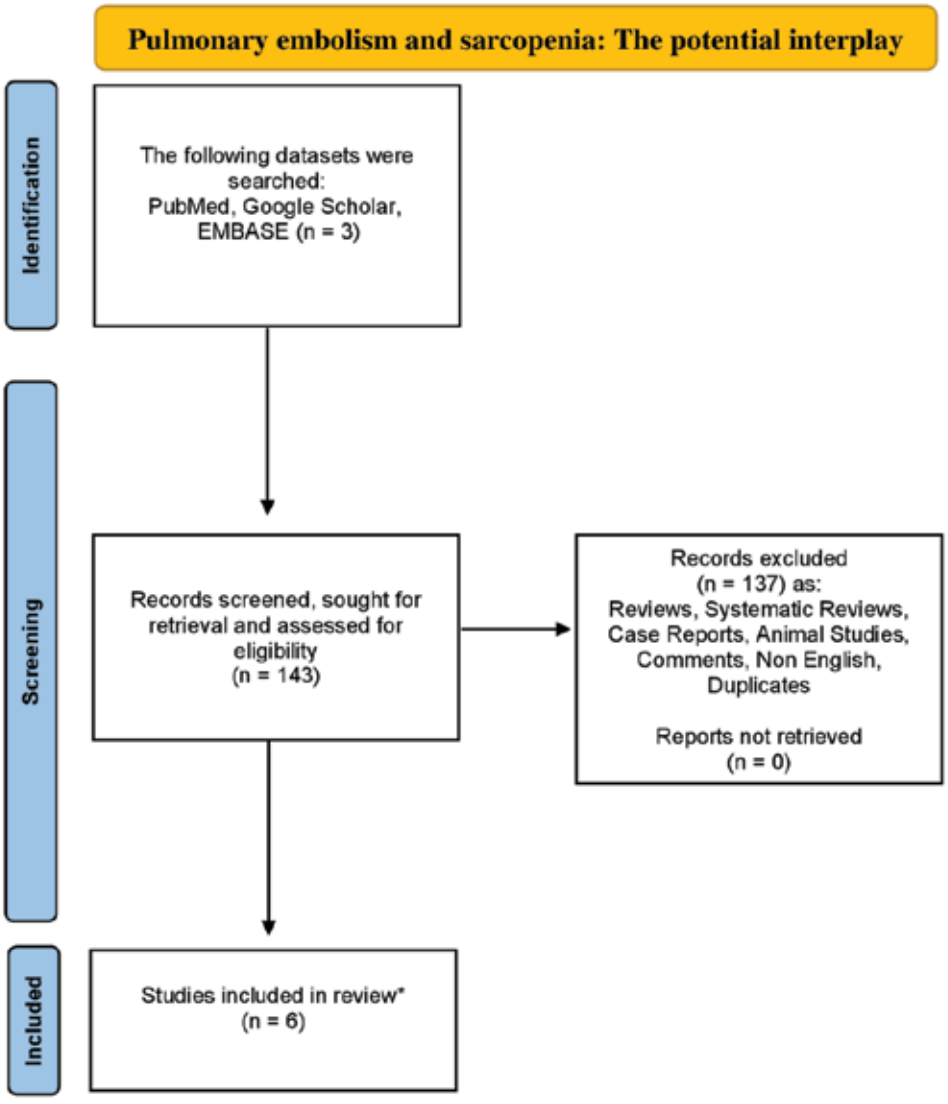
Meyer et al.[23] investigated the potential role that the low skeletal muscle mass (LSMM) diagnosed by thoracic computed tomography (CT) may have for prognosis and the prediction of the mortality risk concerning cases of acute PE. They retrospectively screened the clinical database of their department for subjects who sustained acute PE between 2013 and 2017. A total of 234 patients were included in the study[23]. To assess the muscle mass status and the potential sarcopenia existence, they used contrast-enhanced pulmonary angiography thoracic CT to evaluate axial slides at the thoracic vertebra 5 (Th5) level[23]. They calculated the skeletal muscle index (SMI) by adjusting the muscle area to the subject's height. Of their patients, 64 passed away, representing 27.4% of the initial sample[23]. The authors reported that SMI was slightly higher for acute PE survivors than acute PE non-survivors (57.7 ± 11.9 vs 55.6 ± 14.3 cm^2/m^2; p=0.07), while SMI was related to 30-day mortality in univariate, as well as multivariate analyses (respective hazard ratios, HR=1.06; 95% CI: 1.03–1.09, and HR=1.08; 95% CI: 1.04–1.11)[23]. This study concluded that SMI at Th5 derived from thoracic CT might have a relevant impact on 30 days mortality in subjects with acute PE and could be included in the clinical armamentarium, underlying the potential role of SMI and skeletal muscle mass health in PE[23].

Akkoc et al.[24] evaluated the predictive value of a certain muscle region and more specifically, of the psoas muscle area, which can be evaluated to identify sarcopenia, measured by CT concerning the forecast of in-hospital mortality in subjects with PE at admission to the intensive care unit[24]. A total of 89 subjects with an abdominal CT scan on admission in need of intensive care unit (ICU)

confrontation were examined, while the PE severity index (PESI) was utilized to evaluate the clinical severity of the PE in accordance with the European Society of Cardiology (ESC) guidelines[24]. A radiologist who was blinded to subject outcomes conducted quantitative evaluation of psoas muscle anatomical regions utilizing the available CT scan depictions at the caudal end of L3 vertebra, while the psoas muscle region value was measured by dividing the sum of the right and left psoas muscle areas into the body surface area[24]. The rate of the in-hospital mortality was 22.5% of the subjects included in this study. It was found that the PESI of PE subjects with in-hospital mortality was significantly higher than that of the PE subjects without in-hospital mortality ($p<0.05$)[24]. In addition, the value of psoas muscle region in the PE subjects with in-hospital mortality was significantly lower than that in the PE subjects without in-hospital mortality ($p<0.05$)[24]. They concluded that the growth in the value of psoas muscle area was related to a reduction of the in-hospital mortality rate, while in subjects with in-hospital mortality associated with PE, the increased PESI and the decreased value of psoas muscle area were related to the subjects' outcome[24]. This could point to the significance of psoas muscle area evaluation and sarcopenia assessment in subjects with PE, managed in intensive care units[24].

In another study, Maddox et al.[25] investigated the impact of sarcopenia on surgical morbidity after lower extremity (LE) reconstruction and the risk of postoperative complications[25]. Preoperative CT scans of the abdomen and LEs were examined to identify sarcopenia. Sarcopenia was evaluated by measuring the Hounsfield unit average calculation (HUAC) via two techniques: the 'traditional method' via Philips IntelliSpace Portal (ISP; Amsterdam, Netherlands) and the novel 'ellipse method' via CPACS[25]. The traditional technique was detecting the bilateral psoas at spinal level L4 with the

Figure 1. Flowchart diagram indicative of the literature review strategy



*Only original non-animal studies written in English were included in this non-systematic review.

Table 1. The interplay between pulmonary embolism and sarcopenia

Authors	Study design Year	Study population	Main outcomes	Sarcopenia assessment
Meyer et al.[23]	Retrospective 2022	234 subjects 64 participants passed away	SMI at Th5 from thoracic CT showed relevant impact on 30 days mortality in subjects with acute PE (HR=1.06; 95% CI: 1.03–1.09; HR=1.08; 95% CI: 1.04–1.11). SMI was slightly higher for acute PE survivors than acute PE non-survivors (57.7 ± 11.9 vs 55.6 ± 14.3 cm^2/m^2, p=0.07)	Axial slides at Th5 level of contrast-enhanced pulmonary angiography thoracic CT SMI calculation
Akkoc et al.[24]	Retrospective 2020	89 adults In-hospital mortality rate was 22.5%	PESI of PE subjects with in-hospital mortality was significantly higher than that of the PE subjects without in-hospital mortality (p<0.05). The value of psoas muscle area in PE subjects with in-hospital mortality was significantly lower than that PE subjects without in-hospital mortality (p<0.05)	Psoas muscle area assessment using CT at the caudal end of L3 vertebra
Maddox et al.[25]	Retrospective 2021	A total of 50 subjects receiving free flap-based reconstruction of the LE 12 subjects (24%) sarcopenic via the traditional method and 16 (32%) sarcopenic via the ellipse method	Through ellipse method sarcopenia assessment, sarcopenic subjects were at higher risk for any complication (p=0.002) and were at a higher risk for a deep vein thrombus or PE through the traditional method of sarcopenia evaluation (p=0.047)	L4 level through tracing ('traditional method') and encircling ('ellipse method') to calculate HUAC
Meyer et al.[26]	Retrospective 2023	981 subjects (440 female, 44.9%) with mean age of 63.5 ± 15.9 years 144 subjects (14.6%) died within the 30-days period	Every pectoral muscle value higher in survivors compared to non-survivors (e.g. SMI 9.9 ± 3.5 cm^2/m^2 vs 7.8 ± 2.6 cm^2/m^2, p<0.001). Various muscle variables associated with 30-day mortality such as SMA (OR=0.94; 95% CI: 0.92–0.96, p<0.001); SMI (OR=0.78; 95% CI: 0.72–0.84, p<0.001); muscle density (OR=0.96; 95% CI: 0.94–0.97, p<0.001); muscle gauge (OR=0.96; 95% CI: 0.94–0.99, p<0.001) Both SMI and muscle density were independently related to 30-days mortality: SMI (OR=0.81; 95% CI: 0.75– 0.88, p<0.001); muscle density (OR=0.96: 95% CI: 0.95–0.98, p<0.001)	Axial slices of the thoracic CT at the level of T4 of contrast enhanced pulmonary angiography CT
Aro et al.[27]	Retrospective 2020	348 subjects curatively treated colorectal cancer	Rates of cardiorespiratory complications like heart failure, heart attack, respiratory failure, pleural effusion and PE in sarcopenic colon cancer subjects were higher than cardiorespiratory complication rates in non-sarcopenic (6.3% vs 0.0%, p=0.023)	SMI, L3 level via venous-phase CT
Kemper et al.[28]	Retrospective 2021	98 subjects with histologically confirmed esophageal cancer	If SMI increased by five points, the odds of PE increased by 109.3% (95% CI: 36.6–278.3). Univariate, unadjusted long-term survival analysis demonstrated that lower MRA and lower SMI were associated with shorter survival (p=0.03)	SMI and MRA on an axial CT slice at the height of the L3 vertebra

SMI: skeletal muscle index. Th5: thoracic vertebra 5. CT: computed tomography. PE: pulmonary embolism. HR: hazard ratio. PESI: pulmonary embolism severity index. L3: third lumbar. LE: lower extremity. L4: fourth lumbar. HUAC: Hounsfield unit average calculation. SMA: skeletal muscle area. T4: fourth thoracic vertebra. MRA: muscle radiation attenuation.

spline contour tool and calculating bilateral psoas surface area and HU measurements. On the other hand, to conduct the novel ellipse method, area measurements and bilateral psoas density were acquired from L4, utilizing the ellipse tool instead of the spline tool[25]. In this study, from a total of 50 subjects given free flap-based reconstruction of the LE, 12 subjects (24%) were sarcopenic utilizing the traditional technique and 16 (32%) were sarcopenic utilizing the ellipse method, while ellipse method was shown to be more precise, sensitive, and specific compared to the traditional technique concerning the prediction of postoperative morbidity (p=0.009)[25]. Maddox et al.[25] concluded that utilizing the ellipse technique, sarcopenic subjects were at an increased risk for any complication (p=0.002) and were at an increased hazard for a deep vein thrombus or PE utilizing the traditional technique (p=0.047)[25].

Meyer et al.[26] studied, utilizing thoracic CT, the pectoralis muscle region and density as a prognostic imaging biomarker of 30-day mortality in subjects with acute PE[26]. They retrospectively screened for subjects with thoracic CT in 3 medical centers, while pectoralis musculature was assessed on axial slices of the thoracic CT at the level of T4 of contrast enhanced pulmonary angiography CT. In addition, skeletal muscle area (SMA), SMI, muscle density and gauge were measured[26]. In total, 981 subjects (440 female, 44.9%) with a mean age of 63.5 ± 15.9 years were included in their study and 144 subjects (14.6%) died within the 30-days period[26]. Every pectoral muscle value was higher in survivors in comparison with non-survivors (for example SMI 9.9 ± 3.5 cm^2/m^2 vs 7.8 ± 2.6 cm^2/m^2, p<0.001)[26]. Various muscle variables are associated with 30-day mortality such as SMA (OR=0.94; 95% CI: 0.92–0.96, p<0.001); SMI (OR=0.78; 95% CI: 0.72–0.84, p<0.001); muscle density (OR=0.96; 95% CI: 0.94– 0.97, p<0.001); muscle gauge (OR=0.96; 95% CI: 0.94–0.99, p<0.001)[26]. Both SMI and muscle density were independently related to 30-days mortality: SMI (OR=0.81; 95% CI: 0.75–0.88, p<0.001); muscle density (OR=0.96; 95% CI: 0.95–0.98, p<0.001)[26]. As a result, they have concluded that parameters of the pectoralis musculature are related to 30-day mortality in subjects with acute PE[26].

The impact of sarcopenia on cardiorespiratory complications including PE in subjects with colon cancer

Aro et al.[27] examined whether sarcopenia or myosteatosis influence short- and long-term outcomes in subjects who were surgically managed for colorectal cancer. A total of 348 curatively treated colorectal cancer subjects were included in this retrospective study. Skeletal muscle mass and SMI were evaluated at the L3 level via venous-phase CT, while subjects were divided into sarcopenic, non-sarcopenic, and myosteatotic and non-myosteatotic[27]. Among their intriguing results, they demonstrated that sarcopenia was present at 208 subjects (59.8%) and myosteatosis was present at 108 subjects (31.2%). In addition, they have studied the rates of cardiorespiratory complications, among them heart failure, respiratory failure, heart attack, pleural effusion and PE, and they concluded that sarcopenic colon cancer subjects had higher cardiorespiratory complication rates compared to non-sarcopenic (6.3% vs 0.0%, p=0.023)[27].

The interplay of SMI, PE and survival in subjects with esophageal cancer

Nevertheless, a study conducted by Kemper et al.[28], based on the current knowledge that esophageal cancer subjects usually experience cancer-related malnutrition and consequently sarcopenia, tried to analyze the linear relation of CT-derived muscle parameters with significant clinical short- and long-term results post esophagectomy such as pneumonia, esophagoenteric leak, length of stay in ICU or hospital, pleural effusion, pleural empyema and PE, regardless of cut-offs[28]. In all, 98 subjects with histologically confirmed esophageal cancer were included in this study and with CT scans shortly before or after the operative procedures[28]. SMI, quantifying muscle mass, was evaluated by CT subjects sustaining esophagectomy, while muscle radiation attenuation (MRA) was utilized to assess muscle quality[28]. SMI and MRA were assessed on an axial CT slice at the height of the L3 vertebra. Logistic regression models were utilized to assess the impact of the SMI and MRA on post-surgery complications[28]. Concerning PE, they demonstrated that if the SMI increased by five points, the odds of a PE increased by 109.3% (95% CI: 36.6–278.3), while long-term survival analysis demonstrated that decreased MRA and decreased SMI were related to shorter survival (p=0.03)[28]. All the outcomes of the abovementioned studies are presented in Table 1.

DISCUSSION

This literature review article recorded the current knowledge concerning the intriguing interplay between sarcopenia and PE. These two clinical entities might share a close linkage. Sarcopenia and low muscle mass are associated with medical conditions also related to thrombotic danger such as obesity, cancer and others, resulting in both PE and sarcopenia sharing common trigger factors, even though whether there are possible underlying pathways and mechanisms concerning common pathophysiology is still an unknown matter[29-34]. These common factors could fuel both conditions leading to their coexistence and potentially creating a life-threatening mix with detrimental effects and poor outcomes. In addition, as already mentioned, low physical activity, prolonged bed rest, immobility and hospitalization could fuel both these conditions, leading to a potential and upcoming vicious cycle of reduced activity, disability and increased thrombosis risk[20-22].

Limitations

There are some limitations that should be noted. One is

that the existing literature and data that investigate this interplay are quite limited, and the studies conducted about this medical issue need to be more extensive. In addition, the number of the participants in these studies is small. Significantly, most reviewed studies are retrospective, with certain limitations that should be mentioned. Since they rely on review of charts that were not mainly planned to accumulate data for conducting research, some significant data are almost certain to be missing, and selection and recall biases also might have an impact on the outcomes and reasons for dissimilarities in therapy among subjects, while lost follow-up may often not be noted and might generally result in bias[35]. Moreover, in most studies, they utilized CT method to determine skeletal muscle mass or dysfunction and no other methods such as DXA which is the one most broadly utilized method in the everyday practice, as the sole radiological technique with validated cutoff values to distinguish sarcopenia[36].

Implications

Studies with a greater number of participants are needed to have more validated results and conclusions. Moreover, it would be quite interesting if we could study the existence of specific biomarkers related to both sarcopenia and PE and their prognostic value in sarcopenic subjects who sustained PE while the potential and upcoming validation of prognostic indexes or scores binding these two medical issues could be quite significant. Using other radiological methods, apart from CT scan, to assess sarcopenia could be also of great importance.

An important way of managing sarcopenia is dietary interventions and the utilization of particular exercise and training strategy. On the other hand, obesity is an important hazard for PE. It would be quite remarkable if we could examine the role of specific nutritional and training interventions, which could have a protective role in both sarcopenia and PE development, or nutritional and training interventions in sarcopenic cases sustained PE to prevent recurrent events of PE.

It would be quite important everyday clinicians who treat subjects with increased risk for PE to assess these subjects further for sarcopenia and to evaluate their skeletal muscle mass utilizing existing screening and diagnostic tools, as mentioned above. Additionally, subjects who sustained PE could be evaluated for their skeletal muscle mass. This means that everyday clinical doctors should be aware of the concept of sarcopenia and skeletal muscle mass disorder and dedicate some time to sarcopenia assessment during their clinical examination of subjects having risk factors for PE. Moreover, the collaboration among physicians, dieticians and trainers could benefit subjects living with sarcopenia and having risk factors for PE or having sustained PE. A thorough follow-up of these type of patients by the abovementioned healthcare professionals could provide the optimum management with less adverse outcomes.

CONCLUSIONS

We demonstrated that sarcopenia might have an impact on subjects who sustained PE. Nevertheless, further studies should be conducted in the final analysis to obtain more answers regarding their link. Physicians and clinical doctors should be aware of this upcoming interplay and try to investigate the existence of skeletal muscle disorder and sarcopenia in subjects in danger of PE during their physical examination or in subjects who have already sustained PE, to avoid a recurrent event with potentially detrimental results.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported.

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Ethical approval and informed consent were not required for this study.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

AUTHORS' CONTRIBUTIONS

NDK and OSK: conceptualization, investigation, writing, reviewing and editing of manuscript. NDK: visualization and writing of original draft. OSK and KIG: supervision. All authors read and approved the final version of the manuscript.

PROVENANCE AND PEER REVIEW

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REFERENCES

1. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012;379(9828):1835-1846. doi:10.1016/S0140-6736(11)61904-1
2. Nicholson M, Chan N, Bhagirath V, Ginsberg J. Prevention of Venous Thromboembolism in 2020 and Beyond. J Clin Med. 2020;9(8):2467. doi:10.3390/jcm9082467
3. Essien EO, Rali P, Mathai SC. Pulmonary Embolism. Med Clin North Am. 2019;103(3):549-564. doi:10.1016/j.mcna.2018.12.013
4. Pastori D, Cormaci VM, Marucci S, et al. A Comprehensive Review of Risk Factors for Venous Thromboembolism: From Epidemiology to Pathophysiology. Int J Mol Sci. 2023;24(4):3169. doi:10.3390/ijms24043169
5. Soo Hoo GW. Overview and assessment of risk factors for pulmonary embolism. Expert Rev Respir Med. 2013;7(2):171-191. doi:10.1586/ers.13.7
6. Toplis E, Mortimore G. The diagnosis and management

of pulmonary embolism. Br J Nurs. 2020;29(1):22-26. doi:10.12968/bjon.2020.29.1.22
7. Duffett L, Castellucci LA, Forgie MA. Pulmonary embolism: update on management and controversies. BMJ. 2020;370:m2177. doi:10.1136/bmj.m2177
8. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543-603. doi:10.1093/eurheartj/ehz405
9. Martinez Licha CR, McCurdy CM, Maldonado SM, Lee LS. Current Management of Acute Pulmonary Embolism. Ann Thorac Cardiovasc Surg. 2020;26(2):65-71. doi:10.5761/atcs.ra.19-00158
10. Karakousis ND, Gourgoulianis KI, Kotsiou OS. Sarcopenia and Tuberculosis: Is There Any Connection? J Pers Med. 2023;13(7):1102. doi:10.3390/jpm13071102
11. Bellos TC, Tzelves LI, Manolitsis IS, et al. Sarcopenia in Urinary Bladder Cancer: Definition, Prevalence and Prognostic Value in Survival. Maedica (Bucur). 2022;17(2):427-435. doi:10.26574/maedica.2022.17.2.427
12. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31. doi:10.1093/ageing/afy169
13. Petermann-Rocha F, Balntzi V, Gray SR, et al. Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2022;13(1):86-99. doi:10.1002/jcsm.12783
14. Schweighofer N, Colantonio C, Haudum CW, et al. DXA-Derived Indices in the Characterisation of Sarcopenia. Nutrients. 2022;14(1):186. doi:10.3390/nu14010186
15. Aleixo GFP, Shachar SS, Nyrop KA, Muss HB, Battaglini CL, Williams GR. Bioelectrical Impedance Analysis for the Assessment of Sarcopenia in Patients with Cancer: A Systematic Review. Oncologist. 2020;25(2):170-182. doi:10.1634/theoncologist.2019-0600
16. Dhillon RJS, Hasni S. Pathogenesis and Management of Sarcopenia. Clin Geriatr Med. 2017;33(1):17-26. doi:10.1016/j.cger.2016.08.002
17. Giallauria F, Cittadini A, Smart NA, Vigorito C. Resistance training and sarcopenia. Monaldi Arch Chest Dis. 2016;84(1-2):738. doi:10.4081/monaldi.2015.738
18. Cho MR, Lee S, Song SK. A Review of Sarcopenia Pathophysiology, Diagnosis, Treatment and Future Direction. J Korean Med Sci. 2022;37(18):e146. doi:10.3346/jkms.2022.37.e146
19. Anton SD, Hida A, Mankowski R, et al. Nutrition and Exercise in Sarcopenia. Curr Protein Pept Sci. 2018;19(7):649-667. doi:10.2174/1389203717666161227144349
20. English KL, Paddon-Jones D. Protecting muscle mass and function in older adults during bed rest. Curr Opin Clin Nutr Metab Care. 2010;13(1):34-39. doi:10.1097/MCO.0b013e328333aa66
21. Rogeri PS, Zanella R, Martins GL, et al. Strategies to Prevent Sarcopenia in the Aging Process: Role of Protein Intake and Exercise. Nutrients. 2022;14(1):52. doi:10.3390/nu14010052
22. Engbers MJ, Blom JW, Cushman M, Rosendaal FR, van Hylckama Vlieg A. The contribution of immobility risk factors to the incidence of venous thrombosis in an older population. J Thromb Haemost. 2014;12(3):290-296. doi:10.1111/jth.12480
23. Meyer HJ, Benkert F, Bailis N, Lerche M, Denecke T, Surov A. Low skeletal muscle mass defined by thoracic CT as a prognostic marker in acute pulmonary embolism. Nutrition. 2022;98:111622. doi:10.1016/j.nut.2022.111622
24. Akkoc I, Toptas M, Yalcin M, Demir E, Toptas Y. Psoas Muscle Area Measured with Computed Tomography at Admission to Intensive Care Unit: Prediction of In-Hospital Mortality in Patients with Pulmonary Embolism. Biomed Res Int. 2020;2020:1586707. doi:10.1155/2020/1586707
25. Maddox SS, Palines PA, Hoffman RD, et al. A Novel Technique for Radiographic Diagnosis of Sarcopenia that Accurately Predicts Postoperative Complications in Lower Extremity Free Flap Patients. J Reconstr Microsurg. 2021;37(9):744-752. doi:10.1055/s-0041-1726396
26. Meyer HJ, Kardas H, Schramm D, et al. CT-defined pectoralis muscle mass and muscle density are associated with mortality in acute pulmonary embolism. A multicenter analysis. Clin Nutr. 2023;42(6):1036-1040. doi:10.1016/j.clnu.2023.04.022
27. Aro R, Mäkäräinen-Uhlbäck E, Ämmälä N, et al. The impact of sarcopenia and myosteatosis on postoperative outcomes and 5-year survival in curatively operated colorectal cancer patients - A retrospective register study. Eur J Surg Oncol. 2020;46(9):1656-1662. doi:10.1016/j.ejso.2020.03.206
28. Kemper M, Molwitz I, Krause L, et al. Are muscle parameters obtained by computed tomography associated with outcome after esophagectomy for cancer? Clin Nutr. 2021;40(6):3729-3740. doi:10.1016/j.clnu.2021.04.040
29. Choi KM. Sarcopenia and sarcopenic obesity. Korean J Intern Med. 2016;31(6):1054-1060. doi:10.3904/kjim.2016.193
30. Williams GR, Dunne RF, Giri S, Shachar SS, Caan BJ. Sarcopenia in the Older Adult With Cancer. J Clin Oncol. 2021;39(19):2068-2078. doi:10.1200/JCO.21.00102
31. Bai T, Fang F, Li F, Ren Y, Hu J, Cao J. Sarcopenia is associated with hypertension in older adults: a systematic review and meta-analysis. BMC Geriatr. 2020;20(1):279. doi:10.1186/s12877-020-01672-y
32. Kim SH, Jeong JB, Kang J, et al. Association between sarcopenia level and metabolic syndrome. PLoS One. 2021;16(3):e0248856. doi:10.1371/journal.pone.0248856
33. Hisada Y, Mackman N. Cancer-associated pathways and biomarkers of venous thrombosis. Blood. 2017;130(13):1499-1506. doi:10.1182/blood-2017-03-743211
34. Samad F, Ruf W. Inflammation, obesity, and thrombosis. Blood. 2013;122(20):3415-3422. doi:10.1182/blood-2013-05-427708
35. Talari K, Goyal M. Retrospective studies - utility and caveats. J

R Coll Physicians Edinb. 2020;50(4):398-402. doi:10.4997/JRCPE.2020.409
36. Albano D, Messina C, Vitale J, Sconfienza LM. Imaging of sarcopenia: old evidence and new insights. Eur Radiol. 2020;30(4):2199-2208. doi:10.1007/s00330-019-06573-2

Tuberculosis of the temporomandibular joint: A rare case report and review of the literature

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ABSTRACT

Head and neck tuberculosis represents a rare form of extrapulmonary tuberculosis and usually concerns the cervical lymph nodes. Involvement of the temporomandibular joint (TMJ) is extremely rare and only reported at a level of case report forms. A 20-year-old female patient of African origin presented with pain in the mandible and swelling at the left masticator since one month ago. Head and brain CT scan revealed multiple hyperdense lesions with peripheral enhancement and surrounding swelling. These findings were consistent with multiple abscesses. Moreover, severe impairment and the presence of fluid was observed at the left temporomandibular joint, the mandible and the left masseter muscle. Chest CT scan revealed centrilobular nodules in both upper lung lobes. Treatment with common antibiotics was initiated but the patient did not improve. During hospitalization, the patient experienced an episode of generalized tonic-clonic convulsion. Therefore, a surgical drainage of the mandibular abscess was performed. The AFB smear and the molecular test (XPERT MTB/RIF) were positive for *Mycobacterium tuberculosis* sensitive to rifampicin. The patient was treated with isoniazid, high dose rifampicin (900 mg), pyrazinamide, ethambutol and moxifloxacin. The patient received treatment for 12 months and improved significantly clinically and radiologically. Diagnosis of tuberculosis in the temporomandibular joint is challenging but should be included in the differential diagnosis when a compatible history of exposure and other organ involvement exist.

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INTRODUCTION

In 2021, the estimated number of people diagnosed with tuberculosis (TB) increased by 4.5%, mainly due to the disruption of TB services caused by the COVD-19 pandemic leading to delayed diagnosis and treatment initiation. Although specific data regarding extrapulmonary (EPTB) incidence are not available, it is estimated that EPTB accounts for approximately 15–25% of TB infections[1]. Head and neck TB (HNTB) represents 10% of EPTB cases and mainly affects the cervical lymph nodes, larynx, middle ear, oral cavity and pharynx[2,3]. More specifically, TB affecting the orofacial region is very rare affecting only 0.1–5% of extrapulmonary TB cases[4].

Involvement of the temporomandibular joint (TMJ) is extremely rare, with only a few cases reported in the literature. As a matter of fact, TMJ TB accounts for <2% of skeletal TB sites[5].

Unfortunately, symptoms usually appear at an advanced stage and include mainly preauricular swelling, trismus (difficulty in mouth opening) and joint stiffness[6]. The main abnormality is formation of an abscess along with varying degrees of bone destruction, which can result even in the formation of a fistula[4].

Simple imaging studies such as panoramic dental X-rays, show the osteolytic lesion or lysis and condensation usually with fuzzy limits. CT scans provide a more detailed illustration of the abnormalities, including periodontitis with bone loss, bone remodeling with osteolysis and osteo condensation, and pre-mandibular soft tissue abscess[7]. MRI may be more effective in detecting TB abnormalities in peripheral joints. Even though the presence of pus either on CT or MRI is not always apparent, the presence of fluid favors a diagnosis of TMJ TB[8].

The infection begins in the subchondral region and progresses to affect the cartilage, synovium and joint space. The cancellous portion of the mandibular condyle is particularly susceptible to TB, since this part of the bone is affected in the beginning[4].

TMJ TB accounts for an osteoarticular TB form as it usually involves the cancellous portion of the mandibular condyle. *M. tuberculosis* inoculates there by hematogenous dissemination[4]. Nevertheless, TMJ TB can be a complicated manifestation of TB of the oral cavity. Oral TB, although

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uncommon due to natural defensive mechanisms, can involve the buccal mucosa, tongue, gingiva, and mandible[9]. Interestingly, in an older review concerning TB of the oral cavity, it was reported that the second most commonly affected area was the mandible (21.4%)[10]. Mandibular osteomyelitis presents with signs of atypical osteitis, periodontal disease with vertical bone loss, or destructive osteolysis. Discharge of pus or blood was described either by sinuses, tooth sockets, even by the spicules of bones through the gums[10]. It appears that abnormalities follow gradual involvement of adjacent tissues but it is not known which is the primary site of infection; the mandible or is it the oral cavity? The latter can be explained as it is known that breaks in the continuity of the mucosa, such as trauma, allow invasion of *M. tuberculosis* into deeper tissues, including the facial bones[9]. Local factors that may facilitate invasion of the oral mucosa include poor oral hygiene, leukoplakia, local trauma, and irritation by clove chewing[11]. Interestingly, TMJ TB has even been reported to arise from a fistulous communication from the middle ear[12].

Diagnosing TMJ TB requires confirming the presence of *M. tuberculosis* through microbiological tests such as AFB, molecular or culture, either by bone biopsy or more commonly via a fine needle aspiration of the pus. While TMJ TB can rarely present as a primary form of TB[4], it is more commonly associated with pulmonary disease. When a patient presents with both pulmonary TB and TMJ abnormalities, it is highly likely that TMJ TB is also present. In this case, a good response to treatment, both clinically and based on imaging findings is expected.

Differential diagnosis for TMJ TB includes other conditions like abscess, arthritis, osteomyelitis, neoplasmatic disease, or any systemic diseases that affect the joints. Pathology of the surrounding structures, e.g. teeth and the parotid gland, have to be ruled out.

Treatment of TMJ TB is similar to that of pulmonary TB, although it requires a significant amount of time, typically 6–9 months or even longer. The presence of other affected organs from tuberculosis also determines the final regimen. In our case, which is the first reported to have concomitant pulmonary and CNS tuberculosis, a high dose of rifampicin was used (900 mg), given new data. Moreover, since *M. tuberculosis* was sensitive to all first-class medicines a quinolone was added to increase treatment efficacy regarding CNS involvement. The extent of TMJ destruction at the time of diagnosis and treatment initiation determines the level of functionality afterwards. Early diagnosis is crucial for achieving the best possible quality of life. In fact, around 90–95% of TMJ TB patients regain normal masticatory function, when treatment is initiated at an early stage[13]. Surgical interventions such as decortications and excision are only considered when oral drug treatment seems insufficient[4]. The treatment of orofacial TB varies, depending on its presentation. According to the literature, cases with minimal destructive lesions typically respond to medical intervention with anti-tubercular therapy, leading to resolution, without the need for surgical treatment. On the other hand, moderately destructive lesions may necessitate decortication of bone due to medullary bone destruction and/or cortical bone perforation[14].

CASE PRESENTATION

A 20-year-old female patient of African origin presented to the hospital with pain in the mandible, swelling at the left masticator and inability of complete mouth opening since one month ago. The patient was admitted to the internal medicine department for further investigation and treatment.

The patient had no significant medical history, except for a tooth extraction 3 years ago, and was not taking any medications. She was afebrile, and all her vital signs were within the normal range. Swelling and pain at palpation were observed upon palpation of the left temporomandibular joint and the masticator muscle area. Additionally, the patient had proptosis (exophthalmos) in her right eye without experiencing diplopia. She mentioned a non-productive cough over the past month. Neurologic examination revealed no deficits.

The patient underwent a chest and brain CT scan which revealed multiple hyperdense lesions in the right frontal and temporal lobe with peripheral enhancement and surrounding swelling. The largest lesion was 1.6 cm in the frontal lobe (Figure 1). Leptomeningeal enhancement was also observed. These findings were consistent with multiple abscesses and meningitis. Moreover, severe impairment and the presence of an abscess were observed in the right parietal bone. The

Figure 1. CT brain: hyperdense lesion in the right frontal lobe (1.6 cm) with peripheral enhancement and surrounding swelling

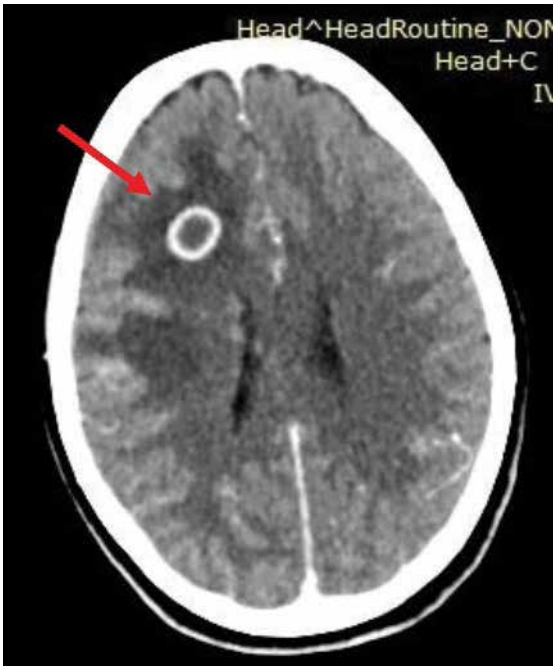


Table 1. Overview of cases of TB infections of the TMJ

Authors	Age	Gender	Symptoms/ clinical findings	Imaging findings	Type of operation	Other sites of TB co-infection	Type and duration of treatment
Geetha et al.[4]	49	Female	Swelling in front of the left tragus	Destruction of the left mandibular condyle with proximal sclerosis and erosion of mandibular foss	Condylectomy	None	6 months standard regimen
Helbling et al.[6]	22	Female	Swelling and pain in the left preauricular area	Destruction of the left condyle and condylar fossa	FNA	None	9 months standard regimen
Park et al.[8]	53	Male	Painful swelling in the right preauricular area + difficulty in mouth opening since 3 months	Destructive changes of the right condyle glenoid fossa and ring enhancement of the preauricular area of the TMJ	Incision and drainage	Lumbar spondylodiscitis	6 months standard regimen
Mohad et al.[15]	12	Male	Swelling in the right preauricular area and difficulty in mouth opening since 2 months	Pronounced rarefaction and destruction of bone in mandibular condyle with discontinuity of the cortical boundary	FNA + incision	None	Unknown duration, standard regimen
Sheikh et al.[16]	20	Male	Swelling in the right preauricular area	Erosion with comminuted destruction of the right mandibular condyle + abscess	Us guided FNA	Bilateral paravertebral and prevertebral abscess at L5–S1 level + right sacroiliac joint	9 months standard regimen
Kumar et al.[17]	35	Male	Swelling in the left preauricular area + difficulty in mouth opening	Erosion with the trabecular destruction of the left mandibular condyle + abscess+ cervical lymphadenopathy	FNA	None	INH/RIF for 9 months + condylectomy
Koul et al.[18]	16	Female	Left-sided preauricular facial swelling + trismus	Rarefaction + destruction of bone with a large mass in retromandibular and inferior temporal fossa	Trucut biopsy	None	9 months standard regimen
Karjodkar et al.[19]	A 18	Female	Swelling on left preauricular region + trismus since 8 months	Osteomyelitic changes in relation to left condyle and ramus	FNA	None	NA
	B 45	Male	Swelling on right side at the angle of the jaw since 2 months + teeth extraction due to pain	Irregular destruction at the angle region + osteomyelitis of the mandible	FNA	None	NA

Figure 2. CT brain: destruction of the tuber of the left mandible, the temporal bone and edema of the left masseter muscle

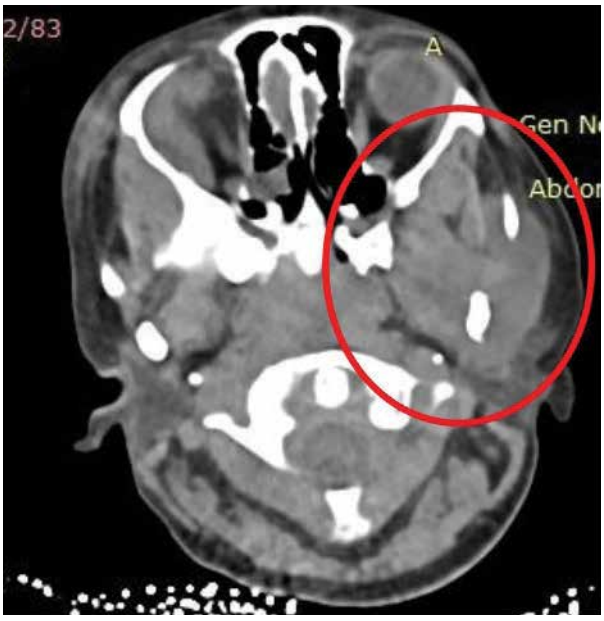
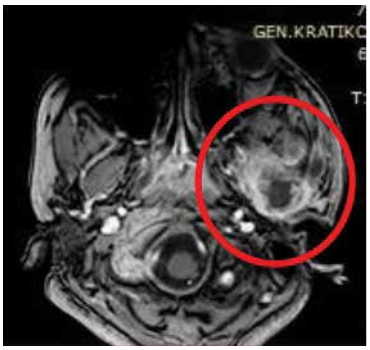


Figure 3. Brain MRI: abscess and edema surrounding at the left temporomandibular joint



tuber of the left mandible, the mandible itself, as well as the left masseter muscle appeared to be affected (Figures 2 and 3). Fluid consistent with an abscess was also present at the area. Since MRI is more sensitive than CT scanning in determining the extent of meningeal and parenchymal involvement, an MRI was performed and confirmed all the aforementioned lesions. Chest CT scan revealed centrilobular nodules and traction bronchiectasis in both upper lung lobes.

Laboratory tests showed elevated inflammatory markers (CRP, ESR). The patient tested negative for HIV, HCV and HBV, while the Quantiferon test was positive.

Initially, the patient received common antibiotics with ceftriaxone and vancomycin but showed no improvement. Therefore, surgical drainage of the mandibular abscess was performed. The drained fluid was examined for common bacteria, fungus, toxoplasma, nocardia and mycobacteria. The AFB smear and the molecular test (XPERT MTB/RIF) were positive for M. tuberculosis. The detected strain was sensitive to rifampicin.

The patient was treated with isoniazid, high dose rifampicin (900 mg), pyrazinamide, ethambutol, and moxifloxacin. Current data support the use of higher doses of rifampicin (i.e. 35 mg/kg) in order to achieve increased CNS penetration. The use of levofloxacin instead of moxifloxacin is preferable due to reduced levels of the latter when co-administered with rifampicin. However, the patient presented an allergic reaction to levofloxacin, and moxifloxacin was administered instead. The patient responded well to the treatment both clinically and radiologically, in terms of CT findings.

During hospitalization, the patient experienced an episode of generalized tonic-clonic convulsions, resulting in a traumatic fracture of the cervical vertebrae A2. A brain CT scan was repeated and revealed further damage of the odontoid process of the A2 vertebrae. The patient was started on daily anticonvulsant treatment (levetiracetam) and no further seizures occurred.

The patient was discharged from the hospital after 34 days and continued follow-up at the Antituberculous Department of the Chest Disease Hospital. She received treatment for another 12 months and improved significantly. Follow-up CT scans showed improvement or remission of most lesions in both the brain and chest.

DISCUSSION

Diagnosis of TMJ TB can be challenging, especially when it presents as the primary symptom. Delayed diagnosis may be observed due to a lack of strong suspicion. Patients often lack pathognomonic signs, and exhibit fewer systemic symptoms, and even the typical tests performed when TB is suspected such as Tuberculin Skin Test (TST) yield positive results in only about half of the patients (53%)[14]. Unlike pulmonary TB, only 20% of head and neck TB patients experience typical symptoms such as cough, fever, or night sweats[14]. An overview of relevant studies of cases of TB infections of the TMJ is given in Table 1.

CONCLUSION

This case presentation emphasizes the importance of considering TB as part of the differential diagnosis, particularly for patients from endemic areas. In such cases investigation for lung involvement reinforces the diagnosis. Regrettably, there is a growing necessity to report and record each case of extrapulmonary TB, in order to guide the diagnostic approach for uncommon sites of infection.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported.

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DATA AVAILABILITY
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REFERENCES
1. Moule MG, Cirillo JD. Mycobacterium tuberculosis Dissemination Plays a Critical Role in Pathogenesis. Front Cell Infect Microbiol. 2020;10:65. doi:10.3389/fcimb.2020.00065
2. Srivanitchapoom C, Sittitrai P. Nasopharyngeal Tuberculosis: Epidemiology, Mechanism of Infection, Clinical Manifestations, and Management. Int J Otolaryngol. 2016;2016:4817429. doi:10.1155/2016/4817429
3. Das S, Das D, Bhuyan UT, Saikia N. Head and Neck Tuberculosis: Scenario in a Tertiary Care Hospital of North Eastern India. J Clin Diagn Res. 2016;10(1):MC04-MC7. doi:10.7860/JCDR/2016/17171.7076
4. Towdur GN, Upasi AP, Veerabhadrappa UK, Rai K. A Rare, Unusual Presentation of Primary Tuberculosis in the Temporomandibular Joint. J Oral Maxillofac Surg. 2018;76(4):806-811. doi:10.1016/j.joms.2017.09.010
5. Mezri S, Chebbi G, Chebbi M, Maamouri S, Mhamed RB, Akkari K. Extranodal Tuberculosis of Head and Neck: A Series of 29 Cases. J Tuberc Res. 2019;7(3):148-158. doi:10.4236/jtr.2019.73015
6. Helbling CA, Lieger O, Smolka W, Iizuka T, Kuttenberger J. Primary tuberculosis of the TMJ: presentation of a case and literature review. Int J Oral Maxillofac Surg. 2010;39(8):834-838. doi:10.1016/j.ijom.2010.03.023
7. Boussel L, Marchand B, Blineau N, et al. Imagerie de la tuberculose ostéo-articulaire. J Radiol. 2002;83(9-C1):1025-1034. doi:JR-09-2002-83-9-C1-0221-0363-101019-ART3
8. Park HJ, Kim BC, Choi EJ, Samayoa SRK, Kim HJ. Tuberculosis of the temporomandibular joint: a case of misdiagnosis. J Oral Facial Pain Headache. 2014;28(2):165-170. doi:10.11607/ofph.1061
9. Wang WC, Chen JY, Chen YK, Lin LM. Tuberculosis of the head and neck: a review of 20 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107(3):381-386. doi:10.1016/j.tripleo.2008.11.002
10. Kakisi OK, Kechagia AS, Kakisis IK, Rafailidis PI, Falagas ME. Tuberculosis of the oral cavity: a systematic review. Eur J Oral Sci. 2010;118(2):103-109. doi:10.1111/j.1600-0722.2010.00725.x
11. Jain P, Jain I. Oral Manifestations of Tuberculosis: Step towards Early Diagnosis. J Clin Diagn Res. 2014;8(12):ZE18-ZE21. doi:10.7860/JCDR/2014/10080.5281
12. Prasad KC, Sreedharan S, Chakravarthy Y, Prasad SC. Tuberculosis in the head and neck: experience in India. J Laryngol Otol. 2007;121(10):979-985. doi:10.1017/S0022215107006913
13. Tuli SM. General principles of osteoarticular tuberculosis. Clin Orthop Relat Res. 2002;398:11-19. doi:10.1097/00003086-200205000-00003
14. Bruzgielewicz A, Rzepakowska A, Osuch-Wójcikewicz E, Niemczyk K, Chmielewski R. Tuberculosis of the head and neck - epidemiological and clinical presentation. Arch Med Sci. 2014;10(6):1160-1166. doi:10.5114/aoms.2013.34637
15. Mohad N, Dabir A, Vahanwala J, Padhye M, Patwardhan J. Tuberculous osteomyelitis in condyle of mandible: A case report. Advances in Oral and Maxillofacial Surgery. 2021;2:100064. doi:10.1016/j.adoms.2021.100064
16. Sheikh S, Pallagatti S, Gupta D, Mittal A. Tuberculous osteomyelitis of mandibular condyle: a diagnostic dilemma. Dentomaxillofac Radiol. 2012;41(2):169-174. doi:10.1259/dmfr/56238546
17. Kumar S, Mohan S, Lav R, John B. Tuberculous osteomyelitis of mandibular condyle: A rare encounter. Natl J Maxillofac Surg. 2015;6(2):214-218. doi:10.4103/0975-5950.183859
18. Koul PA, Khan UH, Jan RA, Shah TH, Bagdadi F, Shah S. Tubercular osteomyelitis of the mandible in a young female. Int J Mycobacteriol. 2014;3(2):155-157. doi:10.1016/j.ijmyco.2014.02.002
19. Karjodkar F, Saxena VS, Maideo A, Sontakke S. Osteomyelitis affecting mandible in tuberculosis patients. J Clin Exp Dent. 2012;4(1):e72-e76. doi:10.4317/jced.50588

Spontaneous pneumothorax following COVID-19 infection in an adolescent: A case report and review of literature

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ABSTRACT

SARS-CoV-2 infection is associated with respiratory complications, especially during the acute phase. We report an unusual case of an adolescent boy who presented with cough, dyspnea and unilaterally absent breath sounds on auscultation. Two weeks prior to the admission, the patient reported low-grade fever and mild cough. A rapid SARS-CoV-2 antigen test was positive. On admission, the child tested positive for SARS-CoV-2 with polymerase chain reaction (PCR). The diagnosis of spontaneous pneumothorax was confirmed by a chest X-ray. A chest tube was inserted, and symptoms gradually resolved. This case report highlights that SARS-CoV-2 infection may cause serious respiratory complications in children, even after the resolution of acute infection.

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KEYWORDS

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INTRODUCTION

SARS-CoV-2 infection has continued to affect many patients since December 2019, when it was first detected. Although most children with SARS-CoV-2 infection present acutely with mild symptoms, vigilance is required for potentially serious complications. Fever, cough, and dyspnea are the most reported respiratory symptoms in children[1]. Spontaneous pneumothorax occurs without any obvious trauma or iatrogenic cause and is classified as primary or secondary. In primary spontaneous pneumothorax, there is an absence of known lung disease, whereas secondary presents as a complication of underlying pulmonary disease[2].

Figure 1. Chest X-ray before (A) and after (B) chest drain insertion

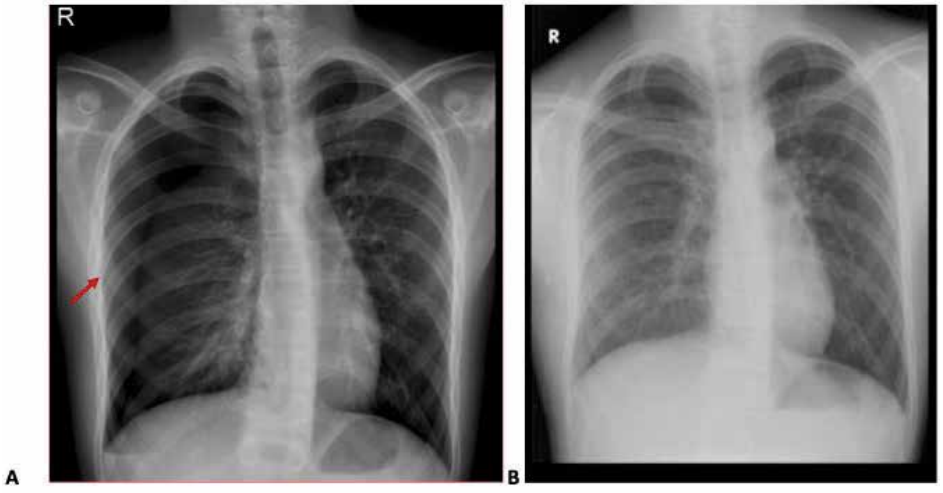

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Table 1. Reports of spontaneous pneumothorax and SARS-CoV-2 infection in children and adolescents

Author Year	Age (years)	Sex	Coexisting conditions	Clinical presentation	CT findings	COVID-19 RT-PCR test	Time of presentation	Therapy	Survival
Buonsenso et al.[4] 2021	17	Male	Negative	Chest pain	Pneumothorax, pneumomediastinum, pneumorrachis	(+)	Incidental finding	Conservative	Yes
Musolino et al.[5] 2021	16	Male	Negative	Chest pain, subcutaneous emphysema, ARDS	Pneumothorax, pneumomediastinum	(+)	Incidental finding	Conservative	Yes
Musolino et al.[5] 2021	17	Male	Negative	Chest pain, respiratory distress	Pneumothorax	(+)	10 days after asymptomatic COVID-19 infection	Pleural drainage with aspiration	Yes
Laaribil et al.[6] 2022	9 months	Male	Epilepsy	Respiratory distress, fever, tachypnoea, O2 desaturation	Pneumothorax, alveolar pneumonitis consolidation	(+)	On admission	Pleural drainage	Yes
Laaribil et al.[6] 2022	1.5	Male	Negative	Dry cough, respiratory distress, fever, O2 desaturation	Alveolar – interstitial pneumonopathy, pneumothorax	(+)	On admission	Pleural drainage	Died due to urosepsis
Oterino et al.[7] 2020	6	Female	Systemic sclerosis	Unknown	Pneumothorax, pneumomediastinum, interstitial emphysema and subcutaneous emphysema	(+)	Incidental finding	Conservative	Died due to respiratory failure
Carroll et al.[8] 2020	9	Female	Medulloblastoma Neurosurgery	ARDS	Bilateral parahilar infiltrates and consolidation. Diffuse ground glass opacity in the right lung- Pneumomediastinum	(+)	Incidental finding	Conservative	Yes
Bellini et al.[9] 2020	17	Male	Negative	Mild dyspnea	Pneumomediastinum	(+)	2 weeks after acute infection	Nil	Yes
Karande et al.[10] 2021	8	Male	Miliary Tuberculosis	ARDS	Bilateral pneumothorax	(-)	Unknown past infection	Intercostal drainage	Yes

Continued

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Table 1. Continued

Author Year	Age (years)	Sex	Coexisting conditions	Clinical presentation	CT findings	COVID-19 RT-PCR test	Time of presentation	Therapy	Survival
Montgomery et al.[11] 2021	17	Male	Negative	Chest pain, dyspnea	Hemo-pneumothorax	(+)	Incidental finding	Bleb dissection, intercostal drainage	Yes
Quintana-Ortega et al.[12] 2021	11	Female	anti-MDA5 juvenile dermatomyositis	Dry cough, skin rash	Pneumothorax, pneumomediastinum	(+)	Onset of symptoms: 5 days before respiratory deterioration	Multiple immunosuppressive and antibiotic therapy	Died due to Multi-organ system failure
Hashemi et al.[13] 2021	2	Male	Hyper IgM syndrome	Fever, cough, shortness of breath, tachypnoea	Pneumothorax	(+)	4 days after symptomatology beginning	Conservative	Yes
Giné et al.[14] 2020	14	Female	Allergy and asthma during infancy	Chest pain, fever, cough, anosmia, ageusia	Pneumothorax, bullae existence	(+)	11 days after symptomatology beginning	Intercostal drainage, bullae dissection	Yes
Soyak et al.[15] 2022	15	Male	Obesity, asthma	Cardiac arrest	Pneumothorax	Unknown	Unknown	Pleural drainage, mechanical ventilator support	Yes
Blondeau et al.[16] 2022	5	Male	Negative	Cough, right shoulder pain	Pneumothorax, pneumonia prior of pneumothorax, multilobulated cystic pulmonary mass	(+)	5 days after positive COVID test and beginning of symptomatology	Pleural drainage, antibiotic, antiviral therapy	Yes
Stewart et al.[17] 2022	13	Male	Autism	Chest pain, cough	Pneumothorax, pneumonia prior to pneumothorax, multiple bullae formation	Unknown	23 days after symptomatology beginning and on readmission	Pleural drainage	Yes

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Spontaneous pneumothorax is an unusual but potentially life-threatening complication of SARS-CoV-2, with an overall incidence of 5–10 cases per 100000 children younger than 18 years[3]. Spontaneous pneumothorax without evidence of concurrent pneumonia or mechanical injury in children with SARS-CoV-2 infection is not often reported[4]. We describe the case of a 16-year-old boy with pneumothorax and no evidence of pneumonia two weeks after the acute phase of SARS-CoV-2 infection, and we review the relative literature.

CASE PRESENTATION

A 16-year-old boy, previously well, presented with chest pain on the right hemithorax lasting for two hours. He was afebrile, with a cough and respiratory distress. There was no history of trauma, vigorous exercise, or cough in the previous days. There was no history of asthma, cystic fibrosis and connective tissue disorder. Family history was clinically insignificant. Two weeks prior to admission, he reported low-grade fever and mild cough, and a rapid SARS-CoV-2 antigen test was positive. On clinical examination, he was tachypneic (respiration rate 40 breaths/min, SpO2 96%, 140 bpm), and on chest auscultation, absent lung sounds were detected on the right chest base.

Lower respiratory tract infection was ruled out based on the absence of fever, raised inflammatory markers and consolidation on chest x-ray. Polymerase Chain Reaction (PCR) was positive for SARS-CoV-2, with a cycle threshold of ORF 26/N 27. Since there were no signs of respiratory distress and oxygen requirements, ARDS was excluded. Pulmonary embolism was a minor consideration, but the patient did not have any predisposing risk factors or CT chest findings consistent with it. Myocardial ischemia, myocarditis, pericarditis, and aortic dissection were included in the differential diagnosis. However, the pain characteristics, negative biochemistry (CK-MB, troponin), and normal ECG have excluded these diagnoses. Marfan syndrome was included in the differential diagnosis since the patient was tall and slender with a BMI of approximately 18 kg/m^2. Nevertheless, a heart ECHO was performed and was reported as normal. Additionally, an ophthalmological examination excluded lens abnormalities. There was no pain on chest palpation; hence, the diagnosis of costochondritis was excluded. Chest X-ray has confirmed the presence of pneumothorax (Figure 1A). Based on the clinical history, examination and initial investigations, no further laboratory tests were performed for rheumatological and inflammatory conditions, since the diagnosis of secondary spontaneous pneumothorax associated with SARS-CoV-2 infection was made.

Subsequently, a chest drain was inserted, and symptoms improved. The chest drain remained for eight days till the complete resolution of pneumothorax (Figure 1 A and B).

DISCUSSION

Based on this case, we have conducted a literature review in PubMed and Google Scholar using the following search terms: SARS-CoV-2, COVID-19, spontaneous pneumothorax, pneumomediastinum, risk factors, predisposing factors, death, children, and adolescents. After searching for pneumothorax as a complication of SARS-CoV-2 infection, we have identified sixteen cases of children/adolescents with spontaneous pneumothorax and SARS-CoV-2 infection (Table 1)[4-17].

Epidemiological and clinical characteristics of children with spontaneous pneumothorax following SARS-CoV-2 infection are presented in Table 1. Most of the reported children in the literature were males (12/16) with a mean age 10.6 ± 6 years and a median age of 12.0 years. Only four cases exhibited spontaneous pneumothorax after the onset of SARS-CoV-2 infection symptoms. The time interval between the beginning of infection symptoms and the pneumothorax presentation was 10 to 23 days. All these four patients were adolescents, but only one was female, who was also the only one with pre-existing conditions, such as allergies and asthma. Underlying medical conditions were described in 9/16 children.

Seven children were identified with symptoms of spontaneous pneumothorax without clearly specifying the chronological relationship between active infection and pneumothorax symptoms. Six of them had positive PCR for SARS-CoV-2, and the seventh had a negative test. The latter patient's current clinical presentation was attributed to COVID-19 because of the existence of positive SARS-CoV-2 IgG serum antibodies. Seven of the patients were referred with chest pain, and ten with respiratory distress. Only two male patients presented with unilateral pneumothorax. A 17-year-old male had hemopneumothorax. In the other five reported cases, pneumothorax was combined with pneumomediastinum, and a 17-year-old male was diagnosed with pneumothorax, pneumomediastinum, and pneumorrachis. A 9-year-old female with a clinical history of medulloblastoma and a 9-month-old male with a history of epilepsy had consolidations and infiltrates along with pneumomediastinum. A 17-year-old adolescent had shown radiological signs of a lung infection after the onset of pneumothorax, and two patients had radiological findings of pneumonia prior to the appearance of pneumothorax. Three patients were reported with bullae coexistence. One patient had a history of miliary tuberculosis. One patient who had pre-existing asthma and obesity developed severe pneumothorax on the base of decreased lung function and was intubated and ventilated due to cardiorespiratory arrest. Three patients who died were females with associated connective tissue disorders, such as multiple sclerosis and juvenile dermatomyositis, and one was a male with urosepsis. Nine patients underwent intercostal drainage, and the rest of the reported cases (seven patients) were treated conservatively.

Here we reported the case of spontaneous pneumothorax following SARS-CoV-2 infection (secondary spontaneous

pneumothorax). In the literature, several adult cases of delayed or secondary spontaneous pneumothorax following SARS-CoV-2 infection have been reported and are associated with SARS-CoV-2 pneumonia and mechanical ventilation[4]. Spontaneous pneumothorax has been documented only in a few cases of a previously healthy adolescent.

Most patients who developed pneumothorax associated with COVID-19 infection were males. In children, the incidence of spontaneous pneumothorax is estimated to be 4.0/100000 population per year in males and 1.1/100000 population per year in females[18]. Male predominance in spontaneous pneumothorax has been previously referred to in the literature with a female/male ratio of 1:3.3[19]. Secondary pneumothorax has an even greater predominance in males.

In the published cases, nine patients were found to suffer from underlying conditions, but only in six of them, the underlying condition could have affected the lungs, hence predisposing them to pneumothorax. Two patients had asthma, and one patient had dermatomyositis, systemic sclerosis, hyper IgM syndrome, and miliary tuberculosis. Connective tissue disorders such as Marfan syndrome and Ehlers-Danlos syndrome, homocystinuria, asthma, cystic fibrosis, a1-antitrypsin deficiency, chronic obstructive pulmonary disease, cystic disorders of the lungs and malignancies are associated with pneumothorax[20-23]. Hyper IgM syndrome is associated with bronchiectasis and a decline in lung function, whereas scleroderma and dermatomyositis can be complicated by interstitial lung disease[24,25]. Medulloblastoma is associated with lung metastasis; nevertheless, this has not been reported in the case by Carroll et al.[8]. In adults, the incidence of spontaneous pneumothorax in all hospitalized patients is 0.3% to 1%, in hospitalized patients with pneumonia, it is 3%, and in patients who underwent mechanical ventilation, it is 12% to 23%[26,27]. However, the presence of SARS-CoV-2 infection in a patient with underlying pulmonary disease could have triggered pneumothorax. The pathophysiological mechanism is not clear, but the hyperproduction of cytokines and exaggerated immune response caused by the viral infection may contribute to pneumothorax forming, especially when there is underlying lung pathology[26-28].

In the previously reported cases, two female patients with connective tissue disorders and pneumothorax died, whereas one male patient with immunodeficiency survived. Autoimmune diseases are known risk factors for SARS-CoV-2 complications due to the presence of a hyper-inflammatory state[29]. The two patients who suffered from juvenile dermatomyositis and systemic sclerosis had both severe predisposing lung involvement since the first had *Pneumonocystis jirovecci* infection and the second had respiratory complications of autoimmunity. Shields et al.19 have reported that adult patients with primary immunodeficiency and symptomatic secondary immunodeficiency display greater morbidity from SARS-CoV-2, particularly if they have associated chronic lung and/or liver disease. Nevertheless, the authors have reported that children with controlled immunodeficiency have lower morbidity compared to the adult population.

In the literature, there are no data to estimate the risk of death due to the coexistence of pneumothorax and SARS-CoV-2 infection in children. Data from adults report older age, male gender, obesity and comorbidities as risk factors for disease severity[21,30]. Laaribi et al.[6], however, reported two cases of SARS-CoV-2 infection in infants and pneumothorax, but only one has survived. The infant who did not survive died from urosepsis, which can be explained by the susceptibility of the immature immune system to more severe inflammation and infection. In the study by Soyak et al.[15], the presence of obesity and asthma in a 15-year-old male adolescent resulted in decreased lung function, which in turn was a risk factor for life-threatening pneumothorax in a child with SARS-Cov-2 infection. In many cases, a SARS-CoV-2 positive test is coincidental and is not considered a risk factor for severe disease due to pneumothorax[30]. The coexistence of neuro disability and respiratory condition further increases the mortality risk; nevertheless, the authors have not described in detail if pneumothorax was included in the respiratory condition[31].

ARDS, dyspnea, and chest pain were reported as the most common presenting symptoms in adolescents. Adult patients report chest pain as the most specific and common symptom at the onset of the disease[32].

CONCLUSION

Spontaneous pneumothorax is a very rare complication during SARS-CoV-2 infection in the pediatric population. It can present up to 4 weeks after the acute onset of the infection. In most cases, no history of preceding lung disease exists. Younger age, underlying respiratory conditions and connective tissue disorder are previously described as risk factors for more severe clinical presentation. Clinicians should be vigilant for pneumothorax diagnosis when a child presents with chest pain and positive SARS-CoV-2 infection history.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported.

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DATA AVAILABILITY

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AUTHORS' CONTRIBUTIONS

All authors were responsible for conceptualization, literature research, creation of table, and writing and revising the manuscript. All authors approved the final version of the manuscript.

REFERENCES

1. Parri N, Lenge M, Buonsenso D; Coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) Research Group. Children with Covid-19 in Pediatric Emergency Departments in Italy. N Engl J Med. 2020;383(2):187-190. doi:10.1056/NEJMc2007617
2. Onuki T, Ueda S, Yamaoka M, et al. Primary and Secondary Spontaneous Pneumothorax: Prevalence, Clinical Features, and In-Hospital Mortality. Can Respir J. 2017;2017:6014967. doi:10.1155/2017/6014967
3. Goldman RD. Spontaneous pneumothorax in children. Can Fam Physician. 2020;66(10):737-738. Accessed November 21, 2023. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7571650/pdf/0660737.pdf
4. Buonsenso D, Gatto A, Graglia B, et al. Early spontaneous pneumothorax, pneumomediastinum and pneumorrhachis in an adolescent with SARS-CoV-2 infection. Eur Rev Med Pharmacol Sci. 2021;25(12):4413-4417. doi:10.26355/eurrev_202106_26152
5. Musolino AM, Boccuzzi E, Supino MC, et al. Point-of-care lung ultrasound in the diagnosis and monitoring of paediatric patients with spontaneous pneumothorax in SARS-CoV-2 infection. J Paediatr Child Health. 2021;57(5):604-606. doi:10.1111/jpc.15410
6. Laaribi I, Mimouni H, Bouayed Z, et al. Bilateral spontaneous pneumothorax in critically-ill COVID-19 infants: About two cases. Ann Med Surg (Lond). 2022;73:103172. doi:10.1016/j.amsu.2021.103172
7. Oterino Serrano C, Alonso E, Andrés M, et al. Pediatric chest x-ray in covid-19 infection. Eur J Radiol. 2020;131:109236. doi:10.1016/j.ejrad.2020.109236
8. Carroll AG, Quinn N, Byrne C, Kassab G, Whelan S, Colleran GC. Pneumomediastinum in a child with severe COVID-19. BJR Case Rep. 2020;7(1):20200062. doi:10.1259/bjrcr.20200062
9. Bellini D, Lichtner M, Vicini S, Rengo M, Ambrogi C, Carbone I. Spontaneous pneumomediastinum as the only CT finding in an asymptomatic adolescent positive for COVID-19. BJR Case Rep. 2020;6(3):20200051. doi:10.1259/bjrcr.20200051
10. Karande S, Mahalawat S, Muranjan M. Spontaneous pneumothoraces complicating acute miliary tuberculosis in a child having recent coronavirus disease 2019. J Postgrad Med. 2021;67(3):177-179. doi:10.4103/jpgm.JPGM_338_21
11. Montgomery AB, Finck C. Spontaneous hemopneumothorax in an adolescent with COVID-19. J Pediatr Surg Case Rep. 2021;69:101852. doi:10.1016/j.epsc.2021.101852
12. Quintana-Ortega C, Remesal A, Ruiz de Valbuena M, et al. Fatal outcome of anti-MDA5 juvenile dermatomyositis in a paediatric COVID-19 patient: a case report. Mod Rheumatol Case Rep. 2021;5(1):101-107. doi:10.1080/24725625.2020.1832755
13. Hashemi SM, Esfahanian N, Ahmadizadeh S, et al. Spontaneous Pneumothorax in a Child with COVID-19. Arch Pediatr Infect Dis. 2022;10(Suppl):e114691. doi:10.5812/pedinfect.114691
14. Giné C, Laín A, García L, López M. Thoracoscopic Bullectomy for Persistent Air Leak in a 14-Year-Old Child with COVID-19 Bilateral Pulmonary Disease. J Laparoendosc Adv Surg Tech A. 2020;30(8):935-938. doi:10.1089/lap.2020.0289
15. Soyak Aytekin E, Sahiner UM, Tuten Dal S, et al. Obesity is a risk factor for decrease in lung function after COVID-19 infection in children with asthma. Pediatr Pulmonol. 2022;57(7):1668-1676. doi:10.1002/ppul.25949
16. Blondeau-Lecomte E, Joseph N. A pneumothorax in the setting of COVID-19 associated pneumatoceles in a pediatric patient. Pediatr Pulmonol. 2022;57(7):1806-1808. doi:10.1002/ppul.25936
17. Stewart B, Alleyne T. Does autism add an extra layer of complexity in a child with COVID-19, blebs, bullae, and pneumothorax? Chest. 2022;161(6):A385. doi:10.1016/j.chest.2021.12.415
18. Savitsky E, Oh SS, Lee JM. The Evolving Epidemiology and Management of Spontaneous Pneumothorax. JAMA. 2018;320(14):1441-1443. doi:10.1001/jama.2018.12878
19. Bobbio A, Dechartres A, Bouam S, et al. Epidemiology of spontaneous pneumothorax: gender-related differences. Thorax. 2015;70(7):653-658. doi:10.1136/thoraxjnl-2014-206577
20. Shields AM, Burns SO, Savic S, Richter AG; UK PIN COVID-19 Consortium. COVID-19 in patients with primary and secondary immunodeficiency: The United Kingdom experience. J Allergy Clin Immunol. 2021;147(3):870-875.e1. doi:10.1016/j.jaci.2020.12.620
21. Tsankov BK, Allaire JM, Irvine MA, et al. Severe COVID-19 Infection and Pediatric Comorbidities: A Systematic Review and Meta-Analysis. Int J Infect Dis. 2021;103:246-256. doi:10.1016/j.ijid.2020.11.163
22. Wilson PM, Rymeski B, Xu X, Hardie W. An evidence-based review of primary spontaneous pneumothorax in the adolescent population. J Am Coll Emerg Physicians Open. 2021;2(3):e12449. doi:10.1002/emp2.12449
23. Zantah M, Dominguez Castillo E, Townsend R, Dikengil F, Criner GJ. Pneumothorax in COVID-19 disease- incidence and clinical characteristics. Respir Res. 2020;21(1):236. doi:10.1186/s12931-020-01504-y
24. Moazzami B, Yazdani R, Azizi G, et al. Respiratory Complications in Patients with Hyper IgM Syndrome. J Clin

Immunol. 2019;39(6):557-568. doi:10.1007/s10875-019-00650-3
25. Tokunaga K, Hagino N. Dermatomyositis with Rapidly Progressive Interstitial Lung Disease Treated with Rituximab: A Report of 3 Cases in Japan. Intern Med. 2017;56(11):1399-1403. doi:10.2169/internalmedicine.56.7956
26. Chong WH, Saha BK, Hu K, Chopra A. The incidence, clinical characteristics, and outcomes of pneumothorax in hospitalized COVID-19 patients: A systematic review. Heart Lung. 2021;50(5):599-608. doi:10.1016/j.hrtlng.2021.04.005
27. Miró Ò, Llorens P, Jiménez S, et al. Frequency, Risk Factors, Clinical Characteristics, and Outcomes of Spontaneous Pneumothorax in Patients With Coronavirus Disease 2019: A Case-Control, Emergency Medicine-Based Multicenter Study. Chest. 2021;159(3):1241-1255. doi:10.1016/j.chest.2020.11.013
28. Martinelli AW, Ingle T, Newman J, et al. COVID-19 and pneumothorax: a multicentre retrospective case series. Eur Respir J. 2020;56(5):2002697. doi:10.1183/13993003.02697-2020
29. Kastritis E, Kitas GD, Vassilopoulos D, Giannopoulos G, Dimopoulos MA, Sfikakis PP. Systemic autoimmune diseases, anti-rheumatic therapies, COVID-19 infection risk and patient outcomes. Rheumatol Int. 2020;40(9):1353-1360. doi:10.1007/s00296-020-04629-x
30. Ward JL, Harwood R, Smith C, et al. Risk factors for PICU admission and death among children and young people hospitalized with COVID-19 and PIMS-TS in England during the first pandemic year. Nat Med. 2022;28(1):193-200. doi:10.1038/s41591-021-01627-9
31. Smith C, Odd D, Harwood R, et al. Deaths in children and young people in England after SARS-CoV-2 infection during the first pandemic year. Nat Med. 2022;28(1):185-192. doi:10.1038/s41591-021-01578-1
32. Marza AM, Petrica A, Lungeanu D, et al. Risk Factors, Characteristics, and Outcome in Non-Ventilated Patients with Spontaneous Pneumothorax or Pneumomediastinum Associated with SARS-CoV-2 Infection. Int J Gen Med. 2022;15:489-500. doi:10.2147/IJGM.S347178

A case report of late pleural effusion and hemoptysis as a result of pulmonary vein stenosis due to atrial fibrillation ablation

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ABSTRACT

Pulmonary vein stenosis (PVS) constitutes an uncommon complication of radiofrequency ablation for atrial fibrillation (RF-ablation for AF), that remains asymptomatic in most cases. We describe a rare case of a male patient who presented pleural effusion and hemoptysis due to PVS, 4 months after the performance of RF-AF. The present work delignates a peculiar clinical presentation of PVS, describes in detail the patient's clinical course, the pathophysiology and differential diagnosis of secondary to RF-ablation for AF PVS, and aims to highlight the key role of pneumonologists' clinical awareness, for the prompt diagnosis and treatment of the present clinical condition.

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INTRODUCTION

Pleural effusion and hemoptysis may present due to multiple etiological factors, but patients with such clinical manifestations are mainly admitted to the pulmonary department for diagnosis and treatment[1]. Nevertheless, misdiagnosis is likely to happen if doctors are not aware of potential, though peculiar, etiological factors[1-3], such as secondary to AF ablation pulmonary vein stenosis-PVS[1,4].

From a multicenter systematic evaluation, PVS due to AF radiofrequency ablation has a reported incidence of 20.8%, and in the majority of cases, remains asymptomatic[4]. In the presented manuscript, we report a rare case of a man that underwent AF ablation 4 months before, presenting pleural effusion and hemoptysis.

The following case report, written according to the CARE checklist, describes in detail the patient's management and clinical course, and aims to highlight the key role of pneumonologists' clinical awareness, for the prompt diagnosis and treatment of PVS.

CASE PRESENTATION

A 43-year-old Caucasian male, smoker, without occupational exposure to inhaling substances, proceeded to our institution on August 2023, complaining about shortness of breath for the past week. The patient's history included dyslipidemia and depression, treated with atorvastatin and escitalopram 20 mg, respectively. On March 2023, due to atrial fibrillation non-responding to anti-arrhythmic medications, the patient underwent radiofrequency AF ablation. The patient's echocardiography at 3 months post-AF ablation was unremarkable.

The patient's vital signs were: BP 140/90 mmHg, PR 109 beats/minute, SpO_2 89%, and a body temperature of 36.8°C. Clinical examination revealed breath sounds' absence at the right base and dullness to percussion. Subsequent CXR verified right pleural effusion. After a Bülau drainage insertion, 2 L of polymorphonuclear exudate was drained. Pleural fluid cytology was negative for cancer cells. Blood tests revealed increased inflammatory markers (CRP 105 mg/L and mild neutrophilia). The patient was immediately administrated with IV moxifloxacin and admitted for further investigation and treatment.

Upon admission, the patient underwent blood test also for: troponins, CK-MB, antinuclear antibodies, rheumatic factor, native-DNA antibody and anti-extractable nuclear antigen analyses, viral infections (such as SARS-CoV-2, HIV, HBV, HCV, CMV, and EBV), blood cultures collected during fever peaks for infectious diseases (leptospirosis, borreliosis, brucellosis, rickettsiosis), and tumor markers. All the laboratory results were negative. Tuberculin skin testing (TST), blood, and urine sample culture tests were also negative and D-dimers were 6.85 μg/mL.

Subsequent HRCT indicated patchy infiltrates of the right pulmonary basis and the CTPA performed due to elevated D-dimers revealed minor filling defects of segmental vessel branches of the right pulmonary artery, without lesions of pulmonary veins. The patient was treated with antibiotics for the pneumonia, and in agreement with the cardiologists, he was finally discharged the 7th day with rivaroxaban 20 mg od.

After a month, on September 2023, the patient proceeded

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Figure 1. Bleeding revealed during bronchoscopy at the RB9 and RB10

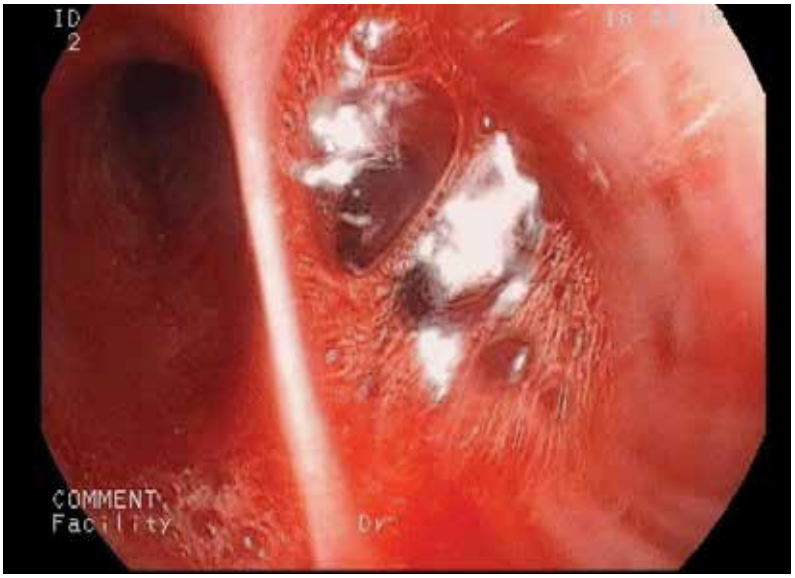
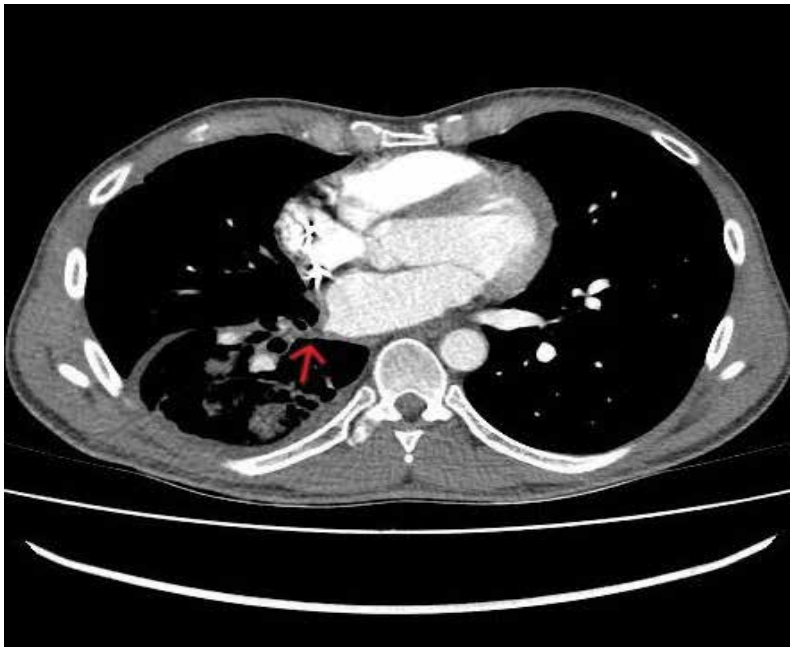


Figure 2. CTA findings, related with post-ablation PVS



once again to our institution complaining about a sole incidence of hemoptysis (<10 cc) and body temperature 37.6℃ for the last 12 hours. Blood tests, urine analysis and blood cultures were unremarkable. CXR did not indicate pleural effusion.

Following these, a bronchoalveolar lavage (BAL) was performed. The bronchial tree anatomy was normal. However, physicians discovered bleeding of RB9 and RB10 (Figure 1). The diagnosis of hemorrhage was confirmed since counting 57% hemosiderin-laden macrophages in BAL fluid. The BAL fluid was negative for common pathogens, Ziehl-Neelsen stain and mucus.

Patient remained asymptomatic and afebrile during admission and treated with piperacillin/tazobactam. The 5th day of hospitalization, he underwent CTA of thoracic aorta and CTV of thoracic veins. The exam revealed severe pulmonary vein stenosis, almost occlusion, which was considered to be a complication of radiofrequency AF ablation due to the patient's history (Figure 2). Afterwards, the patient was admitted to the cardiothoracic surgery department, of another surgical institution where he was scheduled for lobectomy due to his recurrent symptoms of

respiratory infections and hemoptysis. When the patient was discharged, the cardiologic medication remained intact.

In a follow-up appointment after a month, the patient presented with no complications or respiratory symptoms. Physical examination, CXR, blood tests and vital signs were within normal range. Echocardiography was unremarkable.

DISCUSSION

PVS constitutes a rare clinical condition that may be acquired or congenital[1,2]. Congenital PVS is typically presented in childhood, though acquired PVS presents in adults, as a complication of catheter ablation interventions for arrhythmias, including radiofrequency AF ablation[1,2,5-7], rare cases, such as mediastinal tumors[8] and cardiac surgery[7]. From the largest multicenter systematic evaluation, PVS due to AF radiofrequency ablation has an incidence of 20.8%[4].

Although the exact underlying molecular mechanism of PVS remains vague, it is reported that scarring of the pulmonary venous wall, the contraction and the peri-adventitial inflammation of the vein due to the thermal injury provoked by AF ablation, may narrow or even occlude the lumen of the pulmonary vein[2,4].

There are documented predictors of PVS due to AF ablation, such as previous AF ablation and diabetes[1,4]. More specifically, it is reported that diabetes is associated with both structural and electrical remodeling, leading to microvascular and macrovascular complications[4].

In the majority of cases, PVS due to AF ablation is mild or moderate, and remains asymptomatic[4]. The clinical manifestations of PVS vary depending on: 1) the number of pulmonary veins involved, 2) the severity of the stenosis, 3) the response of the pulmonary vasculature to the stenosis, 4) the time course of PVS, 5) the patient's clinical status, and 6) the presence or not of collateral vessels[2]. Patients may present chest pain, dyspnea, orthopnea, cough, pneumonia, recurrent pulmonary infections, and more rarely hemoptysis, as in the presented case[1,2,4].

The incidence of post-ablation PVS may lead to major hemodynamic changes, such as pulmonary hypertension and subsequent complete occlusion of the pulmonary vein[4]. These changes are responsible of the vulnerability to recurrent or/and drug-resistant pulmonary infections, that may present with pleural effusion, as in the presented case[4,5,7]. Hemoptysis, constitutes an infrequent manifestation of PVS, which is related to the increased venous pressure in the pre-stenotic zone and the subsequent lung tissue congestion and bleeding[2].

The diagnosis of PVS is not easily identified, given its rarity, and the variability of its clinical manifestations and non-specific radiological findings[1,4-7]. Differential diagnosis includes other causes of pleural effusion (such as cancer, thoracic mass, and pneumonia), pulmonary embolism[1,3], NOACs, and hemorrhagic pulmonary vasculitis[2]. Common radiological exams, such as CXR and thoracic CT typically demonstrate irrelevant to PVS features[1,2,5].

Herein, CTPA and CTA are of paramount significance when encountering a patient with hemoptysis and previous AF ablation[2,4,5,7]. Indeed, CTA may detect the exact location and extent of probable pulmonary vein stenosis. In addition, following CT-scans, bronchoscopy plays a key role in the differential diagnosis of PVS, especially when encountering a patient with hemoptysis, as in the presented case[2]. Finally, congenital PVS was excluded from the differential diagnosis, since the patient remained asymptomatic through childhood and adulthood, until performing AF ablation.

Post-ablation PVS may be treated via balloon dilatation of the pulmonary vein; however, re-stenosis within 1 year constitutes a common complication, with an incidence of approximately 50%[2]. Therefore, patients with PVS should have regular follow-up and echocardiography[1,2]. In addition, in cases of recurrent episodes of pulmonary infections or respiratory failure or bleeding, as in the presented case, lobectomy should be considered as a therapeutic solution[5,9]. However, the best therapeutic approach is the prevention of PVS[1,4]. This strategy is mostly related to reduction of ablation's temperature and energy, and placing the ablation site from inside to outside the orifice of the pulmonary vein[2].

CONCLUSION

Physicians' clinical awareness is of paramount significance when encountering a patient with pulmonary infection and hemoptysis, who underwent catheter ablation. The presence of pleural effusion and hemoptysis after AF radiofrequency ablation should raise the suspicion of PVS and a CTA should be immediately performed for the prompt diagnosis and the adequate treatment of PVS.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported.

FUNDING

There was no source of funding for this research.

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this study.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer-reviewed.

REFERENCES

1. Zhang G, Yu H, Chen L, Li Y, Liang Z. Pulmonary veins stenosis after catheter ablation of atrial fibrillation as the cause of

haemoptysis: three cases and a literature review. Clin Respir J. 2018;12(1):3-9. doi:10.1111/crj.12501
2. Spadaro S, Saturni S, Cadorin D, et al. An unusual case of acute respiratory failure in a patient with pulmonary veins stenosis late after catheter ablation of atrial fibrillation: a case report and the review of the literature. BMC Pulm Med. 2015;15:128. doi:10.1186/s12890-015-0121-0
3. Jany B, Welte T. Pleural Effusion in Adults-Etiology, Diagnosis, and Treatment. Dtsch Arztebl Int. 2019;116(21):377-386. doi:10.3238/arztebl.2019.0377
4. Samuel M, Khairy P, Mongeon FP, et al. Pulmonary Vein Stenosis After Atrial Fibrillation Ablation: Insights From the ADVICE Trial. Can J Cardiol. 2020;36(12):1965-1974. doi:10.1016/j.cjca.2020.10.013
5. Teunissen C, Velthuis BK, Hassink RJ, et al. Incidence of Pulmonary Vein Stenosis After Radiofrequency Catheter Ablation of Atrial Fibrillation. JACC Clin Electrophysiol. 2017;3(6):589-598. doi:10.1016/j.jacep.2017.02.003
6. De Piccoli B, Rossillo A, Zanella C, et al. Role of transoesophageal echocardiography in evaluating the effect of catheter ablation of atrial fibrillation on anatomy and function of the pulmonary veins. Europace. 2008;10(9):1079-1084. doi:10.1093/europace/eun188
7. Edriss H, Denega T, Test V, Nugent K. Pulmonary vein stenosis complicating radiofrequency catheter ablation for atrial fibrillation: A literature review. Respir Med. 2016;117:215-222. doi:10.1016/j.rmed.2016.06.014
8. Zhang SC, Li RP, Chen JC, et al. Pulmonary vein stenosis with pulmonary infarction secondary to primary mediastinal seminoma: a case report. Article in Chinese. Zhonghua Jie He He Hu Xi Za Zhi. 2023;46(6):592-594. doi:10.3760/cma.j.cn112147-20221026-00847
9. Papakonstantinou NA, Zisis C, Kouvidou C, Stratakos G. Lobectomy due to Pulmonary Vein Occlusion after Radiofrequency Ablation for Atrial Fibrillation. Korean J Thorac Cardiovasc Surg. 2018;51(4):290-292. doi:10.5090/kjtcs.2018.51.4.290

Instructions to authors

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Pneumon considers the following types of articles:

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- Short Reports – brief reports of data from original research.
- Methodology Papers – papers that present different methodological approaches that can be used to investigate problems in a relevant scientific field and to encourage innovation.
- Case Reports – reports and data from interesting cases.
- Images in Pulmonology – images that are related to interesting cases.
- Letters to the Editor – a response to authors of an original publication, or a very small article that may be relevant to readers.
- Editorials – invited articles, or articles written by members of the Editorial Board.

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Articles reporting research may be full length or brief reports. These should report original research findings within the journal's scope. Papers should generally be a maximum of 4000 words in length, excluding tables, references, and abstract and key points of the article, whilst it is recommended that the number of references should not exceed 36.

Review Papers

Comprehensive, authoritative, reviews within the journal's scope. There are two types of review papers:

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Case reports (or clinical case studies) are reports that may refer to classical or rare conditions, their diagnosis and management, as well as feature novel findings, or encourage new management strategies. Cases that focus on key aspects of background pulmonology are also considered important. Case reports usually focus on a valuable clinical lesson, and their text should not exceed 1500 words, excluding references and tables. It is recommended that the number of references should not exceed 15, and a maximum of 3 tables & figures (in total) is preferred. Abstracts for care reports should be unstructured and not more than 250 words. The suggested format for case reports is Introduction, Case Presentation and Conclusion. Depending on their interest and originality, case reports may include a commentary or discussion on the case presented. Generally, it is suggested that case reports follow the CARE Checklist guidelines (https://www.care-statement.org/checklist). Informed consent is required for this type of submissions.

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1. A short introduction which should end with the study's aims. The introduction should state clearly the objective of the paper as well as the context of the research or analysis.
2. A methods section which should describe the study design, setting, participants, measures, variables and statistical analysis performed. This section should also include information on the study's ethics procedures.
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Acknowledgements

This section is for acknowledging individuals and institutions whose support the authors wish to mention (it is not compulsory). Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials. The Acknowledgements section should be kept to a minimum.

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Funding

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Σύντομη Περίληψη Χαρακτηριστικών του Προϊόντος RELVAR Ellipta 92/22 μg

1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ:
Relvar Ellipta 92 μικρογραμμάρια/22 μικρογραμμάρια κόνις για εισπνοή σε δόσεις.

2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ:
Η παρεχόμενη δόση κάθε εφάπαξ εισπνοής (η δόση που εξέρχεται από το επιστόμιο) είναι 92 μικρογραμμάρια φουροϊκής φλουτικαζόνης και 22 μικρογραμμάρια βιλαντερόλης (ως trifenatate). Αυτό αντιστοιχεί σε προκαθορισμένη δόση 100 μικρογραμμαρίων φουροϊκής φλουτικαζόνης και 25 μικρογραμμαρίων βιλαντερόλης (ως trifenatate). Έκδοχα με γνωστές δράσεις: Κάθε παρεχόμενη δόση περιέχει περίπου 25 mg λακτόζης (μονοϋδρική). Για τον πλήρη κατάλογο των εκδόχων, βλ. παράγραφο 6.1

3. ΦΑΡΜΑΚΕΥΤΙΚΗ ΜΟΡΦΗ:
Κόνις για εισπνοή, σε δόσεις (Κόνις για εισπνοή). Λευκή κόνις σε συσκευή εισπνοών χρώματος ανοικτού γκρι, με κάλυμμα επιστομίου χρώματος κίτρινου και δοσομετρητή.

4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ:

4.1 Θεραπευτικές ενδείξεις:
Άσθμα: Το Relvar Ellipta ενδείκνυται για την τακτική αντιμετώπιση του άσθματος σε ενήλικες και εφήβους ηλικίας 12 ετών και άνω στους οποίους η χρήση ενός φαρμακευτικού προϊόντος συνδυασμού (μακράς δράσης β_2–αγωνιστής και εισπνεόμενο κορτικοστεροειδές) είναι κατάλληλη.
• ασθενείς που δεν ελέγχονται επαρκώς με εισπνεόμενα κορτικοστεροειδή και «κατ' επίκληση» εισπνεόμενους βραχείας δράσης β_2–αγωνιστές.
• ασθενείς που έχουν ήδη ελεγχθεί επαρκώς με εισπνεόμενο κορτικοστεροειδές και με β_2–αγωνιστή μακράς δράσης.
ΧΑΠ (Χρόνια Αποφρακτική Πνευμονοπάθεια): Το Relvar Ellipta ενδείκνυται για τη συμπτωματική αντιμετώπιση ενηλίκων με ΧΑΠ με FEV1<70% της προβλεπόμενης φυσιολογικής τιμής (μετά από χρήση βρογχοδιασταλτικού) με ιστορικό παροξυσμών παρά την τακτική θεραπεία με βρογχοδιασταλτικά.

4.2 Δοσολογία και τρόπος χορήγησης:
Δοσολογία: *Άσθμα:* Οι ασθενείς με άσθμα θα πρέπει να λαμβάνουν το Relvar Ellipta στην περιεκτικότητα που περιέχει την κατάλληλη δόση φουροϊκής φλουτικαζόνης (FF) για τη σοβαρότητα της νόσου τους. Οι συνταγογράφοι θα πρέπει να γνωρίζουν ότι σε ασθενείς με άσθμα, 100 μικρογραμμάρια φουροϊκής φλουτικαζόνης (FF) άπαξ ημερησίως ισοδυναμούν με περίπου 250 μικρογραμμάρια προπιονικής φλουτικαζόνης (FP) δύο φορές την ημέρα, ενώ 200 μικρογραμμάρια FF άπαξ ημερησίως ισοδυναμούν με περίπου 500 μικρογραμμάρια FP δύο φορές την ημέρα. *Ενήλικες και έφηβοι ηλικίας 12 ετών και άνω:* Θα πρέπει να εξετάζεται χορήγηση αρχικής δόσης μίας εισπνοής Relvar Ellipta 92/22 μικρογραμμαρίων άπαξ ημερησίως για ενήλικες και εφήβους ηλικίας 12 ετών και άνω που απαιτούν μία χαμηλή έως μεσαία δόση εισπνεόμενου κορτικοστεροειδούς σε συνδυασμό με ένα μακράς δράσης β_2–αγωνιστή. Αν οι ασθενείς δεν ελέγχονται επαρκώς με το Relvar Ellipta των 92/22 μικρογραμμαρίων η δόση μπορεί να αυξηθεί σε 184/22 μικρογραμμάρια, η οποία μπορεί να παρέχει πρόσθετη βελτίωση στον έλεγχο του άσθματος. Οι ασθενείς θα πρέπει να επαναξιολογούνται τακτικά από επαγγελματία του τομέα υγειονομικής περίθαλψης, ώστε η περιεκτικότητα του συνδυασμού φουροϊκής φλουτικαζόνης/βιλαντερόλης που λαμβάνουν να εξακολουθεί να είναι η βέλτιστη και μεταβάλλεται μόνο μετά από ιατρική συμβουλή. Η δόση θα πρέπει να μειώνεται στο χαμηλότερο επίπεδο με το οποίο διατηρείται αποτελεσματικός έλεγχος των συμπτωμάτων. Το Relvar Ellipta 184/22 μικρογραμμαρίων θα πρέπει να εξετάζεται για ενήλικες και εφήβους ηλικίας 12 ετών και άνω που απαιτούν υψηλότερη δόση εισπνεόμενου κορτικοστεροειδούς σε συνδυασμό με ένα μακράς δράσης β_2–αγωνιστή. Οι ασθενείς συνήθως εμφανίζουν βελτίωση της πνευμονικής λειτουργίας εντός 15 λεπτών από την εισπνοή του Relvar Ellipta. Ωστόσο, ο ασθενής πρέπει να ενημερώνεται ότι η τακτική καθημερινή χρήση είναι απαραίτητη για τη διατήρηση του ελέγχου των συμπτωμάτων του άσθματος και ότι η χρήση πρέπει να συνεχιστεί ακόμα και όταν είναι ασυμπτωματικός. Εάν προκύψουν συμπτώματα κατά την περίοδο μεταξύ των δόσεων, για την άμεση ανακούφιση θα πρέπει να χρησιμοποιηθεί ένας εισπνεόμενος β_2-αγωνιστής βραχείας δράσης. *Παιδιά ηλικίας κάτω των 12 ετών:* Η ασφάλεια και η αποτελεσματικότητα του Relvar Ellipta σε παιδιά ηλικίας κάτω των 12 ετών δεν έχουν ακόμα τεκμηριωθεί για την ένδειξη του άσθματος. Δεν υπάρχουν διαθέσιμα δεδομένα.
ΧΑΠ: Ενήλικες από 18 ετών και άνω: Μία εισπνοή Relvar Ellipta 92/22 μικρογραμμαρίων άπαξ ημερησίως. Το Relvar Ellipta 184/22 μικρογραμμαρίων δεν ενδείκνυται για ασθενείς με ΧΑΠ. Δεν υπάρχει πρόσθετο όφελος από τη δόση των 184/22 μικρογραμμαρίων σε σύγκριση με τη δόση των 92/22 μικρογραμμαρίων και υπάρχει πιθανότητα αυξημένου κινδύνου εμφάνισης πνευμονίας και συστηματικών ανεπιθύμητων ενεργειών που σχετίζονται με τα κορτικοστεροειδή (βλέπε παραγράφους 4.4 και 4.8). Οι ασθενείς συνήθως παρουσιάζουν βελτίωση της πνευμονικής λειτουργίας εντός 16-17 λεπτών από την εισπνοή του Relvar Ellipta. *Παιδιατρικός πληθυσμός:* Δεν υπάρχει σχετική χρήση του Relvar Ellipta στον παιδιατρικό πληθυσμό για την ένδειξη ΧΑΠ.
Ειδικοί πληθυσμοί: *Ηλικιωμένοι (>65 ετών)*: Δεν απαιτείται προσαρμογή της δόσης στον συγκεκριμένο πληθυσμό (βλέπε παράγραφο 5.2). *Νεφρική δυσλειτουργία:* Δεν απαιτείται προσαρμογή της δόσης στον συγκεκριμένο πληθυσμό (βλέπε παράγραφο 5.2). *Ηπατική δυσλειτουργία:* Μελέτες σε άτομα με ήπια, μέτρια και σοβαρή ηπατική δυσλειτουργία έδειξαν αύξηση της συστηματικής έκθεσης στη φουροϊκή φλουτικαζόνη (C_{max} και AUC) (βλέπε παράγραφο 5.2). Πρέπει να επιδεικνύεται προσοχή κατά τη χορήγηση σε ασθενείς με ηπατική δυσλειτουργία, οι οποίοι μπορεί να διατρέχουν μεγαλύτερο κίνδυνο εμφάνισης συστηματικών ανεπιθύμητων ενεργειών που σχετίζονται με τα κορτικοστεροειδή. Για ασθενείς με μέτρια έως σοβαρή ηπατική δυσλειτουργία η μέγιστη δόση είναι 92/22 μικρογραμμάρια (βλέπε παράγραφο 4.4).
Τρόπος χορήγησης: Το Relvar Ellipta είναι αποκλειστικά για εισπνεόμενη χρήση. Θα πρέπει να χορηγείται την ίδια ώρα της ημέρας κάθε μέρα. Η τελική απόφαση σχετικά με τη χορήγηση βραδινής ή πρωινής δόσης θα πρέπει να λαμβάνεται σύμφωνα με την κρίση του ιατρού. Εάν παραλειφθεί μία δόση, η επόμενη δόση θα πρέπει να ληφθεί στη συνήθη ώρα την επόμενη ημέρα. Εάν φυλάσσεται σε ψυγείο, η συσκευή εισπνοών θα πρέπει να αφήνεται να επανέλθει σε θερμοκρασία δωματίου τουλάχιστον μία ώρα πριν από τη χρήση. Όταν η συσκευή εισπνοών χρησιμοποιείται για πρώτη φορά, δεν υπάρχει ανάγκη ελέγχου της σωστής λειτουργίας ή ανάγκη ειδικής προετοιμασίας για τη χρήση. Θα πρέπει να ακολουθούνται οι αναλυτικές οδηγίες. Η συσκευή εισπνοών Ellipta συσκευάζεται σε ένα δίσκο που περιέχει ένα φακελίσκο με αφυγραντικό για μείωση της υγρασίας. Ο φακελίσκος με το αφυγραντικό πρέπει να απορρίπτεται και δεν πρέπει να ανοίγεται, να καταναλώνεται ή να εισπνέεται. Ο ασθενής πρέπει να συμβουλεύεται να μην ανοίξει το δίσκο μέχρι να είναι έτοιμος να εισπνεύσει τη δόση. Όταν η συσκευή εισπνοών αφαιρείται από το δίσκο της, θα βρίσκεται στην «κλειστή» θέση. Η ημερομηνία "Απορρίψτε μετά από" πρέπει να είναι γραμμένη στην ετικέτα της συσκευής εισπνοών στο χώρο που παρέχεται. Η ημερομηνία "Απορρίψτε μετά από" είναι 6 εβδομάδες από την ημερομηνία ανοίγματος του δίσκου. Μετά την ημερομηνία αυτή η συσκευή εισπνοών δεν θα πρέπει πλέον να χρησιμοποιείται. Ο δίσκος μπορεί να απορριφθεί μετά το πρώτο άνοιγμα. Μετά την εισπνοή, οι ασθενείς θα πρέπει να ξεπλένουν το στόμα τους με νερό χωρίς να καταπιούν. Οι αναλυτικές οδηγίες που ακολουθούν για τη συσκευή εισπνοών Ellipta 30 δόσεων (επαρκεί για 30 ημέρες) ισχύουν επίσης και για τη συσκευή εισπνοών Ellipta των 14 δόσεων (επαρκεί για 14 ημέρες).
Οδηγίες χρήσεως. **1. Διαβάστε αυτές τις οδηγίες πριν ξεκινήσετε:** Αν το κάλυμμα της συσκευής εισπνοών ανοιχτεί και κλειστεί χωρίς να εισπνευστεί το φάρμακο, η δόση θα χαθεί. Η χαμένη δόση θα παραμείνει με ασφάλεια στο εσωτερικό της συσκευής εισπνοών, αλλά δεν θα είναι πλέον διαθέσιμη για εισπνοή. Δεν είναι δυνατή η τυχαία λήψη επιπλέον ποσότητας φαρμάκου ή διπλής δόσης με μία εισπνοή. **Κάλυμμα** Κάθε φορά που το ανοίγετε, ετοιμάζεται μία δόση του φαρμάκου. **Δοσομετρητής** Δείχνει πόσες δόσεις φαρμάκου απομένουν στην συσκευή εισπνοών. Πριν από την αρχική χρήση της συσκευής εισπνοών δείχνει ακριβώς 30 δόσεις. Μετράει αντίστροφα κατά 1 κάθε φορά που ανοίγεται το κάλυμμα. Όταν έχουν απομείνει λιγότερες από 10 δόσεις, το μισό τμήμα του δοσομετρητή εμφανίζεται κόκκινο. Αφότου χρησιμοποιήσετε την τελευταία δόση, το μισό τμήμα του δοσομετρητή εμφανίζεται κόκκινο και αναγράφεται ο αριθμός 0. Η συσκευή εισπνοών σας είναι πλέον άδεια. Αν ανοίξετε το κάλυμμα μετά από αυτό, το χρώμα του δοσομετρητή θα αλλάξει από μισό κόκκινο σε όλο κόκκινο. ***2. Τρόπος προετοιμασίας της δόσης.*** Ανοίξτε το κάλυμμα όταν είσαστε έτοιμοι να εισπνεύσετε μία δόση. Μην ανακινείτε τη συσκευή εισπνοών. Μετακινήστε το κάλυμμα προς τα κάτω μέχρι να ακουστεί ένα «κλικ». Το φάρμακο είναι πλέον έτοιμο για εισπνοή. Ο δοσομετρητής μετρά αντίστροφα κατά 1 για επιβεβαίωση. Αν ο δοσομετρητής δεν μετρήσει αντίστροφα καθώς ακούγεται το «κλικ», το φάρμακο δεν θα χορηγηθεί από τη συσκευή εισπνοών. Επιστρέψτε τη σε ένα φαρμακοποιό για να σας συμβουλεύσει.
3. Πώς να εισπνεύσετε το φάρμακο. Κρατήστε τη συσκευή εισπνοών μακριά από το στόμα σας και εκπνεύστε στο βαθμό που αισθάνεστε άνετα. Μην εκπνέετε μέσα στη συσκευή εισπνοών. Τοποθετήστε το επιστόμιο ανάμεσα στα χείλη σας και κλείστε τα χείλη σας σφιχτά γύρω από αυτό. Μην φράζετε τους αεραγωγούς με τα δάχτυλά σας. Πάρτε μία μακρά, σταθερή, βαθιά εισπνοή. Κρατήστε την αναπνοή σας όσο το δυνατόν περισσότερο (τουλάχιστον 3 4 δευτερόλεπτα). Απομακρύνετε τη συσκευή εισπνοών από το στόμα σας. Εκπνεύστε αργά και απαλά. Είναι πιθανό να μην μπορέσετε να γευτείτε ή να αισθανθείτε το φάρμακο, ακόμη και όταν χρησιμοποιείτε τη συσκευή εισπνοών σωστά. Εάν θέλετε να καθαρίσετε το επιστόμιο της συσκευής εισπνοών, χρησιμοποιήστε ένα στεγνό χαρτομάντιλο, πριν το κλείσιμο του καλύμματος. ***4. Κλείστε τη συσκευή εισπνοών και ξεπλύνετε το στόμα σας.*** Σπρώξτε το κάλυμμα προς τα επάνω όσο περισσότερο γίνεται για να καλύψετε το επιστόμιο. Ξεπλύνετε το στόμα σας με νερό μετά τη χρήση της συσκευής εισπνοών, μην το καταπιείτε. Αυτό θα μειώσει την πιθανότητα εμφάνισης ανεπιθύμητων ενεργειών όπως ο ερεθισμός του στόματος ή του φάρυγγα.
4.3 Αντενδείξεις: Υπερευαισθησία στις δραστικές ουσίες ή σε κάποιο από τα έκδοχα που αναφέρονται στην παράγραφο 6.1.
4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση. Επιδείνωση νόσου. Ο συνδυασμός φουροϊκής φλουτικαζόνης/βιλαντερόλης δεν πρέπει να χρησιμοποιείται για την αντιμετώπιση οξέων συμπτωμάτων άσθματος ή οξέος παροξυσμού της ΧΑΠ, που απαιτούν ένα βραχείας δράσης βρογχοδιασταλτικό παράγοντα. Η αυξανόμενη χρήση βρογχοδιασταλτικών βραχείας δράσης για την ανακούφιση από συμπτώματα υποδηλώνει επιδείνωση του ελέγχου και οι ασθενείς θα πρέπει να επανεξετάζονται από ιατρό. Οι ασθενείς δεν θα πρέπει να σταματούν τη θεραπεία με το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης για την αντιμετώπιση του άσθματος ή της ΧΑΠ, χωρίς ιατρική επίβλεψη καθώς τα συμπτώματα μπορεί να επανεμφανιστούν μετά τη διακοπή. Σοβαρά ανεπιθύμητα συμβάντα που σχετίζονται με το άσθμα και παροξυσμοί μπορεί να εκδηλωθούν κατά τη διάρκεια της θεραπείας με το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης. Θα πρέπει να ζητηθεί από τους ασθενείς να συνεχίσουν τη θεραπεία αλλά να ζητήσουν ιατρική συμβουλή εάν τα συμπτώματα του άσθματος παραμένουν εκτός ελέγχου ή εάν επιδεινωθούν μετά την έναρξη της θεραπείας με Relvar Ellipta. Παράδοξος βρογχόσπασμος: Μετά τη χορήγηση της δόσης μπορεί να εμφανιστεί παράδοξος βρογχόσπασμος συνοδευόμενος από μία άμεση αύξηση του συριγμού. Αυτό θα πρέπει να αντιμετωπιστεί άμεσα με εισπνεόμενο βρογχοδιασταλτικό βραχείας δράσης. Το Relvar Ellipta θα πρέπει να διακοπεί άμεσα και να αξιολογηθεί ο ασθενής και, αν κριθεί απαραίτητο, να ξεκινήσει εναλλακτική θεραπεία. Καρδιαγγειακές επιδράσεις: Καρδιαγγειακές επιδράσεις όπως καρδιακές αρρυθμίες, π.χ. υπερκοιλιακή ταχυκαρδία και έκτακτες συστολές μπορεί να παρατηρηθούν με συμπαθομιμητικά φαρμακευτικά προϊόντα συμπεριλαμβανομένου του Relvar Ellipta. Σε μια ελεγχόμενη με εικονικό φάρμακο μελέτη σε συμμετέχοντες με μέτρια ΧΑΠ και ιστορικό ή αυξημένο κίνδυνο εμφάνισης καρδιαγγειακής νόσου, δεν παρατηρήθηκε αύξηση του κινδύνου καρδιαγγειακών επεισοδίων στους ασθενείς που λάμβαναν φουροϊκή φλουτικαζόνη/βιλαντερόλη έναντι αυτών που λάμβαναν εικονικό φάρμακο (βλέπε παράγραφο 5.1). Ωστόσο, ο συνδυασμός φουροϊκής φλουτικαζόνης/βιλαντερόλης θα πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με σοβαρή καρδιαγγειακή νόσο ή ανωμαλίες του καρδιακού ρυθμού, θυρεοτοξίκωση, μη διορθωμένη υποκαλιαιμία ή σε ασθενείς με προδιάθεση για χαμηλά επίπεδα καλίου στον ορό. Ασθενείς με ηπατική δυσλειτουργία: Για ασθενείς με μέτρια έως σοβαρή ηπατική δυσλειτουργία θα πρέπει να χρησιμοποιείται η δόση των 92/22 μικρογραμμαρίων και οι ασθενείς θα πρέπει να παρακολουθούνται για την εμφάνιση συστηματικών ανεπιθύμητων ενεργειών που σχετίζονται με τα κορτικοστεροειδή (βλέπε παράγραφο 5.2). Συστηματικές επιδράσεις κορτικοστεροειδών: Συστηματικές επιδράσεις μπορεί να παρουσιαστούν με οποιοδήποτε εισπνεόμενο κορτικοστεροειδές, ιδιαίτερα αν χορηγείται σε υψηλές δόσεις για μεγάλες περιόδους. Αυτές οι επιδράσεις είναι πολύ λιγότερο πιθανό να συμβούν σε σχέση με τα από του στόματος κορτικοστεροειδή. Οι πιθανές συστηματικές επιδράσεις περιλαμβάνουν σύνδρομο Cushing, χαρακτηριστικά συνδρόμου που προσομοιάζει με σύνδρομο Cushing, καταστολή των επινεφριδίων, μείωση της οστικής πυκνότητας, καθυστερημένη ανάπτυξη σε παιδιά και εφήβους, καταρράκτης και γλαύκωμα και σπανιότερα μία σειρά ψυχολογικών ή συμπεριφορικών επιδράσεων συμπεριλαμβανομένων ψυχοκινητικής υπερδραστηριότητας, διαταραχές ύπνου, άγχος, κατάθλιψη ή επιθετικότητα (ιδιαίτερα σε παιδιά). Ο συνδυασμός φουροϊκής φλουτικαζόνης/βιλαντερόλης θα πρέπει να χορηγείται με προσοχή σε ασθενείς με πνευμονική φυματίωση ή σε ασθενείς με χρόνιες ή μη αντιμετωπιζόμενες λοιμώξεις. Οπτική διαταραχή: Ενδέχεται να αναφερθεί οπτική διαταραχή με τη συστηματική και τοπική χρήση κορτικοστεροειδών. Εάν ένας ασθενής παρουσιάζει συμπτώματα, όπως θαμπή όραση ή άλλες οπτικές διαταραχές, τότε θα πρέπει να εξετάζεται το ενδεχόμενο παραπομπής του ασθενούς σε οφθαλμίατρο για την αξιολόγηση των πιθανών αιτιών που ενδέχεται να περιλαμβάνουν καταρράκτη, γλαύκωμα ή σπάνιες ασθένειες, όπως κεντρική ορώδης χοριοαμφιβληστροειδοπάθεια (ΚΟΧΑ) και που έχουν αναφερθεί μετά τη χρήση συστηματικών και τοπικών κορτικοστεροειδών. Υπεργλυκαιμία: Έχουν υπάρξει αναφορές αυξήσεων των επιπέδων της γλυκόζης στο αίμα σε διαβητικούς ασθενείς και αυτό θα πρέπει να λαμβάνεται υπόψη κατά τη χορήγηση σε ασθενείς με ιστορικό σακχαρώδους διαβήτη. Πνευμονία σε ασθενείς με ΧΑΠ: Αύξηση στη συχνότητα εμφάνισης της πνευμονίας, συμπεριλαμβανομένης της πνευμονίας που απαιτεί νοσηλεία, έχει παρατηρηθεί σε ασθενείς με ΧΑΠ που λαμβάνουν εισπνεόμενα κορτικοστεροειδή. Υπάρχουν κάποιες ενδείξεις αυξημένου κινδύνου πνευμονίας με την τάση της δόσης στεροειδών, αλλά αυτό δεν έχει αποδειχθεί με βεβαιότητα σε όλες τις μελέτες. Δεν υπάρχουν οριστικές κλινικές ενδείξεις για διαφορές εντός της κατηγορίας ως προς το μέγεθος του κινδύνου πνευμονίας μεταξύ προϊόντων εισπνεόμενων κορτικοστεροειδών. Οι γιατροί θα πρέπει να παραμένουν σε εγρήγορση για πιθανή ανάπτυξη πνευμονίας σε ασθενείς με ΧΑΠ καθώς τα κλινικά χαρακτηριστικά αυτών των λοιμώξεων επικαλύπτονται με τα συμπτώματα των παροξύνσεων της ΧΑΠ. Οι παράγοντες κινδύνου για πνευμονία σε ασθενείς με ΧΑΠ περιλαμβάνουν το κάπνισμα, τη μεγαλύτερη ηλικία, το χαμηλό δείκτη μάζας σώματος (ΔΜΣ) και τη σοβαρή ΧΑΠ. Πνευμονία σε ασθενείς με άσθμα: Η συχνότητα εμφάνισης πνευμονίας σε ασθενείς με άσθμα ήταν συχνή στην υψηλότερη δόση. Η συχνότητα εμφάνισης πνευμονίας σε ασθενείς με άσθμα που έλαβαν συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης 184/22 μικρογραμμαρίων ήταν αριθμητικά υψηλότερη σε σχέση με αυτούς που έλαβαν το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης των 92/22 μικρογραμμαρίων ή εικονικό φάρμακο (βλέπε παράγραφο 4.8). Δεν εντοπίστηκαν παράγοντες κινδύνου. Έκδοχα: Οι ασθενείς με σπάνια κληρονομικά προβλήματα δυσανεξίας στη γαλακτόζη, ολική έλλειψη λακτάσης ή δυσαπορρόφηση γλυκόζης-γαλακτόζης δεν πρέπει να χρησιμοποιήσουν αυτό το φαρμακευτικό προϊόν.
4.5 Αλληλεπιδράσεις με άλλα φαρμακευτικά προϊόντα και άλλες μορφές αλληλεπίδρασης. Κλινικά σημαντικές φαρμακευτικές αλληλεπιδράσεις με το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης σε κλινικές δόσεις θεωρούνται μη πιθανές λόγω των χαμηλών συγκεντρώσεων που επιτυγχάνονται στο πλάσμα μετά την εισπνοή της δόσης. Αλληλεπίδραση με β-αναστολείς: Οι β_2-αδρενεργικοί αναστολείς μπορεί να εξασθενίσουν ή να ανταγωνίζονται τη δράση των β_2-αδρενεργικών αγωνιστών. Θα πρέπει να αποφεύγεται η ταυτόχρονη χρήση μη εκλεκτικών και εκλεκτικών β_2-αδρενεργικών αναστολέων, εκτός εάν υπάρχουν σοβαροί λόγοι για τη χρήση τους. Αλληλεπίδραση με αναστολείς του CYP3A4: Τόσο η φουροϊκή φλουτικαζόνη όσο και η βιλαντερόλη αποβάλλονται ταχέως μέσω εκτεταμένου μεταβολισμού πρώτης διόδου με τη διαμεσολάβηση του ηπατικού κυτοχρώματος CYP3A4. Συνιστάται προσοχή κατά τη συγχορήγηση με ισχυρούς αναστολείς του CYP3A4 (π.χ., κετοκοναζόλη, ριτοναβίρη, προϊόντα που περιέχουν κομπισστάτη) καθώς υπάρχει πιθανότητα αυξημένης συστηματικής έκθεσης τόσο στη φουροϊκή φλουτικαζόνη όσο και στη βιλαντερόλη. Η συγχορήγηση πρέπει να αποφεύγεται εκτός αν το όφελος υπερτερεί του αυξημένου κινδύνου συστηματικών ανεπιθύμητων ενεργειών των κορτικοστεροειδών, στην οποία περίπτωση οι ασθενείς θα πρέπει να παρακολουθούνται για συστηματικές ανεπιθύμητες ενέργειες των κορτικοστεροειδών. Πραγματοποιήθηκε επαναλαμβανόμενης δόσης μελέτη φαρμακευτικής αλληλεπίδρασης του CYP3A4 σε υγιή άτομα με το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης (184/22 μικρογραμμάρια) και τον ισχυρό αναστολέα του CYP3A4 κετοκοναζόλη (400 mg). Η συγχορήγηση αύξησε τη μέση $AUC_{(0-24)}$ και C_{max} της φουροϊκής φλουτικαζόνης κατά 36% και 33%, αντίστοιχα. Η αύξηση της έκθεσης στη φουροϊκή φλουτικαζόνη συσχετίστηκε με μία μείωση της τάξεως του 27% της σταθμισμένης μέσης τιμής της κορτιζόλης ορού σε διάστημα 0 24 ωρών. Η συγχορήγηση αύξησε τη μέση $AUC_{(0-t)}$ και C_{max} της βιλαντερόλης κατά 65% και 22%, αντίστοιχα. Η αύξηση της έκθεσης στη βιλαντερόλη δεν συσχετίστηκε με αύξηση των σχετιζόμενων με τους β_2-αγωνιστές συστηματικών επιδράσεων στην καρδιακή συχνότητα, το κάλιο αίματος ή το διάστημα QTcF. Αλληλεπίδραση με αναστολείς της P-γλυκοπρωτεΐνης. Η φουροϊκή φλουτικαζόνη και η βιλαντερόλη αποτελούν υποστρώματα της P-γλυκοπρωτεΐνης (P gp). Μία κλινική φαρμακολογική μελέτη που διενεργήθηκε σε υγιή άτομα στα οποία συγχορηγήθηκε η βιλαντερόλη και ο ισχυρός για την P-gp και μέτριος για το CYP3A4 αναστολέας βεραπαμίλη, δεν κατέδειξε καμία σημαντική επίδραση στη φαρμακοκινητική της βιλαντερόλης. Δεν έχουν διενεργηθεί κλινικές φαρμακολογικές μελέτες με ειδικό αναστολέα της P-gp και φουροϊκή φλουτικαζόνη. Συμπαθομιμητικά φαρμακευτικά προϊόντα: Η ταυτόχρονη χορήγηση άλλων συμπαθομιμητικών φαρμακευτικών προϊόντων (μεμονωμένα ή ως μέρος συνδυαστικής θεραπείας) μπορεί να ενισχύσει τις ανεπιθύμητες ενέργειες που προκαλούνται από το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης. Το Relvar Ellipta δεν θα πρέπει να χρησιμοποιείται σε συνδυασμό με άλλους μακράς δράσης β_2-αδρενεργικούς αγωνιστές η φαρμακευτικά προϊόντα που περιέχουν μακράς δράσης β_2-αδρενεργικούς αγωνιστές. Παιδιατρικός πληθυσμός: Μελέτες αλληλεπιδράσεων έχουν πραγματοποιηθεί μόνο σε ενήλικες.
4.6 Γονιμότητα, κύηση και γαλουχία: Κύηση. Μελέτες σε ζώα κατέδειξαν τοξικότητα στην αναπαραγωγική ικανότητα σε εκθέσεις οι οποίες δεν είναι κλινικά σημαντικές (βλέπε παράγραφο 5.3). Δεν διατίθενται ή είναι περιορισμένα τα δεδομένα από τη χρήση της φουροϊκής φλουτικαζόνης και της vilanterol trifenatate στις έγκυες γυναίκες. Η χορήγηση του συνδυασμού φουροϊκής φλουτικαζόνης/βιλαντερόλης σε έγκυες γυναίκες θα πρέπει να εξετάζεται μόνο αν το αναμενόμενο όφελος για τη μητέρα είναι μεγαλύτερο από οποιοδήποτε δυνητικό κίνδυνο για το έμβρυο. Θηλασμός: Υπάρχουν ανεπαρκείς πληροφορίες σχετικά με την απέκκριση της φουροϊκής φλουτικαζόνης ή της vilanterol trifenatate και/ή των μεταβολιτών στο ανθρώπινο γάλα. Ωστόσο, άλλα κορτικοστεροειδή και β_2-αγωνιστές ανιχνεύονται στο ανθρώπινο γάλα (βλέπε παράγραφο 5.3). Ο κίνδυνος για τα νεογνά/βρέφη που θηλάζουν δεν μπορεί να αποκλειστεί. Πρέπει να αποφασιστεί εάν θα διακοπεί ο θηλασμός ή θα διακοπεί η θεραπεία με το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης λαμβάνοντας υπόψη το όφελος του θηλασμού για το παιδί και το όφελος της θεραπείας για τη γυναίκα. Γονιμότητα: Δεν υπάρχουν δεδομένα σχετικά με τη γονιμότητα σε ανθρώπους. Μελέτες σε ζώα δεν έδειξαν επίδραση του συνδυασμού φουροϊκής φλουτικαζόνης/βιλαντερόλης trifenatate στη γονιμότητα (βλέπε παράγραφο 5.3).
4.7 Επιδράσεις στην ικανότητα οδήγησης και χειρισμού μηχανημάτων: Η φουροϊκή φλουτικαζόνη ή η βιλαντερόλη δεν έχουν καμία ή έχουν ασήμαντη επίδραση στην ικανότητα οδήγησης και χειρισμού μηχανημάτων.
4.8 Ανεπιθύμητες ενέργειες: Περίληψη του προφίλ ασφάλειας: Χρησιμοποιήθηκαν δεδομένα από μεγάλες κλινικές δοκιμές του άσθματος και της ΧΑΠ για τον προσδιορισμό της συχνότητας εμφάνισης των ανεπιθύμητων ενεργειών που σχετίζονται με το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης. Στο πρόγραμμα κλινικής ανάπτυξης για το άσθμα συμπεριλήφθηκαν συνολικά 7.034 ασθενείς σε μία συγκεντρωτική αξιολόγηση των ανεπιθύμητων ενεργειών. Στο πρόγραμμα κλινικής ανάπτυξης για τη ΧΑΠ συμπεριλήφθηκαν συνολικά 6.237 ασθενείς σε μία συγκεντρωτική αξιολόγηση των ανεπιθύμητων ενεργειών. Οι ανεπιθύμητες ενέργειες που αναφέρθηκαν συχνότερα με τη φουροϊκή φλουτικαζόνη και τη βιλαντερόλη ήταν κεφαλαλγία και ρινοφαρυγγίτιδα. Με εξαίρεση την πνευμονία και τα κατάγματα, το προφίλ ασφάλειας ήταν παρόμοιο στους ασθενείς με άσθμα και ΧΑΠ. Κατά τη διάρκεια κλινικών μελετών, πνευμονία και κατάγματα παρατηρήθηκαν πιο συχνά σε ασθενείς με ΧΑΠ. Πίνακας ανεπιθύμητων ενεργειών: Οι ανεπιθύμητες αντιδράσεις παρατίθενται ανά κατηγορία οργανικού συστήματος και συχνότητα. Για την ταξινόμηση των συχνοτήτων, χρησιμοποιήθηκε η παρακάτω συνθήκη: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥ 1/10.000 έως< 1/1.000), πολύ σπάνιες (< 1/10.000). Εντός κάθε ομάδας συχνότητας, οι ανεπιθύμητες αντιδράσεις παρουσιάζονται κατά σειρά φθίνουσας σοβαρότητας.

Κατηγορία/Οργανικό σύστημα	Ανεπιθύμητες ενέργειες	Συχνότητα
Λοιμώξεις και παρασιτώσεις	Πνευμονία*, Λοίμωξη του ανώτερου αναπνευστικού, Βρογχίτιδα, Γρίπη, Καντιντίαση του στόματος και του φάρυγγα	Συχνή
Διαταραχές του ανοσοποιητικού συστήματος	Αντιδράσεις υπερευαισθησίας, συμπεριλαμβανομένης αναφυλαξίας, αγγειοοιδήματος, εξανθήματος και κνίδωσης	Σπάνια
Διαταραχές του μεταβολισμού και της θρέψης	Υπεργλυκαιμία	Όχι συχνή
Ψυχιατρικές διαταραχές	Άγχος	Σπάνια
Διαταραχές του νευρικού συστήματος	Κεφαλαλγία Τρόμος	Πολύ συχνή Σπάνια
Οφθαλμικές διαταραχές	Όραση θαμπή (βλέπε παράγραφο 4.4)	Όχι συχνή
Καρδιακές διαταραχές	Έκτακτες συστολές Αίσθημα παλμών, Ταχυκαρδία	Όχι συχνή Σπάνια
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωράκιου	Ρινοφαρυγγίτιδα Στοματοφαρυγγικό άλγος, Παραρρινοκολπίτιδα, Φαρυγγίτιδα, Ρινίτιδα, Βήχας, Δυσφωνία Παράδοξος βρογχόσπασμος	Πολύ συχνή Συχνή Σπάνια

Κατηγορία/Οργανικό σύστημα	Ανεπιθύμητες ενέργειες	Συχνότητα
Διαταραχές του γαστρεντερικού	Κοιλιακό άλγος	Συχνή
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού	Αρθραλγία, Οσφαλγία, Κατάγματα**, Μυϊκοί σπασμοί	Συχνή
Γενικές διαταραχές και καταστάσεις της οδού χορήγησης	Πυρεξία	Συχνή

*, ** Βλέπε παρακάτω «Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών»

Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών **Πνευμονία (Βλέπε παράγραφο 4.4)* Σε μία ενιαία ανάλυση των δύο επαναληπτικών μελετών ενός έτους σε μέτρια έως βαριά ΧΑΠ (μέσος προβλεπόμενος FEV1 μετά το βρογχοδιασταλτικό κατά την προκαταρκτική αξιολόγηση 45%, τυπική απόκλιση (SD) 13%) με παροξυσμό κατά το προηγούμενο έτος (n = 3255), ο αριθμός των εκδηλώσεων πνευμονίας ανά 1000 έτη ασθενών ήταν 97.9 για την FF/VI 184/22, 85.7 για την FF/VI 92/22 και 42.3 για την ομάδα VI 22. Για σοβαρή πνευμονία ο αντίστοιχος αριθμός των συμβάντων ανά 1000 έτη ασθενών ήταν 33.6, 35.5 και 7.6 αντίστοιχα, ενώ για σοβαρή πνευμονία οι αντίστοιχες εκδηλώσεις ανά 1000 έτη ασθενών ήταν 35.1 για την FF/VI 184/22, 42.9 για την FF/VI 92 /22, 12.1 για την VI 22. Τέλος, οι προσαρμοσμένες στην έκθεση περιπτώσεις θανατηφόρας πνευμονίας ήταν 8.8 για την FF/VI 184/22 έναντι 1.5 για την FF/VI 92/22 και 0 για την VI 22. Σε μια ελεγχόμενη με εικονικό φάρμακο μελέτη (SUMMIT) σε συμμετέχοντες με μέτρια ΧΑΠ (μέσο ποσοστό FEV1 μετά το βρογχοδιασταλτικό κατά την προκαταρκτική αξιολόγηση 60%, SD 6%) και ιστορικό ή αυξημένο κίνδυνο εμφάνισης καρδιαγγειακής νόσου, η συχνότητα εμφάνισης πνευμονίας με τη FF/VI, τη FF, τη VI και το εικονικό φάρμακο είχε ως εξής: ανεπιθύμητα συμβάντα (6%, 5%, 4%, 5%), σοβαρά ανεπιθύμητα συμβάντα (3%, 4%, 3%, 3%), αξιολογημένοι θάνατοι λόγω πνευμονίας κατά τη θεραπεία (0,3%, 0,2%, 0,1%, 0,2%), ενώ τα προσαρμοσμένα ως προς την έκθεση ποσοστά (ανά 1.000 έτη θεραπείας) ήταν: ανεπιθύμητα συμβάντα (39,5, 42,4, 27,7, 38,4), σοβαρά ανεπιθύμητα συμβάντα (22,4, 25,1, 16,4, 22,2), αξιολογημένοι θάνατοι λόγω πνευμονίας κατά τη θεραπεία (1,8, 1,5, 0,9, 1,4), αντιστοίχως.Σε μία ενιαία ανάλυση των 11 μελετών στο άσθμα (7.034 ασθενείς), η συχνότητα εμφάνισης πνευμονίας ανά 1000 έτη ασθενών ήταν 18.4 για την FF/VI 184/22 έναντι 9.6 για την FF/VI 92/22 και 8.0 για την ομάδα του εικονικού φαρμάκου. **Κατάγματα: Σε δύο πανομοιότυπες μελέτες διάρκειας 12 μηνών που διενεργήθηκαν σε ένα σύνολο 3.255 ασθενών με ΧΑΠ, η συχνότητα εμφάνισης οστικών καταγμάτων συνολικά ήταν χαμηλή σε όλες τις ομάδες θεραπείας, με υψηλότερη συχνότητα εμφάνισης σε όλες τις ομάδες του Relvar Ellipta (2%) σε σχέση με την ομάδα της βιλαντερόλης των 22 μικρογραμμαρίων (<1%). Παρόλο που παρατηρήθηκαν περισσότερα κατάγματα στις ομάδες του Relvar Ellipta σε σχέση με την ομάδα της βιλαντερόλης των 22 μικρογραμμαρίων, τα κατάγματα που κατά κανόνα σχετίζονται με τη χρήση κορτικοστεροειδών (π.χ., συμπίεση νωτιαίου μυελού /κατάγματα θωρακοοσφϊκών σπονδύλων, κατάγματα ισχίου και κοτύλης) εμφανίστηκαν σε <1% των σκελών θεραπείας με Relvar Ellipta και βιλαντερόλη. Στη μελέτη SUMMIT, η συχνότητα εμφάνισης όλων των συμβάντων κατάγματος με τη FF/VI, τη FF, τη VI και το εικονικό φάρμακο ήταν 2% σε κάθε σκέλος – το ποσοστό των καταγμάτων που συνήθως σχετίζονται με τη χρήση ICS ήταν μικρότερο από 1% σε κάθε σκέλος. Τα προσαρμοσμένα ως προς την έκθεση ποσοστά (ανά 1.000 έτη θεραπείας) για το σύνολο των συμβάντων κατάγματος ήταν 13,6, 12,8, 13,2, 11,5 αντιστοίχως – το ποσοστό των καταγμάτων που συνήθως σχετίζονται με τη χρήση ICS ήταν 3,4, 3,9, 2,4, 2,1 αντιστοίχως. Σε μία ενιαία ανάλυση 11 μελετών για το άσθμα (7.034 ασθενείς), η συχνότητα εμφάνισης καταγμάτων ήταν <1% και συνήθως συνδέονταν με τραυματισμό.

Αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών Η αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών μετά από τη χορήγηση άδειας κυκλοφορίας του φαρμακευτικού προϊόντος είναι σημαντική. Επιτρέπει τη συνεχή παρακολούθηση της σχέσης οφέλους/κινδύνου του φαρμακευτικού προϊόντος. Ζητείται από τους επαγγελματίες υγείας να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες μέσω του εθνικού συστήματος αναφοράς που αναγράφεται παρακάτω: **Ελλάδα**, Εθνικός Οργανισμός Φαρμάκων, Μεσογείων 284, GR-15562 Χολαργός, Αθήνα. Τηλ: + 30 2132040380/337, Φαξ: + 30 2106549585. Ιστότοπος: http://www.eof.gr. **Κύπρος**, Φαρμακευτικές Υπηρεσίες Υπουργείο Υγείας, CY-1475 Λευκωσία, Τηλ: + 357 22608607, Φαξ: + 357 22608649, Ιστότοπος: www.moh.gov.cy/phs.

4.9 Υπερδοσολογία. Συμπτώματα και σημεία: Η υπερδοσολογία από το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης μπορεί να προκαλέσει σημεία και συμπτώματα λόγω της δράσης των επιμέρους συστατικών, συμπεριλαμβανομένων εκείνων που έχουν παρατηρηθεί με υπερδοσολογία από άλλους β_2-αγωνιστές και σύμφωνα με τις γνωστές επιδράσεις της κατηγορίας των εισπνεόμενων κορτικοστεροειδών (βλέπε παράγραφο 4.4). Αντιμετώπιση: Δεν υπάρχει συγκεκριμένη θεραπεία για την υπερδοσολογία από το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης. Αν συμβεί υπερδοσολογία, ο ασθενής θα πρέπει να αντιμετωπιστεί υποστηρικτικά με την κατάλληλη παρακολούθηση κατά περίπτωση. Ο καρδιοεκλεκτικός β αποκλεισμός θα πρέπει να εξετάζεται μόνο για σημαντικές επιδράσεις υπερδοσολογίας από βιλαντερόλη, οι οποίες είναι κλινικά ανησυχητικές και δεν ανταποκρίνονται σε υποστηρικτικά μέτρα. Τα φαρμακευτικά προϊόντα που περιέχουν καρδιοεκλεκτικούς β-αναστολείς θα πρέπει να χρησιμοποιούνται με προσοχή σε ασθενείς με ιστορικό βρογχόσπασμου. Η περαιτέρω αντιμετώπιση θα πρέπει να βασίζεται στις κλινικές ενδείξεις ή τις συστάσεις του εθνικού κέντρου δηλητηριάσεων, εφόσον υπάρχουν.

5. ΦΑΡΜΑΚΟΛΟΓΙΚΕΣ ΙΔΙΟΤΗΤΕΣ.

5.1 Φαρμακοδυναμικές ιδιότητες. Φαρμακοθεραπευτική κατηγορία: Φάρμακα για αποφρακτικές νόσους των αεροφόρων οδών, Αδρενεργικά σε συνδυασμό με κορτικοστεροειδή ή άλλα φάρμακα εξαιρουμένων των αντιχοληνεργικών, Κωδικός ATC: R03AK10.

6. ΦΑΡΜΑΚΕΥΤΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ

6.1 Κατάλογος εκδόχων. Μονοϋδρική λακτόζη, Στεατικό μαγνήσιο

6.2 Ασυμβατότητες: Δεν εφαρμόζεται.

6.3 Διάρκεια ζωής: 2 χρόνια. Διάρκεια ζωής κατά τη χρήση μετά το άνοιγμα του δίσκου: 6 εβδομάδες.

6.4 Ιδιαίτερες προφυλάξεις κατά τη φύλαξη του προϊόντος: Μη φυλάσσετε σε θερμοκρασία μεγαλύτερη των 25ºC. Αν φυλάσσεται σε ψυγείο, η συσκευή εισπνοών θα πρέπει να αφήνεται να επανέλθει σε θερμοκρασία δωματίου τουλάχιστον μία ώρα πριν από τη χρήση. Να φυλάσσεται στην αρχική συσκευασία ώστε να προστατεύεται από την υγρασία. Γράψτε την ημερομηνία που πρέπει να απορριφθεί η συσκευή εισπνοών, στο χώρο που παρέχεται στην ετικέτα. Η ημερομηνία πρέπει να προστεθεί μόλις η συσκευή εισπνοών αφαιρεθεί από το δίσκο.

6.5 Φύση και συστατικά του περιέκτη: Η συσκευή εισπνοών αποτελείται από ένα σώμα χρώματος ανοικτού γκρι, ένα κάλυμμα επιστομίου χρώματος κίτρινου και ένα δοσομετρητή, συσκευασμένα σε δίσκο από φύλλο αλουμινίου που περιέχει ένα φακελίσκο με αφυγραντικό από silica gel. Ο δίσκος είναι σφραγισμένος με αφαιρούμενο κάλυμμα από φύλλο αλουμινίου. Η συσκευή εισπνοών είναι μία πολυσύνθετη συσκευή που αποτελείται από πολυπροπυλένιο, πολυαιθυλένιο υψηλής πυκνότητας, πολυοξυμεθυλένιο, τερεφθαλικό πολυβουτυλένιο, ακρυλονιτρικό βουταδιενικό στυρένιο, πολυανθρακικό και ανοξείδωτο χάλυβα. Η συσκευή εισπνοών περιέχει δύο ταινίες από φύλλο αλουμινίου 14 ή 30 δόσεων. Συσκευασίες Συσκευών Εισπνοών των 14 ή 30 δόσεων. Πολλαπλή συσκευασία Συσκευών Εισπνοών των 3 x 30 δόσεων. Μπορεί να μην κυκλοφορούν όλες οι συσκευασίες.

6.6 Ιδιαίτερες προφυλάξεις απόρριψης: Κάθε αχρησιμοποίητο φαρμακευτικό προϊόν ή υπόλειμμα πρέπει να απορρίπτεται σύμφωνα με τις κατά τόπους ισχύουσες σχετικές διατάξεις.

7. ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ: GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ιρλανδία.

8. ΑΡΙΘΜΟΣ(ΟΙ) ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ: EU/1/13/886/001, EU/1/13/886/002, EU/1/13/886/003

9. ΗΜΕΡΟΜΗΝΙΑ ΠΡΩΤΗΣ ΕΓΚΡΙΣΗΣ / ΑΝΑΝΕΩΣΗΣ ΤΗΣ ΑΔΕΙΑΣ: Ημερομηνία πρώτης έγκρισης: 13 Νοεμβρίου 2013
Ημερομηνία τελευταίας ανανέωσης: 26 Ιουλίου 2018

10. ΗΜΕΡΟΜΗΝΙΑ ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ: 15/08/2022

Λεπτομερείς πληροφορίες για το παρόν φαρμακευτικό προϊόν είναι διαθέσιμες στο δικτυακό τόπο του Ευρωπαϊκού Οργανισμού Φαρμάκων http://www.ema.europa.eu/.

Σύντομη Περίληψη Χαρακτηριστικών του Προϊόντος RELVAR Ellipta 184/22 μg

1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ: Relvar Ellipta 184 μικρογραμμάρια/22 μικρογραμμάρια κόνις για εισπνοή σε δόσεις.

2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ: Η παρεχόμενη δόση κάθε εφάπαξ εισπνοής (η δόση που εξέρχεται από το επιστόμιο) είναι 184 μικρογραμμάρια φουροϊκής φλουτικαζόνης και 22 μικρογραμμάρια βιλαντερόλης (ως trifenatate). Αυτό αντιστοιχεί σε προκαθορισμένη δόση 200 μικρογραμμαρίων φουροϊκής φλουτικαζόνης και 25 μικρογραμμαρίων βιλαντερόλης (ως trifenatate). Εκδοχα με γνωστές δράσεις: Κάθε παρεχόμενη δόση περιέχει περίπου 25 mg λακτόζης (μονοϋδρική). Για τον πλήρη κατάλογο των εκδόχων, βλ. παράγραφο 6.1.

3. ΦΑΡΜΑΚΕΥΤΙΚΗ ΜΟΡΦΗ: Κόνις για εισπνοή, σε δόσεις. (Κόνις για εισπνοή). Λευκή κόνις σε συσκευή εισπνοών χρώματος ανοικτού γκρι, με κάλυμμα επιστομίου χρώματος κίτρινου και δοσομετρητή.

4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ: 4.1 Θεραπευτικές ενδείξεις: Άσθμα: Το Relvar Ellipta ενδείκνυται για την τακτική αντιμετώπιση του άσθματος σε ενήλικες και εφήβους ηλικίας 12 ετών και άνω στους οποίους η χρήση ενός φαρμακευτικού προϊόντος συνδυασμού (μακράς δράσης β_2-αγωνιστής και εισπνεόμενος κορτικοστεροειδές) είναι κατάλληλη. • ασθενείς που δεν ελέγχονται επαρκώς με εισπνεόμενα κορτικοστεροειδή και «κατ' επίκληση» εισπνεόμενους βραχείας δράσης β_2-αγωνιστές. • ασθενείς που έχουν ήδη ελεγχθεί επαρκώς με εισπνεόμενο κορτικοστεροειδές και με β_2-αγωνιστή μακράς δράσης.

4.2 Δοσολογία και τρόπος χορήγησης: Δοσολογία: *Άσθμα:* Οι ασθενείς με άσθμα θα πρέπει να λαμβάνουν το Relvar Ellipta στην περιεκτικότητα που περιέχει την κατάλληλη δόση φουροϊκής φλουτικαζόνης (FF) για τη σοβαρότητα της νόσου τους. Οι συνταγογράφοι θα πρέπει να γνωρίζουν ότι σε ασθενείς με άσθμα, 100 μικρογραμμάρια φουροϊκής φλουτικαζόνης (FF) άπαξ ημερησίως ισοδυναμούν με περίπου 250 μικρογραμμάρια προπιονικής φλουτικαζόνης (FP) δύο φορές την ημέρα, ενώ 200 μικρογραμμάρια FF άπαξ ημερησίως ισοδυναμούν με περίπου 500 μικρογραμμάρια FP δύο φορές την ημέρα. *Ενήλικες και έφηβοι ηλικίας 12 ετών και άνω:* Θα πρέπει να εξετάζεται χορήγηση αρχικής δόσης μίας εισπνοής Relvar Ellipta 92/22 μικρογραμμαρίων άπαξ ημερησίως για ενήλικες και εφήβους ηλικίας 12 ετών και άνω που απαιτούν μία χαμηλή έως μεσαία δόση εισπνεόμενου κορτικοστεροειδούς σε συνδυασμό με ένα μακράς δράσης β_2-αγωνιστή. Αν οι ασθενείς δεν ελέγχονται επαρκώς με το Relvar Ellipta των 92/22 μικρογραμμαρίων η δόση μπορεί να αυξηθεί σε 184/22 μικρογραμμάρια, η οποία μπορεί να παρέχει πρόσθετη βελτίωση στον έλεγχο του άσθματος. Οι ασθενείς θα πρέπει να επαναξιολογούνται τακτικά από επαγγελματία του τομέα υγειονομικής περίθαλψης, ώστε η περιεκτικότητα του συνδυασμού φουροϊκής φλουτικαζόνης/βιλαντερόλης που λαμβάνουν να εξακολουθεί να είναι η βέλτιστη και μεταβάλλεται μόνο μετά από ιατρική συμβουλή. Η δόση θα πρέπει να μειώνεται στο χαμηλότερο επίπεδο με το οποίο διατηρείται αποτελεσματικός έλεγχος των συμπτωμάτων. Το Relvar Ellipta 184/22 μικρογραμμαρίων θα πρέπει να εξετάζεται για ενήλικες και εφήβους ηλικίας 12 ετών και άνω που απαιτούν υψηλότερη δόση εισπνεόμενου κορτικοστεροειδούς σε συνδυασμό με ένα μακράς δράσης β_2-αγωνιστή. Η μέγιστη συνιστώμενη δόση είναι Relvar Ellipta 184/22 μικρογραμμάρια άπαξ ημερησίως. Οι ασθενείς συνήθως εμφανίζουν βελτίωση της πνευμονικής λειτουργίας εντός 15 λεπτών από την εισπνοή του Relvar Ellipta. Ωστόσο, ο ασθενής πρέπει να ενημερώνεται ότι η τακτική καθημερινή χρήση είναι απαραίτητη για τη διατήρηση του ελέγχου των συμπτωμάτων του άσθματος και ότι η χρήση πρέπει να συνεχιστεί ακόμα και όταν είναι ασυμπτωματικός. Εάν προκύψουν συμπτώματα κατά την περίοδο μεταξύ των δόσεων, για την άμεση ανακούφιση θα πρέπει να χρησιμοποιηθεί ένας εισπνεόμενος β_2-αγωνιστής βραχείας δράσης. *Παιδιά ηλικίας κάτω των 12 ετών:* Η ασφάλεια και η αποτελεσματικότητα του Relvar Ellipta σε παιδιά ηλικίας κάτω των 12 ετών δεν έχουν ακόμα τεκμηριωθεί για την ένδειξη του άσθματος. Δεν υπάρχουν διαθέσιμα δεδομένα. Ειδικοί πληθυσμοί: *Ηλικιωμένοι (>65 ετών):* Δεν απαιτείται προσαρμογή της δόσης στον συγκεκριμένο πληθυσμό (βλέπε παράγραφο 5.2). *Νεφρική δυσλειτουργία:* Δεν απαιτείται προσαρμογή της δόσης στον συγκεκριμένο πληθυσμό (βλέπε παράγραφο 5.2). *Ηπατική δυσλειτουργία:* Μελέτες σε άτομα με ήπια, μέτρια και σοβαρή ηπατική δυσλειτουργία έδειξαν αύξηση της συστηματικής έκθεσης στη φουροϊκή φλουτικαζόνη (C_{max} και AUC) (βλέπε παράγραφο 5.2). Πρέπει να επιδεικνύεται προσοχή κατά τη χορήγηση σε ασθενείς με ηπατική δυσλειτουργία, οι οποίοι μπορεί να διατρέχουν μεγαλύτερο κίνδυνο εμφάνισης συστηματικών ανεπιθύμητων ενεργειών που σχετίζονται με τα κορτικοστεροειδή. Για ασθενείς με μέτρια έως σοβαρή ηπατική δυσλειτουργία η μέγιστη δόση είναι 92/22 μικρογραμμάρια (βλέπε παράγραφο 4.4). Τρόπος χορήγησης: είναι αποκλειστικά για εισπνεόμενη χρήση. Θα πρέπει να χορηγείται την ίδια ώρα της ημέρας κάθε μέρα. Η τελική απόφαση σχετικά με τη χορήγηση βραδινής ή πρωινής δόσης θα πρέπει να λαμβάνεται σύμφωνα με την κρίση του ιατρού. Εάν παραλειφθεί μία δόση, η επόμενη δόση θα πρέπει να ληφθεί στη συνήθη ώρα την επόμενη ημέρα. Εάν φυλάσσεται σε ψυγείο, η συσκευή εισπνοών θα πρέπει να αφήνεται να επανέλθει σε θερμοκρασία δωματίου τουλάχιστον μία ώρα πριν από τη χρήση. Όταν η συσκευή εισπνοών χρησιμοποιείται για πρώτη φορά, δεν υπάρχει ανάγκη ελέγχου της σωστής λειτουργίας ή ανάγκη ειδικής προετοιμασίας για τη χρήση. Θα πρέπει να ακολουθούνται οι αναλυτικές οδηγίες. Η συσκευή εισπνοών Ellipta συσκευάζεται σε ένα δίσκο που περιέχει ένα φακελίσκο με αφυγραντικό για μείωση της υγρασίας. Ο φακελίσκος με το αφυγραντικό πρέπει να απορρίπτεται και δεν πρέπει να ανοίγεται, να καταναλώνεται ή να εισπνέεται. Ο ασθενής πρέπει να συμβουλεύεται να μην ανοίξει το δίσκο μέχρι να είναι έτοιμος να εισπνεύσει τη δόση. Όταν η συσκευή εισπνοών αφαιρείται από το δίσκο της, θα βρίσκεται στην «κλειστή» θέση. Η ημερομηνία "Απορρίψτε μετά από" πρέπει να είναι γραμμένη στην ετικέτα της συσκευής εισπνοών στο χώρο που παρέχεται. Η ημερομηνία "Απορρίψτε μετά από" είναι 6 εβδομάδες από την ημερομηνία ανοίγματος του δίσκου. Μετά την ημερομηνία αυτή η συσκευή εισπνοών δεν θα πρέπει πλέον να χρησιμοποιείται. Ο δίσκος μπορεί να απορριφθεί μετά το πρώτο άνοιγμα. Μετά την εισπνοή, οι ασθενείς θα πρέπει να ξεπλένουν το στόμα τους με νερό χωρίς να καταπιούν. Οι αναλυτικές οδηγίες που ακολουθούν για τη συσκευή εισπνοών Ellipta 30 δόσεων (επαρκεί για 30 ημέρες) ισχύουν επίσης και για τη συσκευή εισπνοών Ellipta των 14 δόσεων (επαρκεί για 14 ημέρες).

Οδηγίες χρήσεως. ***1. Διαβάστε αυτές τις οδηγίες πριν ξεκινήσετε:*** Αν το κάλυμμα της συσκευής εισπνοών ανοιχτεί και κλειστεί χωρίς να εισπνευστεί το φάρμακο, η δόση θα χαθεί. Η χαμένη δόση θα παραμείνει με ασφάλεια στο εσωτερικό της συσκευής εισπνοών, αλλά δεν θα είναι πλέον διαθέσιμη για εισπνοή. Δεν είναι δυνατή η τυχαία λήψη επιπλέον ποσότητας φαρμάκου ή διπλής δόσης με μία εισπνοή. **Κάλυμμα** Κάθε φορά που τα ανοίγετε, ετοιμάζετε μία δόση του φαρμάκου. **Δοσομετρητής** Δείχνει πόσες δόσεις φαρμάκου απομένουν στην συσκευή εισπνοών. Πριν από την αρχική χρήση της συσκευής εισπνοών δείχνει ακριβώς 30 δόσεις. Μετράει αντίστροφα κατά 1 κάθε φορά που ανοίγεται το κάλυμμα. Όταν έχουν απομείνει λιγότερες από 10 δόσεις, το μισό τμήμα του δοσομετρητή εμφανίζεται κόκκινο. Αφότου χρησιμοποιήσετε την τελευταία δόση, το μισό τμήμα του δοσομετρητή εμφανίζεται κόκκινο και αναγράφεται ο αριθμός 0. Η συσκευή εισπνοών σας είναι πλέον άδεια. Αν ανοίξετε το κάλυμμα μετά από αυτό, το χρώμα του δοσομετρητή θα αλλάξει από μισό κόκκινο σε όλο κόκκινο. ***2. Τρόπος προετοιμασίας της δόσης.*** Ανοίξτε το κάλυμμα όταν είσαστε έτοιμοι να εισπνεύσετε μία δόση. Μην ανακινείτε τη συσκευή εισπνοών. Μετακινήστε το κάλυμμα προς τα κάτω μέχρι να ακουστεί ένα «κλικ». Το φάρμακο είναι πλέον έτοιμο για εισπνοή. Ο δοσομετρητής μετρά αντίστροφα κατά 1 για επιβεβαίωση. Αν ο δοσομετρητής δεν μετρήσει αντίστροφα καθώς ακούγεται το «κλικ», το φάρμακο δεν θα χορηγηθεί από τη συσκευή εισπνοών. Επιστρέψτε τη σε ένα φαρμακοποιό για να σας συμβουλέψει. ***3. Πώς να εισπνεύσετε το φάρμακο.*** Κρατήστε τη συσκευή εισπνοών μακριά από το στόμα σας και εκπνεύστε στο βαθμό που αισθάνεστε άνετα. Μην εκπνέετε μέσα στη συσκευή εισπνοών. Τοποθετήστε το επιστόμιο ανάμεσα στα χείλη σας και κλείστε τα χείλη σας σφιχτά γύρω από αυτό. Μην φράζετε τους αεραγωγούς με τα δάχτυλά σας. Πάρτε μία μακρά, σταθερή, βαθιά εισπνοή. Κρατήστε την αναπνοή σας όσο το δυνατόν περισσότερο (τουλάχιστον 3 4 δευτερόλεπτα). Απομακρύνετε τη συσκευή εισπνοών από το στόμα σας. Εκπνεύστε αργά και απαλά. Είναι πιθανό να μην μπορέσετε να γευτείτε ή να αισθανθείτε το φάρμακο, ακόμη και όταν χρησιμοποιείτε τη συσκευή εισπνοών σωστά. Εάν θέλετε να καθαρίσετε το επιστόμιο της συσκευής εισπνοών, χρησιμοποιήστε ένα στεγνό χαρτομάντιλο, πριν το κλείσιμο του καλύμματος. ***4. Κλείστε τη συσκευή εισπνοών και ξεπλύνετε το στόμα σας.*** Σπρώξτε το κάλυμμα προς τα επάνω όσο περισσότερο γίνεται για να καλύψετε το επιστόμιο. Ξεπλύνετε το στόμα σας με νερό μετά τη χρήση της συσκευής εισπνοών, μην το καταπιείτε. Αυτό θα μειώσει την πιθανότητα εμφάνισης ανεπιθύμητων ενεργειών όπως ο ερεθισμός του στόματος ή του φάρυγγα.

4.3 Αντενδείξεις: Υπερευαισθησία στις δραστικές ουσίες ή σε κάποιο από τα έκδοχα που αναφέρονται στην παράγραφο 6.1.

4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση: Επιδείνωση νόσου: Ο συνδυασμός φουροϊκής φλουτικαζόνης/βιλαντερόλης δεν πρέπει να χρησιμοποιείται για την αντιμετώπιση οξέων συμπτωμάτων άσθματος, που απαιτούν ένα βραχείας δράσης βρογχοδιασταλτικό παράγοντα. Η αυξανόμενη χρήση βρογχοδιασταλτικών βραχείας δράσης για την ανακούφιση από συμπτώματα υποδηλώνει επιδείνωση του ελέγχου και οι ασθενείς θα πρέπει να επανεξετάζονται από ιατρό. Οι ασθενείς δεν θα πρέπει να σταματούν τη θεραπεία με το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης για την αντιμετώπιση του άσθματος, χωρίς ιατρική επίβλεψη καθώς τα συμπτώματα μπορεί να επανεμφανιστούν μετά τη διακοπή. Σοβαρά ανεπιθύμητα συμβάντα που σχετίζονται με το άσθμα και παροξυσμοί μπορεί να εκδηλωθούν κατά τη διάρκεια της θεραπείας με το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης. Θα πρέπει να ζητηθεί από τους ασθενείς να συνεχίσουν τη θεραπεία αλλά να ζητήσουν ιατρική συμβουλή εάν τα συμπτώματα του άσθματος παραμένουν εκτός ελέγχου ή εάν επιδεινωθούν μετά την έναρξη της θεραπείας με Relvar Ellipta. Παράδοξος βρογχόσπασμος: Μετά τη χορήγηση της δόσης μπορεί να εμφανιστεί παράδοξος βρογχόσπασμος συνοδευόμενος από μία άμεση αύξηση του σφυγμού. Αυτό θα πρέπει να αντιμετωπιστεί άμεσα με εισπνεόμενο βρογχοδιασταλτικό βραχείας δράσης. Το Relvar Ellipta θα πρέπει να διακοπεί άμεσα και να αξιολογηθεί ο ασθενής και, αν κριθεί απαραίτητο, να ξεκινήσει εναλλακτική θεραπεία. Καρδιαγγειακές επιδράσεις: Καρδιαγγειακές επιδράσεις όπως καρδιακές αρρυθμίες, π.χ. υπερκοιλιακή ταχυκαρδία και έκτακτες συστολές μπορεί να παρατηρηθούν με συμπαθομιμητικά φαρμακευτικά προϊόντα συμπεριλαμβανομένου του Relvar Ellipta. . Σε μια ελεγχόμενη με εικονικό φάρμακο μελέτη σε συμμετέχοντες με μέτρια ΧΑΠ και ιστορικό ή αυξημένο κίνδυνο εμφάνισης καρδιαγγειακής νόσου, δεν παρατηρήθηκε αύξηση του κινδύνου καρδιαγγειακών επεισοδίων στους ασθενείς που λάμβαναν φουροϊκή φλουτικαζόνη/βιλαντερόλη έναντι αυτών που λάμβαναν εικονικό φάρμακο. Ωστόσο, ο συνδυασμός φουροϊκής φλουτικαζόνης/βιλαντερόλης θα πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με σοβαρή καρδιαγγειακή νόσο ή ανωμαλίες του καρδιακού ρυθμού, θυρεοτοξίκωση, μη διορθωμένη υποκαλιαιμία ή σε ασθενείς με προδιάθεση για χαμηλά επίπεδα καλίου στον ορό. Ασθενείς με ηπατική δυσλειτουργία: Για ασθενείς με μέτρια έως σοβαρή ηπατική δυσλειτουργία θα πρέπει να χρησιμοποιείται η δόση των 92/22 μικρογραμμαρίων και οι ασθενείς θα πρέπει να παρακολουθούνται για την εμφάνιση συστηματικών ανεπιθύμητων ενεργειών που σχετίζονται με τα κορτικοστεροειδή (βλέπε παράγραφο 5.2). Συστηματικές επιδράσεις κορτικοστεροειδών: Συστηματικές επιδράσεις μπορεί να παρουσιαστούν με οποιοδήποτε εισπνεόμενο κορτικοστεροειδές, ιδιαίτερα αν χορηγείται σε υψηλές δόσεις για μεγάλες περιόδους. Αυτές οι επιδράσεις είναι πολύ λιγότερο πιθανό να συμβούν σε σχέση με τα από του στόματος κορτικοστεροειδή. Οι πιθανές συστηματικές επιδράσεις περιλαμβάνουν σύνδρομο Cushing, χαρακτηριστικά συνδρόμου που προσομοιάζει με σύνδρομο Cushing, καταστολή των επινεφριδίων, μείωση της οστικής πυκνότητας, καθυστερημένη ανάπτυξη σε παιδιά και εφήβους, καταρράκτης και γλαύκωμα και σπανιότερα μία σειρά ψυχολογικών ή συμπεριφορικών επιδράσεων συμπεριλαμβανομένων ψυχοκινητικής υπερδραστηριότητας, διαταραχές ύπνου, άγχος, κατάθλιψη ή επιθετικότητα (ιδιαίτερα σε παιδιά). Ο συνδυασμός φουροϊκής φλουτικαζόνης/βιλαντερόλης θα πρέπει να χορηγείται με προσοχή σε ασθενείς με πνευμονική φυματίωση ή σε ασθενείς με χρόνιες ή μη αντιμετωπιζόμενες λοιμώξεις. Οπτική διαταραχή: Ενδέχεται να αναφερθεί οπτική διαταραχή με τη συστηματική και τοπική χρήση κορτικοστεροειδών. Εάν ένας ασθενής παρουσιάζει συμπτώματα, όπως θαμπή όραση ή άλλες οπτικές διαταραχές, τότε θα πρέπει να εξετάζεται το ενδεχόμενο παραπομπής του ασθενούς σε οφθαλμίατρο για την αξιολόγηση των πιθανών αιτιών που ενδέχεται να περιλαμβάνουν καταρράκτη, γλαύκωμα ή σπάνιες ασθένειες, όπως κεντρική ορώδης χοριοαμφιβληστροειδοπάθεια (ΚΟΧΑ) και που έχουν αναφερθεί μετά τη χρήση συστηματικών και τοπικών κορτικοστεροειδών. Υπεργλυκαιμία: Έχουν υπάρξει αναφορές αυξήσεων των επιπέδων της γλυκόζης στο αίμα σε διαβητικούς ασθενείς και αυτό θα πρέπει να λαμβάνεται υπόψη κατά τη χορήγηση σε ασθενείς με ιστορικό σακχαρώδους διαβήτη. Πνευμονία σε ασθενείς με ΧΑΠ: Αύξηση στη συχνότητα εμφάνισης της πνευμονίας, συμπεριλαμβανομένης της πνευμονίας που απαιτεί νοσηλεία, έχει παρατηρηθεί σε ασθενείς με ΧΑΠ που λαμβάνουν εισπνεόμενα κορτικοστεροειδή. Υπάρχουν κάποιες ενδείξεις αυξημένου κινδύνου πνευμονίας με την αύξηση της δόσης στεροειδών, αλλά αυτό δεν έχει αποδειχθεί με βεβαιότητα σε όλες τις μελέτες. Δεν υπάρχουν οριστικές κλινικές ενδείξεις για διαφορές εντός της κατηγορίας ως προς το μέγεθος του κινδύνου πνευμονίας μεταξύ προϊόντων εισπνεόμενων κορτικοστεροειδών. Οι γιατροί θα πρέπει να παραμένουν σε εγρήγορση για πιθανή ανάπτυξη πνευμονίας σε ασθενείς με ΧΑΠ καθώς τα κλινικά χαρακτηριστικά αυτών των λοιμώξεων επικαλύπτονται με τα συμπτώματα των παροξύνσεων της ΧΑΠ. Οι παράγοντες κινδύνου για πνευμονία σε ασθενείς με ΧΑΠ περιλαμβάνουν το

κάπνισμα, τη μεγαλύτερη ηλικία, το χαμηλό δείκτη μάζας σώματος (ΔΜΣ) και τη σοβαρή ΧΑΠ. Πνευμονία σε ασθενείς με άσθμα: Η συχνότητα εμφάνισης πνευμονίας σε ασθενείς με άσθμα ήταν συχνή στην υψηλότερη δόση. Η συχνότητα εμφάνισης πνευμονίας σε ασθενείς με άσθμα που έλαβαν συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης 184/22 μικρογραμμαρίων ήταν αριθμητικά υψηλότερη σε σχέση με αυτούς που έλαβαν το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης των 92/22 μικρογραμμαρίων ή εικονικό φάρμακο (βλέπε παράγραφο 4.8). Δεν εντοπίστηκαν παράγοντες κινδύνου. Έκδοχα: Οι ασθενείς με σπάνια κληρονομικά προβλήματα δυσανεξίας στη γαλακτόζη, ολική έλλειψη λακτάσης ή δυσαπορρόφηση γλυκόζης-γαλακτόζης δεν πρέπει να χρησιμοποιήσουν αυτό το φαρμακευτικό προϊόν.

4.5 Αλληλεπιδράσεις με άλλα φαρμακευτικά προϊόντα και άλλες μορφές αλληλεπίδρασης: Κλινικά σημαντικές φαρμακευτικές αλληλεπιδράσεις με το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης σε κλινικές δόσεις θεωρούνται μη πιθανές λόγω των χαμηλών συγκεντρώσεων που επιτυγχάνονται στο πλάσμα μετά την εισπνοή της δόσης. Αλληλεπίδραση με β-αναστολείς: Οι β_2-αδρενεργικοί αναστολείς μπορεί να εξασθενίσουν ή να ανταγωνίζονται τη δράση των β_2-αδρενεργικών αγωνιστών. Θα πρέπει να αποφεύγεται η ταυτόχρονη χρήση μη εκλεκτικών και εκλεκτικών β_2-αδρενεργικών αναστολέων, εκτός εάν υπάρχουν σοβαροί λόγοι για τη χρήση τους. Αλληλεπίδραση με αναστολείς του CYP3A4: Τόσο η φουροϊκή φλουτικαζόνη όσο και η βιλαντερόλη αποβάλλονται ταχέως μέσω εκτεταμένου μεταβολισμού πρώτης διόδου με τη διαμεσολάβηση του ηπατικού κυτοχρώματος CYP3A4. Συνιστάται προσοχή κατά τη συγχορήγηση με ισχυρούς αναστολείς του CYP3A4 (π.χ., κετοκοναζόλη, ριτοναβίρη, προϊόντα που περιέχουν κομπισιστάτη) καθώς υπάρχει πιθανότητα αυξημένης συστηματικής έκθεσης τόσο στη φουροϊκή φλουτικαζόνη όσο και στη βιλαντερόλη. Η συγχορήγηση πρέπει να αποφεύγεται εκτός αν το όφελος υπερτερεί του αυξημένου κινδύνου συστηματικών ανεπιθύμητων ενεργειών των κορτικοστεροειδών, στην οποία περίπτωση οι ασθενείς θα πρέπει να παρακολουθούνται για συστηματικές ανεπιθύμητες ενέργειες των κορτικοστεροειδών. Πραγματοποιήθηκε επαναλαμβανόμενης δόσης μελέτη φαρμακευτικής αλληλεπίδρασης του CYP3A4 σε υγιή άτομα με το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης (184/22 μικρογραμμάρια) και τον ισχυρό αναστολέα του CYP3A4 κετοκοναζόλη (400 mg). Η συγχορήγηση αύξησε τη μέση $AUC_{(0-24)}$ και C_{max} της φουροϊκής φλουτικαζόνης κατά 36% και 33%, αντίστοιχα. Η αύξηση της έκθεσης στη φουροϊκή φλουτικαζόνη συσχετίστηκε με μία μείωση της τάξεως του 27% της σταθμισμένης μέσης τιμής της κορτιζόλης ορού σε διάστημα 0 24 ωρών. Η συγχορήγηση αύξησε τη μέση $AUC_{(0-h)}$ και C_{max} της βιλαντερόλης κατά 65% και 22%, αντίστοιχα. Η αύξηση της έκθεσης στη βιλαντερόλη δεν συσχετίστηκε με αύξηση των σχετιζόμενων με τους β_2-αγωνιστές συστηματικών επιδράσεων στην καρδιακή συχνότητα, το κάλιο αίματος ή το διάστημα QTcF. Αλληλεπίδραση με αναστολείς της P-γλυκοπρωτεΐνης: Η φουροϊκή φλουτικαζόνη και η βιλαντερόλη αποτελούν υποστρώματα της P-γλυκοπρωτεΐνης (P-gp). Μία κλινική φαρμακολογική μελέτη που διενεργήθηκε σε υγιή άτομα στα οποία συγχορηγήθηκε η βιλαντερόλη και ο ισχυρός για την P-gp και μέτριος για το CYP3A4 αναστολέας βεραπαμίλη, δεν κατέδειξε καμία σημαντική επίδραση στη φαρμακοκινητική της βιλαντερόλης. Δεν έχουν διενεργηθεί κλινικές φαρμακολογικές μελέτες με ειδικό αναστολέα της P-gp και φουροϊκή φλουτικαζόνη. Συμπαθομιμητικά φαρμακευτικά προϊόντα: Η ταυτόχρονη χορήγηση άλλων συμπαθομιμητικών φαρμακευτικών προϊόντων (μεμονωμένα ή ως μέρος συνδυαστικής θεραπείας) μπορεί να ενισχύσει τις ανεπιθύμητες ενέργειες που προκαλούνται από το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης. Το Relvar Ellipta δεν θα πρέπει να χρησιμοποιείται σε συνδυασμό με άλλους μακράς δράσης β_2-αδρενεργικούς αγωνιστές η φαρμακευτικά προϊόντα που περιέχουν μακράς δράσης β_2-αδρενεργικούς αγωνιστές. Παιδιατρικός πληθυσμός: Μελέτες αλληλεπιδράσεων έχουν πραγματοποιηθεί μόνο σε ενήλικες.

4.6 Γονιμότητα, κύηση και γαλουχία: Κύηση: Μελέτες σε ζώα κατέδειξαν τοξικότητα στην αναπαραγωγική ικανότητα σε εκθέσεις οι οποίες δεν είναι κλινικά σημαντικές (βλέπε παράγραφο 5.3). Δεν διατίθενται ή είναι περιορισμένα τα δεδομένα από τη χρήση της φουροϊκής φλουτικαζόνης και της vilanterol trifenatate στις έγκυες γυναίκες. Η χορήγηση του συνδυασμού φουροϊκής φλουτικαζόνης/βιλαντερόλης σε έγκυες γυναίκες θα πρέπει να εξετάζεται μόνο αν το αναμενόμενο όφελος για τη μητέρα είναι μεγαλύτερο από οποιοδήποτε δυνητικό κίνδυνο για το έμβρυο. Θηλασμός: Υπάρχουν ανεπαρκείς πληροφορίες σχετικά με την απέκκριση της φουροϊκής φλουτικαζόνης ή της vilanterol trifenatate και/ή των μεταβολιτών στο ανθρώπινο γάλα. Ωστόσο, άλλα κορτικοστεροειδή και β_2-αγωνιστές ανιχνεύονται στο ανθρώπινο γάλα (βλέπε παράγραφο 5.3). Ο κίνδυνος για τα νεογνά/ βρέφη που θηλάζουν δεν μπορεί να αποκλειστεί. Πρέπει να αποφασιστεί εάν θα διακοπεί ο θηλασμός ή θα διακοπεί η θεραπεία με το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης λαμβάνοντας υπόψη το όφελος του θηλασμού για το παιδί και το όφελος της θεραπείας για τη γυναίκα. Γονιμότητα: Δεν υπάρχουν δεδομένα σχετικά με τη γονιμότητα σε ανθρώπους. Μελέτες σε ζώα δεν έδειξαν επίδραση του συνδυασμού φουροϊκής φλουτικαζόνης/βιλαντερόλης trifenatate στη γονιμότητα (βλέπε παράγραφο 5.3).

4.7 Επιδράσεις στην ικανότητα οδήγησης και χειρισμού μηχανημάτων: Η φουροϊκή φλουτικαζόνη ή η βιλαντερόλη δεν έχουν καμία ή έχουν ασήμαντη επίδραση στην ικανότητα οδήγησης και χειρισμού μηχανημάτων.

4.8 Ανεπιθύμητες ενέργειες: Περίληψη του προφίλ ασφάλειας: Χρησιμοποιήθηκαν δεδομένα από μεγάλες κλινικές δοκιμές του άσθματος και της ΧΑΠ για τον προσδιορισμό της συχνότητας εμφάνισης των ανεπιθύμητων ενεργειών που σχετίζονται με το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης. Στο πρόγραμμα κλινικής ανάπτυξης για το άσθμα συμπεριλήφθηκαν συνολικά 7.034 ασθενείς σε μία συγκεντρωτική αξιολόγηση των ανεπιθύμητων ενεργειών. Στο πρόγραμμα κλινικής ανάπτυξης για τη ΧΑΠ συμπεριλήφθηκαν συνολικά 6.237 ασθενείς σε μία συγκεντρωτική αξιολόγηση των ανεπιθύμητων ενεργειών. Οι ανεπιθύμητες ενέργειες που αναφέρθηκαν συχνότερα με τη φουροϊκή φλουτικαζόνη και τη βιλαντερόλη ήταν κεφαλαλγία και ρινοφαρυγγίτιδα. Με εξαίρεση την πνευμονία και τα κατάγματα, το προφίλ ασφάλειας ήταν παρόμοιο στους ασθενείς με άσθμα και ΧΑΠ. Κατά τη διάρκεια κλινικών μελετών, πνευμονία και κατάγματα παρατηρήθηκαν πιο συχνά σε ασθενείς με ΧΑΠ.

Πίνακας ανεπιθύμητων ενεργειών: Οι ανεπιθύμητες αντιδράσεις παρατίθενται ανά κατηγορία οργανικού συστήματος και συχνότητα. Για την ταξινόμηση των συχνοτήτων, χρησιμοποιήθηκε η παρακάτω συνθήκη: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥ 1/10.000 έως< 1/1.000), πολύ σπάνιες (< 1/10.000). Εντός κάθε ομάδας συχνότητας, οι ανεπιθύμητες αντιδράσεις παρουσιάζονται κατά σειρά φθίνουσας σοβαρότητας.

Κατηγορία/Οργανικό σύστημα	Ανεπιθύμητες ενέργειες	Συχνότητα
Λοιμώξεις και παρασιτώσεις	Πνευμονία*, Λοίμωξη του ανώτερου αναπνευστικού, Βρογχίτιδα, Γρίπη, Καντιντίαση του στόματος και του φάρυγγα	Συχνή
Διαταραχές του ανοσοποιητικού συστήματος	Αντιδράσεις υπερευαισθησίας, συμπεριλαμβανομένης αναφυλαξίας, αγγειοοιδήματος, εξανθήματος και κνίδωσης	Σπάνια
Διαταραχές του μεταβολισμού και της θρέψης	Υπεργλυκαιμία	Όχι συχνή
Ψυχιατρικές διαταραχές	Άγχος	Σπάνια
Διαταραχές του νευρικού συστήματος	Κεφαλαλγία Τρόμος	Πολύ συχνή Σπάνια
Οφθαλμικές διαταραχές	Όραση θαμπή (βλέπε παράγραφο 4.4)	Όχι συχνή
Καρδιακές διαταραχές	Έκτακτες συστολές Αίσθημα παλμών Ταχυκαρδία	Όχι συχνή Σπάνια Σπάνια
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωράκιου	Ρινοφαρυγγίτιδα Στοματοφαρυγγικό άλγος Παραρρινοκολπίτιδα Φαρυγγίτιδα Ρινίτιδα Βήχας Δυσφωνία Παράδοξος βρογχόσπασμος	Πολύ συχνή Συχνή Σπάνια
Διαταραχές του γαστρεντερικού	Κοιλιακό άλγος	Συχνή
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού	Αρθραλγία, Οσφυαλγία, Κατάγματα**, Μυϊκοί σπασμοί	Συχνή
Γενικές διαταραχές και καταστάσεις της οδού χορήγησης	Πυρεξία	Συχνή

*, ** Βλέπε παρακάτω «Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών»

Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών

*Πνευμονία (βλέπε παράγραφο 4.4): Σε μία ενιαία ανάλυση των δύο επαναληπτικών μελετών ενός έτους σε μέτρια έως βαριά ΧΑΠ (μέσος προβλεπόμενος FEV1 μετά το βρογχοδιασταλτικό κατά την προκαταρκτική αξιολόγηση 45%, τυπική απόκλιση (SD) 13%) με παροξυσμό κατά το προηγούμενο έτος (n = 3255), ο αριθμός των εκδηλώσεων πνευμονίας ανά 1000 έτη ασθενών ήταν 97.9 για την FF/VI 184/22, 85.7 για την FF/VI 92/22 και 42.3 για την ομάδα VI 22. Για σοβαρή πνευμονία ο αντίστοιχος αριθμός των συμβάντων ανά 1000 έτη ασθενών ήταν 33.6, 35.5 και 7.6 αντίστοιχα, ενώ για σοβαρή πνευμονία οι αντίστοιχες εκδηλώσεις ανά 1000 έτη ασθενών ήταν 35.1 για την FF/VI 184/22, 42.9 για την FF/VI 92 /22, 12.1 για την VI 22. Τέλος, οι προσαρμοσμένες στην έκθεση περιπτώσεις θανατηφόρας πνευμονίας ήταν 8.8 για την FF/VI 184/22 έναντι 1.5 για την FF/VI 92/22 και 0 για την VI 22. Σε μια ελεγχόμενη με εικονικό φάρμακο μελέτη (SUMMIT) σε συμμετέχοντες με μέτρια ΧΑΠ (μέσο ποσοστό FEV1 μετά το βρογχοδιασταλτικό κατά την προκαταρκτική αξιολόγηση 60%, SD 6%) και ιστορικό ή αυξημένο κίνδυνο εμφάνισης καρδιαγγειακής νόσου, η συχνότητα εμφάνισης πνευμονίας με τη FF/VI, τη FF, τη VI και το εικονικό φάρμακο είχε ως εξής: ανεπιθύμητα συμβάντα (6%, 5%, 4%, 5%), σοβαρά ανεπιθύμητα συμβάντα (3%, 4%, 3%, 3%), αξιολογημένοι θάνατοι λόγω πνευμονίας κατά τη θεραπεία (0,3%, 0,2%, 0,1%, 0,2%), ενώ τα προσαρμοσμένα ως προς την έκθεση ποσοστά (ανά 1.000 έτη θεραπείας) ήταν: ανεπιθύμητα συμβάντα (39,5, 42,4, 27,7, 38,4), σοβαρά ανεπιθύμητα συμβάντα (22,4, 25,1, 16,4, 22,2), αξιολογημένοι θάνατοι λόγω πνευμονίας κατά τη θεραπεία (1,8, 1,5, 0,9, 1,4), αντιστοίχως. Σε μία ενιαία ανάλυση των 11 μελετών στο άσθμα (7.034 ασθενείς), η συχνότητα εμφάνισης πνευμονίας ανά 1000 έτη ασθενών ήταν 18.4 για την FF/VI 184/22 έναντι 9.6 για την FF/VI 92/22 και 8.0 για την ομάδα του εικονικού φαρμάκου.

*Κατάγματα: Σε δύο πανομοιότυπες μελέτες διάρκειας 12 μηνών που διενεργήθηκαν σε ένα σύνολο 3.255 ασθενών με ΧΑΠ, η συχνότητα εμφάνισης οστικών καταγμάτων συνολικά ήταν χαμηλή σε όλες τις ομάδες θεραπείας, με υψηλότερη συχνότητα εμφάνισης σε όλες τις ομάδες του Relvar Ellipta (2%) σε σχέση με την ομάδα της βιλαντερόλης των 22 μικρογραμμαρίων (<1%). Παρόλο που παρατηρήθηκαν περισσότερα κατάγματα στις ομάδες του Relvar Ellipta σε σχέση με την ομάδα της βιλαντερόλης των 22 μικρογραμμαρίων, τα κατάγματα που κατά κανόνα σχετίζονται με τη χρήση κορτικοστεροειδών (π.χ., συμπίεση νωτιαίου μυελού /κατάγματα θωρακοσφυϊκών σπονδύλων, κατάγματα ισχίου και κατώτερης) εμφανίστηκαν σε <1% των σκελών θεραπείας με Relvar Ellipta και βιλαντερόλη. Στη μελέτη SUMMIT, η συχνότητα εμφάνισης όλων των συμβάντων κατάγματος με τη FF/VI, τη FF, τη VI και το εικονικό φάρμακο ήταν 2% σε κάθε σκέλος – το ποσοστό των καταγμάτων που συνήθως σχετίζονται με τη χρήση ICS ήταν μικρότερο από 1% σε κάθε σκέλος. Τα προσαρμοσμένα ως προς την έκθεση ποσοστά (ανά 1.000 έτη θεραπείας) για το σύνολο των συμβάντων κατάγματος ήταν 13,6, 12,8, 13,2, 11,5 αντιστοίχως – το ποσοστό των καταγμάτων που συνήθως σχετίζονται με τη χρήση ICS ήταν 3,4, 3,9, 2,4, 2,1 αντιστοίχως. Σε μία ενιαία ανάλυση 11 μελετών για το άσθμα (7.034 ασθενείς), η συχνότητα εμφάνισης καταγμάτων ήταν <1% και συνήθως συνδέονταν με τραυματισμό.

Αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών Η αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών μετά από τη χορήγηση άδειας κυκλοφορίας του φαρμακευτικού προϊόντος είναι σημαντική. Επιτρέπει τη συνεχή παρακολούθηση της σχέσης οφέλους/κινδύνου του φαρμακευτικού προϊόντος. Ζητείται από τους επαγγελματίες υγείας να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες μέσω του εθνικού συστήματος αναφοράς που αναγράφεται παρακάτω: Ελλάδα, Εθνικός Οργανισμός Φαρμάκων, Μεσογείων 284, GR-15562 Χολαργός, Αθήνα. Τηλ: + 30 2132040380/337, Φαξ: + 30 2106549585. Ιστότοπος: http://www.eof.gr. Κύπρος, Φαρμακευτικές Υπηρεσίες Υπουργείο Υγείας, CY-1475 Λευκωσία, Τηλ: + 357 22608607, Φαξ: + 357 22608649, Ιστότοπος: www.moh.gov.cy/phs.

4.9 Υπερδοσολογία: Συμπτώματα και σημεία: Η υπερδοσολογία από το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης μπορεί να προκαλέσει σημεία και συμπτώματα λόγω της δράσης των επιμέρους συστατικών, συμπεριλαμβανομένων εκείνων που έχουν παρατηρηθεί με υπερδοσολογία από άλλους β_2-αγωνιστές και σύμφωνα με τις γνωστές επιδράσεις της κατηγορίας των εισπνεόμενων κορτικοστεροειδών (βλέπε παράγραφο 4.4).

Αντιμετώπιση: Δεν υπάρχει συγκεκριμένη θεραπεία για την υπερδοσολογία από το συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης. Αν συμβεί υπερδοσολογία, ο ασθενής θα πρέπει να αντιμετωπιστεί υποστηρικτικά με την κατάλληλη παρακολούθηση κατά περίπτωση. Ο καρδιοεκλεκτικός β αποκλεισμός θα πρέπει να εξετάζεται μόνο για σημαντικές επιδράσεις υπερδοσολογίας από βιλαντερόλη, οι οποίες είναι κλινικά ανησυχητικές και δεν ανταποκρίνονται σε υποστηρικτικά μέτρα. Τα φαρμακευτικά προϊόντα που περιέχουν καρδιοεκλεκτικούς β-αναστολείς θα πρέπει να χρησιμοποιούνται με προσοχή σε ασθενείς με ιστορικό βρογχόσπασμου. Η περαιτέρω αντιμετώπιση θα πρέπει να βασίζεται στις κλινικές ενδείξεις ή τις συστάσεις του εθνικού κέντρου δηλητηριάσεων, εφόσον υπάρχουν.

5. ΦΑΡΜΑΚΟΛΟΓΙΚΕΣ ΙΔΙΟΤΗΤΕΣ.

5.1 Φαρμακοδυναμικές ιδιότητες. Φαρμακοθεραπευτική κατηγορία: Φάρμακα για αποφρακτικές νόσους των αεροφόρων οδών, Αδρενεργικά σε συνδυασμό με κορτικοστεροειδή ή άλλα φάρμακα εξαιρουμένων των αντιχολινεργικών, Κωδικός ATC: R03AK10.

6. ΦΑΡΜΑΚΕΥΤΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ

6.1 Κατάλογος εκδόχων: Μονοϋδρική λακτόζη. Στεατικό μαγνήσιο

6.2 Ασυμβατότητες: Δεν εφαρμόζεται.

6.3 Διάρκεια ζωής: 2 χρόνια. Διάρκεια ζωής κατά τη χρήση μετά το άνοιγμα του δίσκου: 6 εβδομάδες.

6.4 Ιδιαίτερες προφυλάξεις κατά τη φύλαξη του προϊόντος: Μη φυλάσσετε σε θερμοκρασία μεγαλύτερη των 25°C. Αν φυλάσσεται σε ψυγείο, η συσκευή εισπνοών θα πρέπει να αφήνεται να επανέλθει σε θερμοκρασία δωματίου τουλάχιστον μία ώρα πριν από τη χρήση. Να φυλάσσεται στην αρχική συσκευασία ώστε να προστατεύεται από την υγρασία. Γράψτε την ημερομηνία που πρέπει να απορριφθεί η συσκευή εισπνοών, στο χώρο που παρέχεται στην ετικέτα. Η ημερομηνία πρέπει να προστεθεί μόλις η συσκευή εισπνοών αφαιρεθεί από το δίσκο.

6.5 Φύση και συστατικά του περιέκτη: Η συσκευή εισπνοών αποτελείται από ένα σώμα χρώματος ανοικτού γκρι, ένα κάλυμμα επιστομίου χρώματος κίτρινου και ένα δοσομετρητή, συσκευασμένα σε δίσκο από φύλλο αλουμινίου που περιέχει ένα φακελάκιο με αφυγραντικό από silica gel. Ο δίσκος είναι σφραγισμένος με αφαιρούμενο κάλυμμα από φύλλο αλουμινίου. Η συσκευή εισπνοών είναι μία πολυσύνθετη συσκευή που αποτελείται από πολυπροπυλένιο, πολυαιθυλένιο υψηλής πυκνότητας, πολυοξυμεθυλένιο, τερεφθαλικό πολυβουτυλένιο, ακρυλονιτρικό βουταδιενικό στυρένιο, πολυανθρακικό και ανοξείδωτο χάλυβα. Η συσκευή εισπνοών περιέχει δύο ταινίες από φύλλο αλουμινίου 14 ή 30 δόσεων. Συσκευασίες Συσκευών Εισπνοών των 14 ή 30 δόσεων. Πολλαπλή συσκευασία Συσκευών Εισπνοών των 3 x 30 δόσεων. Μπορεί να μην κυκλοφορούν όλες οι συσκευασίες.

6.6 Ιδιαίτερες προφυλάξεις απόρριψης: Κάθε αχρησιμοποίητο φαρμακευτικό προϊόν ή υπόλειμμα πρέπει να απορρίπτεται σύμφωνα με τις κατά τόπους ισχύουσες σχετικές διατάξεις.

7. ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ: GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ιρλανδία.

8. ΑΡΙΘΜΟΣ(ΟΙ) ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ: EU/1/13/886/004, EU/1/13/886/005, EU/1/13/886/006

9. ΗΜΕΡΟΜΗΝΙΑ ΠΡΩΤΗΣ ΕΓΚΡΙΣΗΣ / ΑΝΑΝΕΩΣΗΣ ΤΗΣ ΑΔΕΙΑΣ: Ημερομηνία πρώτης έγκρισης: 13 Νοεμβρίου 2013. Ημερομηνία τελευταίας ανανέωσης: 26 Ιουλίου 2018

10. ΗΜΕΡΟΜΗΝΙΑ ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ: 15/08/2022.

Λεπτομερείς πληροφορίες για το παρόν φαρμακευτικό προϊόν είναι διαθέσιμες στο δικτυακό τόπο του Ευρωπαϊκού Οργανισμού Φαρμάκων http://www.ema.europa.eu.

GR-REL-4-01-2023

Βοηθήστε να γίνουν τα φάρμακα πιο ασφαλή και Αναφέρετε ΟΛΕΣ τις ανεπιθύμητες ενέργειες για ΟΛΑ τα φάρμακα Συμπληρώνοντας την «ΚΙΤΡΙΝΗ ΚΑΡΤΑ»

Τοπικός Αντιπρόσωπος

Menarini Hellas

Menarini Hellas A.E.
Πάτμου 16-18, 151 23 Μαρούσι
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www.menarini.gr

ΣΥΝΤΟΜΗ ΠΕΡΙΛΗΨΗ ΤΩΝ ΧΑΡΑΚΤΗΡΙΣΤΙΚΩΝ ΤΟΥ ΠΡΟΪΟΝΤΟΣ **ANORO Ellipta**

▼Το φάρμακο αυτό τελεί υπό συμπληρωματική παρακολούθηση. Αυτό θα επιτρέψει τον ταχύ προσδιορισμό νέων πληροφοριών ασφάλειας. Ζητείται από τους επαγγελματίες του τομέα της υγειονομικής περίθαλψης να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες. Βλ. παράγραφο 4.8 για τον τρόπο αναφοράς ανεπιθύμητων ενεργειών.

1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΙΟΝΤΟΣ. ANORO ELLIPTA 55 μικρογραμμάρια/22 μικρογραμμάρια, κόνις για εισπνοή, σε δόσεις.

2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ. Η παρεχόμενη δόση κάθε εφάπαξ εισπνοής (η δόση που εξέρχεται από το επιστόμιο) είναι 65 μικρογραμμάρια βρωμιούχου ουμεκλιδινίου που ισοδυναμούν με 55 μικρογραμμάρια ουμεκλιδινίου και 22 μικρογραμμάρια βιλαντερόλης (ως trifenatate). Αυτό αντιστοιχεί σε προκαθορισμένη δόση 74,2 μικρογραμμαρίων βρωμιούχου ουμεκλιδινίου που ισοδυναμούν με 62,5 μικρογραμμάρια ουμεκλιδινίου και 25 μικρογραμμάρια βιλαντερόλης (ως trifenatate). Έκδοχο με γνωστές δράσεις Κάθε παρεχόμενη δόση περιέχει περίπου 25 mg λακτόζης (ως μονοϋδρική). Για τον πλήρη κατάλογο των εκδόχων, βλ. παράγραφο 6.1.

3. ΦΑΡΜΑΚΟΤΕΧΝΙΚΗ ΜΟΡΦΗ. Κόνις για εισπνοή, σε δόσεις (κόνις για εισπνοή). Λευκή κόνις σε συσκευή εισπνοών (ELLIPTA) χρώματος ανοικτού γκρι, με κάλυμμα επιστομίου χρώματος κόκκινου και δοσομετρητή.

4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ.

4.1 Θεραπευτικές ενδείξεις. Το ANORO ELLIPTA ενδείκνυται ως βρογχοδιασταλτική θεραπεία συντήρησης για την ανακούφιση των συμπτωμάτων σε ενήλικες ασθενείς με χρόνια αποφρακτική πνευμονοπάθεια (ΧΑΠ).

4.2 Δοσολογία και τρόπος χορήγησης. Δοσολογία. *Ενήλικες.* Η συνιστώμενη δόση είναι μία εισπνοή ANORO ELLIPTA 55/22 μικρογραμμαρίων άπαξ ημερησίως. Το ANORO ELLIPTA πρέπει να χορηγείται την ίδια ώρα της ημέρας, κάθε ημέρα, προκειμένου να διατηρηθεί η βρογχοδιαστολή. Η μέγιστη δόση είναι μία εισπνοή ANORO ELLIPTA 55/22 μικρογραμμαρίων άπαξ ημερησίως. *Ειδικοί πληθυσμοί.* Ηλικιωμένοι ασθενείς. Δεν απαιτείται προσαρμογή της δόσης σε ασθενείς ηλικίας άνω των 65 ετών. Νεφρική δυσλειτουργία. Δεν απαιτείται προσαρμογή της δόσης σε ασθενείς με νεφρική δυσλειτουργία. Ηπατική δυσλειτουργία. Δεν απαιτείται προσαρμογή της δόσης σε ασθενείς με ήπια έως μέτρια ηπατική δυσλειτουργία. Η χρήση του ANORO ELLIPTA δεν έχει μελετηθεί σε ασθενείς με σοβαρή ηπατική δυσλειτουργία και θα πρέπει να χρησιμοποιείται με προσοχή. *Παιδιατρικός πληθυσμός.* Δεν υπάρχει σχετική χρήση του ANORO ELLIPTA στον παιδιατρικό πληθυσμό (ηλικίας κάτω των 18 ετών) για την ένδειξη της ΧΑΠ. Τρόπος χορήγησης. Το ANORO ELLIPTA είναι αποκλειστικά για εισπνεόμενη χρήση. Οι παρακάτω οδηγίες για την συσκευή εισπνοών 30 δόσεων (επαρκεί για 30 ημέρες) ισχύουν επίσης και για την συσκευή εισπνοών 7 δόσεων (επαρκεί για 7 ημέρες). Η συσκευή εισπνοών Ellipta περιέχει προκαθορισμένες δόσεις και είναι έτοιμη προς χρήση. Η συσκευή εισπνοών συσκευάζεται σε ένα δίσκο που περιέχει ένα φακελίσκο με αφυγραντικό για τη μείωση της υγρασίας. Ο φακελίσκος με το αφυγραντικό πρέπει να απορρίπτεται και δεν πρέπει να ανοίγεται, να καταναλώνεται ή να εισπνέεται. Ο ασθενής πρέπει να συμβουλεύεται να μην ανοίξει το δίσκο μέχρι να είναι έτοιμος να εισπνεύσει τη δόση. Η συσκευή εισπνοών θα βρίσκεται στην «κλειστή» θέση όταν τη βγάλετε για πρώτη φορά από το σφραγισμένο δίσκο. Η ημερομηνία "Απορρίπτε μετά από" πρέπει να είναι γραμμένη στην ετικέτα της συσκευής εισπνοών στο χώρο που παρέχεται. Η ημερομηνία "Απορρίπτε μετά από" είναι 6 εβδομάδες από την ημερομηνία ανοίγματος του δίσκου. Μετά την ημερομηνία αυτή η συσκευή εισπνοών δεν θα πρέπει πλέον να χρησιμοποιείται. Ο δίσκος μπορεί να απορριφθεί μετά το πρώτο άνοιγμα. Εάν το κάλυμμα της συσκευής εισπνοών ανοιχτεί και κλειστεί χωρίς να εισπνεύσετε το φαρμακευτικό προϊόν, η δόση θα χαθεί. Η χαμένη δόση θα παραμείνει με ασφάλεια στο εσωτερικό της συσκευής εισπνοών, αλλά δεν θα είναι πλέον διαθέσιμη για εισπνοή. Δεν είναι δυνατή η τυχαία λήψη επιπλέον ποσότητας φαρμάκου ή διπλής δόσης με μία εισπνοή.

Οδηγίες χρήσης. α) Προετοιμάστε μια δόση. Ανοίξτε το κάλυμμα όταν είστε έτοιμοι να εισπνεύσετε τη δόση. Η συσκευή εισπνοών δεν πρέπει να ανακινείται. Μετακινείστε το κάλυμμα προς τα κάτω μέχρι να ακουστεί ένα «κλικ». Το φάρμακο είναι πλέον έτοιμο για εισπνοή. Ο δοσομετρητής μετρά αντίστροφα κατά 1 για επιβεβαίωση. Αν ο δοσομετρητής δεν μετρήσει αντίστροφα καθώς ακούγεται το «κλικ», το φάρμακο δεν θα χορηγηθεί από τη συσκευή εισπνοών και πρέπει να επιστραφεί σε ένα φαρμακοποιό για να σας συμβουλέψει.

β) Πώς να εισπνεύσετε το φάρμακο. Η συσκευή εισπνοών πρέπει να κρατείται μακριά από το στόμα καθώς εκπνέετε στο βαθμό που αισθάνεστε άνετα. Αλλά μην εκπνέετε μέσα στη συσκευή. Το επιστόμιο πρέπει να τοποθετηθεί ανάμεσα στα χείλη και τα χείλη πρέπει να κλείσουν σφιχτά γύρω από αυτό. Οι αεραγωγοί δεν πρέπει να φράζονται με τα δάχτυλα κατά τη διάρκεια της χρήσης. • Πάρτε μια μακρά, σταθερή, βαθιά εισπνοή. Αυτή η αναπνοή πρέπει να κρατηθεί όσο το δυνατόν περισσότερο (τουλάχιστον 3-4 δευτερόλεπτα). • Απομακρύνετε τη συσκευή εισπνοών από το στόμα. • Εκπνεύστε αργά και απαλά. Είναι πιθανό να μην μπορέσετε να γευτείτε ή να αισθανθείτε το φάρμακο, ακόμη και όταν χρησιμοποιείτε σωστά τη συσκευή εισπνοών. Το επιστόμιο της συσκευής εισπνοών μπορεί να καθαριστεί χρησιμοποιώντας ένα στεγνό χαρτομάντιλο πριν το κλείσιμο του καλύμματος.

γ) Κλείστε τη συσκευή εισπνοών. Σπρώξτε το κάλυμμα προς τα επάνω όσο περισσότερο γίνεται για να καλύψετε το επιστόμιο.

4.3 Αντενδείξεις. Υπερευαισθησία στις δραστικές ουσίες ή σε κάποιο από τα έκδοχα που αναφέρονται στην παράγραφο 6.1.

4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση. *Άσθμα.* Ο συνδυασμός ουμεκλιδινίου/βιλαντερόλη δεν πρέπει να χρησιμοποιείται σε ασθενείς με άσθμα καθώς δεν έχει μελετηθεί σε αυτόν τον πληθυσμό ασθενών. *Παράδοξος βρογχόσπασμος.* Η χορήγηση του συνδυασμού ουμεκλιδινίου/βιλαντερόλη μπορεί να οδηγήσει σε παράδοξο βρογχόσπασμο που ενδέχεται να είναι απειλητικός για τη ζωή. Η θεραπεία με το συνδυασμό ουμεκλιδινίου/βιλαντερόλη θα πρέπει να διακοπεί άμεσα εάν παρουσιαστεί παράδοξος βρογχόσπασμος και αν κριθεί απαραίτητο, θα πρέπει να ξεκινήσει εναλλακτική θεραπεία. Δεν ενδείκνυται για χρήση σε οξείες καταστάσεις. Ο συνδυασμός ουμεκλιδινίου/βιλαντερόλη δεν ενδείκνυται για την αντιμετώπιση οξέων επεισοδίων βρογχόσπασμου. *Επιδείνωση νόσου.* Η αύξηση της χρήσης βρογχοδιασταλτικών βραχείας δράσης για την ανακούφιση από τα συμπτώματα υποδηλώνει επιδείνωση του ελέγχου. Σε περίπτωση επιδείνωσης της ΧΑΠ κατά τη διάρκεια της θεραπείας με το συνδυασμό ουμεκλιδινίου/βιλαντερόλη, θα πρέπει να πραγματοποιηθεί εκ νέου αξιολόγηση του ασθενούς και του θεραπευτικού σχήματος για τη ΧΑΠ. *Επιδράσεις στο καρδιαγγειακό.* Επιδράσεις στο καρδιαγγειακό σύστημα, όπως καρδιακές αρρυθμίες, π.χ., κολπική μαρμαρυγή και ταχυκαρδία, μπορεί να παρατηρηθούν μετά τη χορήγηση ανταγωνιστών των μουσκαρινικών υποδοχέων και συμπαθομιμητικών, συμπεριλαμβανομένου του συνδυασμού ουμεκλιδινίο/βιλαντερόλη. Οι ασθενείς με κλινικά σημαντική μη ελεγχόμενη καρδιαγγειακή νόσο εξαιρέθηκαν από τις κλινικές μελέτες. Ως εκ τούτου, ο συνδυασμός ουμεκλιδινίου/βιλαντερόλη θα πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με σοβαρή καρδιαγγειακή νόσο. *Αντιμουσκαρινική δράση.* Ως συνέπεια της αντιμουσκαρινικής του δράσης, ο συνδυασμός ουμεκλιδίνιο/βιλαντερόλη θα πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με κατακράτηση ούρων ή με γλαύκωμα κλειστής γωνίας. *Υποκαλιαιμία.* Οι β_2-αδρενεργικοί αγωνιστές μπορεί να προκαλέσουν σημαντική υποκαλιαιμία σε ορισμένους ασθενείς, η οποία ενδέχεται να οδηγήσει σε καρδιαγγειακές ανεπιθύμητες ενέργειες. Η μείωση του καλίου ορού είναι συνήθως παροδική και δεν απαιτείται θεραπεία αποκατάστασης. Κλινικές επιδράσεις σχετιζόμενες με υποκαλιαιμία δεν παρατηρήθηκαν σε κλινικές μελέτες με το συνδυασμό ουμεκλιδίνιο/βιλαντερόλη στη συνιστώμενη θεραπευτική δόση. Απαιτείται προσοχή όταν ο συνδυασμός ουμεκλιδίνιο/βιλαντερόλη χρησιμοποιείται μαζί με άλλα φαρμακευτικά προϊόντα που έχουν και αυτά τη δυνατότητα πρόκλησης υποκαλιαιμίας (βλέπε παράγραφο 4.5). *Υπεργλυκαιμία.* Οι β_2-αδρενεργικοί αγωνιστές μπορεί να προκαλέσουν παροδική υπεργλυκαιμία σε ορισμένους ασθενείς. Δεν παρατηρήθηκαν σχετιζόμενες με τη θεραπεία κλινικές επιδράσεις στη γλυκόζη πλάσματος σε κλινικές μελέτες με το συνδυασμό ουμεκλιδίνιο/βιλαντερόλη στη συνιστώμενη θεραπευτική δόση. Κατά την έναρξη της θεραπείας με το συνδυασμό ουμεκλιδινίου/βιλαντερόλη, η γλυκόζη πλάσματος θα πρέπει να παρακολουθείται πιο τακτικά σε διαβητικούς ασθενείς. *Συνυπάρχουσες καταστάσεις.* Ο συνδυασμός ουμεκλιδινίου/βιλαντερόλη πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με διαταραχές που συνοδεύονται από σπασμούς ή θυρεοτοξίκωση και σε ασθενείς που εμφανίζουν ασυνήθιστα ευαίσθητοι στους β_2-αδρενεργικούς αγωνιστές. *Έκδοχα.* Αυτό το φαρμακευτικό προϊόν περιέχει λακτόζη. Οι ασθενείς με σπάνια κληρονομικά προβλήματα δυσανεξίας στη γαλακτόζη, ολικής έλλειψης λακτάσης ή δυσαπορρόφησης γλυκόζης-γαλακτόζης δεν πρέπει να χρησιμοποιήσουν αυτό το φαρμακευτικό προϊόν.

4.5 Αλληλεπιδράσεις με άλλα φαρμακευτικά προϊόντα και άλλες μορφές αλληλεπίδρασης. *β-αδρενεργικοί αναστολείς.* Τα φαρμακευτικά προϊόντα που περιέχουν β-αδρενεργικούς αναστολείς μπορεί να εξασθενίσουν ή να ανταγωνίζονται τη δράση των β_2-αδρενεργικών αγωνιστών, όπως η βιλαντερόλη. Θα πρέπει να αποφεύγεται η ταυτόχρονη χρήση μη εκλεκτικών ή εκλεκτικών β-αδρενεργικών αναστολέων, εκτός εάν υπάρχουν σοβαροί λόγοι για τη χρήση τους. *Αλληλεπιδράσεις που βασίζονται στο μεταβολισμό και μεταφορείς.* Η βιλαντερόλη αποτελεί υπόστρωμα του κυτοχρώματος P450 3A4 (CYP3A4). Η ταυτόχρονη χορήγηση ισχυρών αναστολέων του CYP3A4 (π.χ., κετοκοναζόλη, κλαριθρομυκίνη, ιτρακοναζόλη, ριτοναβίρη, τελιθρομυκίνη) μπορεί να αναστείλει το μεταβολισμό της βιλαντερόλης και να αυξήσει τη συστηματική έκθεση σε αυτό. Η συγχορήγηση με κετοκοναζόλη (400 mg) σε υγιείς εθελοντές αύξησε τη μέση AUC(0-t) και C_{max}, της βιλαντερόλης κατά 65% και 22% αντίστοιχα. Η αύξηση της έκθεσης στη βιλαντερόλη δεν σχετίστηκε με αύξηση των συστηματικών επιδράσεων στην καρδιακή συχνότητα, οι οποίες σχετίζονται με τους β-αδρενεργικούς αγωνιστές,αύξηση στο κάλιο αίματος ή στο διάστημα QT (διορθωμένο με χρήση της μεθόδου Fridericia). Συνιστάται προσοχή κατά τη συγχορήγηση του συνδυασμού ουμεκλιδίνιο/βιλαντερόλη με κετοκοναζόλη καθώς και άλλους γνωστούς ισχυρούς αναστολείς του CYP3A4 καθώς υπάρχει πιθανότητα για αυξημένη συστηματική έκθεση στη βιλαντερόλη, που θα μπορούσε να οδηγήσει σε αύξηση της πιθανότητας εμφάνισης ανεπιθύμητων ενεργειών. Η βεραπαμίλη, ένας μέτριος αναστολέας του CYP3A4, δεν επηρέασε σημαντικά τη φαρμακοκινητική της βιλαντερόλης. Το ουμεκλιδίνιο αποτελεί υπόστρωμα του κυτοχρώματος P450 2D6 (CYP2D6). Η φαρμακοκινητική του ουμεκλιδίνιο σε σταθερή κατάσταση αξιολογήθηκε σε υγιείς εθελοντές με έλλειψη CYP2D6 (ασθενείς με πτωχό μεταβολισμό). Δεν παρατηρήθηκε επίδραση στην AUC ή τη C_{max} του ουμεκλιδινίου σε δόση 8 φορές υψηλότερη. Αύξηση περίπου κατά 1,3 φορές της AUC του ουμεκλιδίνιο παρατηρήθηκε σε δόση υψηλότερη κατά 16 φορές χωρίς καμία επίδραση στη C_{max} του ουμεκλιδινίου. Με βάση το εύρος αυτών των μεταβολών, δεν αναμένεται καμία σχετιζόμενη κλινική φαρμακευτική αλληλεπίδραση όταν ο συνδυασμός ουμεκλιδίνιο/βιλαντερόλη συγχορηγείται με αναστολείς του CYP2D6 ή όταν χορηγείται σε ασθενείς με γενετική ανεπάρκεια όσον αφορά τη δράση του CYP2D6 (άτομα με πτωχό μεταβολισμό). Το ουμεκλιδίνιο και η βιλαντερόλη αποτελούν υποστρώματα του διαβιβαστή της P-γλυκοπρωτεΐνης (P-gp). Αξιολογήθηκε η επίδραση του μέτριου αναστολέα του P-gp, βεραπαμίλη (240 mg άπαξ ημερησίως), στη φαρμακοκινητική του ουμεκλιδινίουκαι της βιλαντερόλης σε σταθερή κατάσταση, σε υγιείς εθελοντές. Δεν παρατηρήθηκε επίδραση της βεραπαμίλης στη C_{max} του ουμεκλιδινίουή της βιλαντερόλης. Παρατηρήθηκε αύξηση της AUC του ουμεκλιδινίουκατά 1,4 φορές περίπου χωρίς καμία επίδραση στην AUC της βιλαντερόλης. Με βάση το εύρος αυτών των μεταβολών, δεν αναμένεται καμία σχετιζόμενη κλινική φαρμακευτική αλληλεπίδραση κατά τη συγχορήγηση του συνδυασμού ουμεκλιδίνιο/βιλαντερόλη με αναστολείς της P-gp. *Άλλα αντιμουσκαρινικά και συμπαθομιμητικά.* Η συγχορήγηση του συνδυασμού ουμεκλιδίνιο/βιλαντερόλη με άλλους μακράς δράσης μουσκαρινικούς ανταγωνιστές, μακράς δράσης β_2-αδρενεργικούς αγωνιστές ή φαρμακευτικά προϊόντα που περιέχουν οποιονδήποτε από αυτούς τους παράγοντες, δεν έχει μελετηθεί και δεν συνιστάται, καθώς ενδέχεται να ενισχύσει γνωστές ανεπιθύμητες ενέργειες των εισπνεόμενων μουσκαρινικών ανταγωνιστών ή των β_2 αδρενεργικών αγωνιστών (βλέπε παραγράφου; 4.4 και 4.9). *Υποκαλιαιμία.* Ταυτόχρονη θεραπεία με παράγωγα μεθυλοξανθίνης, στεροειδή ή μη καλιοσυντηρητικά διουρητικά που επάγουν υποκαλιαιμία, μπορεί να ενισχύσει την πιθανή υποκαλιαιμική δράση των β_2-αδρενεργικών αγωνιστών και, επομένως, θα πρέπει να γίνεται με προσοχή (βλέπε παράγραφο 4.4). *Άλλα φαρμακευτικά προϊόντα για την αντιμετώπιση της ΧΑΠ.* Παρόλο που δεν έχουν διεξαχθεί επίσημες *in vivo* μελέτες φαρμακευτικής αλληλεπίδρασης, ο εισπνεόμενος συνδυασμός ουμεκλιδίνιο/βιλαντερόλη έχει χρησιμοποιηθεί ταυτόχρονα με άλλα φαρμακευτικά προϊόντα για την αντιμετώπιση της ΧΑΠ συμπεριλαμβανομένων βραχείας δράσης συμπαθομιμητικών βρογχοδιασταλτικών και εισπνεόμενων κορτικοστεροειδών χωρίς κλινική ένδειξη φαρμακευτικών αλληλεπιδράσεων.

4.6 Γονιμότητα, κύηση και γαλουχία. *Κύηση.* Δεν διατίθενται δεδομένα από τη χρήση του συνδυασμού ουμεκλιδίνιο/βιλαντερόλη στις έγκυες γυναίκες. Οι μελέτες σε ζώα έδειξαν αναπαρα-

γωγική τοξικότητα σε επίπεδα έκθεσης χωρίς κλινικές επιδράσεις μετά τη χορήγηση βιλαντερόλη (βλέπε παράγραφο 5.3). Ο συνδυασμός ουμεκλιδίνιο/βιλαντερόλη πρέπει να χρησιμοποιείται κατά τη διάρκεια της εγκυμοσύνης μόνο εάν το αναμενόμενο όφελος για τη μητέρα υπερτερεί του δυνητικού κινδύνου για το έμβρυο.

Θηλασμός. Δεν είναι γνωστό εάν το ουμεκλιδίνιο ή η βιλαντερόλη αποβάλλονται στο ανθρώπινο γάλα. Ωστόσο, άλλοι β_2-αδρενεργικοί αγωνιστές ανιχνεύονται στο ανθρώπινο γάλα. Ο κίνδυνος στα νεογέννητα/βρέφη δεν μπορεί να αποκλειστεί. Πρέπει να αποφασιστεί εάν θα διακοπεί ο θηλασμός ή θα διακοπεί η θεραπεία με το συνδυασμό ουμεκλιδίνιο/βιλαντερόλη λαμβάνοντας υπόψη το όφελος του θηλασμού για το παιδί και το όφελος της θεραπείας για τη γυναίκα.

Γονιμότητα. Δεν διατίθενται δεδομένα σχετικά με τις επιδράσεις του συνδυασμού ουμεκλιδίνιο/βιλαντερόλη στην ανθρώπινη γονιμότητα. Μελέτες σε ζώα δεν υποδεικνύουν επίδραση του ουμεκλιδινίου ή της βιλαντερόλης στη γονιμότητα.

4.7 Επίδραση στην ικανότητα οδήγησης και χειρισμού μηχανημάτων. Ο συνδυασμός ουμεκλιδίνιο/βιλαντερόλη δεν έχει καμία ή έχει ασήμαντη επίδραση στην ικανότητα οδήγησης και χειρισμού μηχανημάτων.

4.8 Ανεπιθύμητες ενέργειες. Περίληψη του προφίλ ασφάλειας. Η πιο συχνά αναφερόμενη ανεπιθύμητη ενέργεια με το συνδυασμό ουμεκλιδίνιο/βιλαντερόλη ήταν ρινοφαρυγγίτιδα (9%).

Περιληπτικός πίνακας ανεπιθύμητων ενεργειών. Το προφίλ ασφαλείας του ANORO ELLIPTA βασίζεται στην εμπειρία από την ασφάλεια του συνδυασμού ουμεκλιδίνιο/βιλαντερόλη και των επιμέρους συστατικών από το πρόγραμμα κλινικής ανάπτυξης που συμπεριλάμβανε 6.855 ασθενείς με ΧΑΠ και από αυθόρμητες αναφορές. Το πρόγραμμα κλινικής ανάπτυξης περιελάμβανε 2.354 ασθενείς λάμβαναν το συνδυασμό ουμεκλιδίνιο/βιλαντερόλη άπαξ ημερησίως στις κλινικές μελέτες Φάσης ΙΙΙ διάρκειας 24 εβδομάδων ή μεγαλύτερης, εκ των οποίων 1.296 λάμβαναν τη συνιστώμενη δόση των 55/22 μικρογραμμαρίων σε μελέτες διάρκειας 24 εβδομάδων, 832 λάμβαναν υψηλότερη δόση 113/22 μικρογραμμαρίων σε μελέτες διάρκειας 24 εβδομάδων και 226 λάμβαναν 113/22 μικρογραμμάρια σε μια μελέτη διάρκειας 12 μηνών. Οι συχνότητες των ανεπιθύμητων ενεργειών που αναφέρονται στον παρακάτω πίνακα περιλαμβάνουν μη επεξεργασμένα ποσοστά επίπτωσης που παρατηρήθηκαν στο σύνολο πέντε μελετών διάρκειας 24 εβδομάδων και στη μελέτη ασφαλείας διάρκειας 12 μηνών. Η συχνότητα των ανεπιθύμητων ενεργειών ορίζεται με τη χρήση της ακόλουθης συνθήκης: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥ 1/10.000 έως < 1/1.000), πολύ σπάνιες (< 1/10.000), και μη γνωστές (δεν μπορούν να εκτιμηθούν με βάση τα διαθέσιμα δεδομένα).

Κατηγορία Οργανικού Συστήματος	Ανεπιθύμητες ενέργειες	Συχνότητα
Λοιμώξεις και παρασιτώσεις	Λοίμωξη του ουροποιητικού Παραρρινικολπίτιδα Ρινοφαρυγγίτιδα Φαρυγγίτιδα Λοίμωξη του ανώτερου αναπνευστικού	Συχνή Συχνή Συχνή Συχνή Συχνή
Διαταραχές του ανοσοποιητικού συστήματος	Αντιδράσεις υπερευαισθησίας που περιλαμβάνουν: Εξάνθημα Αναφυλαξία, αγγειοοίδημα και κνίδωση	 Όχι συχνή Σπάνια
Διαταραχές του νευρικού συστήματος	Κεφαλαλγία Τρόμος Δυσγευσία Ζάλη	Συχνή Όχι συχνή Όχι συχνή Μη γνωστή
Οφθαλμικές διαταραχές	Θαμπή όραση Γλαύκωμα Ενδοφθάλμια πίεση αυξημένη Πόνος του οφθαλμού	Σπάνια Σπάνια Σπάνια Σπάνια
Καρδιακές διαταραχές	Κολπική μαρμαρυγή Υπερκοιλιακή ταχυκαρδία Ιδιοκοιλιακός ρυθμός Ταχυκαρδία Υπερκοιλιακές έκτακτες συστολές Αίσθημα παλμών	Όχι συχνή Όχι συχνή Όχι συχνή Όχι συχνή Όχι συχνή Όχι συχνή
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωρακίου	Βήχας Στοματοφαρυγγικό άλγος Δυσφωνία Παράδοξος βρογχόσπασμος	Συχνή Συχνή Όχι συχνή Σπάνια
Διαταραχές του γαστρεντερικού	Δυσκοιλιότητα Ξηροστομία	Συχνή Συχνή
Διαταραχές του δέρματος και του υποδόριου ιστού	Εξάνθημα	Όχι συχνή
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού	Μυϊκοί σπασμοί	Όχι συχνή
Διαταραχές των νεφρών και των ουροφόρων οδών	Κατακράτηση ούρων Δυσουρία Απόφραξη εξόδου ουροδόχου κύστεως	Σπάνια Σπάνια Σπάνια

Αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών Η αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών μετά από τη χορήγηση άδειας κυκλοφορίας του φαρμακευτικού προϊόντος είναι σημαντική. Επιτρέπει τη συνεχή παρακολούθηση της σχέσης οφέλους/κινδύνου του φαρμακευτικού προϊόντος. Ζητείται από τους επαγγελματίες υγείας να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες στον Εθνικό Οργανισμό Φαρμάκων (Μεσογείων 284, GR-15562 Χολαργός, Αθήνα, Τηλ: + 30 213 2040380/337, Φαξ: + 30 210 6549585, Ιστότοπος: http://www.eof.gr) και στην Κύπρο Φαρμακευτικές Υπηρεσίες Υπουργείο Υγείας, CY-1475 Λευκωσία, Τηλ: + 357 22608607, Φαξ: + 357 22608649, Ιστότοπος: www.moh.gov.cy/phs.

4.9 Υπερδοσολογία. Η υπερδοσολογία με το συνδυασμό ουμεκλιδίνιο/βιλαντερόλη μπορεί να προκαλέσει σημεία και συμπτώματα λόγω της δράσης των επιμέρους συστατικών, σύμφωνα με τις γνωστές ανεπιθύμητες ενέργειες των εισπνεόμενων μουσκαρινικών ανταγωνιστών (π.χ. ξηροστομία, διαταραχές της οπτικής προσαρμογής και ταχυκαρδία) ή με αυτές που έχουν παρατηρηθεί με υπερδοσολογία από άλλους β_2-αδρενεργικούς αγωνιστές (π.χ., αρρυθμίες, τρόμος, κεφαλαλγία, αίσθημα παλμών, ναυτία, υπεργλυκαιμία και υποκαλιαιμία). Αν συμβεί υπερδοσολογία, ο ασθενής θα πρέπει να αντιμετωπιστεί υποστηρικτικά με την κατάλληλη παρακολούθηση κατά περίπτωση.

5. ΦΑΡΜΑΚΟΛΟΓΙΚΕΣ ΙΔΙΟΤΗΤΕΣ.

5.1 Φαρμακοδυναμικές ιδιότητες. Φαρμακοθεραπευτική κατηγορία: Φάρμακα για αποφρακτικές παθήσεις των αεραγωγών, αδρενεργικά σε συνδυασμό με αντιχολινεργικά, περιλαμβανομένων τριπλών συνδυασμών με κορτικοστεροειδή, κωδικός ATC: R03AL03.

6. ΦΑΡΜΑΚΕΥΤΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ.

6.1 Κατάλογος εκδόχων. Μονοϋδρική λακτόζη, Μαγνήσιο στεατικό.

6.2 Ασυμβατότητες. Δεν εφαρμόζεται.

6.3 Διάρκεια ζωής. 2 χρόνια. Διάρκεια ζωής κατά τη χρήση μετά το άνοιγμα του δίσκου: 6 εβδομάδες.

6.4 Ιδιαίτερες προφυλάξεις κατά την φύλαξη του προϊόντος. Μη φυλάσσετε σε θερμοκρασία μεγαλύτερη των 30°C. Αν φυλάσσεται σε ψυγείο, αφήστε τη συσκευή εισπνοών τουλάχιστον μία ώρα ώστε να επανέλθει σε θερμοκρασία δωματίου πριν από τη χρήση. Φυλάσσετε τη συσκευή εισπνοών μέσα στο σφραγισμένο δίσκο για να προστατεύεται από την υγρασία και αφαιρέστε μόνο αμέσως πριν από την πρώτη χρήση. Γράψτε την ημερομηνία που πρέπει να απορριφθεί η συσκευή εισπνοών, στο χώρο που παρέχεται στην ετικέτα. Η ημερομηνία πρέπει να προστεθεί μόλις η συσκευή εισπνοών αφαιρεθεί από το δίσκο.

6.5 Φύση και συστατικά του περιέκτη. Η συσκευή εισπνοών ELLIPTA αποτελείται από ένα σώμα χρώματος ανοικτού γκρι, ένα κάλυμμα επιστομίου χρώματος κόκκινου και ένα δοσομετρητή, συσκευασμένα σε δίσκο από φύλλο αλουμινίου που περιέχει ένα φακελίσκο με αφυγραντικό silica gel. Ο δίσκος είναι σφραγισμένος με αφαιρούμενο κάλυμμα από φύλλο αλουμινίου. Η συσκευή εισπνοών είναι μία συσκευή που αποτελείται από πολλά μέρη και είναι κατασκευασμένη από πολυπροπυλένιο, πολυαιθυλένιο υψηλής πυκνότητας, πολυοξυμεθυλένιο, τερεφθαλικό πολυβουτυλένιο, ακρυλονιτρικό βουταδιενικό στυρένιο, πολυανθρακικό και ανοξείδωτο χάλυβα. Η συσκευή εισπνοών περιέχει δύο συσκευασίες τύπου κυψέλης από φύλλο αλουμινίου των 7 ή των 30 δόσεων. Συσκευές εισπνοών των 7 ή 30 δόσεων. Πολυσυσκευασία των 3 συσκευών εισπνοών x 30 δόσεις. Μπορεί να μην κυκλοφορούν όλες οι συσκευασίες.

6.6 Ιδιαίτερες προφυλάξεις απόρριψης. Κάθε αχρησιμοποίητο φαρμακευτικό προϊόν ή υπόλειμμα πρέπει να απορρίπτεται σύμφωνα με τις κατάτόπους ισχύουσες σχετικές διατάξεις.

7. ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ. GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ιρλανδία.

8. ΑΡΙΘΜΟΣ(ΟΙ) ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ.

EU/1/14/898/001,
EU/1/14/898/002,
EU/1/14/898/003.

9. ΗΜΕΡΟΜΗΝΙΑ ΠΡΩΤΗΣ ΕΓΚΡΙΣΗΣ/ΑΝΑΝΕΩΣΗΣ ΤΗΣ ΑΔΕΙΑΣ. Ημερομηνία πρώτης έγκρισης: 08 Μαΐου 2014. Ημερομηνία τελευταίας ανανέωσης: 15 Ιανουάριος 2019.

10. ΗΜΕΡΟΜΗΝΙΑ ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ. 18/11/2022.

Λεπτομερείς πληροφορίες για το παρόν φαρμακευτικό προϊόν είναι διαθέσιμες στο δικτυακό τόπο του Ευρωπαϊκού Οργανισμού Φαρμάκων http://www.ema.europa.eu.

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ΣΥΝΤΟΜΗ ΠΕΡΙΛΗΨΗ ΤΩΝ ΧΑΡΑΚΤΗΡΙΣΤΙΚΩΝ ΤΟΥ ΠΡΟΪΟΝΤΟΣ **TRELEGY ELLIPTA**

1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΙΟΝΤΟΣ: Trelegy Ellipta 92 μικρογραμμάρια/55 μικρογραμμάρια/22 μικρογραμμάρια κόνις για εισπνοή σε δόσεις.

2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ: Η παρεχόμενη δόση κάθε εφάπαξ εισπνοής (η δόση που εξέρχεται από το επιστόμιο) είναι 92 μικρογραμμάρια φουροϊκής φλουτικαζόνης, 65 μικρογραμμάρια βρωμιούχου ουμεκλιδίνιου που ισοδυναμούν με 55 μικρογραμμάρια ουμεκλιδίνιο και 22 μικρογραμμάρια βιλαντερόλης (ως trifenatate). Αυτό αντιστοιχεί σε προκαθορισμένη δόση 100 μικρογραμμαρίων φουροϊκής φλουτικαζόνης, 74,2 μικρογραμμαρίων βρωμιούχου ουμεκλιδίνιου που ισοδυναμούν με 62,5 μικρογραμμάρια ουμεκλιδίνιο και 25 μικρογραμμαρίων βιλαντερόλης (ως trifenatate). Έκδοχο με γνωστή δράση: Κάθε παρεχόμενη δόση περιέχει περίπου 25 mg μονοϋδρικής λακτόζης. Για τον πλήρη κατάλογο των εκδόχων, βλ. παράγραφο 6.1.

3. ΦΑΡΜΑΚΟΤΕΧΝΙΚΗ ΜΟΡΦΗ: Κόνις για εισπνοή, σε δόσεις (κόνις για εισπνοή).Λευκή κόνις σε συσκευή εισπνοών (Ellipta) χρώματος ανοικτού γκρι, με κάλυμμα επιστομίου χρώματος μπεζ και δοσομετρητή.

4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ

4.1 Θεραπευτικές ενδείξεις: Το Trelegy Ellipta ενδείκνυται ως θεραπεία συντήρησης σε ενήλικες ασθενείς με μέτρια έως σοβαρή χρόνια αποφρακτική πνευμονοπάθεια (ΧΑΠ), οι οποίοι δεν αντιμετωπίζονται επαρκώς με συνδυασμό ενός εισπνεόμενου κορτικοστεροειδούς και ενός β_2-αγωνιστή μακράς δράσης ή με συνδυασμό ενός β_2-αγωνιστή μακράς δράσης και ενός ανταγωνιστή των μουσκαρινικών υποδοχέων μακράς δράσης (για τις επιδράσεις στον έλεγχο των συμπτωμάτων και την πρόληψη των παροξύνσεων, βλ. παράγραφο 5.1).

4.2 Δοσολογία και τρόπος χορήγησης: Δοσολογία. Η συνιστώμενη και μέγιστη δόση είναι μία εισπνοή μία φορά ημερησίως, την ίδια ώρα κάθε ημέρα. Εάν παραλειφθεί μία δόση, η επόμενη δόση θα πρέπει να εισπνευστεί στη συνήθη ώρα την επόμενη ημέρα. *Ειδικοί πληθυσμοί: Ηλικιωμένοι* Δεν απαιτείται προσαρμογή της δόσης σε ασθενείς ηλικίας άνω των 65 ετών (βλ. παράγραφο 5.2). Νεφρική δυσλειτουργία: Δεν απαιτείται προσαρμογή της δόσης σε ασθενείς με νεφρική δυσλειτουργία (βλ. παράγραφο 5.2). *Ηπατική δυσλειτουργία:* Δεν απαιτείται προσαρμογή της δόσης σε ασθενείς με ήπια, μέτρια ή σοβαρή ηπατική δυσλειτουργία. Το Trelegy Ellipta θα πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με μέτρια έως σοβαρή ηπατική δυσλειτουργία (βλ. παραγράφους 4.4 και 5.2). *Παιδιατρικός πληθυσμός:* Δεν υπάρχει σχετική χρήση του Trelegy Ellipta στον παιδιατρικό πληθυσμό (ηλικίας κάτω των 18 ετών) για την ένδειξη της ΧΑΠ.

Τρόπος χορήγησης: Αποκλειστικά για εισπνεόμενη χρήση.

Οδηγίες χρήσεως: Οι οδηγίες που ακολουθούν για τη συσκευή εισπνοών 30 δόσεων (επαρκεί για 30 ημέρες) ισχύουν επίσης και για τη συσκευή εισπνοών 14 δόσεων (επαρκεί για 14 ημέρες).

α) Προετοιμασία δόσης: Ανοίξτε το κάλυμμα όταν είσαστε έτοιμοι να εισπνεύσετε μία δόση. Η συσκευή εισπνοών δεν πρέπει να ανακινείται. Σπρώξτε τελείως το κάλυμμα προς τα κάτω μέχρι να ακούσετε ένα «κλικ». Το φαρμακευτικό προϊόν είναι πλέον έτοιμο για εισπνοή. Ο δοσομετρητής μετρά αντίστροφα κατά 1 για επιβεβαίωση. Αν ο δοσομετρητής δεν μετρήσει αντίστροφα καθώς ακούγεται το «κλικ», η δόση δεν θα χορηγηθεί από τη συσκευή εισπνοών και θα πρέπει να την επιστρέψετε στο φαρμακοποιό για να σας συμβουλέψει.

β) Πώς να εισπνεύσετε το φαρμακευτικό προϊόν: Θα πρέπει να κρατήσετε τη συσκευή εισπνοών μακριά από το στόμα και να εκπνεύσετε όσο μπορείτε, αλλά να μην εκπνεύσετε στη συσκευή εισπνοών. Το επιστόμιο θα πρέπει να τοποθετείται ανάμεσα στα χείλη σας και στη συνέχεια τα χείλη σας θα πρέπει να κλείσουν σφιχτά γύρω του. Οι αεραγωγοί δεν πρέπει να φράζονται με τα δάχτυλα κατά τη διάρκεια της χρήσης.

- Πάρτε μία μακρά, σταθερή, βαθιά εισπνοή. Αυτή η αναπνοή πρέπει να κρατηθεί όσο το δυνατόν περισσότερο (τουλάχιστον 3 4 δευτερόλεπτα).
- Απομακρύνετε τη συσκευή εισπνοών από το στόμα.
- Εκπνεύστε αργά και απαλά.

Είναι πιθανό να μην μπορέσετε να γευτείτε ή να αισθανθείτε το φάρμακο, ακόμη και όταν χρησιμοποιείτε τη συσκευή εισπνοών σωστά. Το επιστόμιο της συσκευής εισπνοών μπορεί να καθαριστεί χρησιμοποιώντας στεγνό χαρτομάντιλο, προτού κλείσετε το κάλυμμα.

γ) Κλείστε τη συσκευή εισπνοών και ξεπλύνετε το στόμα σας: Σπρώξτε το κάλυμμα προς τα επάνω όσο περισσότερο γίνεται για να καλύψετε το επιστόμιο. Ξεπλύνετε το στόμα σας με νερό μετά τη χρήση της συσκευής εισπνοών, μην το καταπιείτε. Αυτό θα μειώσει την πιθανότητα εμφάνισης ανεπιθύμητων ενεργειών όπως ο ερεθισμός του στόματος ή του φάρυγγα. Για περισσότερες οδηγίες σχετικά με το χειρισμό της συσκευής, βλ. παράγραφο 6.6.

4.3 Αντενδείξεις: Υπερευαισθησία στις δραστικές ουσίες ή σε κάποιο από τα έκδοχα που αναφέρονται στην παράγραφο 6.1.

4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση:

Άσθμα: Αυτό το φαρμακευτικό προϊόν δεν πρέπει να χρησιμοποιείται σε ασθενείς με άσθμα δεδομένου ότι δεν έχει μελετηθεί σε αυτόν τον πληθυσμό ασθενών.

Δεν ενδείκνυται για χρήση σε οξείες καταστάσεις: Δεν υπάρχουν κλινικά δεδομένα που να υποστηρίζουν τη χρήση του Trelegy Ellipta για την αντιμετώπιση οξέων επεισοδίων βρογχόσπασμου ή για την αντιμετώπιση μίας οξείας παρόξυνσης της ΧΑΠ (δηλ., ως θεραπεία διάσωσης).

Επιδείνωση νόσου: Η αυξανόμενη χρήση βρογχοδιασταλτικών βραχείας δράσης για την ανακούφιση από τα συμπτώματα μπορεί να υποδηλώνει επιδείνωση του ελέγχου της νόσου. Σε περίπτωση επιδείνωσης της ΧΑΠ κατά τη διάρκεια της θεραπείας με Trelegy Ellipta, θα πρέπει να πραγματοποιηθεί εκ νέου αξιολόγηση του ασθενούς και του θεραπευτικού σχήματος για τη ΧΑΠ. Οι ασθενείς δεν θα πρέπει να σταματούν τη θεραπεία με Trelegy Ellipta χωρίς ιατρική επίβλεψη, καθώς τα συμπτώματα μπορεί να επανεμφανιστούν μετά τη διακοπή.

Παράδοξος βρογχόσπασμος: Η χορήγηση του συνδυασμού φουροϊκής φλουτικαζόνης/ουμεκλιδίνιου/βιλαντερόλης μπορεί να προκαλέσει παράδοξο βρογχόσπασμο με άμεσο συριγμό και δυσκολία στην αναπνοή μετά τη χορήγηση της δόσης, ο οποίος μπορεί να είναι απειλητικός για τη ζωή. Εάν εμφανιστεί παράδοξος βρογχόσπασμος η θεραπεία θα πρέπει να διακόπτεται αμέσως. Ο ασθενής θα πρέπει να αξιολογηθεί και, αν κριθεί απαραίτητο, να ξεκινήσει εναλλακτική θεραπεία.

Καρδιαγγειακές επιδράσεις: Καρδιαγγειακές επιδράσεις, όπως καρδιακές αρρυθμίες, π.χ., κολπική μαρμαρυγή και ταχυκαρδία, μπορεί να παρατηρηθούν μετά τη χορήγηση ανταγωνιστών των μουσκαρινικών υποδοχέων και συμπαθομιμητικών, συμπεριλαμβανομένων του ουμεκλιδίνιου και της βιλαντερόλης, αντίστοιχα (βλ. παράγραφο 4.8). Ως εκ τούτου, το Trelegy Ellipta θα πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με ασταθή ή απειλητική για τη ζωή καρδιαγγειακή νόσο.

Ασθενείς με ηπατική δυσλειτουργία: Οι ασθενείς με μέτρια έως σοβαρή ηπατική δυσλειτουργία που λαμβάνουν Trelegy Ellipta θα πρέπει να παρακολουθούνται για την εμφάνιση συστηματικών ανεπιθύμητων ενεργειών που σχετίζονται με τα κορτικοστεροειδή (βλ. παράγραφο 5.2).

Συστηματικές επιδράσεις κορτικοστεροειδών: Συστηματικές επιδράσεις μπορεί να παρουσιαστούν με οποιοδήποτε εισπνεόμενο κορτικοστεροειδές, ιδιαίτερα αν χορηγείται σε υψηλές δόσεις για μεγάλες περιόδους. Αυτές οι επιδράσεις είναι πολύ λιγότερο πιθανό να συμβούν σε σχέση με τα από του στόματος κορτικοστεροειδή.

Οπτική διαταραχή: Ενδέχεται να αναφερθεί οπτική διαταραχή με τη συστηματική και τοπική χρήση κορτικοστεροειδών. Εάν ένας ασθενής παρουσιάζει συμπτώματα, όπως θαμπή όραση ή άλλες οπτικές διαταραχές, τότε θα πρέπει να εξετάζεται το ενδεχόμενο παραπομπής του ασθενούς σε οφθαλμίατρο για την αξιολόγηση των πιθανών αιτιών που ενδέχεται να περιλαμβάνουν καταρράκτη, γλαύκωμα ή σπάνιες ασθένειες, όπως κεντρική ορώδης χοριοαμφιβληστροειδοπάθεια (ΚΟΧΑ) και που έχουν αναφερθεί μετά τη χρήση συστηματικών και τοπικών κορτικοστεροειδών.

Συνυπάρχουσες παθήσεις: Το Trelegy Ellipta θα πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με σπασμωδικές διαταραχές ή θυρεοτοξίκωση, καθώς και σε ασθενείς που παρουσιάζουν ασυνήθιστη ανταπόκριση σε β_2-αδρενεργικούς αγωνιστές.Το Trelegy Ellipta θα πρέπει να χορηγείται με προσοχή σε ασθενείς με πνευμονική φυματίωση ή σε ασθενείς με χρόνιες ή μη αντιμετωπιζόμενες λοιμώξεις.

Αντιχολινεργική δράση: Το Trelegy Ellipta θα πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με γλαύκωμα κλειστής γωνίας. Οι ασθενείς θα πρέπει να ενημερώνονται σχετικά με τα σημεία και τα συμπτώματα του οξέος γλαυκώματος κλειστής γωνίας, να διακόπτουν τη χρήση του Trelegy Ellipta και να επικοινωνούν άμεσα με τον ιατρό τους σε περίπτωση που εμφανίσουν κάποιο από αυτά τα σημεία ή συμπτώματα. Θα πρέπει να συνιστάται προσοχή κατά τη συνταγογράφηση του Trelegy Ellipta σε ασθενείς με κατακράτηση ούρων ή παράγοντες κινδύνου για κατακράτηση ούρων, π.χ. καλοήθης υπερτροφία του προστάτη. Έχουν παρατηρηθεί περιπτώσεις οξείας κατακράτησης ούρων μετά την κυκλοφορία του φαρμάκου (βλ. παράγραφο 4.8).

Πνευμονία σε ασθενείς με ΧΑΠ: Αύξηση στη συχνότητα εμφάνισης της πνευμονίας, συμπεριλαμβανομένης της πνευμονίας που απαιτεί νοσηλεία, έχει παρατηρηθεί σε ασθενείς με ΧΑΠ που λαμβάνουν εισπνεόμενα κορτικοστεροειδή. Υπάρχουν κάποιες ενδείξεις αυξημένου κινδύνου πνευμονίας με την αύξηση της δόσης στεροειδών, αλλά αυτό δεν έχει αποδειχθεί με βεβαιότητα σε όλες τις μελέτες. Δεν υπάρχουν οριστικές κλινικές ενδείξεις για διαφορές εντός της κατηγορίας ως προς το μέγεθος του κινδύνου πνευμονίας μεταξύ προϊόντων εισπνεόμενων κορτικοστεροειδών. Οι γιατροί θα πρέπει να παραμένουν σε εγρήγορση για πιθανή ανάπτυξη πνευμονίας σε ασθενείς με ΧΑΠ καθώς τα κλινικά χαρακτηριστικά αυτών των λοιμώξεων επικαλύπτονται με τα συμπτώματα των παροξύνσεων της ΧΑΠ. Οι παράγοντες κινδύνου για πνευμονία σε ασθενείς με ΧΑΠ περιλαμβάνουν το κάπνισμα, τη μεγαλύτερη ηλικία, το χαμηλό δείκτη μάζας σώματος (ΔΜΣ) και τη σοβαρή ΧΑΠ.

Υποκαλιαιμία: Οι β_2-αδρενεργικοί αγωνιστές μπορεί να προκαλέσουν σημαντική υποκαλιαιμία σε ορισμένους ασθενείς, η οποία έχει τη δυνατότητα να προκαλέσει ανεπιθύμητες καρδιαγγειακές επιδράσεις. Η μείωση του καλίου ορού είναι συνήθως παροδική και δεν απαιτείται αναπλήρωση. Δεν παρατηρήθηκαν κλινικά σημαντικές επιδράσεις υποκαλιαιμίας στις κλινικές μελέτες με το Trelegy Ellipta στη συνιστώμενη θεραπευτική δόση. Θα πρέπει να επιδεικνύεται προσοχή όταν το Trelegy Ellipta χρησιμοποιείται με άλλα φαρμακευτικά προϊόντα που επίσης έχουν τη δυνατότητα να προκαλέσουν υποκαλιαιμία (βλ. παράγραφο 4.5).

Υπεργλυκαιμία: Οι β_2-αδρενεργικοί αγωνιστές μπορεί να προκαλέσουν παροδική υπεργλυκαιμία σε ορισμένους ασθενείς. Δεν παρατηρήθηκαν κλινικά σημαντικές επιδράσεις στα επίπεδα της γλυκόζης στο πλάσμα στις κλινικές μελέτες με φουροϊκή φλουτικαζόνη/ουμεκλιδίνιο/βιλαντερόλη στη συνιστώμενη θεραπευτική δόση. Έχουν υπάρξει αναφορές αυξήσεων των επιπέδων της γλυκόζης στο αίμα σε διαβητικούς ασθενείς που έλαβαν θεραπεία με φουροϊκή φλουτικαζόνη/ουμεκλιδίνιο/βιλαντερόλη και αυτό θα πρέπει να λαμβάνεται υπόψη κατά τη χορήγηση σε ασθενείς με ιστορικό σακχαρώδους διαβήτη. Μετά την έναρξη της θεραπείας με Trelegy Ellipta, η γλυκόζη πλάσματος θα πρέπει να παρακολουθείται πιο στενά σε διαβητικούς ασθενείς.

Έκδοχα: Αυτό το φαρμακευτικό προϊόν περιέχει λακτόζη. Οι ασθενείς με σπάνια κληρονομικά προβλήματα δυσανεξίας στη γαλακτόζη, έλλειψης συνολικής λακτάσης ή δυσαπορρόφηση γλυκόζης γαλακτόζης δεν πρέπει να χρησιμοποιήσουν αυτό το φαρμακευτικό προϊόν.

4.5 Αλληλεπιδράσεις με άλλα φαρμακευτικά προϊόντα και άλλες μορφές αλληλεπίδρασης: Κλινικά σημαντικές φαρμακευτικές αλληλεπιδράσεις με το συνδυασμό φουροϊκής φλουτικαζόνης/ουμεκλιδίνιου/βιλαντερόλης σε κλινικές δόσεις θεωρούνται μη πιθανές λόγω των χαμηλών συγκεντρώσεων που επιτυγχάνονται στο πλάσμα μετά την εισπνοή της δόσης.

Αλληλεπίδραση με β αναστολείς: Οι β_2-αδρενεργικοί αναστολείς μπορεί να εξασθενίσουν ή να ανταγωνίζονται τη δράση των β_2-αδρενεργικών αγωνιστών, όπως η βιλαντερόλη. Εάν απαιτείται η χρήση β-αναστολέων, θα πρέπει να εξετάζεται το ενδεχόμενο χρήσης καρδιοεκλεκτικών β-αναστολέων, ωστόσο, θα πρέπει να επιδεικνύεται προσοχή κατά την ταυτόχρονη χρήση μη εκλεκτικών και εκλεκτικών β-αναστολέων.

Αλληλεπίδραση με αναστολέα του CYP3A4: Η φουροϊκή φλουτικαζόνη και η βιλαντερόλη αποβάλλονται ταχέως μέσω εκτεταμένου μεταβολισμού πρώτης διόδου με τη διαμεσολάβηση του ενζύμου CYP3A4. Συνιστάται προσοχή κατά τη συγχορήγηση με ισχυρούς αναστολείς του CYP3A4 (π.χ., κετοκοναζόλη, ριτοναβίρη, προϊόντα που περιέχουν κομπισιστάτη) καθώς υπάρχει πιθανότητα αυξημένης συστηματικής έκθεσης τόσο στη φουροϊκή φλουτικαζόνη όσο και στη βιλαντερόλη, γεγονός που θα μπορούσε να οδηγήσει σε αυξημένη πιθανότητα εμφάνισης ανεπιθύμητων ενεργειών. Η συγχορήγηση πρέπει να αποφεύγεται εκτός αν το όφελος υπερτερεί του αυξημένου κινδύνου συστηματικών ανεπιθύμητων ενεργειών των κορτικοστεροειδών, στην οποία περίπτωση οι ασθενείς θα πρέπει να παρακολουθούνται για συστηματικές ανεπιθύμητες ενέργειες των κορτικοστεροειδών. Πραγματοποιήθηκε μια μελέτη επαναλαμβανόμενων δόσεων σε υγιή άτομα με συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης (184/22 μικρογραμμάρια) και κετοκοναζόλη (400 χιλιοστόγραμμα, ένας ισχυρός αναστολέας του CYP3A4). Η συγχορήγηση αύξησε τη μέση $AUC_{(0-24)}$ και C_{max} της φουροϊκής φλουτικαζόνης κατά 36% και 33%, αντίστοιχα. Η αύξηση της έκθεσης στη φουροϊκή φλουτικαζόνη συσχετίστηκε με μείωση της τάξεως του 27% της σταθμισμένης μέσης τιμής της κορτιζόλης ορού σε διάστημα 0 24 ωρών. Η συγχορήγηση αύξησε τη μέση AUC(0-t) και C_{max} της βιλαντερόλης κατά 65% και 22%, αντίστοιχα. Η αύξηση της έκθεσης στη βιλαντερόλη δεν συσχετίστηκε με αύξηση των σχετιζόμενων με τους β_2-αγωνιστές συστηματικών επιδράσεων στην καρδιακή συχνότητα ή το κάλιο αίματος.

Αλληλεπίδραση με αναστολείς του CYP2D6/πολυμορφισμός του CYP2D6: Το ουμεκλιδίνιο αποτελεί υπόστρωμα του κυτοχρώματος P450 2D6 (CYP2D6). Η φαρμακοκινητική του ουμεκλιδίνιου σε σταθεροποιημένη κατάσταση αξιολογήθηκε σε υγιείς εθελοντές με έλλειψη CYP2D6 (άτομα με περιορισμένη μεταβολική ικανότητα). Δεν παρατηρήθηκε επίδραση στην AUC ή τη C_{max} του ουμεκλιδίνιου με δόση 8 φορές υψηλότερη από τη θεραπευτική δόση. Αύξηση περίπου κατά 1,3 φορές της AUC του ουμεκλιδίνιου παρατηρήθηκε σε δόση υψηλότερη κατά 16 φορές χωρίς καμία επίδραση στη C_{max} του ουμεκλιδίνιου. Με βάση το μέγεθος αυτών των μεταβολών, δεν αναμένεται καμία κλινικά σημαντική φαρμακευτική αλληλεπίδραση όταν ο συνδυασμός φουροϊκής φλουτικαζόνης/ουμεκλιδίνιου/βιλαντερόλης συγχορηγείται με αναστολείς του CYP2D6 ή όταν χορηγείται σε ασθενείς με γενετική ανεπάρκεια όσον αφορά τη δράση του CYP2D6 (άτομα με περιορισμένη μεταβολική ικανότητα).

Αλληλεπίδραση με αναστολείς της P-γλυκοπρωτεΐνης: Η φουροϊκή φλουτικαζόνη, το ουμεκλιδίνιο και η βιλαντερόλη αποτελούν υποστρώματα του μεταφορέα P γλυκοπρωτεΐνη (P-gp). Αξιολογήθηκε η επίδραση του μέτριου αναστολέα της P-gp βεραπαμίλη (240 mg άπαξ ημερησίως) στη φαρμακοκινητική του ουμεκλιδίνιου και της βιλαντερόλης σε σταθεροποιημένη κατάσταση σε υγιείς εθελοντές. Δεν παρατηρήθηκε επίδραση της βεραπαμίλης στη C_{max} του ουμεκλιδίνιου ή της βιλαντερόλης. Παρατηρήθηκε αύξηση της AUC του ουμεκλιδίνιου κατά 1,4 φορές περίπου, χωρίς καμία επίδραση στην AUC της βιλαντερόλης. Με βάση το μέγεθος αυτών των μεταβολών, δεν αναμένεται καμία κλινικά σημαντική φαρμακευτική αλληλεπίδραση κατά τη συγχορήγηση του συνδυασμού φουροϊκής φλουτικαζόνης/ουμεκλιδίνιου/βιλαντερόλης με αναστολείς της P-gp. Δεν έχουν διενεργηθεί κλινικές φαρμακολογικές μελέτες με ειδικό αναστολέα της P-gp και φουροϊκή φλουτικαζόνη.

Άλλα μακράς δράσης αντιμουσκαρινικά και μακράς δράσης β_2-αδρενεργικοί αγωνιστές: Η συγχορήγηση του Trelegy Ellipta με άλλους μακράς δράσης μουσκαρινικούς ανταγωνιστές ή μακράς δράσης β_2-αδρενεργικούς αγωνιστές δεν έχει μελετηθεί και δεν συνιστάται διότι μπορεί να ενισχύσει τις ανεπιθύμητες ενέργειες (βλ. παραγράφους 4.8 και 4.9).

Υποκαλιαιμία: Η ταυτόχρονη θεραπεία με παράγωγα μεθυλοξανθίνης, στεροειδή ή μη καλιοσυντηρητικά διουρητικά που επάγουν υποκαλιαιμία μπορεί να ενισχύσει την πιθανή υποκαλιαιμική δράση των β2-αδρενεργικών αγωνιστών. Ως εκ τούτου θα πρέπει να επιδεικνύεται προσοχή (βλ. παράγραφο 4.4).

4.6 Γονιμότητα, κύηση και γαλουχία Κύηση: Είναι περιορισμένα τα δεδομένα από τη χρήση του συνδυασμού φουροϊκής φλουτικαζόνης/ουμεκλιδίνιου/βιλαντερόλης στις έγκυες γυναίκες. Μελέτες σε ζώα κατέδειξαν τοξικότητα στην αναπαραγωγική ικανότητα σε εκθέσεις οι οποίες δεν είναι κλινικά σημαντικές (βλ. παράγραφο 5.3). Η χορήγηση του Trelegy Ellipta σε έγκυες γυναίκες θα πρέπει να εξετάζεται μόνο αν το αναμενόμενο όφελος για τη μητέρα δικαιολογεί τον δυνητικό κίνδυνο για το έμβρυο. Θηλασμός: Δεν είναι γνωστό κατά πόσο η φουροϊκή φλουτικαζόνη, το ουμεκλιδίνιο, η βιλαντερόλη ή οι μεταβολίτες τους απεκκρίνονται στο ανθρώπινο γάλα. Ωστόσο, άλλα κορτικοστεροειδή, μουσκαρινικοί ανταγωνιστές και β2-αδρενεργικοί αγωνιστές ανιχνεύονται στο ανθρώπινο γάλα. Ο κίνδυνος για τα νεογνά/βρέφη δεν μπορεί να αποκλειστεί. Πρέπει να αποφασιστεί εάν θα διακοπεί ο θηλασμός ή θα διακοπεί η θεραπεία με το Trelegy Ellipta λαμβάνοντας υπόψη το όφελος του θηλασμού για το παιδί και το όφελος της θεραπείας για τη γυναίκα. Γονιμότητα: Δεν διατίθενται δεδομένα σχετικά με τις επιδράσεις του συνδυασμού φουροϊκής φλουτικαζόνης/ουμεκλιδίνιου/βιλαντερόλης στην ανθρώπινη γονιμότητα. Μελέτες σε ζώα δεν υποδεικνύουν επίδραση της φουροϊκής φλουτικαζόνης, του ουμεκλιδίνιου ή της βιλαντερόλης στη γονιμότητα των αρρένων ή των θηλέων (βλ. παράγραφο 5.3).

4.7 Επιδράσεις στην ικανότητα οδήγησης και χειρισμού μηχανημάτων

Ο συνδυασμός φουροϊκής φλουτικαζόνης/ουμεκλιδίνιου/βιλαντερόλης δεν έχει καμία ή έχει ασήμαντη επίδραση στην ικανότητα οδήγησης και χειρισμού μηχανημάτων.

4.8 Ανεπιθύμητες ενέργειες:

Περίληψη του προφίλ ασφάλειας: Οι πιο συχνά αναφερόμενες ανεπιθύμητες ενέργειεςείναι ρινοφαρυγγίτιδα (7%), κεφαλαλγία (5%) και λοίμωξη του ανώτερου αναπνευστικού συστήματος (2%).

Συνοπτικός πίνακας ανεπιθύμητων ενεργειών: Το προφίλ ασφάλειας του Trelegy Ellipta βασίζεται σε τρεις κλινικές μελέτες φάσης III και σε αυθόρμητες αναφορές. Στις περιπτώσεις στις οποίες η συχνότητα εμφάνισης ανεπιθύμητων ενεργειών διέφερε μεταξύ των μελετών, παρακάτω αναφέρεται η υψηλότερη συχνότητα. Οι ανεπιθύμητες ενέργειες παρουσιάζονται ανά κατηγορία οργανικού συστήματος του MedDRA.

Η συχνότητα των ανεπιθύμητων ενεργειών ορίζεται με τη χρήση της παρακάτω συνθήκης: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥ 1/10.000 έως< 1/1.000), πολύ σπάνιες (< 1/10.000) και μη γνωστές (δεν μπορούν να εκτιμηθούν με βάση τα διαθέσιμα δεδομένα).

Κατηγορία / οργανικό σύστημα	Ανεπιθύμητες ενέργειες	Συχνότητα
Λοιμώξεις και παρασιτώσεις	Πνευμονία, Λοίμωξη του ανώτερου αναπνευστικού, Βρογχίτιδα, Φαρυγγίτιδα, Ρινίτιδα, Παραρινοκολπίτιδα, Γρίπη, Ρινοφαρυγγίτιδα, Καντιντίαση του στόματος και του φάρυγγα, Ουρολοίμωξη	Συχνές
	Ιογενής λοίμωξη του αναπνευστικού συστήματος	Όχι συχνές
Διαταραχές του ανοσοποιητικού συστήματος	Αντιδράσεις υπερευαισθησίας, συμπεριλαμβανομένων αναφυλαξίας, αγγειοοιδήματος, κνίδωσης και εξανθήματος	Σπάνιες
Διαταραχές του νευρικού συστήματος	Κεφαλαλγία	Συχνές
	Δυσγευσία	Όχι συχνές
Οφθαλμικές διαταραχές	Όραση θαμπή (βλ. παράγραφο 4.4), Γλαύκωμα, Πόνος του οφθαλμού	Όχι συχνές
	Αυξημένη ενδοφθάλμια πίεση	Σπάνιες
Καρδιακές διαταραχές	Υπερκοιλιακή ταχυαρρυθμία, Ταχυκαρδία, Κολπική μαρμαρυγή	Όχι συχνές
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωράκιου	Βήχας Στοματοφαρυγγικό άλγος	Συχνές
	Δυσφωνία	Όχι συχνές
Διαταραχές του γαστρεντερικού	Δυσκοιλιότητα	Συχνές
	Ξηροστομία	Όχι συχνές
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού	Αρθραλγία, Οσφυαλγία	Συχνές
	Κατάγματα	Όχι συχνές
Διαταραχές των νεφρών και των ουροφόρων οδών	Κατακράτηση ούρων Δυσουρία	Σπάνιες

Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών

Πνευμονία: Σε συνολικά 1.810 ασθενείς με προχωρημένη ΧΑΠ (μέσος προβλεπόμενος FEV1 μετά από βρογχοδιαστολή κατά την προκαταρκτική αξιολόγηση 45%, τυπική απόκλιση (SD) 13%), εκ των οποίων το 65% είχαν εμφανίσει μέτρια/σοβαρή παρόξυνση της ΧΑΠ κατά το έτος πριν από την ένταξη στη μελέτη (μελέτη CTT116853), αναφέρθηκε υψηλότερη επίπτωση συμβάντων πνευμονίας έως τις 24 εβδομάδες σε ασθενείς που έλαβαν Trelegy Ellipta (20 ασθενείς, 2%) σε σύγκριση με τους ασθενείς που έλαβαν συνδυασμό βουδεσονίδης/φορμοτερόλης (7 ασθενείς, <1%). Πνευμονία για την οποία χρειάστηκε νοσηλεία εμφανίστηκε στο 1% των ασθενών που έλαβαν Trelegy Ellipta και σε <1% των ασθενών που έλαβαν το συνδυασμό βουδεσονίδης/φορμοτερόλης για έως 24 εβδομάδες. Αναφέρθηκε μία θανατηφόρος περίπτωση πνευμονίας σε έναν ασθενή που έλαβε Trelegy Ellipta. Στο υποσύνολο των 430 ασθενών που έλαβαν θεραπεία για έως 52 εβδομάδες, η επίπτωση συμβάντων πνευμονίας που αναφέρθηκε στα σκέλη που έλαβαν Trelegy Ellipta και συνδυασμό βουδεσονίδης/φορμοτερόλης ήταν ίδια και ανερχόταν σε 2%. Η επίπτωση πνευμονίας με Trelegy Ellipta είναι συγκρίσιμη με εκείνη που παρατηρήθηκε στο σκέλος φουροϊκής φλουτικαζόνης/βιλαντερόλης (FF/VI) 100/25 των κλινικών μελετών με FF/VI στη ΧΑΠ. Σε μία μελέτη διάρκειας 52 εβδομάδων, στην οποία συμπεριλήφθηκαν συνολικά 10.355 ασθενείς με ΧΑΠ και ιστορικό μέτριων ή σοβαρών παροξύνσεων εντός των προηγούμενων 12 μηνών (μέσος προβλεπόμενος FEV1 μετά από βρογχοδιαστολή κατά την προκαταρκτική αξιολόγηση 46%, SD 15%) (μελέτη CTT116855), η επίπτωση συμβάντων πνευμονίας ήταν 8% (317 ασθενείς) για το Trelegy Ellipta (n = 4.151), 7% (292 συμμετέχοντες) για τον συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης (n = 4.134) και 5% (97 συμμετέχοντες) για τον συνδυασμό ουμεκλιδίνιου/βιλαντερόλης (n = 2.070). Θανατηφόρος περίπτωση πνευμονίας εμφανίστηκε σε 12 από τους 4.151 ασθενείς (3,5 ανά 1.000 ασθενείς έτη) που έλαβαν Trelegy Ellipta, σε 5 από 4.134 ασθενείς (1,7 ανά 1.000 ασθενείς έτη) που έλαβαν συνδυασμό φουροϊκής φλουτικαζόνης/βιλαντερόλης και σε 5 από 2.070 ασθενείς (2,9 ανά 1.000 ασθενείς έτη) που έλαβαν συνδυασμό ουμεκλιδίνιου/βιλαντερόλης.

Αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών Η αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών μετά από τη χορήγηση άδειας κυκλοφορίας του φαρμακευτικού προϊόντος είναι σημαντική. Επιτρέπει τη συνεχή παρακολούθηση της σχέσης οφέλους/κινδύνου του φαρμακευτικού προϊόντος. Ζητείται από τους επαγγελματίες υγείας να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες μέσω του εθνικού συστήματος αναφοράς που αναγράφεται παρακάτω.

Ελλάδα: Εθνικός Οργανισμός Φαρμάκων: Μεσογείων 284, GR-15562 Χολαργός, Αθήνα, Τηλ: + 30 2132040380 /337, Φαξ: + 30 2106549585, Ιστότοπος: http://www.eof.gr

Κύπρος: Φαρμακευτικές Υπηρεσίες, Υπουργείο Υγείας, CY-1475 Λευκωσία, Τηλ: + 357 22608607, Φαξ: + 357 22608649, Ιστότοπος: www.moh.gov.cy/phs

4.9 Υπερδοσολογία: Η υπερδοσολογία μπορεί να προκαλέσει σημεία, συμπτώματα ή ανεπιθύμητες ενέργειες που σχετίζονται με τη φαρμακολογική δράση των επιμέρους συστατικών (π.χ., σύνδρομο Cushing, χαρακτηριστικά συνδρόμου που προσομοιάζει με σύνδρομο Cushing, καταστολή των επινεφριδίων, μείωση της οστικής πυκνότητας, ξηροστομία, διαταραχή της οπτικής προσαρμογής, ταχυκαρδία, αρρυθμίες, τρόμος, κεφαλαλγία, αίσθημα παλμών, ναυτία, υπεργλυκαιμία και υποκαλιαιμία). Δεν υπάρχει συγκεκριμένη θεραπεία για την υπερδοσολογία από το Trelegy Ellipta. Αν συμβεί υπερδοσολογία, ο ασθενής θα πρέπει να αντιμετωπιστεί υποστηρικτικά με την κατάλληλη παρακολούθηση κατά περίπτωση. Ο καρδιοεκλεκτικός β-αποκλεισμός θα πρέπει να εξετάζεται μόνο για σημαντικές επιδράσεις υπερδοσολογίας από βιλαντερόλη, οι οποίες είναι κλινικά ανησυχητικές και δεν ανταποκρίνονται σε υποστηρικτικά μέτρα. Τα φαρμακευτικά προϊόντα που περιέχουν καρδιοεκλεκτικούς β-αναστολείς θα πρέπει να χρησιμοποιούνται με προσοχή σε ασθενείς με ιστορικό βρογχόσπασμου. Η περαιτέρω αντιμετώπιση θα πρέπει να βασίζεται στις κλινικές ενδείξεις ή τις συστάσεις του εθνικού κέντρου δηλητηριάσεων, εφόσον υπάρχουν.

5. ΦΑΡΜΑΚΟΛΟΓΙΚΕΣ ΙΔΙΟΤΗΤΕΣ

5.1 Φαρμακοδυναμικές ιδιότητες: Φαρμακοθεραπευτική κατηγορία: Φάρμακα για αποφρακτικές νόσους των αεροφόρων οδών, αδρενεργικά σε συνδυασμό με αντιχολινεργικά, συμπεριλαμβανομένων των τριπλών συνδυασμών με κορτικοστεροειδή, Κωδικός ATC: R03AL08.

6. ΦΑΡΜΑΚΕΥΤΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ

6.1 Κατάλογος εκδόχων: Μονοϋδρική λακτόζη. Στεατικό μαγνήσιο.

6.2 Ασυμβατότητες: Δεν εφαρμόζεται.

6.3 Διάρκεια ζωής: 2 χρόνια

Διάρκεια ζωής μετά το άνοιγμα του δίσκου: 6 εβδομάδες

6.4 Ιδιαίτερες προφυλάξεις κατά τη φύλαξη του προϊόντος: Μην φυλάσσετε σε θερμοκρασία μεγαλύτερη των 30°. Εάν φυλάσσεται σε ψυγείο, η συσκευή εισπνοών θα πρέπει να αφήνεται να επανέλθει σε θερμοκρασία δωματίου τουλάχιστον μία ώρα πριν τη χρήση. Φυλάσσετε τη συσκευή εισπνοών μέσα στο σφραγισμένο δίσκο για να προστατεύεται από την υγρασία και αφαιρέστε τη από αυτόν μόνο αμέσως πριν από την πρώτη χρήση.

6.5 Φύση και συστατικά του περιέκτη: Η συσκευή εισπνοών Ellipta αποτελείται από ένα σώμα χρώματος ανοικτού γκρι, ένα κάλυμμα επιστομίου χρώματος μπεζ και ένα δοσομετρητή, συσκευασμένα σε δίσκο από φύλλο αλουμινίου που περιέχει ένα φακελίσκο με αφυγραντικό silica gel. Ο δίσκος είναι σφραγισμένος με αφαιρούμενο κάλυμμα από φύλλο αλουμινίου. Η συσκευή εισπνοών είναι μία πολυσύνθετη συσκευή που αποτελείται από πολυπροπυλένιο, πολυαιθυλένιο υψηλής πυκνότητας, πολυοξυμεθυλένιο, τερεφθαλικό πολυβουτυλένιο, ακρυλονιτρικό βουταδιενικό στυρένιο, πολυανθρακικό και ανοξείδωτο χάλυβα.

Η συσκευή εισπνοών περιέχει δύο ταινίες κυψελών από φύλλο αλουμινίου οι οποίες παρέχουν συνολικά 14 ή 30 δόσεις (επαρκεί για 14 ή 30 ημέρες). Κάθε κυψέλη σε μία ταινία περιέχει φουροϊκή φλουτικαζόνη, κάθε κυψέλη στην άλλη ταινία περιέχει ουμεκλιδίνιο (ως βρωμιούχο) και βιλαντερόλη (ως trifenatate).

Συσκευασίες 1 συσκευής εισπνοών των 14 ή 30 δόσεων. Πολλαπλές συσκευασίες που περιέχουν 90 δόσεις (3 συσκευές εισπνοών των 30 δόσεων). Μπορεί να μην κυκλοφορούν όλες οι συσκευασίες.

6.6 Ιδιαίτερες προφυλάξεις απόρριψης: Μετά την εισπνοή, οι ασθενείς θα πρέπει να ξεπλένουν το στόμα τους με νερό χωρίς να καταπιούν. Η συσκευή εισπνοών συσκευάζεται σε ένα δίσκο που περιέχει ένα φακελίσκο με αφυγραντικό για μείωση της υγρασίας. Ο φακελίσκος με το αφυγραντικό πρέπει να απορρίπτεται και δεν πρέπει να ανοίγεται, να καταναλώνεται ή να εισπνέεται. Ο ασθενής πρέπει να συμβουλεύεται να μην ανοίξει το δίσκο μέχρι να είναι έτοιμος να εισπνεύσει τη δόση.

Όταν η συσκευή εισπνοών αφαιρείται από το σφραγισμένο δίσκο της για πρώτη φορά, θα βρίσκεται στην «κλειστή» θέση. Η ημερομηνία «Απορρίψτε μετά από» πρέπει να είναι γραμμένη στην ετικέτα και στο κουτί της συσκευής εισπνοών στο χώρο που παρέχεται. Η ημερομηνία πρέπει να προστεθεί μόλις η συσκευή εισπνοών αφαιρεθεί από το δίσκο. Η ημερομηνία «Απορρίψτε μετά από» είναι 6 εβδομάδες από την ημερομηνία ανοίγματος του δίσκου. Μετά την ημερομηνία αυτή η συσκευή εισπνοών δεν θα πρέπει πλέον να χρησιμοποιείται. Ο δίσκος μπορεί να απορριφθεί μετά το πρώτο άνοιγμα.

Αν το κάλυμμα της συσκευής εισπνοών ανοιχτεί και κλειστεί χωρίς να εισπνευστεί το φαρμακευτικό προϊόν, η δόση θα χαθεί. Η χαμένη δόση θα παραμείνει με ασφάλεια στο εσωτερικό της συσκευής εισπνοών, αλλά δεν θα είναι πλέον διαθέσιμη για εισπνοή.

Δεν είναι δυνατή η τυχαία λήψη επιπλέον δόσης ή η λήψη διπλής δόσης με μία εισπνοή.

Κάθε αχρησιμοποίητο φαρμακευτικό προϊόν ή υπόλειμμα πρέπει να απορρίπτεται σύμφωνα με τις κατά τόπους ισχύουσες σχετικές διατάξεις.

7. ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ

GlaxoSmithKline Trading Services Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ιρλανδία.

8. ΑΡΙΘΜΟΣ(ΟΙ) ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ

EU/1/17/1236/01, EU/1/17/1236/02, EU/1/17/1236/03

9. ΗΜΕΡΟΜΗΝΙΑ ΠΡΩΤΗΣ ΕΓΚΡΙΣΗΣ/ΑΝΑΝΕΩΣΗΣ ΤΗΣ ΑΔΕΙΑΣ

Ημερομηνία πρώτης έγκρισης: 15 Νοεμβρίου 2017. Ημερομηνία τελευταίας ανανέωσης: 15 Ιουλίου 2022

10. ΗΜΕΡΟΜΗΝΙΑ ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ: 16-02-2023

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GR-TRE-8-05-2023

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