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ABOUT

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Thoracic Research and Practice is a peer reviewed, open access, online-only journal published by the Turkish Thoracic Society.

Thoracic Research and Practice is a bimonthly journal that is published in English in January, March, May, July, September, and November.

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Thoracic Research & Practice
Official Journal of the Turkish Thoracic Society

CONTENTS

Thorac Res Pract. 2026;27(2):77-82 **DOI:** 10.4274/ThoracResPract.2025.2025-7-3

Original Article

Air Pollution, COVID-19–related Air-quality Changes, and Premature Mortality in Türkiye (2019–2023)

Didem Han Yekdeş[1], Ali Cem Yekdeş[2]

[1]Edirne Provincial Health Directorate, Public Health Center, Edirne, Türkiye
[2]Department of Public Health, Trakya University Faculty of Medicine, Edirne, Türkiye

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ABSTRACT

OBJECTIVE: Long-term exposure to fine particulate matter ($PM_{2.5}$) contributes to about 8 million premature deaths worldwide annually. In Türkiye, few studies have examined long-term health impacts, particularly during and after the coronavirus disease-2019 (COVID-19) pandemic. This study aimed to estimate premature mortality and the respiratory disease burden attributable to $PM_{2.5}$ from 1 January 2019 to 31 December 2023.

MATERIAL AND METHODS: Premature deaths attributable to $PM_{2.5}$ were estimated using the World Health Organization's (WHO) AirQ+ software. Inputs included annual provincial $PM_{2.5}$ concentrations (measured directly or at stations without $PM_{2.5}$ measurements, converted from PM_{10} using the WHO-recommended factor of 0.67 for Türkiye), mortality data for individuals aged ≥25 years, and demographic data from Turkish Statistical Institute. The Estimates focused on chronic obstructive pulmonary disease (COPD) and lung cancer. Population attributable fractions were calculated. Temporal comparisons were made across pre-pandemic (2019), pandemic (2020–2021), and post-pandemic (2022–2023) periods to capture potential effects of COVID-19–related reductions in industrial production and traffic. Differences were assessed using one-way ANOVA.

RESULTS: An annual average of 85,344 premature deaths (95% confidence interval: 79,129–91,559) was attributable to $PM_{2.5}$. COPD and lung cancer accounted for a significant share of $PM_{2.5}$-related deaths, with about one in seven linked to COPD. Although temporary improvements in air quality occurred during the COVID-19 pandemic, no statistically significant difference was observed in COPD-attributable mortality across the three study periods ($P = 0.687$).

CONCLUSION: Air pollution remains a major public health challenge in Türkiye. Sustained, region-specific strategies are needed to reduce the burden of $PM_{2.5}$-related mortality. Inadequate monitoring coverage continues to limit precision in exposure and risk assessment.

KEYWORDS: $PM_{2.5}$, COVID-19, lung cancer, premature mortality, Türkiye, air pollution

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INTRODUCTION

Air pollution, defined as the contamination of the atmosphere by physical, chemical, or biological agents, can occur naturally or from anthropogenic sources, such as the burning of fossil fuels.[1] According to the World Health Organization's (WHO) Global Air Quality Guidelines, the principal ambient air pollutants of concern are fine particulate matter ($PM_{2.5}$), coarse particulate matter (PM_{10}), ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO).[2]

Each year, outdoor and household air pollution contribute to 6.7 million premature deaths worldwide by causing a range of health problems.[3] Its effects often overlooked by healthcare professionals and individuals, include both acute issues such as asthma attacks and infections,[4,5] and chronic conditions like ischemic stroke,[6,7] ischemic heart diseases,[8] chronic obstructive pulmonary disease (COPD),[9] and lung cancer, driven by chronic inflammatory processes.[10] Moreover, climate change, fueled by air pollution, alters the geographical distribution of infectious diseases and intensifies natural disasters. Tackling this global threat demands public awareness and a multidisciplinary approach involving scientific experts and national and international organizations that propose sustainable solutions.[11]

Corresponding author: Didem Han Yekdeş, MD, e-mail: dhanyekdes@gmail.com

Long-term exposure to air pollution substantially increases mortality risk. A meta-analysis conducted in 2020 reported that each 10 μg/m^3 increase in $PM_{2.5}$ concentration was associated with a 1.08-fold increase in mortality [95% confidence interval (CI): 1.06–1.09].[12] The AirQ+ software, developed by the WHO, incorporates cohort-based risk estimates to quantify the health impacts of air pollution.[13] Although national-level assessments of long-term (annual) $PM_{2.5}$ exposure in Türkiye have been published,[14] these analyses were restricted to single-year estimates.

The coronavirus disease-2019 (COVID-19) pandemic created exceptional conditions: nationwide restrictions reduced industrial production and traffic, resulting in temporary improvements in air quality in many countries, while widespread mask use may also have influenced individual-level exposure patterns.[15,16] To address these gaps, the present study aimed to compare the pre-pandemic (2019), pandemic (2020–2021), and post-pandemic (2022–2023) periods to capture these exceptional circumstances and estimate the burden of premature mortality attributable to long-term exposure to ambient $PM_{2.5}$ in Türkiye. Specifically, this study seeks to answer the following questions:

1. What is the estimated burden of premature mortality attributable to long-term exposure to ambient $PM_{2.5}$ (per AirQ+) in Türkiye?

2. How are premature deaths due to long-term exposure to ambient $PM_{2.5}$ (per AirQ+) distributed across regions and provinces in Türkiye?

3. What are the temporal trends in the estimated proportion of premature mortality from COPD attributable to long-term exposure to ambient $PM_{2.5}$ (per AirQ+) before and after the COVID-19 pandemic?

Main Points

- Long-term exposure to particulate matter ($PM_{2.5}$) air pollution is a major contributor to premature deaths and chronic respiratory diseases globally.
- World Health Organization's AirQ+ software is widely used to estimate health impacts of air pollution using exposure and incidence data.
- Most studies in Türkiye have focused on short-term effects; national long-term analyses remain limited.
- This study presents the first multi-year (2019–2023) national estimate of premature mortality 40 from $PM_{2.5}$-related air pollution in Türkiye using AirQ+.
- It reveals notable regional disparities in chronic obstructive pulmonary disease (COPD) and lung cancer mortality, with the greatest burden in Southeastern provinces. Although air quality briefly improved during coronavirus disease-2019, no significant reduction in $PM_{2.5}$-related COPD deaths was observed, highlighting the need for ongoing interventions.

MATERIAL AND METHODS

Design

This ecological study covered the 2019–2023 five-year period at the national scale. To capture potential effects of COVID-19 restrictions, three temporal strata were defined: pre-pandemic (01-Jan-2019–31-Dec-2019), pandemic (01-Jan-2020–31-Dec-2021), and post-pandemic (01-Jan-2022–31-Dec-2023).

Data Collection Tools

Air quality data were based on PM (PM_{10} and $PM_{2.5}$), which were used as pollutant parameters. These data were obtained retrospectively from the official website of the Ministry of Environment, Urbanization and Climate Change.[17] For PM_{10} and $PM_{2.5}$ data to be included, a minimum annual measurement availability of at least 60% was considered acceptable.[18] Since $PM_{2.5}$ measurements were not available at some national ground-based air quality monitoring stations, PM_{10} data were converted to $PM_{2.5}$. Household air pollution was not included in this assessment.

Country-specific conversion factors were calculated as the mean ratio of PM_{10} to $PM_{2.5}$ concentrations among stations reporting both pollutants in the same year. If country-specific conversion factors were not available, regional conversion factors obtained by averaging the available country-specific factors were used. As the conversion factor $PM_{2.5}/PM_{10}$ may vary according to location, the converted PM_{10} (or $PM_{2.5}$) values for individual settlements may deviate from the actual values (generally between 0.4 and 0.8) and should be considered approximate only.[19] The conversion factor of 0.67 recommended by the WHO for converting PM_{10} to $PM_{2.5}$ in Türkiye was applied.

Population data for Türkiye, from 2019 to 2023, were obtained from the Turkish Statistical Institute (TURKSTAT) database.[20] In AirQ+ calculations, the population at risk was defined as the total population excluding individuals younger than 25 years of age.

The data on COPD mortality rates were taken from the COPDTURKEY-1 study, which provides community-based data for 2020.[21] For the lung cancer mortality rate, data from the Globocan (GCO) statistics for Türkiye[22] were used in the calculations. The mortality rate for COPD was 420 per 100,000 population, while that for lung cancer was 35.1 per 100,000 population (GCO).

Ethical Considerations

Ethical approval and institutional permissions were not obtained because the data were collected from online open-access databases for this research. Informed consent was not obtained because disease-specific mortality data were used in the study.

AirQ+ Methodology

The AirQ+ program, developed by the WHO European Region, estimates the health impacts of air pollution by evaluating both

short-term (e.g., hospital admissions, workday losses) and long-term effects (e.g., all-cause and cause-specific mortality) of pollutants such as $PM_{2.5}$, PM_{10}, NO_2, O_3, and black carbon. All calculations, which use an integrated risk function rather than relative risks, are based on meta-analyses of studies published since 2013. Required inputs include the cause-specific mortality rate and the exposed adult population. In this study, $PM_{2.5}$-related premature mortality rates were calculated specifically using the burden of disease (BoD) module for long-term mortality. Due to limited $PM_{2.5}$ data, PM_{10} measurements from 2019–2023 were converted using WHO-recommended factors, and disease burden was estimated following the AirQ+ methodology. For this study, long-term (annual) exposure to ambient $PM_{2.5}$ was used to estimate attributable premature mortality. Inputs included annual provincial $PM_{2.5}$ concentrations, baseline cause-specific mortality rates, and the exposed population (aged 25 and above). Outputs were calculated at the provincial level.

Estimation of Premature Mortality (Non-accidental Deaths) Attributable to $PM_{2.5}$

Mortality estimates were calculated using the BoD module of the WHO AirQ+ software. For input data, cause-specific mortality rates were derived from official TURKSTAT datasets stratified by province and selected causes of death. In this process, the total number of deaths was adjusted by excluding deaths due to accidents and injuries to obtain non-accidental deaths [non-communicable deaths + acute lower respiratory infection (ALRI)]. One required input for the premature mortality calculation is the mortality rate for non-communicable diseases and ALRIs. For each province and year, the total number of deaths was adjusted by excluding external causes (ICD-10 codes V01–Y98). Using the adjusted death counts and the at-risk population obtained from AirQ+, the mortality rate per 100,000 population was calculated. The cut-off value for annual mean $PM_{2.5}$ concentration was set at 2.4 $\mu g/m_3$, consistent with the Global Exposure Mortality Model.[23] This approach enabled estimation of premature mortality attributable to long-term exposure to ambient $PM_{2.5}$ at the provincial level in Türkiye for individuals aged 25 years and older.

Province-specific population attributable fractions (PAFs) were calculated using the AirQ+ BoD module based on annual mean $PM_{2.5}$ concentrations and cause-specific mortality rates. All calculations were performed for individuals aged 25 years and above.

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation. For Türkiye, the estimated proportion of COPD mortality attributable to long-term exposure to $PM_{2.5}$ was derived from the provincial average proportions. These estimated proportions were then compared across the pre-pandemic (2019), pandemic (2020–2021), and post-pandemic (2022–2023) periods using one-way ANOVA. Assumptions of normality and homogeneity were tested with Shapiro–Wilk and Levene tests. Results were reported with 95% CIs, and $P < 0.05$ was considered statistically significant.

RESULTS

Descriptive data on PM_{10} levels in Türkiye from 2019 to 2023 are summarized in Supplementary Table 1. Over the past five years, the provinces with the highest PM_{10} pollution levels were Muş (96.70 $\mu g/m^3$), Batman (82.83 $\mu g/m^3$), Iğdır (79.29 $\mu g/m^3$), Şırnak (74.64 $\mu g/m^3$), and Malatya (72.72 $\mu g/m^3$). Among these, Muş showed a decreasing trend in pollution, Malatya exhibited an increasing trend, while the other provinces displayed a fluctuating pattern. The four provinces with the cleanest air quality during this period, based on the lowest 5-year PM_{10} averages, were Bitlis (22 $\mu g/m^3$), Artvin (24 $\mu g/m^3$), Bilecik (27 $\mu g/m^3$), and Rize (28 $\mu g/m^3$).

Total non-accidental deaths at the provincial level are presented in Supplementary Table 2. In 2023, The highest annual number of deaths occurred in İstanbul (67,985), followed by İzmir (29,715) and Ankara (28,572). The lowest numbers were observed in Bayburt (468), Ardahan (676), and Hakkari (651).

Provincial-level premature deaths attributable to long-term $PM_{2.5}$ exposure are summarized in Supplementary Table 3. From 2019 to 2023, the annual national mean number of premature deaths was 85,344 (95% CI: 79,129–91,559). At the provincial scale, attributable mortality rates ranged from 100 to 300 per 100,000 population. The highest rates were observed in Sinop (295.81), Çorum (289.56), and Kastamonu (284.28), while the lowest rates were observed in Bitlis (100.29) and Çanakkale (100.58), with Rize (177.57) having the next lowest rate (Supplementary Table 3).

Between 2019 and 2023, the PAF values attributable to $PM_{2.5}$ for COPD and lung cancer mortality in Türkiye showed significant regional differences. For COPD, the highest PAF values were observed in Muş (34.4%), Batman (30.9%), and Şırnak (29.4%), while the lowest values were recorded in Bitlis (9.5%), Artvin (10.1%), and Kırşehir (11.7%) (Figure 1). Similarly, for lung cancer, the highest PAF values were found in Muş (29.1%), Iğdır (26.8%), and Şırnak (26.5%), whereas the lowest values were observed in Bitlis (10.3%), Artvin (10.9%), and Bilecik (12.1%). These findings highlight the significant public health impact of air pollution. Particularly in the Eastern and Southeastern Anatolia regions (Figure 1).

Figure 2 shows PAF percentages for deaths from COPD and lung cancer attributable to $PM_{2.5}$ across Türkiye from 2019 to 2023. The highest PAF values for COPD in 2023 were observed in Balıkesir (20.42%) and Aydın (21.86%). For lung cancer, Balıkesir (20.18%) and Aydın (21.30%) also stand out with high PAF values. Meanwhile, cities such as Kırklareli and Çanakkale exhibit lower percentages, suggesting differing levels of pollution exposure or the presence of other risk factors. The persistence of high PAF values in certain regions over multiple years underscores the ongoing health challenges posed by air pollution.

Supplementary Table 4. presents detailed on COPD-specific and lung-cancer-specific burdens associated with long-term $PM_{2.5}$ exposure in 2019 and 2023. For COPD in 2023, the highest PAFs were observed in Balıkesir (20.42%), Aydın (21.86%), Denizli (19.05%), and Manisa (23.92%). For lung cancer, the corresponding highest PAFs were in Balıkesir (20.18%), Aydın

(21.30%), and İzmir (18.21%). The lowest COPD PAFs were found in Bitlis (10.29%), Rize (17.57%), and Bilecik (10.16%), while the lowest lung cancer PAFs were found in Bitlis (10.30%), Artvin (10.90%), and Bilecik (12.10%).

The percentage of COPD mortality attributable to long-term exposure to $PM_{2.5}$ in Türkiye showed minimal variation across the pre-, during-, and post-COVID-19 periods, with means of 18.89% (95% CI: 17.49–20.29), 19.34% (95% CI: 18.14–20.54), and 18.58% (95% CI: 17.45–19.70), respectively. These differences were not statistically significant (P = 0.687; Supplementary Table 5).

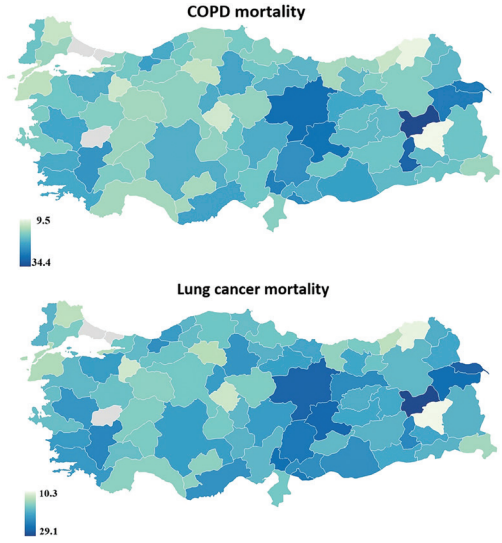

Figure 1. Chronic obstructive pulmonary disease (COPD) and lung cancer mortality attributable to $PM_{2.5}$ in Türkiye (2019–2023)

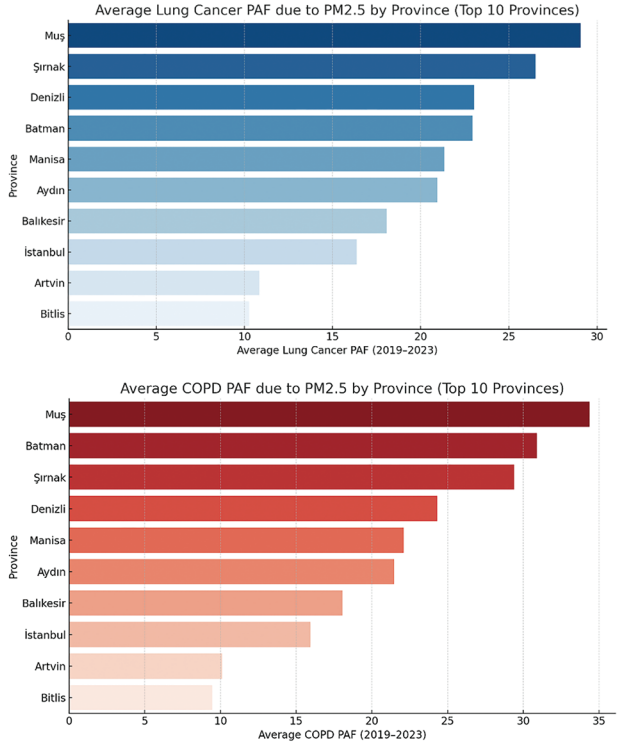

Figure 2. Population of attributable fraction (PAF) of chronic obstructive pulmonary disease (COPD) and lung cancer deaths due to $PM_{2.5}$ in Türkiye (2019–2023)

DISCUSSION

This study aimed to examine long-term trends in premature mortality attributable to air pollution exposure in Türkiye and the burden of respiratory diseases associated with it. Between 2019 and 2023, the provinces with the highest PM_{10} levels were Muş, Batman, Iğdır, Şırnak, and Malatya. The Black Report by the Clean Air Platform (2020–2022) also identified these provinces as among the most polluted areas in the country 24. High pollution levels in Batman may be linked to industrial activities, such as the Petkim Petroleum Refinery, while in Iğdır, geographical conditions and heating-related emissions may be prominent contributors. In Muş, southwestern winds have been identified as a significant factor. Although PM_{10} concentrations in Muş declined from 136 μg/m³ in 2019 to 73 μg/m³ in 2023, they still exceed the acceptable limits.[24] Although Hakkari and Bitlis are listed among the cities with the best air quality, the insufficient number of national ground-based air quality monitoring stations in these cities may not fully reflect the actual situation.[25]

The AirQ+ program, which plays a crucial role in assessing the health effects of air pollution, was widely used in studies conducted between 2002 and 2022. A meta-analysis on this subject found that the majority of these studies were conducted in Iran, followed by India. Additionally, one of the main challenges in this field is the quality and validity of air quality data. The lack of justification for essential data in AirQ+ studies, such as demographic data, relative risks, and incidence rates, has also been noted as a significant issue.[26] In this study, the demographic and mortality data used for premature mortality calculations were obtained from official statistics covering the relevant years, cities, and regions. The mortality rate data for respiratory diseases were obtained from the latest statistical reports published by GCO and national sources.[21,22] These factors eliminate some of the methodological limitations commonly associated with AirQ+ studies. The findings of this research indicate that, between 2019 and 2023, the total annual number of premature deaths attributed to $PM_{2.5}$ pollution in Türkiye was 85,344. The total number of deaths reported in Türkiye for 2022 was approximately 500,000.[27] A global study investigating trends in premature deaths attributed to air pollution found that these deaths increased from approximately 6.87 million in 2000 to approximately 8.89 million in 2015.[28] This figure corresponds to approximately 12% of the 68 million deaths reported worldwide.[29] Our study findings are consistent with the literature; premature mortality rates due to air pollution vary by city and average between 100 and 200 per 100,000 people. A Global Burden of Disease study analyzing premature deaths due to air pollution between 1990 and 2019 reported a similar global average of.[30] These findings not only underscore the reliability and relevance of using official and locally validated data sources in AirQ+ modeling but also reinforce the critical need for country-specific analyses when assessing the health burden of air pollution. The consistency of Türkiye's estimates with global trends highlights the universal impact of $PM_{2.5}$ exposure, while the city-level variability in mortality rates further emphasizes the importance of regionally tailored mitigation strategies. Future research should aim to integrate more granular exposure data and expand temporal coverage to better capture both short- and long-term health effects, thereby

informing more effective public health interventions and policy planning.

COPD and lung cancer are well-known health conditions that are caused by air pollution. This study examines the burden of COPD and lung cancer attributable to air pollution. During the study period, the long-term percentages of COPD and lung cancer attributable to air pollution were particularly high in the southeastern regions of Türkiye, where air pollution levels were also notably elevated. In this study, approximately 70,000 annual deaths were attributed to air pollution, of which approximately 10,000 were linked to COPD. One in every seven air pollution-related deaths was attributable to COPD. According to the WHO, 14% of air pollution-related deaths are associated with COPD, which aligns with our study findings.[3] These findings are consistent with a 2024 study that reported a statistically significant association between ambient air pollution levels and hospital admissions for respiratory diseases.[31] Taken together, these results reinforce the evidence that air pollution poses a substantial public health threat, not only in terms of increased morbidity but also in terms of premature mortality, as observed in our analysis across the pre, during-, and post-COVID-19 periods in Türkiye. Although studies have reported improvements in air quality due to nationwide measures taken during the COVID-19 pandemic, this study did not observe a significant change in the proportion of deaths attributable to air pollution during the COVID-19 pandemic. This finding aligns with literature suggesting that changes in air pollution levels, or improvements in air quality, do not necessarily lead to a significant change in the trend of attributable premature deaths.[28] The absence of a significant COVID-period difference may reflect the lag between exposure and mortality, demographic shifts, limited statistical power, and possible exposure misclassification resulting from conversion of PM_{10} to $PM_{2.5}$.

These results provide further evidence that respiratory diseases such as COPD serve as critical indicators of the long-term health impacts of air pollution. The alignment with WHO estimates and recent empirical studies reinforces the validity of our findings and underscores the persistent nature of air pollution-related health risks, even during periods of temporary environmental improvements. This highlights the importance of sustained, structural interventions rather than relying solely on short-term reductions in pollutant levels.

Study Limitations

The study has some limitations. To ensure data adequacy, a minimum threshold of 60% valid annual measurements was used. However, the Black Report recommends at least 75% for reliability. Due to limited monitoring stations in certain provinces, regional disparities emerged. To address data gaps, the threshold was lowered, allowing broader geographic inclusion and more comprehensive pollutant distribution analysis. This adjustment improved study validity and highlighted infrastructure limitations, offering insights for future research. Additionally, the fixed $PM_{10} \rightarrow PM_{2.5}$ conversion factor (0.67) recommended by the WHO for Türkiye may introduce bias in high-dust regions; this was noted among the study's limitations. Moreover, the inability to use temporal trend analyses, such as Joinpoint, is another limitation, primarily because the five-year evaluation period is too short to detect meaningful changes in trends.

CONCLUSION

This study presents a comprehensive, national-level, multi-year assessment of premature mortality attributable to $PM_{2.5}$ exposure in Türkiye. According to our findings, an average of 85,344 premature deaths per year—approximately 17.0% of all deaths in the country—are attributed to air pollution. The highest provincial premature-death rates were recorded in Sinop (295.8 per 100,000) and Çorum (289.6 per 100,000), while the lowest were observed in Bitlis (100.3 per 100,000) and Çanakkale (100.6 per 100,000). Although temporary improvements in air quality were observed during the COVID-19 pandemic, no statistically significant change was detected in COPD deaths attributable to $PM_{2.5}$. However, the limited number of $PM_{2.5}$ measurements and insufficient distribution of national ground-based air-quality monitoring stations in certain regions of Türkiye may preclude full characterization of the health risks associated with long-term exposure to ambient $PM_{2.5}$ (per AirQ+). The findings suggest that the Western Black Sea and Aegean regions should be prioritized for targeted interventions. Populations with high baseline mortality and populations in areas with dense urban or industrial activity represent key risk groups. Policy measures should focus on tightening national $PM_{2.5}$ standards, ensuring continuous $PM_{2.5}$ monitoring across all provinces, and expanding clean-heating and industrial emission control programs, particularly in high-burden areas. These region-specific interventions would contribute more effectively to reducing long-term air pollution–related health impacts in Türkiye.

Ethics

Ethics Committee Approval: Ethical approval was not obtained because the data were collected from online open-access databases for this research.

Informed Consent: Because anonymous online datasets were used, informed consent was not required.

Footnotes

Authorship Contributions

Concept: D.H.Y., Data Collection or Processing: D.H.Y., A.C.Y., Analysis or Interpretation: D.H.Y., A.C.Y., Literature Search: D.H.Y., Writing: D.H.Y., A.C.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Does Pulmonary Function Testing Affect Autonomic Nervous System Activity?

Gülay Yalçın[1], Server Erdoğmuş Gülcan[1], Erdoğan Kavlak[2]

[1]Department of Physiotherapy and Rehabilitation, Mudanya University Faculty of Health Sciences, Bursa, Türkiye
[2]Department of Physiotherapy and Rehabilitation, Pamukkale University Faculty of Health Sciences, Denizli, Türkiye

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ABSTRACT

OBJECTIVE: The autonomic nervous system (ANS) regulates vital functions such as heart rate (HR) and respiration. Pulmonary function tests (PFTs), which require forced breathing maneuvers, may influence ANS activity, potentially affecting the accuracy of autonomic measurements. This study aimed to investigate the effects of PFT on ANS activity and to assess the reliability of the test order.

MATERIAL AND METHODS: Forty-eight healthy university students (32 women, 16 men; mean age 19±0.92 years) participated. ANS activity was assessed by heart rate variability (HRV) analysis using the Elite HRV Corsense device. HRV was recorded at rest in a seated position (first measurement), was repeated after a 5-minute rest (second measurement), and was recorded again following PFT performed with a Medwelt SP10 spirometer (third measurement).

RESULTS: Comparison of the first and second measurements showed a statistically significant increase only in the root mean square of successive differences (RMSSD) parameter, with no significant changes in other indices. Comparison of the second and third measurements revealed no significant differences in RMSSD or average HR; however, significant changes were observed in the low-frequency (LF) and high-frequency (HF) components and in the LF/HF ratio.

CONCLUSION: Respiratory maneuvers during PFT may temporarily alter ANS activity, particularly affecting parasympathetic–sympathetic balance. The differences between the first and second measurements emphasize the importance of adequate rest periods before HRV assessment. Measurements taken prior to PFT appear to be more reliable for the accurate evaluation of autonomic function.

KEYWORDS: Autonomic nervous system, heart rate variability, pulmonary function test, health economics

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INTRODUCTION

The autonomic nervous system (ANS) is a component of the peripheral nervous system that helps regulate arterial blood pressure, sweating, body temperature, gastrointestinal motility and secretions, bladder emptying, and various other visceral functions.[1] The ANS is primarily activated by several centers located in the hypothalamus, brainstem, and spinal cord. Additionally, signals from the cerebral cortex, particularly the limbic cortex, are transmitted to lower centers, thereby influencing autonomic control. Autonomic efferent signals are transmitted to different regions of the body through two main subdivisions: the sympathetic and parasympathetic nervous systems. Many body regions and visceral functions are predominantly regulated by these two systems.[2]

Heart rate variability (HRV) represents the variation in time intervals between consecutive heartbeats and is one of the most significant cardiovascular and autonomic health indices. HRV, a biomarker of cardiac vagal control is a non-invasive

Corresponding author: Assoc. Prof. Gülay Yalçın, gulay.yalcin@mudanya.edu.tr

electrocardiographic (ECG) measure that can be obtained from long-term Holter monitoring or short-term ECG recordings. Studies suggest that HRV is a reliable test for confirming the presence of dysautonomia.[3,4]

HRV is measured using two main parameters. In time-domain measurements, calculated from the intervals between successive beats in ECG recordings, the intervals between consecutive regular beats originating from the sinoatrial node [referred to as normal-to-normal (NN) intervals] are assessed. The most commonly used indices in a 24-hour HRV recording include the mean heart rate (HR), the percentage of successive R–R intervals (RR) differing by more than 50 ms (pNN50), and the root mean square of successive differences (RMSSD). While mean HR reflects average HR over an hour, RMSSD and pNN50 represent the parasympathetic component of autonomic tone. The other primary parameters, frequency-domain measurements, involve classifying HR signals based on their frequency and power. Evaluated parameters include high-frequency (HF), low-frequency (LF), medium-frequency, ultra-LF, and very-LF.

Regarding autonomic tone, LF reflects sympathetic activity, whereas HF represents the parasympathetic component; therefore, the LF/HF ratio indicates sympathetic/parasympathetic balance.[5,6] Respiration is essential for the survival of all living organisms. The respiratory system comprises organs, tissues, and supporting structures involved in breathing. Spirometric assessment is one of the most common methods for measuring lung capacities and volumes. Although spirometry alone is insufficient for diagnosis, it provides measurements of inhaled and exhaled air volumes over time, expressed in liters. The volume of air generated by the lungs is expressed in liters per second.[7,8]

The respiratory and ANSs are interconnected. Respiration, a physiological process, is regulated both voluntarily and involuntarily; the ANS mediates its involuntary control. The vagus nerve and sympathetic nerve fibers innervate the lungs. Vagus nerve fibers stimulate the muscles and glands of the bronchi, causing bronchoconstriction and increased secretion. Efferent sympathetic nerve fibers relax bronchial smooth muscle, producing bronchodilation.[9]

The ANS and the respiratory system are two essential physiological systems that interact. In this context, pulmonary function tests (PFT) may affect an individual's ANS activity. This study investigates whether PFTs should be administered before or after tests assessing ANS activity. The findings will contribute to a better understanding of the interaction between these two systems and to establishing a scientific foundation regarding the accuracy and reliability of the sequence in which the tests are applied.

Main Points

- Pulmonary function testing (PFT) can cause temporary changes in autonomic nervous system (ANS) activity, as measured by heart rate variability (HRV).
- Both parasympathetic and sympathetic balance are affected following PFT maneuvers.
- A sufficient rest period before HRV measurement is crucial for reliable assessment of autonomic function.
- The findings highlight the importance of considering respiratory testing effects in studies evaluating ANS activity.

MATERIAL AND METHODS

This study was conducted between October 10 and November 30, 2024, and involved students enrolled in the Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Mudanya University. The Ethics Committee for Human Research at Mudanya University approved the research on October 4, 2024 (reference number E-40839601-50.04-44).

In the referenced study, a power analysis based on the HF parameter of HRV conducted with a 95% confidence level, 80% power, a $P = 0.05$ statistical significance level, and an effect size of 0.44 calculated using the G*Power 3.1 program, determined that 33 cases were required.[10]

Forty-eight university students (aged 18–25 years) who volunteered and who had no systemic diseases, no active disease diagnoses, and no cooperation issues were included. Exclusion criteria for the study included pregnancy, malignancy, presence of a pacemaker, current use of medications, smoking within 2 hours of measurements, and alcohol consumption within 24 hours of measurements. All students included in the study were informed and signed informed consent forms. Evaluations were conducted by the same physiotherapist through face-to-face interviews.

Participants' demographic data (age, height, body weight, education level, exercise habits, and smoking habits) were recorded on the demographic data form. PFTs were performed using the Medwelt SP10 spirometer. A separate mouthpiece was used for each individual, and three measurements were taken, with the highest values recorded. All spirometric assessments were conducted in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines. Participants were evaluated in a seated position with a nose clip in place, and an experienced physiotherapist provided standardized verbal instructions and encouragement throughout the procedure.

Each maneuver was initiated following a maximal inspiration and continued with a rapid, forceful, and sustained expiration lasting at least 6 seconds. At least three acceptable maneuvers were obtained for each participant; acceptability and reproducibility were assessed according to ATS/ERS criteria. Reproducibility was confirmed when the difference between the two highest FEV1 and forced vital capacity (FVC) values was ≤150 mL; otherwise, additional trials were performed.

The measured FEV1, FVC, and FEV1/FVC values were documented in the participant follow-up form.[8] In accordance with guideline recommendations, the highest FEV1 and FVC values (not necessarily from the same maneuver) were used in the analysis, and the FEV1/FVC ratio was calculated accordingly.

FEV1: This value represents the maximum volume of air exhaled during the first second of forced expiration following maximal inspiration.

FVC: This refers to the total volume of air forcefully exhaled after a long, deep inspiration.

FEV1/FVC: This ratio is used to diagnose airway obstruction and in the differential diagnosis of restrictive diseases. In young adults, this ratio is typically above 75%; however, it decreases with age. In individuals with airway obstruction, this ratio is below 70%, whereas in restrictive diseases, this ratio is usually normal or increased.

Assessment of the ANS cannot be performed directly using physiological tests. With advances in technology, new methods have been developed, and many of these are used in scientific research. The most commonly used method for measuring ANS activity is HRV analysis. HRV analysis is based on the observation of RR waves present at rest, and in our study this method was applied with the Elite HRV Corsense device, which operates on this principle. The values measured by the device are as follows:[11]

- RMSSD is used as an instantaneous index of the parasympathetic branch of the ANS and forms the basis for the HRV score.

- LF power refers to power in the frequency range between 0.04 and 0.15 Hz. It is directly proportional to sympathetic nervous system activity and thus represents sympathetic activity.

HF power refers to the spectral power in the frequency range between 0.15 and 0.40 Hz. The HF band reflects parasympathetic activity and is highly correlated with time-domain measures such as PNN50 and RMSSD.

- The LF/HF ratio is the ratio of LF power to HF power and is commonly used to indicate the sympathovagal balance. It represents the balance between the opposing branches of the ANS.

- Mean HR.

Study Plan

After participants signed the voluntary consent form, ANS activity was measured while participants were seated. Following this, a 5-minute rest period was allowed for the body to relax, after which ANS activity was measured again. The difference between the two measurements will help to understand the balance between the sympathetic and parasympathetic branches of the nervous system and to indicate whether any change has occurred in the participants' ANS activity. Subsequently, while still seated, participants underwent PFT. Participants were asked to take a maximal inspiration and then exhale as forcefully and rapidly as possible for the measurement. This measurement was repeated three times at one-minute intervals, and the highest value was recorded. This approach aimed to prevent issues such as incorrect respiratory patterns, insufficient motivation, or technical errors during the test. One minute after completion of the PFT, ANS activity was measured again. In this way, statistical answers were sought to determine whether ANS activity remained at the same level before and after the PFT or was affected, and to identify the correct order of measurements.

Statistical Analysis

The data were analyzed using the SPSS 25.0 software package. Continuous variables were presented as mean ± standard deviation, and categorical variables were presented as frequency and percentage. The normality of the data was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. If the data were normally distributed, the parametric Paired samples test was used; otherwise, the non-parametric Wilcoxon signed-ranks test was applied. In our study, the mean HR was usually distributed in the initial measurements, whereas RMSSD, LF, HF, and LF/HF were not. The mean HR and RMSSD were approximately normally distributed in the second and third measurements, but LF, HF, and LF/HF did not follow a normal distribution.

RESULTS

Sociodemographic Data

The study included 48 participants, of whom 32 were female and 16 were male. The average age of the individuals was 19±0.92 years, their mean height was 1.70±0.11 m, and their average body weight was 65.22±14.87 kg. The average body mass index of the individuals was 22.09±3.19 kg/m^2. Data related to the demographic characteristics of the cases are presented in Table 1.

Table 2 presents the ANS activity values—RMSSD, HF, LF, LF/HF, and mean HR— measured three times, and the participants' pulmonary function test (PFT) scores.

Table 3 shows the results of the Wilcoxon signed-rank test and the paired-samples test applied to determine the relationship between the first and second measurements of ANS activity. When examining the results of autonomic activity markers, no statistically significant change was observed in any autonomic activity measure except for the RMSSD parameter.

Table 4 shows the results of the Paired samples test and the Wilcoxon signed ranks test, which were applied to determine the relationship between the second and third measurements of the ANS, the latter taken after the PFT. The results indicate that RMSSD and mean HR did not change, whereas LF, HF, and LF/HF showed statistically significant changes.

DISCUSSION

This study investigated the effect of the PFT on ANS activity. To ensure methodological accuracy, particular attention was

Table 1. Sociodemographic data

	n (%)	X ± SD	Min–max
Gender			
Female	32 (66.7)	-	-
Male	16 (33.3)	-	-
Age		19±0.92	18–21
Height (m)		1.70±0.11	1.56–1.99
Weight (kg)		65.22±14.87	42–105
BMI		22.09±3.19	16–29.32

n: number of cases, X: mean, SD: standard deviation, Min: minimum, max: maximum, BMI: body mass index

given to the timing of autonomic measurements and resting conditions. Participants were allowed to rest for five minutes after the first measurement, after which the same autonomic assessment was repeated.

When the results were examined, most HRV parameters did not show statistically significant differences between the two measurements. However, a statistically significant increase in RMSSD, an indicator of parasympathetic activity, was observed. This finding suggests that a short resting period following the initial measurement may be necessary to obtain a more stable and reliable assessment of autonomic activity. The increase in parasympathetic modulation after rest indicates that the first measurement, taken without adequate recovery, may reflect transient autonomic responses rather than baseline autonomic function.

From a clinical perspective, this finding highlights the importance of standardizing rest intervals prior to autonomic measurements, particularly in protocols involving respiratory maneuvers or physical effort. The observed difference between the two measurements contributes to understanding the balance between sympathetic (stress-related) and parasympathetic (relaxation-related) activity. An increase in parasympathetic activity after rest may also indicate adequate autonomic adaptability in healthy individuals.

PFTs are widely used tools for the evaluation and monitoring of respiratory system function. These tests require participants to perform standardized respiratory maneuvers involving maximal inspiration and forceful expiration to assess lung volumes and airflow.[12] According to current guidelines, at least three acceptable and reproducible maneuvers are required to ensure measurement reliability. Because these maneuvers demand maximal effort, they may act as an acute physiological stressor capable of altering ANS activity.

For this reason, autonomic activity was measured both before and after the PFT in the present study. When pre- and post-test autonomic parameters were compared, statistically significant changes were observed. Specifically, a significant increase in LF and LF/HF ratio—indices associated with sympathetic modulation—and a significant decrease in HF, reflecting parasympathetic activity, were detected. These findings indicate that PFT-related respiratory maneuvers transiently shift autonomic balance toward sympathetic dominance. Consequently, autonomic measurements intended to reflect baseline autonomic function should be performed before PFT administration. This recommendation may be particularly relevant in clinical or research settings in which HRV is used as an outcome measure.

HRV provides a quantitative assessment of beat-to-beat fluctuations in HR and reflects complex interactions between the cardiovascular and ANSs. HRV is considered a sensitive marker of neurocardiac regulation and physiological adaptability.[13-15] In the present study, HRV analysis using the Elite HRV device enabled an objective and non-invasive evaluation of autonomic responses to respiratory maneuvers. The observed changes support the notion that respiratory effort can significantly modulate cardiac autonomic function.

Previous studies have also demonstrated the influence of respiratory maneuvers on autonomic activity. Ajudia et al.[16] investigated the effects of intensive spirometry on cardiac autonomic function in healthy young adults and reported

Table 2. Autonomic nervous system activity (1st, 2nd, and 3rd measurements) and PFT scores

		X ± SD	Min–max
First measurement	RMSSD	64.39±32.51	9.11–187.32
	LF	5935.05±4342.30	42.12–18730.44
	HF	1950.37±2419.57	143.2–14953.42
	LF/HF	5.43±5.53	0.06–31.60
	Mean heart rate	93.89±13.00	72.02–137.04
Second measurement	RMSSD	69.37±29.38	8.90–132.00
	LF	5472.70±4161.81	92.39–18485.00
	HF	1867.72±1808.34	56.90–7301.00
	LF/HF	4.91±5.10	0.10–29.90
	Mean heart rate	92.35±10.93	71.03–129.08
Third measurement	RMSSD	67.77±27.04	10.00–138.90
	LF	6511.81±3974.23	80.10–14944.30
	HF	2117.79±2217.09	46.64–10467.78
	LF/HF	5.41±5.07	0.54–21.99
	Mean heart rate	92.97±12.32	72.07–129.09
Pulmonary function test measurement	FEV1 (L)	2.67±1.026	0.60–5.20
	FVC (L)	3.79±0.95	2.43–6.37
	FEV1/FVC (%)	0.73±0.24	0.15–1.34

PFT: pulmonary function test, X: mean, SD: standard deviation, Min: minimum, max: maximum, RMSSD: root mean square of successive differences, LF: low-frequency, HF: high-frequency, LF/HF: ratio of low-frequency to high-frequency, L: liter, FVC: forced vital capacity

changes in HR parameters following prolonged respiratory training. Although the magnitude and direction of autonomic responses differed between their study and ours, both studies confirm that respiratory maneuvers are capable of altering autonomic regulation. Methodological differences, including intervention duration, breathing frequency, and resting conditions, may explain the variability in outcomes.

Memarian et al.[17] used deep breathing tests to assess cardiovagal function and demonstrated associations between respiratory sinus arrhythmia (RSA) and HRV indices. However, because RSA was not directly measured in the present study, only the HRV-derived parameters included in our results were emphasized in the discussion to avoid interpretative ambiguity. This distinction is important to ensure consistency between reported results and literature comparisons. Nonetheless, both studies underscore the broader concept that controlled respiratory maneuvers have a measurable impact on autonomic regulation.

Ali et al.[18] evaluated parasympathetic reactivity during deep breathing and reported discrepancies between RMSSD and RSA responses. Consistent with their findings, our study observed that RMSSD did not always increase following respiratory maneuvers, suggesting that RMSSD alone may not fully capture parasympathetic reactivity in such contexts. These results indicate that incorporating multiple autonomic indices may provide a more comprehensive assessment of autonomic responses to respiratory interventions.

Malhotra et al.[19] examined the acute effects of slow and deep breathing on HRV and found increased parasympathetic modulation following controlled breathing exercises. Although our study did not involve respiratory training, the shared finding is that respiratory patterns and effort can acutely influence autonomic balance. This supports the hypothesis that even short-term respiratory interventions or tests can transiently modify autonomic function.

Despite these findings, the present study has limitations regarding the temporal dynamics of autonomic recovery. Autonomic activity was assessed only at a single post-test time point, and different rest durations were not compared. Future studies evaluating autonomic responses at multiple intervals following PFT (e.g., immediately after, at 5 and 10 minutes, and during longer recovery periods) may provide deeper insight into autonomic recovery patterns.

Clinically, such information could contribute to optimizing PFT protocols and improving the interpretation of autonomic measurements obtained in conjunction with respiratory testing. Comparing different rest durations may also help establish standardized guidelines for autonomic assessment following PFTs, thereby enhancing the clinical and research utility of these measurements.

Study Limitations

This study has several limitations. Firstly, the limited sample size may restrict the generalizability of the findings. The inclusion of only healthy adults, while strengthening internal validity and allowing for a clearer interpretation of autonomic responses, limits the applicability of the results to clinical populations and different age groups. Therefore, the effects of PFTs on ANS activity should be interpreted with caution when extrapolating to individuals with cardiopulmonary or neurological conditions. Another important limitation is the lack of a detailed evaluation of autonomic responses at multiple time points following the PFT. Autonomic activity was assessed at a single post-test time interval, and the effects of different recovery durations were not

Table 3. The relationship between autonomic nervous system activity in the first and second measurements

	1. measurement	2. measurement	*P*
RMSSD			
Mean ± SD	64.39±32.51	69.37±29.38	0.036[1]
Min–max	5–187	8.90–132.00	
LF			
Mean ± SD	5935.05±4342.30	5472.70±4161.81	0.644[1]
Min–max	42–18730	92.39–18485.00	
HF			
Mean ± SD	1950.37±2419.57	1867.72±1808.34	0.300[1]
Min–max	14–14953	56.90–7301.00	
LF/HF			
Mean ± SD	5.43±5.53	4.91±5.10	0.460[1]
Min–max	0.06–31.60	0.10–29.90	
Mean heart rate			
Mean ± SD	93.89±13.00	92.35±10.93	0.228[2]
Min–max	72.0–137.0	71.0–129.0	

[1]Wilcoxon signed-ranks test, [2]Paired samples test
SD: standard deviation, Min: minimum, max: maximum, RMSSD: root mean square of successive differences, LF: low-frequency, HF: high-frequency, LF/HF: ratio of low-frequency to high-frequency

Table 4. The relationship between autonomic nervous system activity in the second and third measurements

	1. measurement	2. measurement	*P*
RMSSD			
Mean ± SD	69.37±29.38	67.77±27.04	0.588[2]
Min–max	8.90–132.00	10.00–138.00	
LF			
Mean ± SD	5472.70±4161.81	6511.81±3974.23	**0.041[1]**
Min–max	92.39–18485.00	80.00–14944.00	
HF			
Mean ± SD	1867.72±1808.34	2117.79±2217.09	**0.052[1]**
Min–max	56.90–7301.00	46.00–10467.00	
LF/HF			
Mean ± SD	4.91±5.10	5.41±5.07	**0.049[1]**
Min–max	0.10–29.90	0.50–21.99	
Mean heart rate			
Mean ± SD	92.35±10.93	92.97±12.32	0.614[2]
Min–max	71.0–129.0	72.0–129.0	

[1]Wilcoxon signed-ranks test, [2]Paired samples test
SD: standard deviation, Min: minimum, max: maximum, RMSSD: root mean square of successive differences, LF: low-frequency, HF: high-frequency, LF/HF: ratio of low-frequency to high-frequency

systematically compared. Because autonomic responses may vary with the duration of the rest period following respiratory maneuvers, this limitation may have reduced the depth of interpretation and the study's overall contribution to the literature.

Future studies comparing ANS responses at different recovery intervals after PFT (e.g., immediate, short-term, and longer rest periods) may provide more comprehensive insights and contribute to the development of optimized and standardized testing protocols. Additionally, comparing different test types and autonomic measurement parameters may further enhance the consistency and clinical relevance of future findings.

CONCLUSION

This study investigated the effects of PFTs on ANS activity. The findings suggest that respiratory maneuvers can influence autonomic activity, particularly by altering parasympathetic reactivity. The rest period provided after the initial measurement was important in explaining the increase in parasympathetic activity. The observed increase in RMSSD highlights the importance of rest periods in accurately measuring autonomic activity.

Measurements taken before and after the PFT showed an increase in sympathetic nervous system activity, indicated by LF and the LF/HF ratio, and a decrease in parasympathetic nervous system activity, reflected by HF. These results suggest that PFTs temporarily affect ANS activity, and this effect can be validated using different measurement methods.

The HRV analysis method used in our study proved to be an effective tool for objectively assessing the dynamics of the autonomic system. However, further research is needed to understand how different respiratory maneuvers and measurement parameters affect autonomic activity. Despite methodological differences across studies, respiratory maneuvers significantly influence autonomic activity, and selecting appropriate measurement methods is crucial for accurately evaluating this interaction. These findings may provide valuable insights into the potential effects of PFTs on the ANS and serve as an important reference for future studies.

Ethics

Ethics Committee Approval: The Ethics Committee for Human Research at Mudanya University approved the research on October 4, 2024 (reference number E-40839601-50.04-44).

Informed Consent: Written informed consent was obtained from all participants prior to their inclusion in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.Y., S.E.G., E.K., Concept: G.Y., S.E.G., E.K., Design: G.Y., S.E.G., E.K., Data Collection or Processing: G.Y., S.E.G., Analysis or Interpretation: G.Y., S.E.G., Literature Search: G.Y., S.E.G., E.K., Writing: G.Y., S.E.G.

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Original Article

Household Tobacco Smoke Exposure in Asthmatic Children in Algeria: A Multicenter Study

Redouene Sid Ahmed Benazzouz[1], Massinissa Benyagoub[1], Azeddine Mekideche[2], Mohamed Safouane Benazzouz[3,4], Faiza Hadjersi[5]

[1]Department of Medicine, Faculty of Medicine, Laghouat University, Laghouat, Algeria
[2]Private Pulmonology Medical Office (Dr. Azzeddine Mekideche), Jijel, Algeria
[3]Department of Therapeutic Serum Production, Pasteur Institute of Algeria, Algiers, Algeria
[4]Department of Pharmacy, Faculty of Pharmacy, University of Algiers, Algiers, Algeria
[5]Department of Medicine, Laghouat Public Hospital, Laghouat, Algeria

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ABSTRACT

OBJECTIVE: Passive and active tobacco smoke exposure can worsen asthma outcomes in children, yet data on its prevalence in Algeria are limited. To assess the prevalence and characteristics of tobacco smoke exposure, including prenatal and adolescent active smoking, among asthmatic children in Algeria.

MATERIAL AND METHODS: A multicenter cross-sectional study was conducted from December 1, 2024, to January 31, 2025, in five pediatric consultation centers across Algeria. A total of 135 children with physician-diagnosed asthma, aged 2 months to 15 years, were enrolled. Data on demographic, clinical, socioeconomic, and environmental factors were collected.

RESULTS: Tobacco smoke exposure was documented in 37.8% of participants, most commonly attributable to paternal smoking. In utero exposure was reported in 40% of the study population. Low-income households showed a higher prevalence of exposure compared with higher-income groups (P = 0.009). The geographic distribution of exposure varied significantly (P = 0.001). No significant association was found between tobacco smoke exposure and asthma severity or asthma control. Three adolescent patients reported active smoking.

CONCLUSION: Over one-third of Algerian children with asthma are exposed to tobacco smoke, with a substantial proportion exposed prenatally. These findings highlight the need for family-focused cessation programs and region-specific preventive actions to reduce children's exposure to tobacco smoke in Algeria.

KEYWORDS: Asthma, passive smoking, prenatal tobacco exposure, health disparities, Algeria

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INTRODUCTION

Asthma is one of the most common chronic diseases in children worldwide, with prevalence estimates ranging from 5% to 20% depending on the region.[1] Environmental factors play a key role in its onset and progression, and tobacco smoke remains one of the most important and preventable contributors.[2,3] Exposure to passive smoke, whether during pregnancy, in early childhood, or through ongoing household smoking, has consistently been linked to increased respiratory symptoms, reduced treatment efficacy, and higher morbidity among children with asthma.[4-6]

The impact of early-life exposure is particularly well established. A systematic review and meta-analysis by Burke et al.[7] demonstrated that prenatal maternal smoking increased the risk of incident asthma in children ≤2 years of age by 85% [odds ratio (OR): 1.85, 95% confidence interval (CI): 1.35–2.53], whereas postnatal maternal smoking increased the risk of wheezing in the same age group by 70% (OR: 1.70, 95% CI: 1.24–2.35).

Corresponding author: Prof. Assoc. Redouene Sid Ahmed Benazzouz, e-mail: r.benazzouz@lagh-univ.dz

In Algeria, tobacco smoking remains a significant public health issue: adult smoking prevalence is estimated at 15.6%, reaching 30.2% among men and just 0.6% among women, with tobacco-related mortality contributing to approximately 8.4% of all deaths.[8] Despite the high prevalence of tobacco use in Algeria, multicenter data describing the prevalence and patterns of household tobacco smoke exposure among asthmatic children are lacking. In particular, national evidence on prenatal exposure, parental smoking patterns, and socioeconomic and geographic disparities is limited.

This multicenter study primarily aimed to describe the prevalence and characteristics of household tobacco smoke exposure among asthmatic children in Algeria, including prenatal, early-life, and current passive exposure. Secondary objectives were to examine parental smoking behavior and to explore sociodemographic and geographic variations in exposure.

MATERIAL AND METHODS

Study Design and Setting

This was a prospective, multicenter, cross-sectional study conducted over two months, from 1 December 2024 to 31 January 2025. It took place in five pediatric outpatient respiratory consultation centers located in different regions of Algeria, specifically in the cities of Laghouat, Djelfa, Blida, Algiers, and Jijel. The five participating centers were selected to ensure geographic and socioeconomic diversity across Algeria, representing the capital coastal metropolis (Algiers), an inland urban center (Blida), a coastal province (Jijel), a high-plateau region (Djelfa), and a semi-arid southern region (Laghouat). All centers host specialized pulmonology consultation units staffed by qualified personnel and sufficient patient volume to support standardized, multicenter data collection. The pulmonologists responsible for each site shared a common postgraduate training in respiratory medicine, ensuring consistency in diagnostic and clinical assessment practices across centres.

Study Population

The study included all children under 18 years of age who had a confirmed diagnosis of asthma and attended routine outpatient consultations during the study period. Asthma was diagnosed by a pneumologist specializing in respiratory diseases, in accordance with the 2024 Global Initiative for Asthma (GINA) guidelines,[9] based on clinical symptoms such as recurrent wheezing, dyspnea, nocturnal cough, and bronchodilator responsiveness, and/or on spirometric evidence of reversible airway obstruction.

Asthma severity was determined retrospectively according to the GINA 2024 classification, based on the treatment level required to achieve and maintain control (steps 1–5). Mild asthma corresponded to steps 1–2, moderate asthma to step 3, and severe asthma to steps 4–5.

Children with comorbid chronic respiratory conditions, including cystic fibrosis and bronchopulmonary dysplasia, as well as those with incomplete medical records, were excluded. Cases of active smoking in children were identified and documented, but were excluded from the final analysis. The overall recruitment and selection process is summarized in Figure 1.

Data Collection

After obtaining informed consent from the parents or legal guardians, the attending physician collected data using a standardized, structured questionnaire administered in person. The questionnaire included variables related to demographic characteristics (age, sex, region of residence), asthma-related clinical history (age of onset, severity, current treatment, and previous exacerbations), tobacco smoke exposure, smoking behavior of both parents, and household socioeconomic status.

Assessment of Tobacco Smoke Exposure

Tobacco smoke exposure was assessed through parental report. Passive smoking exposure was defined as the presence of one or more household members actively smoking inside the home, regardless of frequency. In utero, or prenatal, exposure refers to maternal smoking during pregnancy, whether active or resulting from significant passive exposure to tobacco smoke. Early-life exposure was defined as household smoking during the child's early years. Active smoking was recorded when children, particularly adolescents, reported smoking more than 100 cigarettes. These individuals were excluded from the analysis.

The smoking habits of both parents were systematically documented, including current smoking status and typical patterns of consumption and exposure within the household.

Main Points

- This is the first multicenter study assessing household tobacco smoke exposure in asthmatic children in Algeria.
- More than one-third of Algerian children with asthma are exposed to secondhand smoke.
- Prenatal exposure to tobacco smoke was reported in 40% of the study population.
- Tobacco smoke exposure was more prevalent in socioeconomically disadvantaged households.
- Exposure rates varied significantly across geographic regions in Algeria.

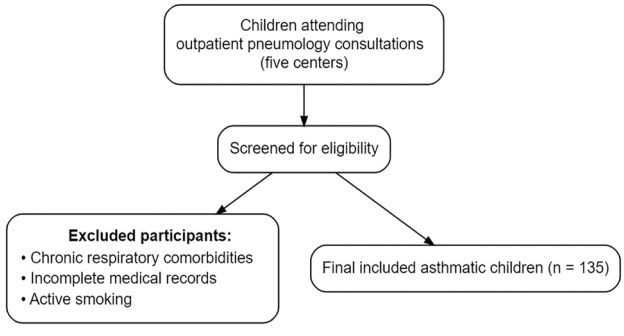

Figure 1. Flow diagram of patient recruitment and inclusion process

Socioeconomic Status Classification

Socioeconomic status was assessed subjectively by the attending physician based on an overall impression that integrated several observable and reported indicators, including estimated family income relative to the national average net income in Algeria (approximately 42,800 DZD per month according to the 2021 ONS report),[10] stability of parental occupation, education level, housing conditions, type of schooling (public or private), and social security coverage. Reported financial difficulties or limited access to healthcare were also considered. The evaluation followed a descending logic, in which the accumulation of indicators suggesting financial limitations led to classification into a lower socioeconomic category. No single factor was used as a determinant. Socioeconomic status was then categorized into three levels: low, middle, and high.

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Laghouat University Faculty of Medicine (protocol no. 13/2024; decision date: 20 November 2024). Written informed consent was obtained from the parents or legal guardians of all participants. All data were anonymized prior to analysis and stored in a secure, password-protected database.

Statistical Analysis

Data entry and analysis were performed using R Project for Statistical Computing, version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were presented as frequencies and percentages, and continuous variables as medians with interquartile ranges (IQR). The prevalence of passive smoking exposure was calculated with 95% CIs. Differences in the distribution of tobacco smoke exposure across sociodemographic and clinical variables were examined using the chi-square test or Fisher's exact test for categorical variables, and the Mann-Whitney U test for continuous variables. A *P* value less than 0.05 was considered statistically significant.

RESULTS

A total of 135 children with physician-diagnosed asthma were included in the analysis. The participants ranged in age from 2 months to 15 years, with a median age of 7.0 years (IQR: 4.0–

Table 1. Baseline characteristics of the study population according to smoke exposure

	Study population	Smoke exposure	No smoke exposure	*P*
Total (%)	135 (100.0)	51 (37.8)	84 (62.2)	
Age[a]	7.0 [4.0, 9.0]	7.0 [4.0, 9.0]	7.0 [4.0, 9.0]	0.523
Paternal age[a]	40.0 [37.0, 44.0]	40.0 [38.0, 45.5]	40.0 [37.0, 44.0]	0.464
Maternal age[a]	37.0 [32.0, 40.0]	37.0 [31.5, 40.0]	36.0 [32.0, 40.0]	0.994
Male (%)	75 (55.56)	29 (56.86)	46 (54.76)	0.953
Asthma severity (%)				
Step 1	32 (24.43)	10 (19.61)	22 (27.50)	0.373
Step 2	29 (22.14)	15 (29.41)	14 (17.50)	
Step 3	63 (48.09)	24 (47.06)	39 (48.75)	
Step 4	7 (5.34)	2 (3.92)	5 (6.25)	
Step 5	0 (0.00)	0 (0.00)	0 (0.00)	
Asthma control (%)				
Well controlled	68 (50.37)	29 (56.86)	39 (46.43)	0.140
Partly controlled	37 (27.41)	9 (17.65)	28 (33.33)	
Uncontrolled	30 (22.22)	13 (25.49)	17 (20.24)	
Socioeconomic level (%)				
Low-income	27 (20.00)	16 (31.37)	11 (13.10)	**0.009**
Middle-income	50 (37.04)	12 (23.53)	38 (45.24)	
High-income	58 (42.96)	23 (45.10)	35 (41.67)	
Geographic location (%)				
Blida	8 (5.93)	3 (5.88)	5 (5.95)	**0.001**
Jijel	72 (53.33)	22 (43.14)	50 (59.52)	
Djelfa	40 (29.63)	25 (49.02)	15 (17.86)	
Laghouat	4 (2.96)	0 (0.00)	4 (4.76)	
Algiers	11 (8.15)	1 (1.96)	10 (11.90)	

[a]Results expressed as median [interquartile range]. Asthma severity and control levels according to GINA criteria[9]
GINA: Global Initiative for Asthma

9.0). Males accounted for 55.6% of the sample. The median age of fathers was 40.0 years (IQR: 37.0–44.0), and that of mothers was 37.0 years (IQR: 32.0–40.0) (Table 1).

Overall, 51 children [37.8% (95% CI: 29.6–45.9)] were exposed to passive tobacco smoke at home. Exposure was strongly associated with socioeconomic status: approximately 60% of low-income households reported exposure, compared with 24% of middle-income households and 40% of high-income households ($P = 0.009$).

No statistically significant differences were observed with respect to the child's sex ($P = 0.953$), the child's age ($P = 0.523$), or the age of either parent ($P = 0.464$ and $P = 0.994$ for fathers and mothers, respectively). The distribution of asthma severity and control status did not differ significantly between children with and without current passive exposure.

Geographic Disparities

Marked differences were observed between cities. Djelfa exhibited the highest prevalence of exposure (62.5%), whereas all other locations reported prevalences below 50%. This difference was statistically significant ($P = 0.001$).

Sources and Timing of Exposure

Regarding parental smoking, 41.5% of fathers and 1.5% of mothers reported current smoking. Prenatal exposure was reported in 40% of participants, and early-life exposure (during the first year of life) was reported in a similar proportion.

The median number of cigarettes smoked per day by fathers was 20 (IQR: 20–30), consistent with that reported by the two smoking mothers. Among fathers, 4.6% reported quitting smoking, with a median duration of smoking cessation of 10 years (IQR: 4.75–13.75).

Three adolescents reported active smoking (≥100 cigarettes in their lifetime) and were excluded from the main analysis.

DISCUSSION

More than one in three asthmatic children in our multicenter Algerian cohort were exposed to tobacco smoke at home, and approximately 40% had been exposed prenatally or during early life. Exposure levels varied significantly across socioeconomic groups and geographic regions. These findings provide one of the first multicenter estimates of household tobacco smoke exposure among asthmatic children in Algeria.

Prevalence in the Context of Existing Literature

Our prevalence (37.8%) is lower than the 53.3% prevalence reported by Tamim et al.[11] in Beirut in 2006 among preschool children. Some countries have reported a gradual decline in children's exposure over recent decades.[12] Algerian data on this topic remain scarce.

A single-centre study from Annaba, Eastern Algeria, reported passive smoke exposure in about one-third of asthmatic children.[13] This figure is consistent with our multicentre findings, but its representativeness is limited by the study's localized scope and lack of socioeconomic stratification.

According to the most recent World Health Organization country profile, adult smoking prevalence in Algeria remains around 15–16% overall (about 30% in men and 1% in women), with no clear downward trend documented over the past two decades.[8] In our cohort, the proportion of smoking fathers (41.5%) was considerably higher than the national average for males, whereas maternal smoking (1.5%) slightly exceeded the national estimate.[8]

Our participants were recruited from outpatient pediatric respiratory clinics rather than from hospital wards, which makes this sample broadly representative of community-based asthma care in Algeria. The higher prevalence of parental smoking in our cohort, particularly among fathers, aligns with international evidence linking parental smoking to the onset and exacerbation of childhood asthma.[4,7] However, causality cannot be inferred from this cross-sectional observation, and further population-based studies are warranted to confirm whether elevated parental smoking rates are a contributing factor or simply reflect shared socio-environmental conditions.

Lack of Sex and Age Differences

Contrary to the findings of Murray and Morrison[14], who reported greater susceptibility to passive smoking among boys and older children, our study did not reveal significant differences by sex or age. This absence of differences may indicate that the overall exposure levels in our sample were sufficient to produce similar effects across demographic subgroups. It is also possible that our design, which did not include objective physiological measurements such as bronchial hyperresponsiveness or airway inflammatory markers, was not sensitive enough to detect subtle sex- or age-related variations in response to passive smoke exposure.

Prenatal and Early-life Exposure

The persistence of high prenatal (40%) and early-life (40%) exposures is of concern, given the robust evidence linking these exposures to respiratory morbidity. The meta-analysis by Burke et al.[7] showed that prenatal maternal smoking increases asthma risk by up to 85% in children aged ≤2 years (OR: 1.85, 95% CI: 1.35–2.53), while postnatal maternal smoking increases the risk of wheezing by up to 70%. Mechanistically, prenatal exposure may impair fetal lung development via nicotine-induced alterations in airway structure and immune function.[15]

Socioeconomic and Geographic Disparities

The higher prevalence of passive smoking exposure among low-income families in our study mirrors the social gradient reported in other countries.[16,17]

The higher prevalence of passive smoking exposure among low-income families in our study reflects the patterns observed in the United Kingdom and Bangladesh, where children from lower socioeconomic backgrounds are disproportionately affected.[16,17] Similar mechanisms are likely at play in Algeria, where socioeconomic disparities may influence household crowding, parental awareness, and adherence to smoke-free home recommendations.

The markedly higher exposure in Djelfa may reflect regional variation, but the reasons for this difference remain to be clarified. No prior data from Algeria have examined regional patterns of household exposure to tobacco.

Study Limitations

This cross-sectional design precludes causal inference, and exposure assessment relied on parental self-report, which may have led to underestimation of prevalence. No biomarker validation was performed. The study included all eligible cases during the two-month multicenter collection period, which limited sample size and may have reduced statistical power, particularly given the unequal distribution of participants across centers. Finally, contextual factors, such as the time children spent at home or outdoors, were not recorded, which could have led to misestimation of exposure.

Policy and Research Implications

Our findings highlight the need for targeted health promotion campaigns, especially in high-prevalence regions and low-income households. Interventions should prioritize smoking cessation among fathers, who are the main household source of exposure, and integrate counselling on tobacco risks during prenatal and early-life visits. Region-specific awareness programs, particularly in areas such as Djelfa, could further strengthen prevention.

Future studies could integrate biomarkers such as cotinine to quantify exposure and assess its longitudinal impact on asthma control.

CONCLUSION

In this multicenter study of 135 asthmatic children in Algeria, more than one-third (37.8%) were currently exposed to household tobacco smoke, with prenatal and early-life exposures were each reported in 40% of cases. Paternal smoking was the predominant household source, and exposure was significantly more frequent in low-income families and in certain geographic regions.

Although asthma severity did not differ significantly between children with and without current passive exposure, the high rates of prenatal and early-life exposure underscore a substantial, preventable risk to pediatric respiratory health. These findings emphasize the urgent need for targeted public health actions—particularly smoking cessation programs for fathers, prenatal smoking counseling, and implementation of smoke-free home environments.

Reducing household tobacco exposure must now become a national priority within Algeria's child and maternal health agenda, combining clinical counselling, media-based awareness, and community-level prevention programs. Future research should include objective biomarkers of exposure and longitudinal tracking to better evaluate effects of exposure on asthma progression.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Laghouat University Faculty of Medicine (protocol no. 13/2024; decision date: 20 November 2024).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of all participants.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: R.S.A.B., M.B., A.M., Concept: R.S.A.B., M.B., A.M., F.H., Design: R.S.A.B., A.M., F.H., Data Collection or Processing: R.S.A.B., A.M., F.H., Analysis or Interpretation: R.S.A.B., M.B., A.M., M.S.B., Literature Search: R.S.A.B., M.B., A.M., M.S.B.,F.H., Writing: R.S.A.B., M.B., A.M., M.S.B., F.H.

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Original Article

The Relationship Between Peripheral Eosinophilia, Lower Respiratory Tract Pathogens, Age at First Pneumonia, and Malnutrition in Children with Non-cystic Fibrosis Bronchiectasis

Esin Gizem Olgun, Gizem Özcan, Fazılcan Zirek, Merve Nur Tekin, Secahattin Bayav, Mahmut Turğut, Mukaddes Ağırtıcı, Semra Küçük Öztürk, Seyhan Çelik Merteşe, Nazan Çobanoğlu

Department of Pediatric Pulmonology, Ankara University Faculty of Medicine, Ankara, Türkiye

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ABSTRACT

OBJECTIVE: Non-cystic fibrosis (non-CF) bronchiectasis is a chronic lung disease, primarily characterised by neutrophilic inflammation, with *Haemophilus influenzae* (HI) frequently isolated from respiratory cultures. Recent adult studies have suggested a potential role for eosinophils in the frequency of pulmonary exacerbations and in lung function decline. This study aimed to evaluate the relationships among peripheral eosinophilia, lower respiratory tract pathogens, age at first pneumonia, and malnutrition in children with non-CF bronchiectasis.

MATERIAL AND METHODS: In this retrospective study, children who were diagnosed with non-CF bronchiectasis were grouped based on nutritional status, eosinophilia, age at first pneumonia, and the most frequently isolated microorganisms. Clinical outcomes were compared across groups.

RESULTS: Among 106 patients (61.3% male), malnutrition was present in 48.1% and eosinophilia in 39.6%. Primary immunodeficiency was the most common etiology (39.6%). HI and *Pseudomonas aeruginosa* (PA) were isolated in 61.3% and 24.5% of respiratory cultures, respectively. Patients with malnutrition had significantly lower forced expiratory volume in one second and forced vital capacity (FVC) values ($P = 0.023$ and $P = 0.005$, respectively). Eosinophilia was more prevalent in patients with PA isolation; was associated with younger ages at first pneumonia and bronchiectasis diagnoses ($P = 0.009$ and $P = 0.017$). PA isolation was associated with a higher frequency of aspiration syndromes ($P < 0.001$) and lower FVC values ($P = 0.040$). Patients who experienced their first episode of pneumonia before the age of two had more frequent exacerbations and were diagnosed with bronchiectasis at an earlier age.

CONCLUSION: Non-CF bronchiectasis in childhood may be preventable and/or non-progressive when diagnosed early. Clinical features such as malnutrition, eosinophilia, PA isolation, and early-onset pneumonia may help identify children who could benefit from closer clinical monitoring. Further pediatric studies are needed to validate these associations.

KEYWORDS: Bronchiectasis, eosinophilia, malnutrition, *Pseudomonas aeruginosa*

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Corresponding author: Esin Gizem Olgun, MD, e-mail: esingizemolgun@outlook.com

INTRODUCTION

Non-cystic fibrosis (non-CF) bronchiectasis is a chronic lung disease clinically characterized by recurrent pulmonary exacerbations accompanied by a wet or productive cough. Although bronchiectasis is typically regarded as irreversible bronchial dilation, early and effective treatment may lead to partial or complete reversal of airway damage.[1,2] Although chronic productive cough is the most common symptom of non-CF bronchiectasis, patients may also present with dyspnea, recurrent wheezing, persistent purulent sputum, hemoptysis, growth failure, and chest wall deformities.[3] Computed tomography (CT) of the chest is the gold standard for diagnosis.[4] Management strategies should be age-appropriate and individualized, including airway clearance techniques, mucoactive agents, pulmonary rehabilitation, and appropriate antibiotic therapy.[5-7] Given that the inflammation is typically neutrophilic, long-term macrolide therapy is often recommended.[8-12]

While the incidence of pediatric non-CF bronchiectasis has decreased due to improvements in antibiotic therapy and immunization programs, it still represents a significant cause of respiratory morbidity and mortality.[1,5] Global incidence rates in children are heterogeneous: reported rates range from 0.2 to 2.3 per 100,000 in Europe, 13.3 per 100,000 in the United Arab Emirates, and as high as 735 per 100,000 in Australia.[13,14] Though data from developing countries are scarce, poor living conditions and inadequate immunization in low-income settings have been associated with increased prevalence of non-CF bronchiectasis.[3,6,13,15]

The pathophysiology of non-CF bronchiectasis is explained by a vicious cycle of infection and inflammation, in which airway infections trigger inflammatory responses that impair mucociliary clearance, leading to further airway injury and increased susceptibility to infection.[16] Beyond persistent bacterial bronchitis and foreign body aspiration, other etiologies include bronchiolitis obliterans, gastroesophageal reflux disease, aspiration syndromes, primary immunodeficiencies (PID), airway hyperreactivity, primary ciliary dyskinesia (PCD), sleep-related disorders, heart failure, and rheumatologic diseases.[6,17] Although neutrophilic inflammation is typically predominant in bronchoalveolar lavage (BAL), some cohorts have reported eosinophilic predominance.[5,16,18] Adult studies suggest that patients with eosinophilia experience more frequent exacerbations and greater declines in forced expiratory volume in one second (FEV_1).[19] Among microbial pathogens, *Haemophilus influenzae* (HI) is the most frequently isolated organism in children with non-CF bronchiectasis.

Main Points

- This study evaluates the associations between peripheral eosinophilia, lower respiratory tract pathogens, nutritional status, and age at first pneumonia in children with non-cystic fibrosis (non-CF) bronchiectasis.
- To our knowledge, this is among the few studies focusing specifically on pediatric non-CF bronchiectasis and its clinical predictors.
- Peripheral eosinophilia and early-life respiratory infections may serve as markers to guide clinical management in this patient group.
- Our findings highlight the need for increased awareness and multicenter collaborations to improve outcomes in pediatric bronchiectasis.

This study examines the associations between peripheral eosinophilia, early respiratory infections, nutritional status, and airway pathogens in children with non-CF bronchiectasis, aiming to identify clinical features and potential markers relevant to disease management. Evidence regarding these associations in children is limited. Therefore, this study aims to characterise clinical features and potential markers that may help guide management in this population.

MATERIAL AND METHODS

This study was approved by the Ethics Committee of the Ankara University Faculty of Medicine in Ankara, Türkiye (approval no: 2025/235, date: 14.04.2025). Written consent was obtained from all participating children and their parents.

Medical records of patients under 18 years of age who were followed at our pediatric pulmonology outpatient clinic between 2015 and 2024 and who were diagnosed with bronchiectasis were retrospectively reviewed. One hundred and twenty patients under the age of 18 were diagnosed with bronchiectasis. Thirteen patients were excluded from the study because of a positive sweat test and detection of a *CFTR* gene mutation, resulting in a diagnosis of CF. One patient was also excluded following genetic testing that identified Hyperimmunoglobulin E syndrome (*STAT 3* gene defect). Data collected included age at first pneumonia, age at diagnosis of bronchiectasis, annual frequency of pulmonary exacerbations, malnutrition, peripheral eosinophilia, extent of bronchiectasis, spirometric parameters, lower airway microbiology, and underlying etiologies of bronchiectasis.

Malnutrition was assessed using body mass index (BMI) Z-scores adjusted for age; a Z-score below -1 was considered indicative of malnutrition.[20] Eosinophilia was defined as a total eosinophil count (TEC) >500 cells/μL on at least two separate complete blood counts, performed at intervals of at least 4 weeks.[21] Patients with PID associated with eosinophilia were excluded. The spirometry results included the percentages of FEV_1 and forced vital capacity (FVC) values in cooperative subjects. Respiratory pathogens identified from sputum, tracheal aspirate cultures, or BAL cultures were recorded, focusing on HI and PA. Etiological classifications of non-CF bronchiectasis were determined for all patients. Disease extent was evaluated using chest CT and categorized as localized (single lobe) or widespread (multiple lobes). Patients were grouped and compared based on nutritional status, eosinophilia presence, age at first pneumonia (<2 years vs. ≥2 years), and type of isolated microorganism. Outcomes were analyzed across groups.

To minimize potential sources of bias, we applied uniform diagnostic criteria for non-CF bronchiectasis and confirmed diagnoses by high-resolution CT. Peripheral eosinophil counts, microbiological cultures, and nutritional assessments were obtained using standardized laboratory and clinical protocols. Patients were included consecutively from our clinic to reduce

selection bias; only those with complete clinical and laboratory data were analyzed. These methodological approaches aimed to enhance the reliability of our findings despite the single-center setting.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). The distribution of quantitative variables was assessed using the Shapiro-Wilk test. Categorical variables were expressed as frequencies and percentages. Descriptive statistics were presented as mean and standard deviation for normally distributed variables. Student's t-test was used to compare continuous variables between groups, and the chi-square test was used for categorical variables. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

A total of 106 patients diagnosed with non-CF bronchiectasis were included in the study. Demographic, clinical, and laboratory characteristics, as well as etiologies, are summarized in Table 1.

Of the patients, 61.3% were male. Chronic productive cough was reported in 89.6%, malnutrition in 48.1%, and eosinophilia in 39.6%. PID was the most frequent etiology (39.6%). HI and PA were isolated in 61.3% and 24.5% of respiratory cultures, respectively. The mean age at first pneumonia was 3.6±4.3 years, and the mean age at bronchiectasis diagnosis was 8.59±4.8 years. The average number of annual exacerbations was 5.8±2.0. Mean FEV_1 and FVC values were 73% and 75%, respectively.

When patients were compared by nutritional status, those with malnutrition had significantly lower FEV_1 and FVC values ($P = 0.023$ and $P = 0.005$, respectively) and a lower frequency of bronchial hyperreactivity ($P = 0.031$). No significant differences were observed in other clinical or etiological variables (Table 2).

Table 1. Demographic, clinical and laboratory characteristics and aetiologies of patients with non-CF bronchiectasis

	n (%)
Male	65 (61.3%)
Chronic productive cough	95 (89.6%)
Malnutrition	51 (48.1%)
Isolation of *Haemophilus influenzae*	65 (61.3%)
Isolation of *Pseudomonas aeruginosa*	26 (24.5%)
Eosinophilia	42 (39.6%)
PID	42 (39.6%)
Bronchial hyperreactivity	29 (27.3%)
Aspiration syndromes/GERD	28 (26.4%)
Bronchiolitis obliterans	23 (21.6%)
PCD	11 (10.3%)
Rheumatological diseases	5 (4.7%)
	Mean ± SD
Age at first pneumonia (year)	3.66±4.3
Age at diagnosis of bronchiectasis (year)	8.59±4.8
Number of pulmonary exacerbations per year	5.85±2.0
FEV_1 (%)	73±23
FVC (%)	75±19

non-CF: non-cystic fibrosis, PID: primary immunodeficiency, GERD: gastroesophageal reflux disease, PCD: primary ciliary dyskinesia, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity

Table 2. Comparison of demographic, clinical, and laboratory characteristics and etiologies of non-CF bronchiectasis patients with and without malnutrition

	Malnutrition present (n = 51)	**Malnutrition absent (n = 55)**	***P* value**
Multiple lobes bronchiectasis	20	24	0.068*
Chronic productive cough	48	47	0.144*
Isolation of *Haemophilus influenzae*	33	32	0.491*
Isolation of *Pseudomonas aeruginosa*	13	13	0.825*
PID	19	23	0.631*
Bronchial hyperreactivity	9	20	**0.031***
Aspiration syndromes/GERD	14	14	0.816*
Bronchiolitis obliterans	14	9	0.166*
PCD	6	5	0.652*
Rheumatological diseases	2	3	0.710*
Age at first pneumonia mean ± SD (years)	3.85±4.4	3.92±4.0	0.554#
Age at bronchiectasis diagnosis mean ± SD (years)	8.72±5.3	8.91±4.2	0.864#
Annual exacerbation mean ± SD (attacks/year)	3.98±3.3	3.67±3.1	0.715#
FEV_1 mean ± SD (%)	65.5±18.8	77.7±23.2	**0.023#**
FVC mean ± SD (%)	67.8±16.6	79.7±17.6	**0.005#**

#Chi-square test was used

*Student-t test was used

non-CF: non-cystic fibrosis, PID: primary immunodeficiency, GERD: gastroesophageal reflux disease, PCD: Primary ciliary dyskinesia, SD: standard deviation, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity

Eosinophilia was more commonly observed in patients with PA isolation ($P = 0.03$), while it was significantly less common among patients with chronic productive cough, bronchial hyperreactivity, and PCD ($P < 0.001$, 0.004, and 0.016, respectively). Patients with eosinophilia were significantly younger at first diagnosis of pneumonia and bronchiectasis ($P = 0.009$ and 0.017), though no significant differences were found in annual exacerbation frequency or spirometric values (Table 3).

When patients with isolation of HI were compared with those with isolation of PA, aspiration syndromes were more frequent in those with PA ($P < 0.001$), and FVC values were significantly lower in this group ($P = 0.040$) (Table 4).

Patients who experienced their first pneumonia before age 2 were diagnosed with bronchiectasis at a younger age ($P = 0.005$), experienced more frequent exacerbations ($P < 0.001$), had a higher prevalence of PCD ($P = 0.045$), and had lower rates of rheumatologic disease ($P = 0.041$) (Table 5).

Table 3. Comparison of demographic, clinical, and laboratory characteristics and etiologies of non-CF bronchiectasis patients with and without eosinophilia

	Eosinophilia present (n = 42)	Eosinophilia absent (n = 64)	*P* value
Multiple lobes bronchiectasis	15	29	0.327
Malnutrition	22	29	0.476
Chronic productive cough	39	56	**<0.001***
Isolation of *Haemophilus influenzae*	29	36	0.328*
Isolation of *Pseudomonas aeruginosa*	15	11	**0.03***
PID	16	26	0.860*
Bronchial hyperreactivity	5	24	**0.004***
Aspiration syndromes/GERD	13	15	0.679*
Bronchiolitis obliterans	8	15	0.599*
PCD	1	10	0.016*
Rheumatological diseases	2	3	0.491*
Age at first pneumonia mean ± SD (years)	2.67±3.3	4.73±4.5	**0.009#**
Age at bronchiectasis diagnosis mean ± SD (years)	7.48±4.9	9.69±4.4	**0.017#**
Annual exacerbation mean ± SD (attacks/year)	6±2.12	5.76±2.0	0.091#
FEV_1 mean ± SD (%)	68.9±18.4	73.4±22.5	0.154#
FVC mean ± SD (%)	73.0±15.7	75.4±19.0	0.456#

#Chi-square test was used
*Student-t test was used
non-CF: non-cystic fibrosis, PID: primary immunodeficiency, GERD: gastroesophageal reflux disease, PCD: Primary ciliary dyskinesia, SD: standard deviation, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity

Table 4. Comparison of demographic, clinical, and etiological aspects of non-CF bronchiectasis patients based on isolation of HI or PA

	H. influenzae (n = 50)	*P. aeruginosa* (n = 11)	*P* value
Multiple lobes bronchiectasis	19	5	0.647*
Eosinophilia	19	5	0.647*
Malnutrition	26	6	0.878*
Chronic productive cough	48	10	0.480*
PID	21	3	0.365*
Bronchial hyperreactivity	18	3	0.581*
Aspiration syndromes/GERD	7	8	**<0.001***
Bronchiolitis obliterans	11	1	0.330*
PCD	8	0	0.155*
Rheumatological diseases	2	0	0.493*
Age at first pneumonia mean ± SD (years)	3.37±3.6	2.88±2.8	0.683#
Age at bronchiectasis diagnosis mean ± SD (years)	9.23±4.6	8.21±4.4	0.511#

Table 4. Continued

	H. influenzae (n = 50)	P. aeruginosa (n = 11)	*P* value
Annual exacerbation mean ± SD (attacks/year)	4.18±3.3	5.27±2.9	0.322#
FEV_1 mean ± SD (%)	72.1±18.4	48.0±47.6	0.064#
FVC mean ± SD (%)	74.6±14.2	53.3±40.4	**0.040#**

#Chi-square test was used
*Student-t test was used
non-CF: non-cystic fibrosis, HI: *Haemophilus influenzae*, PA: *Pseudomonas aeruginosa*, PID: primary immunodeficiency, GERD: gastroesophageal reflux disease, PCD: Primary ciliary dyskinesia, SD: standard deviation, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity

Table 5. Comparison of demographic, clinical, and etiological aspects of non-CF bronchiectasis patients based on age at first pneumonia

	Age at first pneumonia <2 years (n = 47)	Age at first pneumonia ≥2 years (n = 59)	*P* value
Multiple lobes bronchiectasis	18	26/33	0.549*
Chronic productive cough	44	51	0.229*
Malnutrition	23	28	0.880*
Eosinophilia	22	20	0.177*
Isolation of *Haemophilus influenzae*	28	37	0.742*
Isolation of *Pseudomonas aeruginosa*	9	17	0.251*
PID	20	22	0.582*
Bronchial hyperreactivity	9	20	0.091*
Aspiration syndromes/GERD	14	14	0.482*
Bronchiolitis obliterans	10	13	0.925*
PCD	8	3	**0.045***
Rheumatological diseases	0	5	**0.041***
Age at bronchiectasis diagnosis mean ± SD (years)	7.39±4.6	9.95±4.5	**0.005#**
Annual exacerbation mean ± SD (attacks/year)	5.17±3.0	2.74±3.0	**<0.001#**
FEV_1 mean ± SD (%)	70.9±23.0	73.7±21.0	0.619#
FVC mean ± SD (%)	74.2±17.0	75.0±18.0	0.856#

#Chi-square test was used
*Student-t test was used
non-CF: non-cystic fibrosis, PID: primary immunodeficiency, GERD: gastroesophageal reflux disease, PCD: Primary ciliary dyskinesia, SD: standard deviation, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity

DISCUSSION

In this study of children with non-CF bronchiectasis, we found that patients with malnutrition had lower FEV_1 and FVC values; those with isolation of PA had a higher incidence of aspiration syndromes and lower FVC values; and eosinophilic patients were diagnosed at a younger age and had more frequent isolation of PA and less frequent chronic cough, PCD, and bronchial hyperreactivity, reflecting an association rather than disease severity. Furthermore, patients who experienced pneumonia before the age of two had more frequent annual exacerbations, an earlier onset of bronchiectasis, a higher prevalence of PCD, and fewer rheumatologic diagnoses.

Study Limitations

There are also some limitations to our study. Since our centre is a tertiary care facility, our patients completed their treatment without being admitted to us during each pulmonary exacerbation. The number of pulmonary exacerbations per patient was reported as a mean value based on parents' reports obtained during routine follow-up visits. In addition, patients who had their first pneumonia before the age of 2 years were less cooperative during spirometry at follow-up because they were younger. This may be the reason why there was no significant difference in FEV_1 and FVC values. We are aware that the results of our study involving 106 children with non-CF bronchiectasis cannot be generalised because of the uneven distribution of participants among groups; however, we believe that the similarity of conditions such as eosinophilia, malnutrition, and PA isolation between our cohort and previous adult studies is a strength of the study.

In our cohort, the majority of patients (89.6%) presented with a chronic productive cough. The mean age at first pneumonia was 3.66 years, and the mean age at bronchiectasis diagnosis was 8.59 years. Nearly half of the patients (48.1%) were malnourished. Previous studies in low- to middle-income countries report similarly high rates of productive cough (53–96%).[22-25] A Thai study involving 35 children with non-CF bronchiectasis reported a mean age at diagnosis of 36

months.[26] An Italian study involving 105 children reported that the mean age at first pneumonia was 1.3 years, and the mean age at diagnosis of bronchiectasis was 7 years.[27] The longer interval between initial pneumonia and diagnosis, observed in developed countries, may be attributed to better healthcare access and lower rates of malnutrition.

While CF is the most common cause of bronchiectasis in high-income countries, epidemiological data for non-CF bronchiectasis remain unclear. Although reported causes are influenced by local diagnostic capabilities, PID, aspiration syndromes, post-infectious conditions, PCD, and congenital malformations are the most common causes worldwide.[6] Among pediatric populations in low- and middle-income countries, non-CF bronchiectasis is more common due to insufficient immunization coverage and higher rates of malnutrition. Although it is often classified as idiopathic due to limited diagnostic facilities, in our study the most common cause of non-CF bronchiectasis was PID (39.6%), a rate similar to that reported in studies from developed countries (10-34%).[13]

Consistent with the literature, HI (61.3%) was the most frequently isolated pathogen in our study, followed by PA (24.5%).[2,25] PA was more frequently identified in children with aspiration syndromes than in those with HI, and it was associated with significantly lower FVC. While this has been linked to higher morbidity in adults, pediatric data are lacking.[2,25,28]

Li et al.[29] reported a positive correlation of low BMI and low serum albumin/prealbumin levels with bronchiectasis severity on chest CT in adults. Similar pediatric studies are lacking. Similar to Li et al.[29], we also found that patients with malnutrition had lower FEV_1 and FVC values, indicating a greater reduction in lung capacity. Because children often have difficulty performing spirometry, further studies are needed to evaluate the relationship between lung capacity and malnutrition in patients with non-CF bronchiectasis.

Although neutrophilic inflammation predominates in non-CF bronchiectasis, some cohorts have shown eosinophilic involvement.[30,31] Previous studies suggest that PA may suppress Th1 responses via exotoxins and promote type 2 inflammation through elastase B and other virulence factors.[32] Guan et al.[33] defined eosinophilic bronchiectasis in adults as peripheral TEC >300 cells/μL (excluding eosinophilic syndromes), and found that eosinophilic patients more frequently had PA isolation and experienced higher morbidity and mortality. Consistent with previous studies in adults, eosinophilic children in our cohort showed a higher frequency of PA isolation; however, lung function parameters did not differ significantly between the groups. These findings may be associated with a different clinical profile, though conclusions regarding disease severity cannot be drawn from this study. Whether targeted anti-inflammatory approaches could be beneficial in selected pediatric patients requires validation in future controlled studies.

Among patients whose first episode of pneumonia occurred before age two, we observed higher exacerbation rates, earlier diagnosis of bronchiectasis, and higher frequency of PCD. These findings align with a study by Santamaria et al.[27] in Italy, which reported that early-onset pneumonia in children with non-CF bronchiectasis was often associated with underlying conditions, such as PCD, PID, and aspiration syndromes.

CONCLUSION

In our study of children with non-CF bronchiectasis, we demonstrated that malnutrition and PA isolation were associated with reduced lung capacity; eosinophilic patients had higher rates of poor-prognosis PA isolation; and age at first pneumonia was associated with earlier bronchiectasis diagnosis and higher annual exacerbation frequency. Non-CF bronchiectasis in childhood may be preventable or nonprogressive when diagnosed early, as suggested by previous studies. Greater attention to clinical features such as malnutrition, eosinophilia, PA isolation, and early-onset pneumonia may help identify children who could benefit from closer follow-up. Nevertheless, further research is needed in the pediatric population to better understand and manage this disease.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Ankara University Faculty of Medicine in Ankara, Türkiye (approval no: 2025/235, date: 14.04.2025).

Informed Consent: Written consent was obtained from all participating children and their parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.Ö., M.T., M.A., S.K.Ö., N.Ç., Concept: E.G.O., F.Z., N.Ç., Design: E.G.O., N.Ç., Data Collection or Processing: F.Z., M.N.T., S.B., Analysis or Interpretation: M.N.T., N.Ç., Literature Search: E.G.O., Writing: E.G.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

CT-defined Emphysema Morphology as a Predictor for Histological Subtypes of Lung Cancer: A Single-center Retrospective Study

Fadlan Adima Adrianta[1], Dini Rachma Erawati[1], Suryanti Dwi Pratiwi[2], Nanik Setijowati[3]

[1]Department of Radiology, Faculty of Medicine, Universitas Brawijaya, Dr. Saiful Anwar Regional General Hospital, Malang, Indonesia
[2]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Brawijaya, Dr. Saiful Anwar Regional General Hospital, Malang, Indonesia
[3]Department of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

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ABSTRACT

OBJECTIVE: Lung cancer and pulmonary emphysema share common risk factors and pathophysiological pathways. Emerging evidence suggests that emphysema morphology, rather than emphysema burden, may influence lung cancer histology. This study evaluated the association between computed tomography (CT)-defined emphysema characteristics and histological subtypes of lung cancer.

MATERIAL AND METHODS: A retrospective observational cohort study was conducted that included 144 patients with histologically confirmed lung cancer who underwent diagnostic thoracic CT between January 2020 and June 2024 at Dr. Saiful Anwar General Hospital in Indonesia. Emphysema morphology was visually classified as centrilobular emphysema (CLE), paraseptal emphysema, or mixed, and emphysema volume was quantified using 3D Slicer software. Associations with histological subtypes were analyzed using bivariate analyses and multivariate logistic regression, adjusted for age, sex, tumor size, and tumor location. Model performance was assessed using receiver operating characteristic analysis.

RESULTS: Adenocarcinoma (ADC) was the most common subtype (65.3%). Emphysema was present in 37.5% of patients and occurred more frequently in non-ADC subtypes. Emphysema morphology was significantly associated with histological subtype ($P < 0.001$). Multivariate analysis identified CLE as an independent predictor of ADC (adjusted odds ratio: 8.5; 95% confidence interval: 1.24–57.9; $P = 0.029$), and CLE remained significant after adjustment for tumor size and tumor location. The model demonstrated excellent discrimination (area under the curve: 0.89). Emphysema volume did not differ significantly between groups ($P = 0.339$).

CONCLUSION: CT-defined CLE is independently associated with lung ADC, whereas emphysema volume is not predictive of lung ADC. Emphysema morphology may serve as a non-invasive imaging biomarker to support histological risk stratification when tissue diagnosis is limited.

KEYWORDS: Lung cancer, adenocarcinoma, emphysema morphology, CT scan, biomarker

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INTRODUCTION

Lung cancer remains the most commonly diagnosed cancer worldwide, accounting for 12.4% of all cancer cases according to the latest GLOBOCAN 2022 data, and contributing to approximately 1.8 million deaths, or 18.7% of total cancer mortality. In Indonesia, lung cancer accounts for 12.6% of all cancer-related deaths, making it the leading cause of cancer mortality and the fourth most common cancer overall, after breast, cervical, and colorectal cancers. The annual incidence is projected to almost double from 30,023 cases in 2018 to 54,983 cases by 2040.[1-3]

Corresponding author: Fadlan Adima Adrianta, MD, e-mail: adimaadrianta@gmail.com

Lung cancer is broadly classified as small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC), with the latter accounting for approximately 85% of cases. According to the 2015 World Health Organization classification, the main NSCLC subtypes are adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell carcinoma, with ADC the most prevalent, comprising about 40% of NSCLC cases globally in 2022.[4-6]

Over the last decade, advances in molecularly targeted therapies have increased the importance of accurate histologic and genotypic classification of NSCLC. However, some conditions, such as clinical contraindications in patients with lung cancer, may make it impossible to perform invasive procedures, thereby delaying histologic diagnosis.[7]

Emphysema and lung cancer share common risk factors, inflammatory pathways, and molecular pathophysiology. Emerging evidence suggests that emphysema may serve as an independent risk factor for lung cancer; this is supported by several studies reporting that ADC is the histologic subtype of lung cancer most frequently associated with emphysema on CT.[8,9] Nevertheless, the relationship between emphysema characteristics and lung cancer histology and genotype remains unclear. This study aims to further explore and strengthen the evidence linking emphysema characteristics with lung cancer subtypes, potentially aiding in non-invasive diagnosis for biopsy-contraindicated patients and informing personalized screening protocols for high-risk populations.

MATERIAL AND METHODS

Study Population

This retrospective observational cohort study was conducted at Dr. Saiful Anwar General Hospital, East Java, Indonesia. All patients included in this study had primary lung cancer confirmed by histopathologic examination and had undergone diagnostic thoracic computed tomography (CT) scans between January 2020 and June 2024. CT images obtained before patients received cancer treatment were evaluated. Histopathologic examinations included both small (core needle and transbronchial biopsies) and large (surgical biopsies) specimens, which were evaluated by board-certified pathologists. Exclusion criteria were as follows: (1) patients with incomplete imaging data or poor CT image quality precluding emphysema assessment; (2) patients with secondary lung cancer and coexistence of other primary cancers; (3) patients with concomitant lung diseases, such as interstitial lung disease, that could confound emphysema interpretation. A total of 144 patients who met these criteria were enrolled by total sampling from the hospital's radiology and pathology archives. Ethical approval was granted by the Ethics Committee of Dr. Saiful Anwar General Hospital (approval no: 400/277/K.3/302/2023, approved on December 04, 2023).

Main Points

- Centrilobular emphysema (CLE) morphology on computed tomography is strongly and independently associated with the adenocarcinoma (ADC) subtype of lung cancer.
- Emphysema volume did not differ significantly between the ADC and non-ADC groups, suggesting that morphology is a more relevant predictor.
- CLE demonstrated excellent predictive performance for ADC, even after adjustment for tumor size and tumor location, with receiver operating characteristic curve analysis yielding an area under the curve of 0.89.
- Emphysema morphology may serve as a simple, non-invasive imaging biomarker to support histological prediction, especially when invasive biopsy is contraindicated.
- The predictive value of emphysema morphology could be further improved when integrated with additional radiologic features of the primary lung mass.

Tumor Size and Location Assessment

Tumor size was categorized according to the tumor–node–metastasis staging system as ≤5 cm (T1–T2) and >5 cm (T3–T4), based on established clinical prognostic thresholds that reflect differences in tumor burden and potential biological behavior.[10] Tumor location on CT images was classified as central or peripheral using radiologic criteria from previous studies. A tumor was defined as central if the lesion involved the main, lobar, or segmental bronchi or if the tumor epicenter was located within the inner one-third of the lung parenchyma. Tumors were classified as peripheral when the epicenter was in the outer two-thirds of the lung parenchyma without central bronchial involvement. In cases of large tumors extending across both central and peripheral regions, classification was based on the tumor epicenter at the level of the largest axial diameter.[11,12]

Emphysema Assessment

Emphysema characteristics were assessed on high-resolution thoracic CT images acquired with a 128-slice Toshiba Aquilion scanner (model TSX-101A). The evaluation comprised two components: emphysema morphology and emphysema volume. Two experienced radiologists independently assessed emphysema morphology by visual analysis to evaluate interobserver reliability. Emphysema was classified by the Fleischner Society into three morphological subtypes: centrilobular emphysema (CLE), paraseptal emphysema (PSE), and mixed-type emphysema (defined by the coexistence of centrilobular and paraseptal features). Quantitative emphysema volume, expressed in cubic centimeters (cm^3), was measured with the open-source 3D Slicer software (version 5.6.2; https://www.slicer.org/), with segmentation techniques employed to identify low-attenuation areas with a threshold range of −950 to −1024 Hounsfield units.[13] The independent variables were emphysema morphology and emphysema volume; the dependent variable was the histological subtype of lung cancer (ADC, SCC, small cell carcinoma, and adenosquamous carcinoma).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 25. Descriptive statistics were employed to summarize patient characteristics, including means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. For statistical analysis, the chi-square

test was used to assess the association between emphysema morphology and histological subtypes of lung cancer. Independent t-tests were applied to compare emphysema volumes between groups. Multivariable logistic regression analysis was conducted to identify independent predictors of specific histological subtypes (e.g., ADC), adjusting for age, sex, emphysema morphology, tumor size, and tumor location. Receiver operating characteristic (ROC) curve analysis was subsequently performed using the multivariable logistic regression model to evaluate the discriminative performance of emphysema morphology in differentiating ADC from non-ADC histological subtypes, and the area under the curve (AUC) was reported. A *P* value of <0.05 was considered statistically significant. Interobserver agreement for emphysema morphology classification was evaluated using Cohen's kappa statistic.

RESULTS

A total of 144 lung cancer patients participated in this study. The average age of the patients was 59.58 years; 62 (43.1%) were under 60 years and 82 (56.9%) were 60 years or older. The sex distribution among the subjects was 91 males (63.2%) and 53 females (36.8%). Histopathological data showed that ADC was the most frequent lung cancer subtype, diagnosed in 94 patients (65.3%), followed by SCC (29 patients, 20.1%), small cell carcinoma (12 patients, 8.3%), and adenosquamous carcinoma (9 patients, 6.3%). All characteristics of the subjects are presented in Table 1. No significant differences in demographic variables were observed between histological subtypes.

Interobserver agreement analysis revealed substantial agreement between the two expert radiologists in the assessment of emphysema morphology, with a Cohen's kappa value of 0.71. This finding indicates good interobserver consistency in determining emphysema morphology.

In bivariate analysis, tumor size was significantly associated with histological subtype: non-ADC tumors more frequently presented as larger than 5 cm compared with ADC (*P* = 0.041). In contrast, tumor location (central vs. peripheral) did not show a significant association with histological subtype (*P* = 0.155).

Emphysema was detected on CT images in 54 patients (37.5%), whereas 90 patients (62.5%) showed no emphysematous changes. Emphysema prevalence differed significantly between histological groups, with a higher prevalence observed in the non-ADC group than in the ADC group (*P* < 0.05; Table 1). Among those with emphysema, CLE was present in 19 patients (35.2%), PSE in 10 patients (18.5%), and mixed-type emphysema in 25 patients (46.3%) (Table 2). Although overall emphysema prevalence was higher in the non-ADC group, subsequent analyses restricted to emphysema-positive patients demonstrated that emphysema morphology differed significantly by histological subtype.

In the restricted analysis of emphysema-positive patients, a significant association was observed between emphysema morphology and histological subtype of lung cancer (*P* < 0.001), with pairwise comparisons demonstrating a pronounced difference between centrilobular and mixed-emphysema types (*P* < 0.001) (Table 3). Multivariate logistic regression analysis identified CLE as an independent predictor of ADC, with an adjusted odds ratio (OR) of 8.5 [95% confidence interval (CI): 1.247–57.931; *P* = 0.029] (Table 4). This association remained significant after adjustment for age, sex, tumor size, and tumor location, none of which showed an independent association with ADC in the final model. ROC curve analysis based on the multivariable logistic regression model—including age, sex, emphysema morphology, tumor size, and tumor location—demonstrated excellent discrimination between ADC and non-ADC subtypes, with an AUC of 0.89 (95% CI: 0.801–0.987; *P* < 0.001) (Figure 1).

Meanwhile independent t-test analysis showed no significant difference between the mean emphysema volume in ADC (542.71±406.72 cm^3) compared with non-ADC patients (449.73±394.70 cm^3) (*P* = 0.339). The standard deviations in both groups were relatively large, suggesting considerable variability in emphysema volume among individuals. These findings imply that, within this study population, volumetric emphysema measurements did not differ meaningfully across the major histological subtypes of lung cancer.

Table 1. Patient characteristics and emphysema status

Characteristics	Total (n = 144)	Adenocarcinoma	Squamous cell carcinoma	Small cell carcinoma	Adenosquamous carcinoma	*P* value**
Age in years (mean ± SD)	59.58 ± 10.31					
<60	62 (43.1%)	41 (43.6%)	14 (48.3%)	4 (33.3%)	3 (33.3%)	0.992
≥60	82 (56.9%)	53 (56.4%)	15 (51.7%)	8 (66.7%)	6 (66.7%)	
Sex						
Male	91 (63.2%)	55 (58.5%)	20 (69%)	11 (91.7%)	5 (55.6%)	0.157
Female	53 (36.8%)	39 (41.5%)	9 (31%)	1 (8.3%)	4 (44.4%)	
Emphysema status						
Presence	54 (37.5%)	24 (27.1%)	18	8 (66.7%)	4 (44.4%)	<0.001*
Absent	90 (62.5%)	70 (72.9%)	11	4 (33.3%)	5 (55.6%)	

*Statistically significant
**Hypothetical analysis was measured using chi-square for adenocarcinoma vs. non-adenocarcinoma
SD: standard deviation

Table 2. Morphological characteristics and volume of emphysema according to lung cancer subtypes

Variable	Total (n = 54)	Lung cancer subtype		*P* value
		Adenocarcinoma	Non-adenocarcinoma	
Age in years (mean ± SD)	61.22±9.92			
<60	21 (38.9%)	8 (33.3%)	13 (43.3%)	0.453
≥60	33 (61.1%)	16 (66.7%)	17 (56.7%)	
Emphysema morphology				
Centrilobular	19 (35.2%)	17 (70.8%)	2 (6.7%)	<0.001*
Paraseptal	10 (18.5%)	5 (20.8%)	5 (16.7%)	
Mix	25 (46.3%)	2 (8.3%)	23 (76.7%)	
Tumor location				
Peripheral	13 (24.1%)	8 (33.3%)	5 (16.7%)	0.27
Central	41 (75.9%)	16 (66.7%)	25 (83.3%)	
Tumor size				
>5 cm	40 (74.1%)	14 (58.3%)	26 (86.7%)	0.041*
≤5 cm	14 (25.9%)	10 (41.7%)	4 (13.3%)	
Emphysema volume (cm^3) (mean ± SD)	491.06±399.05	542.71±406.72	449.73±394.70	0.339

*Statistically significant
SD: standard deviation

Table 3. Pairwise comparison between emphysema morphology subtype

Variable (n = 54)	*P* value <0.05
Emphysema morphology	
Centrilobular-paraseptal	0.132
Centrilobular-mixed type	<0.001*
Paraseptal-mixed type	0.076

*Statistically significant difference based on post-hoc pairwise comparison analysis ($P < 0.05$)

Table 4. Multiple logistic regression analysis of emphysema morphology and the risk of lung adenocarcinoma

Variable	Adjusted OR	B	95% CI	*P* value
Centrilobular emphysema	8.50	2.14	1.247–57.931	0.029
Mixed-type emphysema	0.08	-2.44	0.013–0.584	0.012

OR: odds ratio, CI: confidence interval

DISCUSSION

Our study provides compelling evidence that ADC is the predominant histological subtype of lung cancer, accounting for 65.3% of diagnosed lung malignancies. This finding aligns with well-documented global epidemiological trends that demonstrate a progressive increase in ADC incidence over recent decades, with ADC now representing approximately 40% of all lung cancers and 60% of non-small-cell lung cancer cases in Western populations.[6,14] Several factors may contribute to this epidemiological shift, including changing smoking patterns, such as increased use of filtered cigarettes leading to greater peripheral lung deposition of carcinogens, evolving histological classification systems, and improving detection of asymptomatic peripheral tumors through the widespread implementation of CT screening.[15] We observed a significantly higher prevalence of emphysema in the non-ADC group than in the ADC group. The strong correlation between smoking-related lung injury and specific histological subtypes, especially SCC and SCLC, may account for the higher prevalence of emphysema in the non-ADC group. The main risk factor for the development of emphysema—heavy tobacco exposure—is traditionally associated with these subtypes.[4,16] On the other hand, patients with lower cumulative smoking exposure or even those who have never smoked may develop ADC, which could account for the lower overall prevalence of emphysema in this population.[17] Importantly, this apparent discrepancy reflects differences in emphysema prevalence rather than in emphysema pattern, and the presence of emphysema alone does not sufficiently explain histological differences. In the present study, analyses of emphysema morphology were restricted to emphysema-positive patients, allowing a clear distinction between emphysema presence and emphysema morphology. Crucially, results from this restricted emphysema-positive cohort indicate that emphysema morphology, particularly CLE, remains important in differentiating ADC from other histological subtypes, even though the presence

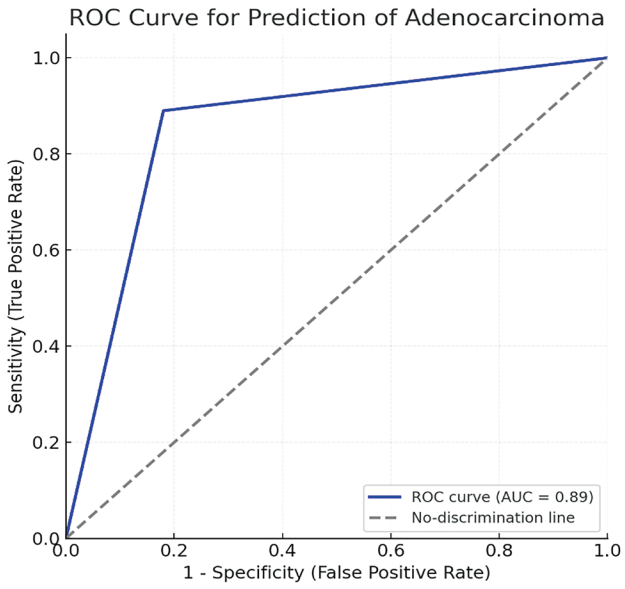

Figure 1. ROC curve for the logistic regression model predicting adenocarcinoma subtype based on emphysema morphology

ROC: receiver operating characteristic

of emphysema is more common in non-ADCs. Of particular clinical significance, our analysis revealed a robust and statistically significant association between CLE morphology and ADC histology (OR: 8.5, 95% CI: 1.247–57.93; $P = 0.029$). This finding corroborates and extends previous observations by Zhang et al.[18], who reported that 68.5% of lung cancer patients with radiologically confirmed emphysema presented with ADC, with CLE representing the predominant emphysema pattern (67% of cases). Even after adjustment for tumor size and location, CLE remained independently associated with ADC. This suggests that the observed relationship is not merely a reflection of tumor distribution or extent, but may instead indicate underlying pathophysiological mechanisms linking specific emphysema morphology to ADC development.

Tumor size and location were also investigated to further elucidate whether this association could be affected by tumor-related characteristics. Tumor size and histological subtype were significantly correlated in the bivariate analysis, but this correlation diminished after multivariate adjustment. This implies that rather than acting as a separate predictor of histological subtype, tumor size may reflect downstream effects of tumor growth dynamics and common etiologic factors. Conversely, emphysema morphology, especially CLE, remained independently associated with ADC, highlighting its potential role as a biologically significant imaging biomarker rather than as a proxy for tumor size.[9,19]

The pathophysiological mechanisms underlying the association between CLE and ADC likely involve complex interactions among chronic inflammation, protease-antiprotease imbalance, and hypoxia-mediated carcinogenesis. At the molecular level, the observed MMP-9/TGF-β1 imbalance in CLE patients may create a permissive microenvironment for ADC development through multiple pathways: (1) promotion of extracellular matrix degradation, facilitating tumor invasion, (2) activation of epithelial-mesenchymal transition programs, and (3) generation of reactive oxygen species leading to DNA damage and oncogenic mutations. Furthermore, the characteristic peripheral distribution of CLE lesions may preferentially expose the terminal bronchiolar and alveolar epithelium –the putative cells of origin for ADC– to sustained inflammatory insults and mitogenic stimuli.[16]

In contrast to the clear association between CLE and ADC, our analysis of PSE revealed more nuanced relationships with lung cancer subtypes. While PSE alone did not demonstrate statistically significant associations with specific histological patterns, we observed notable synergistic effects when PSE coexisted with CLE in non-ADC cases, particularly in SCC. This finding parallels recent work by Durawa et al.[20] demonstrating that combined PSE + CLE morphology, but not PSE in isolation, conferred a substantially elevated cancer risk (OR: 4.0).[19] The apparent subtype-specificity of these emphysema-cancer associations likely reflects fundamental differences in underlying molecular mechanisms: whereas CLE-associated ADC may develop through MMP-9 mediated pathways as discussed above, PSE's inhibition of MMP-2 could preferentially drive squamous carcinogenesis by altering tissue remodeling dynamics and disrupting normal epithelial differentiation programs.[16] Additionally, the coexistence of CLE and PSE may create a unique pulmonary microenvironment characterized by both proximal and distal airway injury, potentially explaining the observed association with SCC, which typically arises from more central bronchial epithelium.[21]

A particularly noteworthy finding from our study was the lack of significant correlation between quantitative emphysema volume measures and specific histological subtypes ($P = 0.339$). This observation, consistent with multiple previous investigations, strongly suggests that qualitative morphological characteristics of emphysema –rather than the disease burden alone– represent the critical determinants of subtype-specific cancer risk.[22,23] From a clinical perspective, this emphasizes the importance of detailed pattern analysis in the interpretation of thoracic imaging and suggests that current lung cancer screening protocols might benefit from incorporating assessments of emphysema morphology into risk-stratification algorithms.

The clinical implications of our findings are potentially substantial. The robust association between CLE morphology and ADC risk identifies a readily detectable imaging biomarker that could enhance early detection efforts, particularly in high-risk populations, such as current or former smokers. Furthermore, the distinct relationships between different emphysema patterns and specific cancer subtypes may eventually inform personalized surveillance strategies and even targeted prevention approaches. However, several important limitations must be acknowledged when interpreting these results. First, the retrospective study design inherently limits our ability to control for all potential confounding variables, particularly detailed smoking exposure measures, such as smoking status and cumulative pack-year history, which may influence both emphysema development and lung cancer histology. Consequently, the observed associations should be interpreted as associative rather than causal. Accordingly, despite good discriminative performance on ROC analysis, these findings

should be interpreted as exploratory and hypothesis-generating rather than as evidence of definitive clinical predictive utility. Second, while our sample size (n = 144) provides adequate power to detect major associations, rare histological subtypes (e.g., small cell carcinoma, adenosquamous carcinoma) were underrepresented, thereby limiting the statistical power for meaningful subgroup analyses. Third, the single-center nature of our study may limit generalizability to more diverse populations.

CONCLUSION

Future research should include prospective, multicenter studies that incorporate detailed environmental exposure data, molecular profiling of emphysematous lung tissue, and advanced imaging analytics to further elucidate the mechanisms linking specific emphysema patterns to lung cancer pathogenesis. Additionally, investigation of potential interactions between emphysema morphology and emerging biomarkers such as circulating tumor DNA or specific mutational signatures could yield valuable insights for precision prevention strategies.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Ethics Committee of Dr. Saiful Anwar General Hospital (approval no: 400/277/K.3/302/2023, approved on December 04, 2023).

Informed Consent: The requirement for informed consent was waived due to the retrospective design.

Footnotes

Authorship Contributions

Concept: F.A.A., D.R.E., S.D.P., N.S., Design: F.A.A., D.R.E., S.D.P., N.S., Data Collection or Processing: F.A.A., Analysis or Interpretation: F.A.A., D.R.E., S.D.P., N.S., Literature Search: F.A.A., Writing: F.A.A., D.R.E., S.D.P.

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Original Article

Underutilization of Bacteriological Testing in Extrapulmonary Tuberculosis: A Retrospective Single-center Study from Mardin, Türkiye

Barış Çil[1], Mehmet Sinan Bodur[2], Mehmet Kabak[3]

[1]Clinic of Pulmonology, Mardin Training and Research Hospital, Mardin, Türkiye
[2]Clinic of Pulmonology, University of Health Sciences Türkiye, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Türkiye
[3]Department of Pulmonology, Mardin Artuklu University Faculty of Medicine, Mardin, Türkiye

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ABSTRACT

OBJECTIVE: Extrapulmonary tuberculosis (EPTB) poses diagnostic challenges due to the low bacillus burden of the disease and the limited use of bacteriological tests. The aim of this study was to evaluate bacteriological confirmation rates, diagnostic methods, and sampling practices among patients diagnosed with tuberculosis (TB) in a southeastern province of Türkiye.

MATERIAL AND METHODS: This retrospective study included a total of 456 TB cases diagnosed between 2014 and 2019. The cases were classified as pulmonary tuberculosis (PTB), EPTB, and cases with both types of involvement. Bacteriological and histopathological confirmation rates were compared between the groups.

RESULTS: 41.0% of all cases were classified as EPTB. The most commonly involved site was lymph node TB (22.4%). Bacteriological confirmation rates were significantly lower in EPTB cases: acid-fast bacilli (AFB) smear positivity was 3.2% and culture positivity was 4.3%, whereas the histopathological confirmation rate was 88.8%. No bacteriological samples were taken from 63.1% of patients in the EPTB group. Among PTB cases, AFB smear positivity (71.4%) and culture positivity (66.5%) were significantly higher ($P < 0.001$).

CONCLUSION: The findings suggest that bacteriological tests are both underused and of low diagnostic efficiency in EPTB cases. Most diagnoses are based on histopathology rather than on bacteriological confirmation. Strengthening sampling strategies and promoting the use of rapid molecular testing are critical for enhancing bacteriological validation in EPTB.

KEYWORDS: Tuberculosis, extrapulmonary tuberculosis, bacteriological confirmation, culture, AFB (acid-fast bacilli), histopathology

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INTRODUCTION

Tuberculosis (TB) remains among the leading infectious diseases, with approximately 10.8 million new cases and 1.25 million deaths worldwide in 2023, according to data from the World Health Organization's Global Tuberculosis Report 2024. In line with the objectives of the "End TB Strategy", the main component of TB control programs is bacteriological confirmation of TB. This confirmation, conducted using smear microscopy, culture, and molecular methods, not only ensures a definitive diagnosis but is also critical for identifying drug resistance, selecting the appropriate treatment regimen, and guiding public health policies.[1,2]

However, bacteriological confirmation rates, especially in extrapulmonary tuberculosis (EPTB) cases, are well below the desired level worldwide. This deficiency reduces the reliability of clinical decision-making processes and hinders the early diagnosis of resistant strains, posing serious risks to public health.

While molecular and culture-based diagnostic methods have been integrated into routine clinical practice in developed countries, limited use of bacteriological methods for EPTB cases in many developing countries creates an important diagnostic gap.[3-5]

Corresponding author: Assoc. Prof. Barış Çil, MD, e-mail: drbariscil@hotmail.com

This study was conducted to examine the use of bacteriological methods for the diagnosis of TB and to identify existing deficiencies.

MATERIAL AND METHODS

A total of 456 patients diagnosed with TB between 2014 and 2019 were included in this retrospective, single-center study. The data were obtained from TB treatment records. Due to the extraordinary conditions affecting diagnosis and reporting during the coronavirus disease-2019 pandemic, data from 2020 onward were excluded. Therefore, the study period covered January 2014 to December 2019.

TB case classifications and terminology were based on the World Health Organization (WHO) diagnostic and classification standards.[6] Sites of disease involvement were classified according to WHO definitions and categorized into 11 sites: pulmonary tuberculosis (PTB) (lung parenchyma) and 10 extrapulmonary sites (pleura, lymph nodes, peritoneum, bone and joint, genitourinary system, skin, meninges, pericardium, breast, and other extrapulmonary sites such as sialoadenitis, liver, and psoas abscess).

Based on the Site of Involvement, Patients were Classified Into Three Diagnostic Groups

1. PTB: Cases with involvement limited to lung parenchyma.

2. EPTB: Cases with involvement of one or more extrapulmonary organs without lung parenchymal involvement.

3. PTB + EPTB: Cases with both pulmonary and extrapulmonary involvement.

This classification was used to compare the diagnostic efficiency of different methods, including acid-fast bacilli (AFB) smear, culture, and histopathological examination, across groups.

Demographic and clinical variables recorded for analysis included age, sex, presence of Bacille Calmette-Guérin (BCG) scar, case definition, histopathological diagnosis, AFB smear results, type of microbiological specimen, mycobacterial culture results, drug resistance status, and treatment outcomes.

Main Points

- Low bacteriological confirmation in extrapulmonary tuberculosis (EPTB): bacteriological tests (acid-fast bacilli smear and culture) for EPTB are significantly underutilized, with positivity rates of only 3.2% and 4.3%, respectively.
- Histopathology as the primary diagnostic tool: the diagnosis of EPTB relies predominantly on histopathological findings (88.8%), indicating gaps in microbiological sampling and diagnostic algorithms.
- Need for improved sampling and molecular testing: strengthening sampling strategies and expanding rapid molecular diagnostic methods are essential to increase bacteriological confirmation rates and enhance diagnostic efficiency in EPTB.

Ethical Approval

The study was approved by the Mardin Artuklu University Ethics Committee (approval number: 2025/10-3, date: 07.10.2025), and all procedures were conducted in accordance with the principles of the Declaration of Helsinki (1975; revised 2008). Informed consent was obtained from all participants.

Statistical Analysis

Statistical analysis of the data was performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test. Fisher's exact test was used for comparisons of positivity rates of diagnostic methods and sample materials between groups. Categorical variables were expressed as frequency (n) and percentage (%), and continuous variables were expressed as mean ± standard deviation or median (minimum-maximum). The statistical significance level was set at $P < 0.05$.

RESULTS

A total of 456 patients diagnosed with TB between 2014 and 2019 were included in the study. Of these patients, 229 (50.2%) were male and 227 (49.8%) were female. Most cases (n = 400, 87.7%) were newly diagnosed. A BCG scar was present in 423 patients (92.8%) (Table 1).

PTB was the most frequent form of the disease, observed in 248 patients (54.4%). EPTB was identified in 187 patients (41.0%), while combined pulmonary and extrapulmonary involvement was detected in 21 patients (4.6%). Among extrapulmonary cases, lymph node TB was the most common site of involvement, accounting for 102 patients (22.4%).

Treatment outcomes showed that 413 patients (90.6%) successfully completed treatment or were cured. Loss to follow-up occurred in 10 patients (2.2%), and treatment failure

Table 1. General distribution and clinical characteristics of the patient population (n = 456)

Features	Category	n	%
Sex	Female	227	49.8
	Male	229	50.2
Disease involvement site	PTB	248	54.4
	EPTB	187	41.0
	Both PTB and EPTB	21	4.6
Case definitions	New case	400	87.7
	Relapse	19	4.2
	Treatment after failure	2	0.4
	Treatment after loss to follow-up	2	0.4
	Transfer-in	33	7.2
BCG scar	Present	423	92.8
	Absent	33	7.2

Percentages (%) were calculated over the total number of cases (n = 456)
PTB: pulmonary tuberculosis, EPTB: extrapulmonary tuberculosis, BCG: Bacille Calmette-Guérin

was observed in 3 patients (0.7%). At least one major drug-resistance mutation was detected in 28 patients (6.1%).

The positivity rates of diagnostic methods differed by the site of TB involvement (Table 2). AFB smear positivity was high in patients with PTB (71.4%) but markedly lower in those with predominant extrapulmonary involvement (3.2%). Similarly, culture positivity was higher in PTB cases (66.5%) and remained relatively high in patients with combined pulmonary and extrapulmonary disease (61.9%).

In contrast, EPTB was predominantly diagnosed by histopathological examination, with a diagnostic yield of 88.8%. Microbiological confirmation in extrapulmonary cases was limited, with AFB smear and culture positivity rates remaining below 5%.

Microbiological specimen selection varied substantially according to the site of disease involvement (Table 3). In the EPTB group, microbiological sampling and culture were performed in a limited proportion of cases, with no microbiological testing conducted in 63.1% of patients, indicating a substantial underutilization of bacteriological testing in EPTB. Consequently, culture-based positivity rates could be assessed only in a restricted subset of extrapulmonary cases. Among patients with PTB, sputum was the primary diagnostic specimen, obtained from 88.3% of patients, whereas bronchoalveolar lavage was used in a minority (6.5%). Microbiological testing was not performed or was not available in only 0.8% of PTB cases.

In EPTB, microbiological testing was not performed or was not available in a large proportion (63.1%) of patients. Specimens obtained through invasive procedures, such as lymph node aspiration or tissue and bone biopsies showed very low rates of microbiological positivity, indicating that diagnosis in these cases was based mainly on histopathological findings. Among microbiological samples, pleural fluid and other sterile-site specimens were the most frequently collected.

In patients with combined pulmonary and extrapulmonary involvement, sputum specimens were commonly used (71.4%) because of pulmonary disease.

DISCUSSION

In this study, 456 TB cases diagnosed between 2014 and 2019 were evaluated. The findings indicate that bacteriological confirmation in the diagnosis of EPTB remains limited. While AFB smear and culture positivity rates were relatively high in PTB, these methods showed a substantially lower diagnostic yield in extrapulmonary disease. In addition, the absence of microbiological sampling in a considerable proportion of EPTB cases points to important gaps in diagnostic algorithms at the regional level.

Although sputum smear microscopy and clinical or radiological findings are generally useful in PTB, biopsy and histopathological examination are often required to establish a diagnosis in EPTB. *Mycobacterium tuberculosis* culture is widely accepted as the gold standard for definitive diagnosis; however, its diagnostic yield is frequently reduced in EPTB because of the

Table 2. Comparison of positivity rates of diagnostic methods and 95% confidence interval in different tuberculosis involvement groups (n = 456)

Diagnostic method	Group 1: lung TB (n = 248)	Group 2: extrapulmonary TB (n = 187)	Group 3: both (pulmonary + extrapulmonary TB) (n = 21)	*P* value (Fisher's exact test)
AFB smear positivity	71.4% (95% CI: 65.5–76.6)	3.2% (95% CI: 1.4–6.8)	38.1% (95% CI: 19.8–60.1)	<0.001
Histopathological diagnosis positivity	2.4% (95% CI: 1.1–5.2)	88.8% (95% CI: 83.3–92.7)	71.4% (95% CI: 50.4–86.1)	<0.001
Culture positivity	66.5% (95% CI: 60.6–72.0)	4.3% (95% CI: 2.1–8.3)	61.9% (95% CI: 40.0–79.9)	<0.001

Percentages (%) were calculated based on the total number of cases in the relevant group. Ninety-five percent confidence intervals (95% CI) were calculated using the Wilson score method

AFB: acid-fast bacilli, TB: tuberculosis, CI: confidence interval

Table 3. Distribution of microbiological sample material by tuberculosis involvement groups (n = 456)

Sample material	Group 1: lung TB (n = 248)	Group 2: extrapulmonary TB (n = 187)	Group 3: both (n = 21)	*P* value (Fisher's exact test)
Sputum	88.3% (CI: 83.7–91.7)	20.9% (CI: 15.6–27.2)	71.4% (CI: 50.4–86.1)	<0.001
Bronchoalveolar lavage	6.5% (CI: 3.8–10.7)	0.0% (CI: 0.0–2.0)	4.8% (CI: 0.8–20.8)	<0.001
Pleural fluid	0.4% (CI: 0.1–2.4)	8.6% (CI: 5.1–13.9)	4.8% (CI: 0.8–20.8)	<0.001
Peritoneal/abdominal fluid	0.0% (CI: 0.0–1.5)	2.7% (CI: 1.1–6.4)	0.0% (CI: 0.0–16.1)	<0.001
Lymph node aspiration/ biopsy	0.0% (CI: 0.0–1.5)	0.5% (CI: 0.1–3.0)	0.0% (CI: 0.0–16.1)	<0.001
Biopsy/bone tissue	0.0% (CI: 0.0–1.5)	1.1% (CI: 0.3–4.0)	0.0% (CI: 0.0–16.1)	<0.001
No test/not tested	0.8% (CI: 0.2–3.2)	63.1% (CI: 55.9–69.8)	14.3% (CI: 4.8–36.3)	<0.001
Other	4.0% (CI: 2.1–7.5)	15.0% (CI: 10.5–20.8)	9.5% (CI: 2.6–28.5)	<0.001

Percentages (%) were calculated based on the total number of cases in the relevant group. Ninety-five percent confidence intervals (95% CI) were calculated using the Wilson score method

TB: tuberculosis, CI: confidence interval

paucibacillary nature of the disease and limitations related to specimen acquisition and processing.[7]

WHO has emphasized bacteriological confirmation as a key component of TB control strategies and has recommended the widest possible use of microscopy, culture, and molecular diagnostic methods.[1] Despite these recommendations, bacteriological diagnosis remains challenging worldwide, particularly in EPTB. In a large multicenter meta-analysis conducted by Diriba et al.[3], the pooled bacteriological confirmation rate in EPTB was reported as 43%, with substantial heterogeneity across studies, even among developing countries.

Comparative data from different regions further illustrate this variability. Wilmink et al.[8] reported considerably higher bacteriological confirmation rates among EPTB cases at a tertiary care center in Germany with high laboratory capacity, highlighting the role of infrastructure and diagnostic resources in improving microbiological yield. In contrast, studies from developing countries report lower confirmation rates. Mbuh et al.[9] demonstrated that bacteriological confirmation of EPTB could be improved under field conditions if adequate laboratory infrastructure is available, although diagnostic heterogeneity persists due to insufficient sampling and the limitations of invasive procedures.

Similarly, Pang et al.[10] reported low culture confirmation rates among EPTB cases in a large epidemiological study from China, with marked variation according to the site of disease involvement. These findings indicate that microbiological confirmation is particularly challenging in lymph node and meningeal forms of TB, for which diagnostic sensitivity is lowest.[10]

Recent advances in molecular diagnostic techniques represent a significant development in the diagnosis of EPTB. Sharma et al.[4] reported that next-generation molecular tests, including GeneXpert and related platforms, have improved diagnostic sensitivity in extrapulmonary specimens despite the intrinsic limitations of conventional microbiological methods. Nevertheless, the effective use of these technologies remains highly dependent on appropriate specimen selection and adequate laboratory infrastructure.[4] In this context, comprehensive clinical evaluation and imaging modalities—such as ultrasonography, contrast-enhanced computed tomography, magnetic resonance imaging, and positron emission tomography—continue to play a critical role in guiding accurate diagnosis and sampling strategies.[4]

Data from Türkiye are consistent with the global literature and demonstrate persistent limitations in bacteriological confirmation of EPTB. Previous studies have reported wide variability in confirmation rates, with diagnoses frequently relying on histopathological evidence rather than on microbiological testing.[11,12] A multicenter study conducted between 2010 and 2014 similarly showed that histopathological methods constituted the primary diagnostic approach in EPTB, while microbiological confirmation was achieved in only a minority of cases.[13]

Taken together, these findings suggest that microbiological confirmation in EPTB remains suboptimal and is strongly influenced by regional laboratory capacity, sampling practices, and access to advanced diagnostic techniques. The predominance of histopathology-based diagnosis and the limited use of bacteriological testing restrict early detection of drug-resistant strains and hinder optimization of treatment strategies. Addressing these challenges will require improved coordination between clinical and laboratory services, standardized sampling protocols, and broader implementation of rapid molecular diagnostic methods to strengthen TB control efforts.

Study Limitations

This study has certain limitations. First, it was designed as a retrospective analysis; the data were obtained from medical records. This may have led to an incomplete assessment of some variables due to missing or non-standardized documentation. Because the study was conducted at a single center, the generalizability of the findings is limited.

CONCLUSION

In conclusion, our study demonstrates that the insufficiency of bacteriological diagnosis in EPTB remains a significant challenge. Histopathological methods frequently substitute for microbiological confirmation, and systematic sampling practices are often inadequate. The low rate of bacteriological testing observed in EPTB cases may be partly due to patients being often first evaluated in non-pulmonary specialties. Increasing awareness of TB diagnostic methods among physicians in these disciplines may therefore contribute to improving bacteriological confirmation rates. Overall, these findings underscore the need to standardize sampling strategies and to expand access to rapid molecular diagnostics. Strengthening sampling protocols, scaling up molecular testing capacity, and enhancing laboratory infrastructure should be prioritized to improve bacteriological confirmation and support progress toward the WHO "End TB" targets.

Ethics

Ethics Committee Approval: The study was approved by the Mardin Artuklu University Ethics Committee(approval number: 2025/10-3, date: 07.10.2025), and all procedures were conducted in accordance with the principles of the Declaration of Helsinki (1975; revised 2008).

Informed Consent: Informed consent was obtained from all participants.

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Footnotes

Authorship Contributions

Concept: B.Ç., M.S.B., Design: B.Ç., M.S.B., Data Collection or Processing: B.Ç., Analysis or Interpretation: B.Ç., M.S.B., M.K., Literature Search: M.S.B., Writing: B.Ç., M.K.,

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Review

Emrelis: A New Approach in Treating MET-high Locally Advanced or Metastatic Non-squamous NSCLC; A Mini Review

Saim Mahmood Khan[1], Areeba Naveed[2], Aleena Amir[2], Yumna Saifullah[3], Surraiya Riaz Mahmood Khan[4]

[1]Karachi Medical and Dental College, Department of Medicine, Karachi, Pakistan
[2]Allama Iqbal Medical College, Department of Medicine, Lahore, Pakistan
[3]Jinnah Sindh Medical University, Department of Medicine, Karachi, Pakistan
[4]Sohail University, Department of Pharmacy, Karachi, Pakistan

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ABSTRACT

Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers; however, a subset of patients experiences disease progression associated with alterations in the Mesenchymal-Epithelial Transition Factor (c-MET) pathway. These include MET exon 14–skipping mutations, which promote tumor growth, metastasis, and resistance to epidermal growth factor receptor (EGFR)-targeted therapies. Telisotuzumab vedotin (TV-t, Emrelis), a novel first-in-class c-MET inhibitor, is under investigation as a targeted therapy for c-MET-high NSCLC. This article highlights the therapeutic potential of TV-t as a targeted therapy for advanced NSCLC patients with limited post-treatment options. A targeted literature review was conducted using PubMed and ClinicalTrials.gov (2018 and 2025) with terms including "Telisotuzumab Vedotin," "c-MET," "c-MET–high," "c-MET overexpression," "MET exon 14," and "NSCLC." Both clinical and preclinical studies of the efficacy, safety, and pharmacological properties of TV-t were included. Also, those studies reported clinical findings relevant to TV-t in c-MET-altered NSCLC. In the pivotal LUMINOSITY phase II trial, TV-t showed a 28.6% overall response rate (ORR) in EGFR-wildtype, c-MET-overexpressing NSCLC, with 34.6% ORR in c-MET-high patients. Median duration of response was 9.0 months, overall survival 14.5 months, and progression-free survival (PFS) 5.7 months for the c-MET-high subgroup. In phase Ib studies, TV-t combined with osimertinib achieved a 50% ORR and 7.4-month PFS, while TV-t with nivolumab, the median PFS was 7.2 months, but ORR was low (7.4%). Common grade 3 or higher toxicities occurred in 27.9% of patients and included neuropathy, anemia, and pulmonary embolism, with no hepatotoxicity. Remarkable cardiac safety was observed. TV-t demonstrated promising efficacy and tolerability in patients, highlighting its clinical potential. However, further studies are needed to confirm its survival advantage, the durability of response, and safety profile, and to establish its long-term value and support its integration into routine clinical practice.

KEYWORDS: Non-squamous NSCLC, Emrelis, telisotuzumab vedotin, MET-high NSCLC, c-MET overexpression

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INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer in adults. Approximately 85% of lung cancers are classified as NSCLC.[1] The three main histological subtypes of NSCLC according to the World Health Organization/ International Association for the Study of Lung Cancer classification are squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma. Among these subtypes, non-squamous subtypes (adenocarcinoma and large cell carcinoma) are the most prevalent, making these subtypes the leading cause of preventable death from lung cancer.[2] Mesenchymal-Epithelial Transition Factor (c-MET) is a receptor tyrosine kinase that, upon activation by hepatocyte growth factor (HGF), triggers downstream signaling pathways (e.g., PI3K/AKT), promoting cellular growth, tissue infiltration, and motility. Its abnormal activation causes persistent endosomal signalling, which leads to oncogenesis and is implicated in NSCLC.

Corresponding author: Saim Mahmood Khan, MBBS, e-mail: saimmahmoodkhanrajput@gmail.com

More recently, evidence indicates that c-MET is also involved in resistance to conventional cytotoxic chemotherapy through downstream activation of several endosomal pathways, particularly the PI3K/AKT pathway. It raises the clinical need for targeted therapies in previously treated, c-MET-high NSCLC patients, for whom the HGF-MET pathway has a confirmed vital role.[3] Food and Drug Administration (FDA) has recently granted accelerated approval to telisotuzumab vedotin (TV-t), a first-in-class c-MET-directed antibody-drug conjugate (ADC), for the treatment of NSCLC in adult patients.[4] This article aims to highlight the therapeutic potential of TV-t as a promising targeted therapy for adult patients with advanced NSCLC who have limited treatment options following prior therapies.

Biological Role of c-MET in NSCLC

c-MET is a transmembrane receptor tyrosine kinase that is activated by its ligand, HGF, which belongs to the family of plasminogen-related growth factors. HGF/c-MET signalling leads to tissue repair, wound healing, tissue regeneration, angiogenesis, and epithelial-mesenchymal transition (EMT).[5] The HGF/c-MET axis works together with other tyrosine kinases and activates several key downstream signaling networks within tumor cells. These pathways include the PI3K/AKT, JAK/STAT, Ras/MAPK, SRC, and Wnt/β-catenin, all of which play crucial roles in cancer growth, metastasis, and survival.[5]

The c-MET tyrosine kinase receptor is overexpressed and overrepresented in NSCLC.[6] Activation of c-MET triggers phosphorylation at key tyrosine residues (Y1003, Y1313, Y1230/1234/1235, Y1349, Y1365), initiating downstream signaling cascades. Moreover, c-MET-mediated SRC activation promotes EMT, which contributes to the initiation of malignant transformation.[6] MET exon 14 skipping mutation (METΔex14) is present in three of every hundred patients with NSCLC.[7] When exon 14 is skipped, the CBL-mediated degradation of the c-MET protein is disrupted, preventing normal receptor turnover. This results in accumulation of c-MET receptors on the cell surface and sustained activation of oncogenic c-MET signaling, driving tumor growth and progression.[7] Both c-MET overexpression and exon 14 skipping contribute to an increased incidence of NSCLC.

Main Points

- Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer cases, making it the most prevalent form in adults.
- The three main histological subtypes of NSCLC are squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Non-squamous types (adenocarcinoma and large cell carcinoma) are more common.
- Non-squamous subtypes of NSCLC are a leading cause of preventable lung cancer deaths, highlighting their clinical significance.
- The Mesenchymal-Epithelial Transition Factor (c-MET) receptor tyrosine kinase, activated by hepatocyte growth factor (HGF), plays a key role in regulating cell proliferation, motility, and invasion.
- Aberrant activation of the c-MET/HGF pathway contributes to oncogenesis in NSCLC due to sustained endosomal signaling and uncontrolled cellular behavior.

The c-MET receptor promotes resistance to standard chemotherapeutic agents by activating the PI3K/AKT signaling axis. The epidermal growth factor receptor (EGFR) T790M mutation primarily mediates acquired resistance to EGFR-tyrosine kinase inhibitor (TKI) in NSCLC, whereas KRAS mutations are mainly associated with primary resistance. Chronic co-activation of the ERK and AKT signaling pathways drives EGFR-TKI resistance in NSCLC cells. Oncogenic SRC and RAS proteins can trigger the EMT, leading to the breakdown of E-cadherin complexes at cell junctions. This disruption enhances cellular invasiveness and metastatic potential.[6]

Mechanism of Action

Receptor-mediated Internalization

TV-t is a novel ADC that advances targeted therapy for NSCLC with MET overexpression. The anti-c-MET monoclonal antibody moiety exhibits remarkable selectivity for its targets. It is about tenfold stronger than the binding of natural HGF. Due to its potent binding to c-MET, the drug selectively targets c-MET-overexpressing tumor cells while having minimal effect on normal tissues. The binding initiates the drug's endocytosis. The complex is rapidly internalized via clathrin-mediated endocytosis, with 80% of surface-bound drug internalized within 30 minutes.

MMAE Payload and Microtubule Disruption

Another noteworthy feature of the drug is the cleavable valine-citrulline linker, which remains intact during circulation but is cleaved by lysosomal proteases.[8] This potent microtubule-disrupting payload, monomethyl auristatin E (MMAE), is directly delivered to tumor cells via a controlled-release approach, resulting in intracellular concentrations that are 50- to 100-fold higher than levels in the normal surrounding tissues. The binding of MMAE causes severe disruption of the microtubule network, leading to cell death within 24-48 hours. The bystander effect, in which hydrophobic MMAE molecules permeate cell membranes and affect neighboring tumor cells, is particularly useful.[9]

Comparison with MET Inhibitors

Unlike small-molecule inhibitors such as capmatinib and tepotinib, which target the MET exon 14-skipping mutation, TV-t acts on all c-MET-overexpressing tumors, regardless of mutation status. The mechanism of action, showing TV-t delivery via c-MET, is illustrated in Figure 1.

Clinical Trial Evidence

First-in-Human Phase I Trials

The earliest multicenter phase I study (NCT02099058) established the safety and dosing of TV-t and provided early signals of efficacy in adults with advanced solid tumors, including c-MET-overexpressing NSCLC. The overall response rate (ORR) was 18.8% (3 PRs) among 16 c-MET-positive NSCLC patients at doses of 2.4-3.0 mg/kg, with a median progression-free survival (MPFS) of 5.7 months and a median duration of response (DOR) of 4.8 months. Non-NSCLC tumors showed no reaction. TV-t drug levels were dose-proportional, with a terminal elimination half-life of two to four days.[10] A Japanese phase I trial confirmed

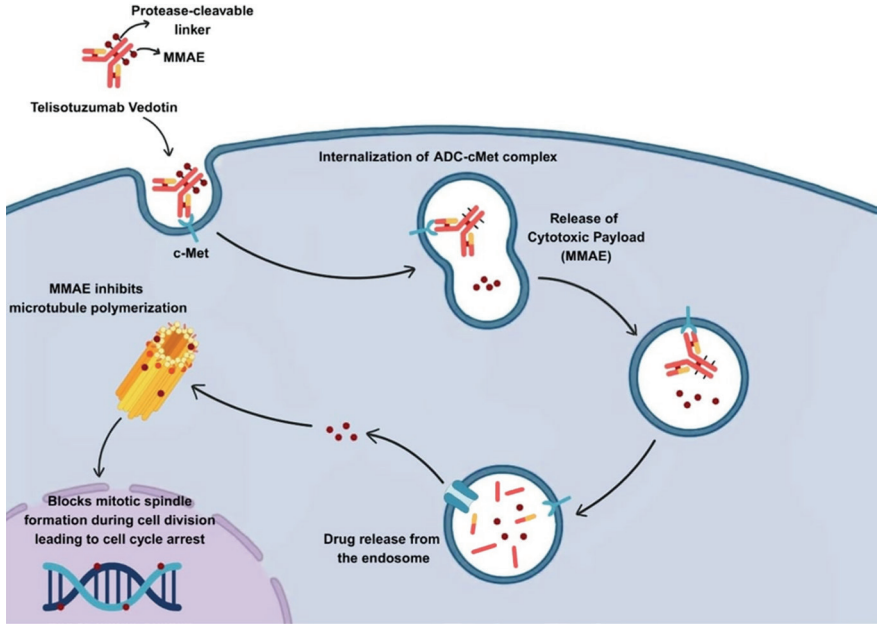

Figure 1. The mechanism of action of telisotuzumab vedotin

MMAE: monomethyl auristatin E, ADC: antibody–drug conjugate, c-MET: Mesenchymal-Epithelial Transition Factor

TV-t's tolerability and effectiveness in an Asian population. With a disease control rate of 89% (8/9 patients), the observed ORR was 22% and the MFS was 7.1 months.[11]

LUMINOSITY Phase II Trial

In the pivotal LUMINOSITY phase II trial (NCT03539536), TV-t monotherapy was administered to 172 patients with treated EGFR-wildtype non-squamous NSCLC and c-Met overexpression. It was a phase II, open-label, single-arm, multicenter trial evaluating the effectiveness of TV-t. An ORR of 28.6% was achieved. Patients with c-MET overexpression had an ORR of 34.6%. For the intermediate group, ORR was 22.9%. Response duration was 9.0 months in the MET-high subgroup and 7.2 months in the intermediate subgroup. Although survival outcomes were favorable across the entire cohort, the median overall survival and progression-PFS were 14.5 months and 5.7 months, respectively.[12]

Phase Ib Combination Studies

The combination potential of TV-t has been evaluated in two significant phase Ib studies.

TV-t + osimertinib: Among patients with EGFR mutations who progressed on osimertinib, TV-t with continued EGFR blockade demonstrated notable activity, achieving a 50% response rate and an MPFS of 7.4 months.[13]

TV-t + nivolumab: The phase Ib nivolumab combination study (NCT02099058) offered insights into TV-t's possible synergy with immunotherapy, albeit with relatively subtle efficacy signals. Among the 27 c-MET-positive patients, the combination showed acceptable safety. However, very limited antitumor activity was demonstrated, with an ORR of 7.4%. Interestingly, an MPFS of 7.2 months was achieved overall and was similar between programmed death-ligand 1-positive and -negative subgroups. This trial showed that TV-t's pharmacokinetic profile did not change when nivolumab was administered, which is an important consideration for combination therapies.[14]

TV-t + erlotinib: An earlier phase Ib trial of erlotinib plus TV-t in patients pretreated with EGFR TKIs showed similarly optimistic outcomes and a notable response rate of 52.6% in the c-MET-high group.[15]

Comparative Clinical Interpretation

Divergence in response rates between combination regimens: The difference in ORR for osimertinib (50%) versus nivolumab (7.4%) combinations appears multifactorial: First, mechanistic distinctions exist: by co-inhibiting EGFR and c-MET, osimertinib is more effective than nivolumab in targeting acquired c-Met amplification, a known EGFR-evasive pathway, because immune-modulatory mechanisms do not synergize with telisotuzumab vedotin's cytotoxic activity. Second, patient enrichment: osimertinib studies limited inclusion to EGFR-mutant patients with evidence of acquired resistance, whereas nivolumab enrolled an unselected, heterogeneous patient population.

Comparison with other c-MET targeted therapies (tepotinib, capmatinib): Telisotuzumab vedotin, with an ORR of 28.6%, has a lower ORR than tepotinib, which has reported ORRs of 40-45% in cases with MET exon 14-skipping mutations, likely because telisotuzumab is indicated based on c-MET overexpression rather than specific genetic alterations. The DOR associated with TV-t (9.0 months in MET-high cohorts) is similar to that observed with capmatinib (8.3 to 9.7 months in METex14), although established differences in trial design prevent firm cross-trial inference.

Safety differentiation from other antibody-drug conjugates: The TV-t construct demonstrates certain hematologic advantages: the incidence of severe neutropenia (grade ≥3) is reported as a comparatively modest 4%, lower than the rates

observed with trastuzumab deruxtecan. When unique toxicity events are investigated, the profile of TV-t regarding interstitial lung disease warrants emphasis. c-MET receptor blockade is associated with a decreased incidence of this complication relative to conjugates that target HER2. Peripheral neuropathy attributable to the bridged MMAE cytotoxic payload is consistent with patterns observed in other ADCs that employ this payload class. Table 1 summarizes clinical trials.

Adverse Effects and Safety Profile

Common adverse effects observed in the phase II trial include peripheral sensory neuropathy, fatigue, and peripheral edema. Grade 3 or higher events occurred in 27.9% of patients; peripheral neuropathy was the most common (7%).[12] Anemia (11%) and pulmonary embolism (8%), the most frequent grade 3 treatment-related side effects, were observed in a phase Ib study of TV-t in combination with osimertinib.[13]

The absence of certain toxicities in the toxicity profile greatly enhances its benefit. Unlike most targeted therapies, telisotuzumab vedotin has not been associated with interstitial lung disease or pneumonitis, which represents a notable lack of pulmonary toxicity. No hepatotoxicity was observed. Cardiac safety is also notable.

Patients should be closely monitored for signs of peripheral neuropathy, such as burning sensations, neuropathic pain, or muscle weakness. Upfront management strategies have been designed to enhance tolerability. For osimertinib combination

Table 1. Summary of all the clinical trials

Study/phase	Study population and design	ORR (%)	Median DOR (months)	Median PFS (months)	Median OS (months)	Common any-grade AEs	Common grade ≥3 AEs
First-in-human phase I (10)	48 advanced solid tumors (incl. NSCLC)	c-MET + NSCLC: 18.8%	4.8	5.7	NR	Fatigue (42%), nausea (27%), constipation (27%), decreased appetite (23%), vomiting (21%), dyspnea (21%), diarrhea (19%), peripheral edema (19%), and neuropathy (17%)	Fatigue, anemia, neutropenia, and hypoalbuminemia (4% each)
Phase I study in Japanese (11)	Japanese patients with advanced solid tumors	22%	8.2 (overall DCR 89%)	7.1	NR	Peripheral sensory neuropathy (44%), and nausea, decreased appetite, and decreased WBC count (33% each)	Neutropenia and hypoalbuminemia in two patients (22%) each, and hypophosphatemia and fatigue in one patient (11%) each
Phase II LUMINOSITY trial (12)	172 patients with EGFR-wildtype NSCLC	Overall: 28.6%; c-MET high: 34.6%; c-MET intermediate: 22.9%	Met high: 9.0 Met intermediate: 7.2	5.7	14.5	Peripheral sensory neuropathy 30%, peripheral edema 16%, fatigue 14%	Peripheral sensory neuropathy 7%
Phase Ib (TV-t+ osimertinib) (13)	38 patients with EGFR-mutant NSCLC	50.0%	NR	7.4	NR	Peripheral sensory neuropathy 50%, peripheral edema 32%, nausea 24%	Anemia 11%, pulmonary embolism 8%
Phase Ib (Teliso-V + Nivolumab) (14)	37 patients; 27 c-Met IHC+ NSCLC (PD-L1 + n = 15; PD-L1– n = 9; PD-L1 unknown n = 3)	7.4	NR	Overall: 7.2; PD-L1+: 7.2; PD-L1–: 4.5	NR	Fatigue 27%, peripheral sensory neuropathy 19%	Not specified
Phase Ib (Teliso-V + Erlotinib) (15)	42 EGFR-mutant NSCLC	Overall: 32.1%; MET-high: 52.6%	NR	5.9 overall; 6.8 in non-T790M+ / unknown		Peripheral sensory neuropathy	

NSCLC: non-small cell lung cancer, c-MET: Mesenchymal-Epithelial Transition Factor, EGFR: epidermal growth factor receptor, PD-L1: programmed death-ligand 1, IHC: immunohistochemistry, TV-t: telisotuzumab vedotin, ADC: antibody–drug conjugate, MMAE: monomethyl auristatin E, ORR: overall response rate, DOR: duration of response, PFS: progression-free survival, OS: overall survival, DCR: disease control rate, NR: not reported, AE: adverse event, PR: partial response, WBC: white blood cell, EMT: epithelial–mesenchymal transition

therapy, hematologic monitoring is crucial. In patients with mild to moderate organ impairment, a dosage of 1.9 mg/kg every two weeks, up to a maximum of 190 mg, exhibits linear pharmacokinetics and does not require adjustment. Research continues into different dosing approaches that may broaden the therapeutic window.

Diagnostic Tool: VENTANA MET RxDx Assay

The VENTANA MET SP44 rxdx assay is approved by the FDA as a companion diagnostic test for the detection of c-MET protein overexpression in patients eligible for treatment with TV-t.[16] It is an immunohistochemistry based test that employs the rabbit monoclonal anti-MET clone SP44 expression in formalin-fixed paraffin-embedded non-squamous NSCLC specimens by light microscopy.[17] The assay has been used in clinical studies, including the phase II LUMINOSITY trial and phase Ib combination trials, where it was used as a pre-screening tool. It stratifies patients into MET-high and MET-intermediate groups based on staining intensities and the proportion of tumor cells that stain strongly. In LUMINOSITY, MET-high was defined as ≥50% of tumor cells exhibiting strong (3+) staining; this demonstrated higher response rates to telisotuzumab vedotin.[18] This standardized diagnostic approach ensures accurate patient selection and enables oncologists to target therapy to patients most likely to respond, thereby avoiding unnecessary treatment in others.

Clinical Relevance and Future Directions

TV-t represents an important advance in precision oncology by providing a targeted treatment option for patients with NSCLC who exhibit high c-MET protein expression but lack MET exon 14-skipping mutations, a group for whom MET TKIs such as capmatinib are ineffective. For this population with limited options for targeted therapies, TV-t offers a biomarker-driven alternative.[10] Due to its favorable safety profile, TV-t also has potential for combination with immune checkpoint inhibitors (anti-PD-1/PD-L1 agents) or conventional chemotherapy. Ongoing phase II and Ib trials are refining patient selection and optimizing treatment approaches. However, the knowledge gaps remain regarding the durability of the response, the mechanisms of resistance, and the long-term survival outcomes. Beyond NSCLC, the success of TV-t highlights the broader role of companion diagnostics and biomarker-driven therapies in guiding precision medicine across oncology.

CONCLUSION

The approval of Emrelis by the FDA represents a major step forward in the treatment of locally advanced or metastatic non-squamous NSCLC and is expected to reduce the number of deaths it causes globally. In its LUMINOSITY trial, it demonstrated a notable ORR and a favorable tolerability profile in patients, highlighting its clinical potential. However, its real-world data and long-term results remain limited. Further studies are needed to confirm its survival benefits, assess the durability of responses, and characterize its toxicity profile, thereby validating its long-term benefits; these data will be critical for defining its role in routine clinical practice.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.M.K., A.A., Concept: S.M.K., A.N., A.A., Design: S.M.K., A.N., A.A., Data Collection or Processing: S.M.K., A.N., A.A., Y.S., Analysis or Interpretation: S.M.K., A.A., Y.S., S.R.M.K., Literature Search: S.M.K., A.N., Y.S., S.R.M.K., Writing: S.M.K., A.N., Y.S., S.R.M.K.

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Review

The Interplay Between Obstructive Sleep Apnea and Respiratory Infections: A Review Article

Safy Kaddah[1], Antonio M. Esquinas[2]

[1]Department of Chest Diseases, Cairo University, Kasr Alainy Hospital Faculty of Medicine, Giza, Egypt
[2]Intensive Care Unit, Hospital Meseguer, NIV-ICM, Biomedical Research Institute of Murcia Pascual Parrilla–IMIB, Murcia, Spain

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ABSTRACT

Obstructive sleep apnea (OSA) is a prevalent sleep-related breathing disorder characterized by recurrent upper airway collapse, intermittent hypoxia, and sleep fragmentation. Increasing evidence suggests a bidirectional association between OSA and lower respiratory tract infections (LRTIs), including pneumonia, bronchitis, and exacerbations of chronic lung disease. Multiple mechanisms may underlie this relationship. Intermittent hypoxia and sleep disruption promote systemic inflammation and immune dysregulation. Impaired mucociliary clearance, microaspiration, alterations in airway microbiota, together with obesity and related comorbidities, further contribute to increased susceptibility to and severity of infections. Observational studies demonstrate that individuals with untreated OSA have higher rates of pneumonia, more severe infections, and delayed recovery from infections compared with non-OSA populations. These risks are particularly evident among older adults and patients with cardiopulmonary comorbidities. Continuous positive airway pressure (CPAP) therapy may mitigate infection risk by maintaining airway patency, reducing hypoxemia, and improving mucociliary clearance. However, concerns remain regarding CPAP device-associated microbial colonization, highlighting the importance of strict hygiene practices and equipment maintenance. OSA appears to be an underrecognized risk factor for LRTIs; this association is driven by overlapping pathophysiological mechanisms and is supported by emerging epidemiological data. Recognizing this interplay may guide infection prevention strategies and improve clinical outcomes in high-risk populations.

KEYWORDS: Obstructive sleep apnea, lower respiratory tract infections, immune dysregulation, CPAP therapy, airway microbiota, COVID-19, community-acquired pneumonia

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INTRODUCTION

Obstructive sleep apnea (OSA) is the most common sleep-breathing disorder, characterized by collapse of the soft tissues of the upper airway during sleep, causing recurrent intermittent hypoxia and hypercapnia, and resulting in frequent nocturnal awakenings and sleep fragmentation.[1] Those alterations induce sympathetic activation, oxidative stress, and metabolic dysregulation,[2] which lead to various cardiovascular diseases and pulmonary, neurological, and cognitive dysfunctions.[3,4] The exact prevalence of OSA is underestimated; available data indicate that about 20% of middle-aged Americans have OSA, and a higher prevalence has been observed among Asian populations.[5,6] The incidence is higher in males aged 50–70 years (17%) than in females diagnosed with moderate-to-severe OSA (9%).[7]

Lower respiratory tract infections (LRTIs) are a major public health problem associated with increased morbidity and mortality. LRTIs include bronchitis, bacterial and viral pneumonia.[8] The host immune response and the virulence of the susceptible organism determine the outcomes of respiratory infections.[9] The proinflammatory state induced by OSA[10] has highlighted the coexistence of OSA and respiratory infections through enhancement of proinflammatory stimuli.[11] The coronavirus disease 2019 (COVID-19) pandemic has heightened awareness of viral LRTIs.[12] In 2019, LRTIs were recognized as one of the leading causes of mortality worldwide. An American observational study in Chicago, using healthcare

Corresponding author: Prof. Safy Kaddah, MD, e-mail: safykaddah@kasralainy.edu.eg

system records, reported that OSA patients had an increased risk of COVID-19 infection, hospitalization, and worse sequelae compared with patients of the same age who received similar treatment.[13] It was assumed that elevated inflammatory markers in OSA patients contributed to unfavorable COVID-19 outcomes. Moreover, COVID-19 and OSA share several risk factors, such as diabetes, hypertension, cardiovascular disease, and obesity.[13,14]

This review explores the potential link between OSA and LRTIs and the burden of both conditions in adults.

Objective

To evaluate, through a literature review, the impact of OSA on susceptibility, pathogenesis, and clinical outcomes of respiratory infections, and to discuss potential management strategies.

METHODS LITERATURE SEARCH

A systematic search of PubMed, Web of Science, and CENTRAL, using specified keywords, was conducted to identify publications up to January 31, 2025. Our search strategy followed a stepwise approach to ensure comprehensive capture of relevant literature. We began with search terms for obstructive sleep apnea (Search #1), combining MeSH terms such as "Obstructive Sleep Apnea" and "Sleep Apnea, Obstructive" with title and abstract keywords, including "Sleep-related breathing disorders" and "OSA". We also included broader MeSH terms like "Sleep-Disordered Breathing" and "Sleep Apnea Syndromes" to ensure comprehensive coverage for respiratory infections, we constructed three separate search sets: one for bacterial pneumonia (Search #2) using terms such as "Pneumonia"[MeSH], "bacterial pneumonia," community-acquired pneumonia, and "Lower Respiratory Tract Infections"[MeSH]; another for influenza (Search #3) using "Influenza, Human"[MeSH] and related terms; and a third for COVID-19 (Search #4) using appropriate MeSH terms and keywords. These respiratory infection searches were combined using the Boolean operator "OR" (Search #5) and were then intersected with the OSA search using "AND" (Search #6). Finally, we applied filters for English-language publications, human studies, an adult population (19+ years), and publication year 2025 (Search #7). The summary of the research strategy is listed in Table 1.

Main Points

- Emerging evidence suggests that obstructive sleep apnea (OSA) may increase lower respiratory tract infections, particularly in individuals with severe disease and higher hypoxic burden.
- Biological mechanisms such as intermittent hypoxia, systemic inflammation, immune dysregulation, impaired mucociliary clearance, and microaspiration may contribute to the observed association between OSA and infection severity.
- Consideration of preventive strategies-including vaccination, comorbidity optimization, and careful continuous positive airway pressure hygiene- may help reduce infectious morbidity in patients with moderate-to-severe OSA.

SEARCH STRATEGY LITERATURE

Both authors (A.M.E., S.K.) searched for, and conducted a full-text review of, the retrieved literature. The two authors discussed the exclusion and inclusion criteria of the retrieved studies and reached a consensus.

Results of Literature Search

A systematic search of the literature was conducted in PubMed, CENTRAL, and Web of Science to evaluate whether OSA in adults is associated with an increased risk of respiratory infections.

The search strategies included free-text terms and controlled vocabulary for OSA ("Sleep Apnea, Obstructive," "OSA," "Sleep-related breathing disorders") and for respiratory infections ("respiratory tract infections," "pneumonia," "bronchitis," "influenza," "COVID-19," and related terms).

The search retrieved a total of 3,975 records (PubMed: 1,440; CENTRAL: 1,294; Web of Science: 1,241). After removal of 1,070 duplicate records, 2,905 unique records remained for title and abstract screening. Full-text articles were subsequently assessed for eligibility, and the reasons for exclusion were recorded. The final numbers of included studies are presented in the PRISMA flow diagram Figure 1.

PATHOPHYSIOLOGICAL MECHANISMS

Hypoxia and Inflammation

Healthy sleep plays a crucial role in regulating the immune system.[15,16] OSA patients experience chronic sleep deprivation and intermittent hypoxia. Immune perturbations secondary to disrupted sleep led to increased oxidative stress and systemic inflammation, which may render those patients susceptible

Table 1. Summary of the research strategy

Items	Specification
Search date	January 31, 2025
Databases searched	PubMed; Web of Science; CENTRAL
Search terms	"Obstructive Sleep Apnea"; "Sleep-related breathing disorders"; OSA; Pneumonia; bacterial pneumonia; community-acquired pneumonia; CAP; respiratory infection; bronchopneumonia
Timeframe	Up to January 31, 2025
Inclusion criteria	English language; non-randomized trials; randomized controlled trials (RCTs); proof-of-concept studies; observational studies (cross-sectional, cohort, case-control); case reports; research protocols
Exclusion criteria	Unavailable full text (abstracts and letters to the editor)
Selection process	Article screening: S.K. and A.M.E.; Literature classification: S.K. and A.M.E.; Review content preparation: S.K. and A.M.E.

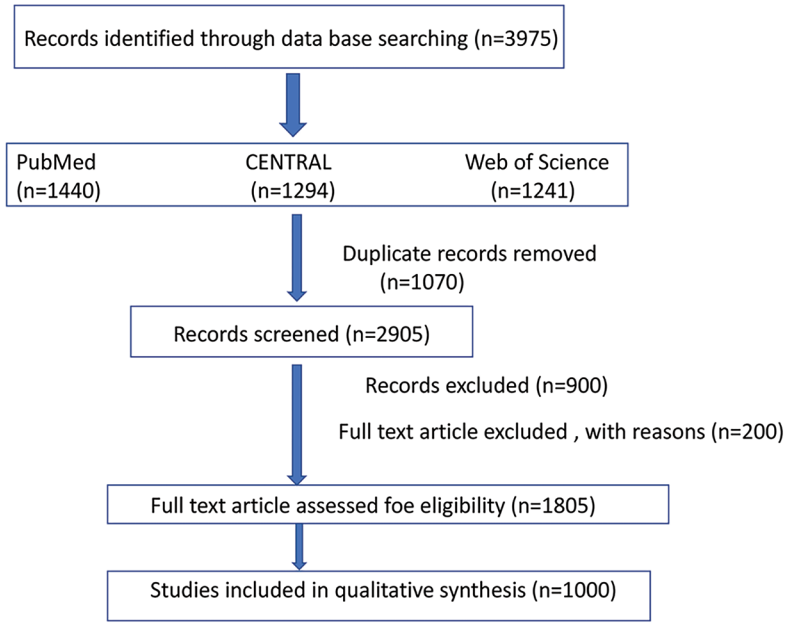

Figure 1. PRISMA flow diagram

to pathogen invasion and LRTIs.[15-18] Impaired lung neutrophil function resulting from hypercapnia that may be associated with OSA could render those patients susceptible to LRTIs.[19]

Impaired Mucociliary Clearance

OSA is associated with alterations in intrathoracic pressure and breathing patterns. Those alterations are more frequently observed during rapid eye movement sleep. They are attributed to inhibition of cortical input to the brainstem cough center. Moreover, at night there is an increase in the peripheral nerves threshold that cause a weak or even an absent cough reflex that leads to an inability to clear pathogens from the airways.[20,21]

Microaspiration Risk

During the night, aspiration of small amounts is normal in healthy individuals.[22] During sleep, patients with OSA have a higher risk of pulmonary aspiration than individuals without OSA. Following episodes of apnea-hypopnea, patients are stimulated to breathe against a closed airway, leading to a greater increase in negative intrathoracic pressure. As a result, the pressure gradient increases, creating a vacuum effect in the upper airway that leads to excessive microaspiration. Excessive microaspirations lead to increases in bacterial pathogens and upper airway and laryngeal inflammation.[23-28] Treatment of gastroesophageal reflux (GER) may lead to a significant decrease in the apnea-hypopnea index (AHI).[25,29]

The Role of Comorbidities and Obesity

There is evidence that obesity and comorbid conditions such as diabetes, hypertension, cardiovascular disorders, cerebrovascular disease, GER, Parkinson's disease, epilepsy, and chronic liver and kidney diseases are associated with greater OSA risk. Those comorbidities increase the risk of infections, including LRTIs. Also, in patients with comorbid chronic obstructive pulmonary disease (COPD) and asthma, those who receive corticosteroids have an increased risk of LRTIs.[30]

Obesity increases the risk of complications in critically ill patients.[31-33] However, the "obesity paradox" confers a protective effect against mortality from LRTIs among obese patients. This effect is the result of an early presentation in those patients, increased hospital admission, and changed immune response characterized by lesser inflammation in those patients (Figure 2).[34-36]

EVIDENCE FROM THE STUDIES

In this retrospective cohort study, adult OSA patients (aged ≥20 years) were enrolled from the Research Database of the Taiwan National Health Insurance. Compared to a cohort control group without OSA, having the same age, sex, and comorbidities. The two cohorts were followed for the occurrence of pneumonia. The study included 34,100 patients (6,816 with OSA and 27,284 controls). During a follow-up period of approximately 4.50 years, 2,757 (8.09%) participants developed pneumonia, including 638 (9.36%) OSA patients and 2,119 (7.77%) in the control cohort. They concluded that pneumonia incidence was higher among OSA patients, based on Kaplan-Meier analysis (log-rank test, $P < 0.001$), and a 1.20-fold increased risk (95% confidence interval 1.10–1.31) after multivariate adjustment. They also stated that the risk was even greater among patients who were treated by continuous positive airway pressure (CPAP).[37] CPAP is the gold-standard therapy for moderate-to-severe OSA. It may decrease sputum expectoration, thereby increasing the risk of aspiration. In addition, humidifiers provide a potential source of bacterial contamination.[38] Therefore, maintenance and regular cleaning of CPAP devices are crucial to avoid the risk of infection.[39]

Chiner et al.[40] conducted a study that included 82 community-acquired pneumonia (CAP) patients and 41 patients with non-respiratory infections. They found that severe OSA patients

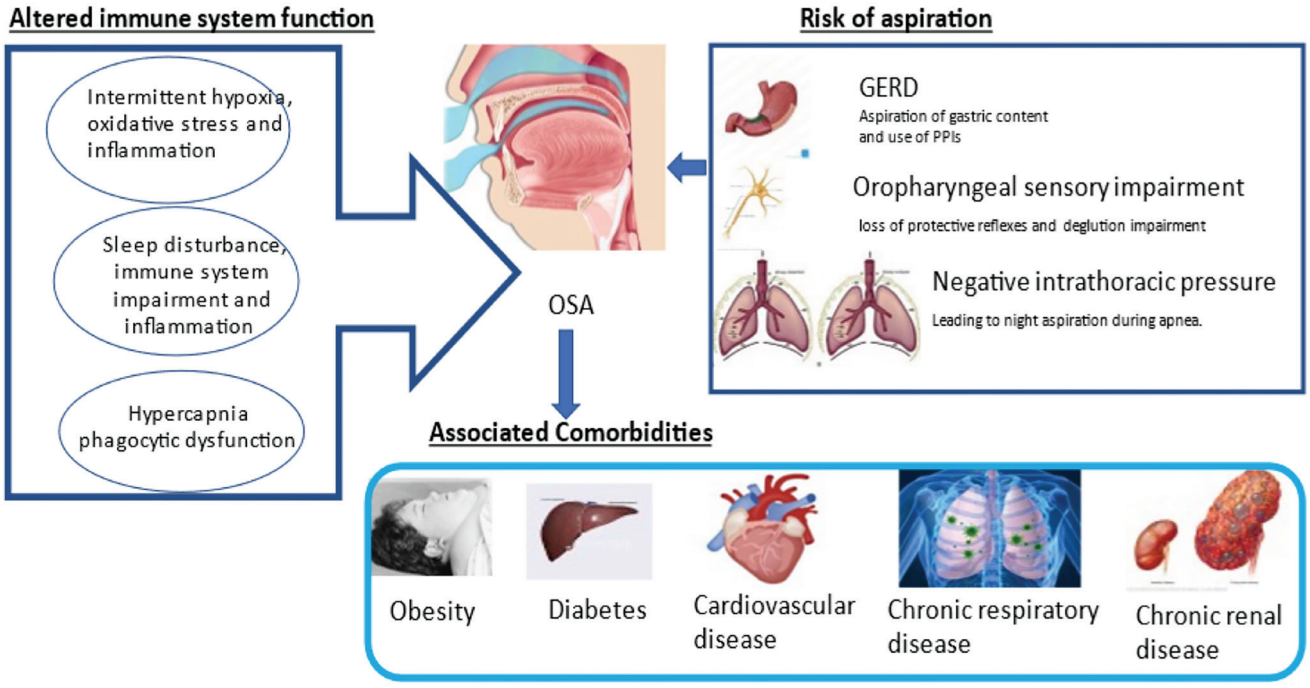

Figure 2. Risk factors and pathophysiological interaction of LRT infections and OSA

LRT: lower respiratory tract infection, OSA: obstructive sleep apnea

had threefold greater odds (odds ratio: 3.18; 1.11–11.56) of developing pneumonia during sleep than normal-breathing patients. They also concluded that, based on AHI results and various indices of oxygen saturation, higher OSA grade was associated with more severe CAP presentation, which highlights the role of OSA as a risk factor that increases susceptibility and influences the clinical outcomes of CAP.[40]

Notably, during a follow-up period of up to 20.4 years, the Atherosclerosis Risk in Communities prospective cohort study reported that severe OSA increased the risk of pneumonia by 87%. Also, they found that a hypoxic burden [which is the time of oxygen saturation below 90% during total time of sleep (T90)] greater than 5%, compared with less than 1%, was associated with a 50% increased risk of pneumonia. This association suggests that the hypoxic burden and its physiological consequences increase the risk of pneumonia, extending beyond the effects of obesity alone.[41]

Moreover, a nationwide Finnish retrospective population-based case-control study, using data from the national primary and secondary health care registers from 2015–2019, investigated the incidence of LRTs in the first year before and after diagnosis of OSA. They included controls matched for sex, age, and multimorbidity. They analyzed the effect of comorbidities and patient characteristics on the risk of LRTIs and on their recurrence. They reported that OSA patients develop LRTIs at a higher incidence than controls. Hazard ratios were 1.35 (95% confidence interval 1.16–1.57) one year before the diagnosis of OSA and 1.39 (95% confidence interval 1.22–1.58) one year after the diagnosis of OSA. They found that in OSA patients, a previous LRTI before OSA diagnosis, having more than one morbidity, asthma, COPD, and age greater than 65 years increased the incidence and recurrence of LRTIs in those patients.

DIAGNOSTIC AND SCREENING CONSIDERATIONS

OSA and LRTIs

CAP is defined as an acute disease characterized by one or more of the following symptoms: cough with or without sputum production, dyspnea, pleuritic chest pain, and fever. On auscultation, adventitious and bronchial breath sounds may be heard. An increased total leucocytic count and the presence of infiltrates on the chest X-ray were observed.[42] Investigations include a complete blood picture, serum C-reactive protein (CRP) levels, and arterial blood gas analysis. Detection of the causative organism is performed by sputum culture or by protected bronchial lavage via fiberoptic bronchoscopy.

After hospitalization, CAP patients suspected of having OSA should be screened with sleep questionnaires to assess OSA symptoms. Daytime sleepiness is screened by the Epworth sleepiness scale.[43] During history taking, smoking status, alcohol consumption, and the presence of associated comorbidities (COPD, diabetes, previous pneumonia, heart failure, asthma, steroid intake during the last 6 months, hospitalization during the previous 3 months, liver and kidney failure, and cerebrovascular disease) should be assessed. Physical examinations include height, weight, body mass index, and the Mallampati scale. The Diagnosis of OSA is confirmed by polysomnography when the AHI is equal to or greater than 5 events per hour of sleep.

Sleep deprivation in OSA patients leads to altered immunity and increases the risk of LRTIs. Hypoxemia and related oxidative stress are linked to activation of the immune system, and inflammatory marker levels increase [proinflammatory cytokines, e.g., interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and CRP].[44-47] Moreover, sleep deprivation without

hypoxemia induces inflammation and elevates inflammatory markers in untreated sleep apnea patients.[48,49]

OSA and Pneumonia Severity

Chronic inflammation, hypoxia, and sleep fragmentation associated with the pathogenesis of OSA lead to alterations in immune system activity and an increased risk of severe infection.[50-52] Gastro-esophageal reflux disease associated with OSA increases the risk of pulmonary aspiration and the subsequent development of aspiration pneumonia.[53] The airway microbiome in OSA patients is altered compared with that in healthy individuals. It increases predisposition to respiratory infection as its severity increases.[54]

CLINICAL IMPLICATION AND MANAGEMENT

Role of CPAP Therapy

Treatment with a positive airway pressure device, together with lifestyle interventions, remains the gold-standard treatment for moderate-to-severe OSA. CPAP use for at least four hours per night has been shown to decrease sleep fragmentation and improve oxygenation, thereby reducing inflammation and enhancing sleep quality. Special consideration of the use of a suitable interface and its proper hygiene to decrease the risk of infections.[55]

Role of Antibiotic Therapy

Determining the causal agent of CAP is challenging. The American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) 2019 guidelines recommended empirical antibiotic therapy.[56] Regimen choice is based on the patient characteristics, the pneumonia severity index (PSI), the presence of comorbidities, risk of complications, and the clinical decision to hospitalize.[56-58]

OSA may augment PSI scores and lead to hospitalization because associated comorbid conditions necessitate broader antimicrobial coverage.

The ATS/IDSA guidelines for outpatient management recommend regimens that depend on the risk of complications.[56]

Table 2. The summary of the most relevant literature on the association between OSA and LRTIs

Author and date	Design	Total n (OSA n)	Inclusion and exclusion criteria	Outcomes	Key Findings	Limitations
Maas et al.,[13] 2021	Multicentric, retrospective cohort	5544,884 (~44,877)	I: All patient encounters; January to June 2020	COVID-19, hospitalization, respiratory failure.	OSA: ↑ COVID-19, OR: 8.6, ↑ hospitalization, OR: 1.65, ↑ respiratory failure, OR: 1.98	No PSG data, no data on OSA treatment
Cade et al.,[14] 2020	Multicentric, retrospective cohort	4668 (443)	I: Positive COVID-19 PCR; A minimum of two clinical notes, two encounters, and three ICD diagnoses	Mortality, composite (mortality, MV, ICU), hospitalization.	OSA or CPAP not linked with mortality, MV, ICU, and hospitalization	No PSG data, no data on OSA treatment
Chiner et al.,[40] 2016	Single center case-control	123 (85)	I: Cases: Hospitalized for CAP; Controls: Hospitalized for non-respiratory/non-ENT infection. E: Previous OSA diagnosis and CPAP	Pneumonia, PSI	AHI ≥10: ↑ pneumonia OR: 2.86; AHI ≥30: ↑ pneumonia OR: 3.184; AHI positively correlated with PSI	Small sample size, no data on OSA treatment
Keto et al.,[49] 2023	Case-control from Finland	50,648 (25,324)	I: ICD code for OSA. E: OSA in the two years preceding the index date	LRTI, recurring LRTI	↑ LRTI in the year preceding OSA RR: 1.35, and during the year after OSA RR: 1.39	No PSG data, no data on OSA treatment, no BMI data
Girardin et al.,[59] 2021	Retrospective cohort from NYC and LI	4446 (290)	I: Positive COVID-19 PCR	Hospital mortality	OSA not linked to mortality	No PSG data, no data on OSA treatment, no BMI data
Lutsey et al.,[41] 2023	Post-hoc analysis of the multicentric prospective cohort	1586 (772)	I: Valid PSG data; Self-identify as White. E: CSA; Already had the outcome of interest at the time of visit	Hospitalization: with pneumonia; with respiratory infection; with any infection	OSA not linked to outcomes; T90 >5% ↑ hospitalized pneumonia HR: 1.59, ↑ hospitalized respiratory infection HR: 1.53, ↑ hospitalized any infection HR: 1.25	No data on OSA treatment, mostly White population

AHI: apnea-hypopnea index, BMI: body mass index, CAP: community-acquired pneumonia, CA: Canada, CPAP: continuous positive airway pressure, CSA: central sleep apnea E: exclusion criteria, HR: hazard ratio, I: inclusion criteria, ICD: International Classification of Diseases, ICU: intensive care unit, LRTI: lower respiratory tract infection, n: number of subjects included, NYC: New York City, OSA: sleep apnea, PCR: polymerase chain reaction, PSG: polysomnography, ↑: increased risk, (OSA N): number of study participants with obstructive sleep apnea, ~: approximation based on presented data

Patients with chronic comorbidities should be treated with dual therapy combining a beta-lactam anti-pneumococcal agent (cefuroxime or amoxicillin-clavulanate) and either doxycycline or a macrolide (e.g., azithromycin or clarithromycin). Fluoroquinolones (e.g., levofloxacin or moxifloxacin) can be used as monotherapy.

Patients with OSA are at increased risk of pneumococcal and streptococcal pneumonia.[60] Therefore, those patients require a more aggressive approach. The recommendations of the Specific Risks Guiding Empiric Antibiotic Therapy Guideline for regimens of antibiotics for CAP recommend to cover the most common and typical (*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Haemophilus influenzae*) also the atypical pathogens such as (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* species). Furthermore, the CDC recommends specific antiviral therapies for OSA patients with influenza or COVID-19 infection.[56]

Pseudomonas aeruginosa is identified in more than 10% of patients diagnosed with OSA who present with bacterial pneumonia.[40] OSA is associated with several comorbidities[59] that increase the risk of *Pseudomonas* infection. Thus, in severe LRTI cases with one or more associated comorbidities or with OSA, it is advisable to use a fluoroquinolone or an antipseudomonal beta-lactam as early coverage for *Pseudomonas*.[56]

Case reports have documented Legionnaires' disease in OSA patients using CPAP.[61,62] Legionnaires' disease is characterized by neurological disturbances, bradycardia, diarrhea, and hyponatremia.[63] Diagnosis is confirmed by detecting Legionella antigen in urine. Treatment includes respiratory fluoroquinolones.[64]

PREVENTIVE STRATEGIES

Current CDC guidelines recommend pneumococcal vaccination for individuals aged 65 years and older and for patients under 65 years with asthma, COPD, or emphysema.[65] They also recommend annual influenza vaccinations for individuals aged six months or older.[66] COVID-19 vaccinations are advisable in light of new variants.[67,68] We recommend prioritizing patients with OSA for vaccination against these infections.

DISCUSSION

This review highlights the emerging and clinically significant association between OSA and LRTIs. Traditionally, the clinical focus of OSA research has been directed toward cardiovascular, metabolic, and neurocognitive sequelae. However, the accumulating evidence reviewed here suggests that infectious complications —particularly bacterial and viral pneumonias— represent an underrecognized dimension of OSA-related morbidity.

Pathophysiological Insights: The pathophysiological mechanisms outlined in this review support a biologically plausible interplay between OSA and increased LRTIs. Intermittent hypoxia, systemic inflammation, immune dysregulation, impaired mucociliary clearance, microaspiration, and comorbid conditions such as obesity and diabetes converge to create a microenvironment favorable for respiratory pathogens. Importantly, these mechanisms extend beyond simple epidemiological associations, strengthening the argument for causality rather than coincidence. Moreover, the interplay between OSA and gastroesophageal reflux disease (GERD) adds another layer of complexity, as chronic aspiration may act as a critical driver of recurrent infections.

Clinical Evidence: Several cohort and case–control studies reinforce this biological plausibility by demonstrating higher rates of pneumonia and hospitalization among patients with OSA, with evidence of dose–response relationships linked to OSA severity and hypoxic burden. However, heterogeneity across studies should be acknowledged. Some cohort studies suggest an increased risk only in the year before or the year after OSA diagnosis, raising questions about surveillance bias and the role of comorbidities.

Although CPAP therapy improves sleep-related outcomes, observational studies caution that it may increase the risk of aspiration or lead to microbial colonization of equipment, underscoring that therapy can be both preventive and risk-enhancing when hygiene protocols are not strictly followed.

Strengths and Limitations of Current Evidence

The strengths of the available evidence include large-scale population studies, long-term prospective cohorts, and consistent findings across different geographical regions. Nonetheless, several limitations must be considered. First, most studies rely on administrative databases, which may underestimate undiagnosed OSA and introduce misclassification bias. Second, confounding by obesity, smoking, or comorbid cardiopulmonary disease is difficult to eliminate, even with multivariable adjustments. Third, mechanistic studies directly linking OSA-related immune dysfunction to clinical infections remain scarce. Finally, heterogeneity in the definitions of both OSA (AHI thresholds and diagnostic modalities) and LRTIs (clinical versus microbiological confirmation) complicates direct comparisons. A summary of the most relevant studies on the association between OSA and LRTIs is listed in Table 2.

Clinical and Public Health Implications: From a clinical standpoint, recognition of OSA as a risk factor for LRTIs warrants heightened vigilance. Early identification of OSA in patients presenting with recurrent pneumonia, aspiration events, or unexplained severe CAP could guide tailored management strategies. Preventive interventions such as vaccinations (pneumococcal, influenza, and COVID-19), optimization of comorbid conditions, and patient education regarding CPAP hygiene may have additional benefits in reducing infectious morbidity. In the intensive care setting, awareness of OSA may aid in risk stratification for ventilatory support needs, infection risk, and prognosis.

At the public health level, the intersection of two highly prevalent conditions —OSA and LRTIs— magnifies the global burden. In low- and middle-income countries, where OSA remains underdiagnosed and access to diagnostic sleep studies is limited, the potential additive impact of OSA on pneumonia outcomes warrants urgent attention. Screening strategies integrated into primary care and chronic disease management may provide cost-effective opportunities for risk reduction.[69,70]

Future Research Directions: Several important research gaps remain. Future studies should (1) explore biomarkers of OSA-related immune dysfunction (e.g., CRP, IL-6, TNF-α) as predictors of infection risk. (2) Clarify the temporal relationship among OSA onset, diagnosis, and LRTI incidence to disentangle causal pathways from detection bias. (3) Assess the risks and benefits of CPAP therapy in relation to infection outcomes, including prospective studies with microbiome analyses. (4) Investigate whether OSA indices beyond the AHI (e.g., hypoxic burden, sleep fragmentation, nocturnal desaturation) better predict infection susceptibility. (5) Evaluate preventive strategies, including targeted vaccination campaigns and GERD management, among individuals with OSA.

CONCLUSION

The authors conclude that OSA may increase susceptibility to acute LRTIs and the risk of more severe forms of these infections, although there is no clear evidence that it increases pneumonia-related mortality. They emphasize that preventive strategies, such as vaccination and infection control measures, should be considered, particularly for patients with severe OSA.

This review article examines the association between OSA and both acute and chronic LRTIs, including CAP, viral pneumonia (influenza), and COVID-19. It provides a comprehensive synthesis of the existing literature on pathophysiological mechanisms (hypoxia, inflammation, impaired mucociliary clearance, microaspiration, obesity, and comorbidities), epidemiological data, diagnostic approaches, management strategies, and preventive measures.

To our knowledge, there is no indication that a work of this scope and structure has been published previously.

Footnotes

Authorship Contributions

Concept: A.M.E., S.K., Design: A.M.E., S.K., Data Collection or Processing: A.M.E., S.K., Analysis or Interpretation: A.M.E., S.K., Literature Search: S.K., Writing: S.K.

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Research Letter

Temporal Trends in the Use of Pulmonary Function Tests Before, During, and After the COVID-19 Pandemic: Experience from a University Hospital in Türkiye

Mustafa Ersözlü, Deniz Doğan Mülazimoğlu, Miraç Öz Kahya, Öznur Yıldız, Özlem Özdemir Kumbasar

Department of Chest Diseases, Ankara University Faculty of Medicine, Ankara, Türkiye

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The coronavirus disease-2019 (COVID-19) pandemic has disrupted healthcare globally, including diagnostic services.[1] In Türkiye, healthcare restrictions began shortly after March 11, 2020. Pulmonary function test (PFT) use, especially spirometry, declined because of concerns about transmission, which may indicate unmet healthcare needs.[2] The use and quality of PFTs declined during the pandemic due to concerns about infection transmission.[3]

A recent nationwide study by Görek Dilektaşlı et al.[4] highlighted substantial reductions in PFT practices and variability in adherence to safety protocols across Türkiye during the pandemic. We conducted a study reviewing trends in the use of PFTs before, during, and after the COVID-19 pandemic in the outpatient pulmonology clinic of a university hospital.

This retrospective, cross-sectional, single-center study reviewed outpatient visits and the number of PFTs performed at the Ankara University Hospital Chest Diseases Department from May 1, 2019, to December 31, 2024. Data were grouped into pre-pandemic (pre-COV), before the World Health Organization's declaration of the global pandemic on March 11, 2020; pandemic (COV), until the official end of the emergency status on May 31, 2023; and post-pandemic (post-COV), through December 31, 2024. The PFT laboratory data included monthly totals for spirometry, lung volumes measured by the multiple-breath nitrogen washout method and by body plethysmography, and carbon monoxide diffusing capacity. Monthly counts of new COVID-19 cases were extracted from online open data sources.[5] Data were summarized as mean ± standard deviation or median [25th–75th percentiles], with normality assessed by the Shapiro-Wilk test and by visual inspection. ANOVA or Kruskal-Wallis tests were used for comparisons. Statistical analyses were performed using SPSS v27; significance was set at $P < 0.05$.

The mean monthly number of outpatient clinic admissions ($P < 0.001$), the median monthly number of spirometry tests ($P < 0.001$), the median monthly number of diffusing lung capacity measurements ($P < 0.001$), and the mean monthly number of lung volume measurements ($P < 0.001$) all varied significantly. The spirometry-to-outpatient-admission ratio differed significantly ($P < 0.001$), while no significant difference was observed between the pre-COV and post-COV periods ($P = 0.19$) (Table 1). A comparison of the spirometry-to-admission ratio across the periods is illustrated in Figure 1. Trends in cases and healthcare statistics over time are shown in Figure 2.

Corresponding author: Mustafa Ersözlü, MD, e-mail: mersozlu@outlook.com

Table 1. Comparison of the monthly admission and test numbers between periods

	Pre-COV	COV	Post-COV	*P*
Outpatient clinic admissions; mean ± SD	2775±495	2174±817[a]	3173±610[b]	0.001[1]
Spirometry; median [25th–75th percentiles]	751 [595–865][a]	101 [45–345][b]	738 [672–854][a]	<0.001
Diffusing lung capacity; median [25th–75th percentiles]	251 [200–291][a]	145 [79–260][b]	234 [188–273][a]	<0.001
Lung volume measurements; mean ± SD	18±21[a]	34±32[b]	84±59[a]	0.001[1]
Spirometry/outpatient clinic admission (%); median [25th–75th percentiles]	27.1 [26.5–28.9][a]	4.3 [0.2–12.5][b]	24.9 [19–26][a]	<0.001

[1] *P* value for ANOVA test. Other *P* values were obtained from the Kruskal-Wallis test. The same letter in the mean or median values denoted by a, b indicates that there is no statistical difference (*P > 0.05)*
SD: standard deviation, Pre-COV: pre-pandemic period, COV: pandemic period, Post-COV: post-pandemic period

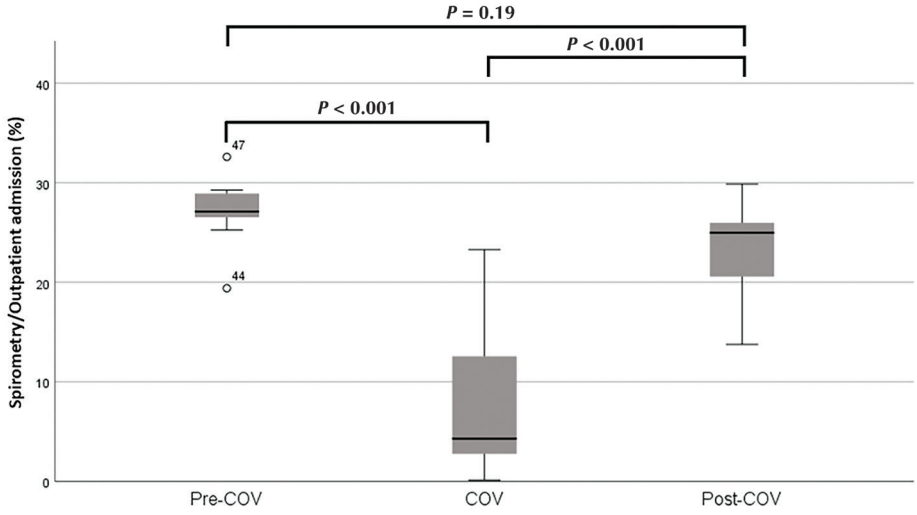

Figure 1. Boxplot of the ratio of spirometry to the number of outpatient admissions between periods

Pre-COV: pre-pandemic period, COV: pandemic period, Post-COV: post-pandemic period

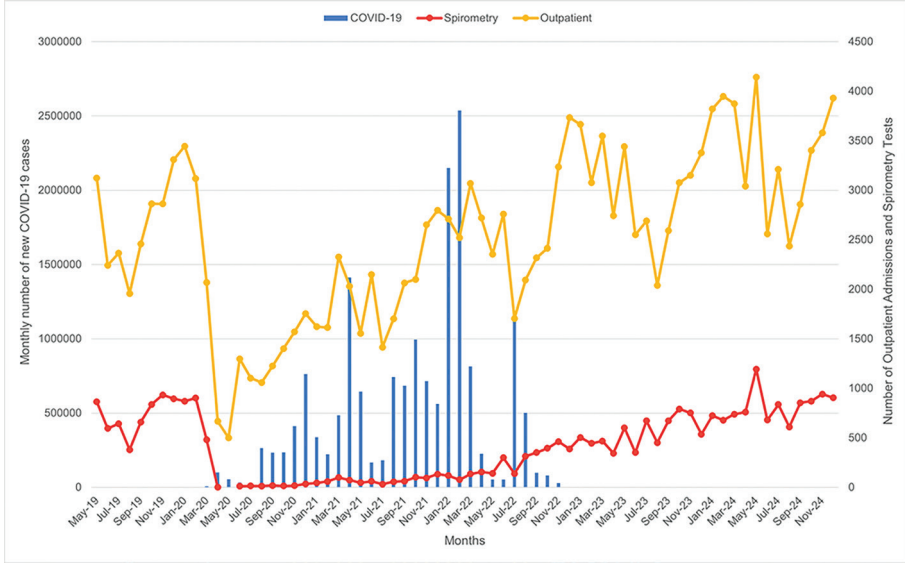

Figure 2. Monthly trends in outpatient admissions (yellow line), spirometry tests performed (red line), and COVID-19 cases (blue bars) between May 2019 and December 2024

COVID-19: coronavirus disease-2019

Our findings demonstrated a reduction in the use of PFTs, consistent with previous studies. One study reported an 88% drop during the pandemic; another study from Türkiye noted fewer spirometry tests in 2021 than in 2019; and a recent study found that 73% of PFT laboratories suspended testing during the first pandemic peak, with some restricting procedures such as diffusing capacity tests.[3,4,6] As recommended in consensus reports, spirometry testing was restricted to reduce the risk of transmission, which likely contributed to this outcome.

Limitations include the single-center design, which limits generalizability, and potential confounders such as seasonal variation. The shorter pre-COV period results from missing data. The data lacked patient characteristics, such as new- or follow-up status, and did not indicate whether follow-ups were missed or diagnoses were delayed.

This study found a slight but comparable decline in PFTs during the post-pandemic period, consistent with previous reports.[3] The relatively modest decline in lung diffusion capacity testing may be explained by its essential role in diagnosing certain diseases, such as interstitial lung disease, and by its link to insurance reimbursement.

In conclusion, spirometry use per outpatient admission declined significantly during the pandemic, while the spirometry-to-visit ratio showed a slight reduction from pre-COV to post-COV. This trend reflects the pandemic's broader impact on healthcare utilization and highlights a potential unmet need. Future efforts should focus on developing safe, resilient testing strategies to ensure continuity of care during public health crises.

Ethics

Ethics Committee Approval: This study was approved by the ethics review boards at Ankara University Faculty of Medicine (decision no: 2025/500, 2025000500-1, approval date: 25.06.2025). The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: The requirement for informed consent was waived due to the retrospective design and use of anonymized, aggregated data.

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Footnotes

Authorship Contributions

Concept: M.E., D.D.M., M.Ö.K., Ö.Y., Ö.Ö.K., Design: M.E., D.D.M., Ö.Ö.K., Data Collection or Processing: M.E., D.D.M., Analysis or Interpretation: M.E., D.D.M., M.Ö.K., Literature Search: M.E., D.D.M., Writing: M.E., D.D.M., M.Ö.K., Ö.Y., Ö.Ö.K.

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