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ABOUT

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Thoracic Research and Practice aims to publish studies of the highest scientific and clinical value, and encourages the submission of high-quality research that advances the understanding and treatment of pulmonary diseases.

Thoracic Research and Practice covers a wide range of topics related to adult and pediatric pulmonary diseases, as well as thoracic imaging, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery, including diagnostic methods, treatment techniques, and prevention strategies. The journal is interested in publishing original research that addresses important clinical questions and advances the understanding and treatment of these conditions. This may include studies on the effectiveness of different treatments, new diagnostic tools or techniques, and novel approaches to preventing or managing pulmonary diseases.

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The target audience of the journal includes healthcare professionals and researchers who are interested in or working in the pulmonary diseases field, and related disciplines.

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Original Article

Pulmonary Function and Diffusing Capacity of Carbon Monoxide in Hypersensitivity Pneumonitis: An Observational Study of 152 Patients

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Abstract

OBJECTIVE: Hypersensitivity pneumonitis (HP) is an inflammatory and/or fibrotic lung disease. The restrictive lung function with low diffusing capacity of carbon monoxide (DLCO) is common in interstitial lung diseases (ILD). There are limited data on pulmonary function test (PFT) in HP and its role for diagnosis is questionable. We analyzed the data of 152 HP patients for type of defect, lung volume, and DLCO.

MATERIAL AND METHODS: The present study is a retrospective analysis of 152 patients at one of the tertiary chest institutes in India. All diagnosed cases with at least spirometry were included. PFT findings were classified and graded as obstructive, restrictive, and mixed patterns. The correlation of PFT was calculated with disease duration and 6MWT distance.

RESULTS: The majority were female [106 (70%)], with a mean age of 47.8 ± 12.3 years. Spirometry with lung volume data were available for 97% patients. PFT was abnormal in 118 (80%) cases. Among the patterns of abnormality, the most common type was restrictive (74%) followed by mixed (15%) and obstructive (11%) with the majority in the severe to very severe grade. The mean total lung capacity (TLC) and residual volume (RV) were reduced, with the grade more severe when the pattern of abnormality was restrictive while the RV/TLC was higher suggestive of air tapping. DLCO data were available for 132 (87%) cases, with levels decreased in 67%. The severity of DLCO was highest when the pattern of abnormality was restrictive. One of the PFT parameters was abnormal in 137 (90%) cases, with isolated decreased DLCO levels seen in 16 (10%) cases. Forced vital capacity (FVC), TLC, and DLCO showed positive correlation with 6MWT distance (FVC $r = .22$, $P = .02$; TLC $r = .28$, $P = .003$; DLCO $r = .30$, $P = .002$).

CONCLUSION: The PFT abnormality is seen in >80% of HP patients. All types of abnormality were seen, with the restrictive pattern being the most common. Isolated decreased DLCO levels were seen in 10% of cases. We advised to do full PFT for diagnosis and follow-up of HP.

KEYWORDS: Hypersensitivity pneumonitis, lung volumes, spirometry, diffusion capacity, pulmonary function test

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INTRODUCTION

Hypersensitivity pneumonitis (HP) is an inflammatory and/or fibrotic lung disease that typically results from an immune-mediated reaction to inhaled antigen in susceptible host.[1] The prevalence of HP varies considerably with geographic location, climatic condition with history of occupational and environmental exposures. As per published data the incidence range 0.3-0.9 per 100 000 in western world.[2,3] There is lack of prevalence study from India however available studies shown HP account for 2.4 to 10.7% of all interstitial lung disease (ILD). As per Indian ILD registry, HP was the most common type of ILD (nearly 47%).[4-7] Till recently there is lack of internationally accepted uniform diagnostic criteria for diagnosis of HP, leads to substantial varies in diagnosis over different region. Recently a Clinical Practice Guideline for diagnosis of HP has been published. The diagnosis is mainly done on basis of exposure to antigen, high-resolution computed tomography (HRCT) finding, bronchoalveolar lavage (BAL) cellular analysis, and lung biopsy findings.[1]

The pulmonary function test (PFT) is a simple, noninvasive test, primarily used to determine the physiologic abnormalities of lung. It is one of the commonly used test for diagnosis and management of ILD. There are limited data on PFT in HP. However the restrictive pattern abnormality with low diffusing capacity of carbon monoxide (DLCO) is the common type.[8-10] The role of PFT in diagnosis of HP is questionable. As the only one of the four proposed diagnostic criteria mentioned restrictive ventilator defect as one of the minor criteria of diagnosis. Similarly the decreased DLCO was also mentioned as minor diagnostic criteria in only 2 criteria.[11-14] Even recent ATS document on HP diagnosis also did not mentioned it.[1,15,16] However, Salisbury et al[16] suggested it for disease monitoring during treatment and follow-up. In the present study, we analyzed the data of PFT in 152 HP patients for type of defect, lung volume, and DLCO.

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MATERIAL AND METHODS

This study was a retrospective analysis of 152 patients, registered in 6 years (2014-2020) at one of the tertiary care chest institute in Delhi, India. The study was done after approval from human ethical committee of V.P. Chest Institute, University of Delhi (Approval No: VPCI/DIR/IHEC/2023/2258, Date: 2023). At the time of registration, all ILD suspected patients underwent a symptom screening with examination. Investigations including routine hematology/biochemical blood tests, sputum examination, connective tissue serology, 6 minute work test (6MWT), PFT with DLCO, chest x-ray, HRCT chest, and bronchoscopy with BAL and bronchial biopsy whenever required. The detailed data of patients in standardized file were available for all the cases as per hospital protocol. The case files of all diagnosed HP patients were screened for PFT including spirometry, lung volumes, and DLCO with 6MWT findings. All diagnosed HP patients with at least spirometry were included in the analysis. Data were extracted and entered in standard research forms. The written consent was taken from all the participants. Finally we included 152 diagnosed cases of HP, who have at least baseline spirometry report with or without other PFT parameters reports for analysis in the study.

Diagnosis of Hypersensitivity Pneumonitis

The diagnosis of HP was done on the basis of a multidisciplinary approach. Diagnosis of HP was considered when the following criteria were present: (1) Exposure history to an inciting antigen, (2) Respiratory symptoms suggestive of ILD, (3) HRCT suggestive of HP, (4) rule out all other known causes of ILDs, (5) TBLB consistent with HP findings, and (6) BAL lymphocytosis (≥30%).

Exposure History

The exposure history to any inciting agent is consider positive when there is a history of exposure for a minimum of 3-6 months at patient's resident or working place. The history of exposure was considered and taken particularly for birds (pigeon, parrot), hay, molds, and occupational dust.

Pulmonary Function Test

Spirometry and lung volume were conducted on a dry, roll-seal spirometer of the Benchmark design lung function machine (P.K. Morgan, Kent, UK). Full expiratory flow volume curves have been produced as suggested by ATS. Forced expiratory volume in the first second of expiration (FEV_1)/Forced vital capacity (FVC) and total lung capacity (TLC) were taken for assessing the obstructive, restrictive, and mixed patterns. FEV_1 was taken for assessing the severity of impairment of lung function and TLC for restrictive severity. The DLCO was performed by helium dilution method with correction with hemoglobin on same machine. The percentage predicted of corrected DLCO was taken for assessing the capacity of CO diffusion. PFT was interpreted as obstructive when FEV_1/FVC was <0.80 with TLC >80% predicted; restrictive when FEV_1/FVC > 0.80 and TLC <80% predicted and mixed pattern defined as coexistence of both types. The severity of lung impairment grading was done as per standard guideline.[17-19]

Main Points

- The pulmonary function test abnormality is a common finding in hypersensitivity pneumonitis subtype interstitial lung disease patients, that is, in >80% of cases.
- The commonest type lung function abnormality on spirometry was the restrictive pattern.
- The severity of abnormality grade was moderately severe to very severe in nearly 60% of cases.
- The isolated decrease in diffusing capacity of carbon monoxide (DLCO) with normal spirometry was seen in nearly 10% of cases.
- The forced vital capacity, total lung capacity, and DLCO showed significant positive correlation with 6MWT distance.

Statistical Analysis

The data accrued on all the HP patients was compiled and analysed using Microsoft Office Excel software. Continuous data is presented as mean with standard deviation or median and interquartile range (due to extreme values) and categorical data is presented as number and percentages. Figures are presented as bar diagram, table, and flowchart. The correlation was calculated between PFT parameters and DLCO with duration of disease and 6MWT distance. $P < .05$ is considered as significant.

RESULTS

The majority of cases were female [106 (70%)], with a mean age of 47.8 ± 12.3 years. The most common occupation was housewife in 79 (51%). Most of patients 136 (89%) were nonsmokers. The most common presenting symptoms were breathlessness 146 (96%) and cough 143 (94%) with median duration symptoms of 18 months. The history of exposure to allergen was present in 116 (76.3%) with pigeon is the most common seen in 103 (67.7%) patients. The details of demographic parameters are given in Table 1.

We analyzed the data of 152 patients, who have at least spirometry report. The PFT including spirometry with lung volume was available for 147 (97%) patients. Out of 147 cases the PFT was normal in 29 (20%) and abnormal in 118 (80%) cases. The most common abnormality was restrictive defect in 87 (59%) followed by mixed 18 (12%) and obstructive 13 (9%) with mean FVC of 1.91 ± 0.76 L, FEV1 of 1.61 ± 0.6lts and TLC of 3.32 ± 1.06 L. In the remaining five cases only spirometry report was available. Of that five spirometry showed 2 cases of normal, 2 cases of restrictive, and 1 case of obstructive pattern. The detail of patients with different PFT and DLCO abnormalities is shown in Figure 1. The overall severity of abnormality was mild in 28 (24%), moderate in 21 (18%), moderately severe in 36 (30%), severe in 26 (22%), and very severe in 7 (6%) (Figure 2). The mean predicted TLC was 70.50 ± 18.14. Overall 132 patients able to performed diffusion capacity with mean predicted of 67.7 ± 28.7.

Out of 118 abnormal PFT, all the parameters of spirometry and lung volumes were decrease except FEV1/FVC and residual volume (RV)/TLC ratio. The most common type of abnormality is restrictive type (74%) followed by mixed (15%) and obstructive (11%). The majority of patient 69 (58%) with abnormal PFT had moderately severe to very severe grade

Table 1. Demographic Details of Patients at Presentation

Patients Characteristics	Patients (n, %)
Total population	152
Female	106 (70%)
Mean age (years)	47.8 ± 12.3
History of smoking	36 (11%)
Median duration of symptom (years)	18
Occupation	
Housemaker	79 (51%)
Office work	14 (9%)
Shopkeeper	11 (7%)
Symptoms	
Breathlessness	146 (96%)
Cough	143 (94%)
Fever	14 (9%)
Exposure	
Pigeon	103 (68%)
Parrot	4 (2%)
Hay	3 (2%)
Mean 6MWT (m)	324 ± 112

of abnormality. The severity of lung function impairment was highest seen in mixed type followed by restrictive and least in obstructive (Figure 1 and Table 2). The forced expiratory flow $(FEF)_{25\%-75\%}$ was reduced in overall patients with mean predicted percentage of 76.4 ± 41.89%. The impairment of $FEF_{25\%-75\%}$ was highest in mixed followed by obstructive pattern and normal in restrictive pattern (Table 2).

About lung volume values, overall the TLC was reduced with a mean predicted% of 65.69 ± 16.40. The severity of reduced lung volumes was more in restrictive than mixed type. However, it was normal in obstructive pattern with mean percentage of 96.53 ± 14.79. The RV was just below normal range with mean predicted% of 78.93 ± 32.82, it was reduced in restrictive pattern, normal in mixed and increase in obstructive. The RV/TLC was higher suggestive of air tapping with overall mean of 40.96%. It was increased in all types. It was highest in obstructive followed by mixed and least in restrictive (Table 2). The severity of restriction on basis of TLC was mild in 21 (24%) moderate in 25 (29%) and severe in 41 (47%) cases.

The DLCO value was available for 132 (87%) cases. Overall the mean predicted% was 64.66 ± 29.93 and decreased in 89/132 (67%) with normal in remaining 43/132 (33%) cases. The severity of DLCO was mild in 21%, moderate in 30% and severe in 16% cases. Out of 132 patients with DLCO report, the other PFT parameters were normal in 28 (21%) and abnormal in 104 (79%) cases. Sixteen patients with normal PFT had decreased DLCO (Figure 1). The severity of decreased DLCO was again also higher in restrictive pattern. The detail of DLCO severity in different types of spirometry pattern is shown in Figure 3. Overall 6MWT report was available in 119 (77%) patients. The mean distance on 6MWT was 324.5 ± 112.8 m with an oxygen desaturation of >4% seen in 70 (59%) patients. The oxygen desaturation was highest in restrictive pattern and the mean duration of distance was lowest in mixed pattern and highest in obstructive pattern.

One of the PFT parameter was abnormal in 137 (90%) cases of HP subtype ILD patients, i.e., either spirometry, lung volume, or diffusion capacity. Even if both spirometry and lung volume were normal, isolated DLCO was decreased in (16/29) 50% cases (Figure 1). We did the correlation of various PFT parameters and DLCO with duration of disease using Pearson's correlation. All the PFT parameters including DLCO did not showed significant correlation with disease duration. We also did the correlation of various PFT parameters and DLCO with 6MWT distance on Pearson's correlation coefficient. The FVC, TLC, and DLCO data showed statistically

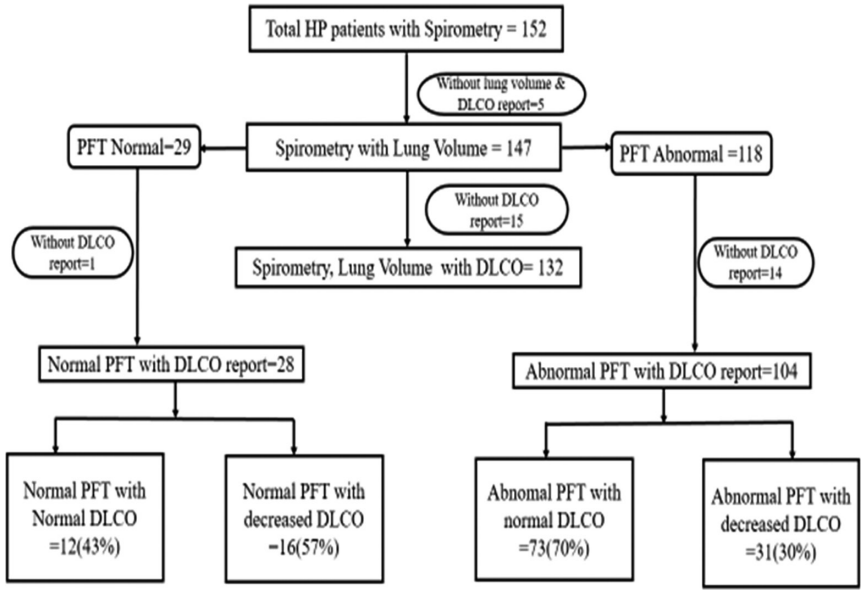


Figure 1. Overall detail flowchart of hypersensitivity pneumonitis patients with different pulmonary function test and diffusing capacity of carbon monoxide findings. HP, hypersensitivity pneumonitis; PFT, pulmonary function test; DLCO, diffusing capacity of carbon monoxide.

Table 2. The Details of Lung Functions Parameters with Various Types of Abnormality Pattern Among Abnormal PFT Patients (n = 118)

Parameter	Obstructive (n = 13)		Restrictive (n = 87)		Mixed (n = 18)		Total (n = 118)	
	Observed Value (Mean)	Pred%(Mean)	Observed Value (Mean)	Pred%(Mean)	Observed Value (Mean)	Pred%(Mean)	Observed Value (Mean)	Pred%(Mean)
FVC	2.41 ± 0.83	79.46 ± 21.20	1.65 ± 0.56	54.21 ± 13.08	1.85 ± 0.73	60.50 ± 14.40	1.76 ± o.66	57.96 ± 16.27
FEV1	1.72 ± 0.60	68.00 ± 18.04	1.47 ± 0.48	57.92 ± 14.37	1.31 ± 61	50.88 ± 16.14	1.47 ± 0.53	57.95 ± 15.56
FEV_1/FVC	72.00 ± 6.49		89.54 ± 4.95		69.22 ± 8.95		84.51 ± 10.30	
$FEF_{25\%-75\%}$	1.52 ± 1.17	46.61 ± 24.42	2.49 ± 0.97	90.66 ± 38.43	0.91 ± 0.59	31.33 ± 17.49	2.13 ± 1.112	76.4 ± 41.89
TLC	4.45 ± 1.10	96.53 ± 14.79	2.80 ± 0.72	60.17 ± 12.08	3.31 ± 0.69	70.11 ± 7.39	3.06 ± 0.92	65.69 ± 16.40
RV	1.97 ± 0.57	128.23 ± 29.45	3.41 ± 20.96	70.49 ± 24.42	1.35 ± 0.39	82.75 ± 25.49	2.95 ± 18.03	78.93 ± 32.82
RV/TLC	44.92 ± 10.16		39.99 ± 10.14		42.72 ± 12.38		40.96 ± 10.55	
DLCO	18.69 ± 6.40	79.08 ± 22.12	14.36 ± 6.18	61.55 ± 23.66	15.59 ± 8.99	67.83 ± 38.40	15.27 ± 6.81	64.66 ± 29.93

DLCO, diffusing capacity of carbon monoxide; FEV1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; PFT, pulmonary function test; RV, residual volume; TLC, total lung capacity.

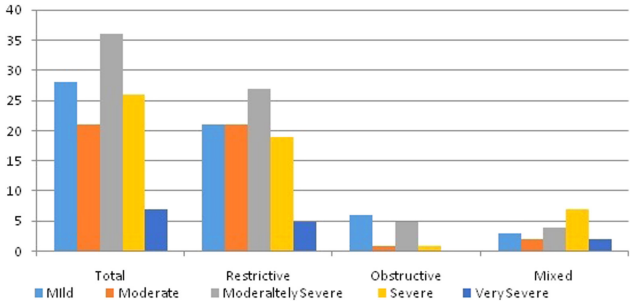


Figure 2. Severity of lung function abnormality with different pulmonary function test patterns.

significant positive correlation with 6MWT distance (FVC r = 0.22 P = .02; TLC r = 0.28 P = .003; DLCO r = 0.30 P = .002)

DISCUSSION

Hypersensitivity pneumonitis is one of the types of ILD. The restrictive type of lung function abnormality with decrease DLCO is one of the characteristics of most of the ILD. Pulmonary function test is commonly used for diagnosis, prognosis, and management follow-up of ILD. There is a lack of published data on PFT in HP subtype of ILD. So the utility of this test in HP is questionable or unclear. Even the recent ATS document on HP diagnosis and Delphi HP diagnostic criteria for chronic HP also did not mentioned it for diagnosis of HP.[1,20] Not only the recent, even all the previous proposed diagnostic criteria for HP also did not mentioned it as a major diagnostic criteria.[11-14] For definitive diagnosis of HP minimum, we need exposure history, HRCT finding with either lung biopsy finding or BAL lymphocytosis.[1,20] The history of exposure difficult to find in all HP suspected as studies had shown that the history of exposure is identified in 50%-70% cases.[16,21] So PFT with typical finding can be considered for diagnosis of HP in cases where the invasive procedure are not possible or refused by patients. Every patient with HP should undergone PFT with DLCO at the time of diagnosis for prognosis and treatment follow-up.

The most common type of lung function defect in ILD is restrictive type in most of the ILDs. In the present study we found that the lung function abnormality was seen in 80% of HP patients. Some available data on PFT in HP also showed that PFT abnormality is common and seen in 75%-90% cases (Table 3).[14,21-24] As early as in 1986 a study of farmer's lung found that the carbon monoxide transfer factor was <80%

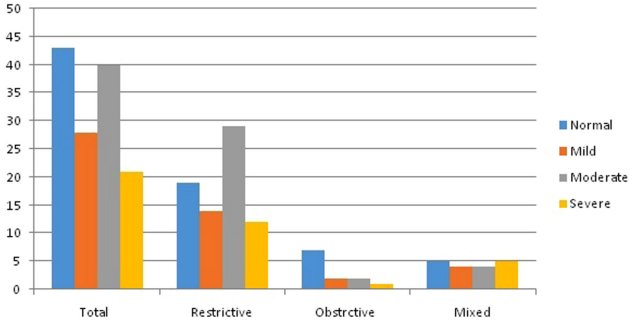


Figure 3. The detail of decreased diffusing capacity of carbon monoxide and diffusing capacity of carbon monoxide levels in different spirometry patterns.

Table 3. Various Studies of HP with PFT Findings

Author	Year	No of patients with PFT	PFT abnormality	TLC	DLCO
Cormier et al[14]	1986	92/94 (98%)	FEV1/FVC normal in all	Decreased 10/76 (13%)	Decreased 27/92 (29%)
Morais et al[22]	2004	92/113 (82%)	Normal 26%, restrictive 63%, obstructive 9%		Decreased 55%
Hanak et al[23]	2007	83/85 (98%)	Normal 8 (10%), restrictive 44 (53%), obstructive 13 (16%) & nonspecific 10 (12%)		Isolated decreased 8 (10%)
Morell et al[24]	2008	78/86 (91%)	Normal 8 (10%), restrictive 60 (77%), obstructive 7 (9%) & Mixed 3 (4%)	Decreased 19/57 (33%)	Decreased 45/53 (85%)
Kumar et al[21]	2020	101/103 (98%)	Normal 23 (23%), restrictive 69 (68%), obstructive 4 (5%) & Mixed 5 (6%)		Decreased78/101 (77%)
Present study	2022	152 (100%)	Normal 29 (20%), restrictive 87 (59%), obstructive 13 (9%) & Mixed 18 (12%)	Decreased 105/147 (71%)	Decreased 47/132 (36%)

predicted in 27/92 (29%) and TLC was <80% predicted in 10/76 (13%) cases with normal mean FEV1/FVC. They also found that the both TLCO and TLC were negatively correlated with the radiographic score.[25] Studies had shown that the PFT can be performed in HP patients. We found that the PFT was totally normal in 20% cases. Similar to our finding, various studies had also shown that the PFT was normal in 10%-25% cases (Table 3). The present study showed that the most common type of defect was restrictive (59%) followed by mixed (12%) and obstructive (9%). Similar to our finding the most common type of abnormality in HP patients was restrictive type seen in 53%-77% cases. The obstructive and mixed types of defect were seen in 5%-15% and 4%-12% cases respectively.[21-25]

Lung volume measurement is an important part of complete lung function test. Ideally restrictive type of defect and its severity should label according to TLC rather than FVC. In the present study the overall lung volume parameters, i.e., TLC and RV were reduced and RV/TLC was increased. There is scarcity of published data on lung volume in HP. An early study of farmer's lung disease patients in 1986 found that the TLC was <80% predicted in 13% cases.[25] Morell et al[24] in a study found that the lung volume measurement was present 57 (73%) cases. They found that the TLC was <80% predicted in 19 (33%) with RV increases in 26% cases.[24] Morais et al[22] in a study of 113 HP patients found that the TLC and RV/TLC impairment were more severe in bird fancier's disease than suberosis patients. Overall the reduced TLC with maintaining of RV and increased RV/TLC is seen in HP patients suggestive of air trapping among this group of patients. However, further larger multicenter studies with all lung parameters and its correlations are needed to confirm of our findings.

The DLCO is one of the important parameters of PFT. The measurement of DLCO is important, as this identify the gas exchange abnormality and involvement of interstitium and parenchyma in the disease. The decreased DLCO is one of the characteristics finding of ILD. However again there is limited published data on HP subtype. Also the procedure is slightly difficult than other as patient needs to hold the breath for at least 10seconds, which is difficult among ILD patients. In the present study the DLCO parameter was available in 132 (87%) cases with decreased in 67%. Various studies reported variable findings of DLCO. Studies reported the decreased DLCO varies from 29%-85% cases in HP subtype.[21,22,24,25] We found that out of 28 normal PFT finding the isolated decreased DLCO seen in 16 cases, which is nearly 10% of total patients. Similar to our finding Hank et al[23] in a study also found that the isolated decreased DLCO in 8 (10%) cases.Another study from same institute also found that the decreased DLCO with normal spirometry in 7% cases.[21] The decreased DLCO is also mentioned as minor diagnostic criteria for HP in two proposed diagnostic criteria.[13-14] The overall various findings of all PFT parameters in various published literature is summarized in Table 3. It is clear from above discussion that the decreased DLCO is common in HP patients. Even with normal lung function parameters the isolated decrease DLCO is seen in nearly 10% cases. This may be the early finding before involvement of airway. This may explained that the early involvement of interstitium with gas exchange abnormality in HP before clinical and other PFT manifestation. However there is need of prospective larger study with all parameters of PFT for further confirmation of this finding.

About strength of study, this is a large sample size study with involved HP subtype of ILD. As per best of our knowledge this is only study primary on lung function test in HP subtype ILD. Another strength of the study is that more than 85% of patients have all the parameters of PFT including lung volume and DLCO.

About the limitation, there are few limitations of this study. The study was retrospective analysis of patient's records from a single center. As the lung volume and DLCO parameters were not available in records of nearly 5%-15% cases. This might be either due to not able to perform the procedure or patient might take their report with them. The author proposed a multicenter, prospective study with follow-up for further confirmation of findings.

The PFT abnormality is common and seen in >80% of cases with the HP subtype ILD. All types of lung function abnormality are seen in HP cases, with the restrictive pattern being the most common type of defect. Isolated decreased DLCO levels are seen in nearly 10% of cases. We advised to do the full PFT in all HP patients for diagnosis and follow-up.

Ethics Committee Approval: This study was approved by Ethics Committee of V.P. Chest Institute, University of Delhi (Approval No: VPCI/DIR/IHEC/2023/2258, Date: 2023).

Informed Consent: The written consent was taken from all the participants. The data was collected from hospital patients' records.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.K., S.S.; Design – R.K., S.S.; Supervision – R.K., S.S.; Resources – R.K., S.S.; Materials – R.K., S.S., P.M.; Data Collection and/or Processing – S.S., P.M., R.N.; Analysis and/or Interpretation – R.K., S.S., P.M., R.N.; Literature Search – R.K., S.S., P.M.; Writing – R.K., S.S., P.M.; Critical Review – R.K., S.S., P.M., R.N.

Declaration of Interests: The authors have no conflict of interest to declare.

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Original Article

Assessing the Prevalence of Pulmonary Embolism and the Clot Burden in Hospitalized Patients with Chronic Obstructive Pulmonary Disease Exacerbation

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Abstract

OBJECTIVE: This prospective cohort study aimed to assess the pulmonary embolism (PE) rate and clot burden in patients with chronic obstructive pulmonary disease (COPD) exacerbation.

MATERIAL AND METHODS: A total of 248 patients entered the study, and their clinical probability of PE was assessed using the Geneva score. Patients with high clinical probability underwent computed tomographic pulmonary angiography, while those with low or intermediate probability underwent a D-dimer test.

RESULTS: Among the patients analyzed, 14 individuals (5.6%) were confirmed to have PE using computed tomographic pulmonary angiography. A 3-month follow-up revealed 3 cases of PE out of 232 patients initially deemed PE-free. Mortality rates were higher among patients with venous thromboembolism at admission than those diagnosed with PE during follow-up. Pulmonary embolism (PE) prevalence among patients with COPD exacerbation was 5.6%.

CONCLUSION: The results of this study show the importance of screening for PE in patients with COPD presenting with dyspnea. Not all of them are due to COPD exacerbation; a small minority of them can be due to PE, which needs prompt screening, confirmation, and therapy. However, further research with larger cohorts is required to understand better the potential benefits and implications of systematic screening for pulmonary embolism in this specific patient population.

KEYWORDS: Qanadli index, embolism, pulmonary CT angiography

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a debilitating respiratory condition characterized by persistent airflow constriction and gradual lung function deterioration. It leads to substantial sickness and loss of life annually. The fatality linked to COPD is impacted by sudden worsening episodes known as acute exacerbations, necessitating alterations in treatment due to sudden respiratory symptom aggravation.[1]

Triggers of these acute COPD exacerbations encompass multiple factors, including bronchial infections and exposure to air pollutants. Intriguingly, several investigations have indicated a notable prevalence of pulmonary embolism occurrences in patients undergoing COPD exacerbations.[2-5] A comprehensive analysis found that approximately 16% of hospitalized patients encountering unexplained acute COPD exacerbations simultaneously suffered from pulmonary embolism. Furthermore, a retrospective assessment disclosed that regardless of the initial suspected cause of exacerbation, pulmonary embolism emerged as the primary cause of fatality in 21% of patients admitted for acute COPD exacerbations.[6,7] The connection between exacerbations of COPD and the occurrence of pulmonary embolism poses a complex clinical situation, given that the symptoms of both conditions can overlap, leading to challenges in diagnosis and possible delays in appropriate treatment. However, determining the most effective approach for screening and diagnosing pulmonary embolism in hospitalized patients experiencing acute COPD exacerbation remains a formidable task. The current diagnostic methods employed for suspected acute pulmonary embolism in the general population might not yield the same results when applied to COPD exacerbations, particularly in the context of ventilation–perfusion lung scans. Furthermore, the clinical manifestations of acute pulmonary embolism and COPD exacerbation exhibit similarities, complicating the decision of whether pulmonary embolism should be considered in this specific clinical scenario.[8,9]

It is crucial to establish the precise frequency of pulmonary embolism among patients undergoing COPD exacerbation in order to enhance patient care and outcomes. This study, conducted with prospective follow-up, aimed primarily to

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determine the prevalence of pulmonary embolism in COPD patients admitted to the hospital due to sudden worsening of respiratory symptoms. Additionally, we aimed to evaluate the extent of clot presence through pulmonary CT angiography.[10,11] Our intention is to raise health-care professionals' awareness about the concealed risk of pulmonary embolism in cases of COPD exacerbations, prompting them to remain vigilant and factor in this potential complication when assessing patients with abruptly deteriorating respiratory symptoms.

MATERIAL AND METHODS

Ethical Review and Study Organization

The Ethics Committee of IAU (Approval number: 9716, Date: July 25, 2017) approved our prospective cohort study. Informed consent was obtained. This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Study Participants

From September 2017 to December 2022, a continuous series of adult outpatients (18 years or older) were enrolled to the teaching hospital due to sudden worsening of respiratory symptoms associated with COPD. To confirm the COPD diagnosis, patients were required to show either previous pulmonary function test results indicating a post-bronchodilator forced expiratory volume in the first second of expiration to forced vital capacity ratio of less than 70%, or a COPD diagnosis previously established by a pulmonologist. The criteria for defining acutely worsening respiratory symptoms in COPD encompassed a sustained deterioration in the patient's typical symptoms (such as dyspnea, cough, and sputum production) beyond the expected day-to-day fluctuations, necessitating an alteration in treatment.

Exclusion criteria consisted of individuals with contraindications for undergoing computed tomographic pulmonary angiography (specifically those with a known allergy to iodine contrast agents), a creatinine clearance level below 30 mL/min/1.73 m² (indicative of severe kidney impairment), pregnancy, hospitalization exceeding 48 hours before inclusion, and anticoagulant therapy administered for reasons unrelated to venous thromboembolism**.**

Pulmonary Embolism Diagnostic Procedure

Patients were enrolled within 48 hours of being admitted to the hospital and categorized based on whether they displayed clinically suggestive symptoms of pulmonary embolism or not, as well as whether an alternative diagnosis more or less likely than pulmonary embolism was established.

The clinical likelihood of pulmonary embolism was evaluated for all patients using the Geneva score.[12] Patients with a high clinical likelihood (defined as a Geneva score ≥11) underwent computed tomographic pulmonary angiography. For patients with a low or moderate clinical likelihood (Geneva score <11), a D-dimer test was conducted and interpreted using the standard threshold of 500 ng/mL, denoted as Fibrinogen Equivalent Units. In cases where the D-dimer test yielded a negative result, the presence of pulmonary embolism was ruled out, and no further testing was conducted.

Follow-up visits were conducted monthly over a period of 3 months to identify any indications of venous thromboembolism.

Pulmonary Computed Tomography Angiography

Chest CT scans were performed using a multidetector CT scanner (Brilliance 64, Philips Medical Systems, Cleveland, Ohio, USA). The scan slice thickness was configured at 1mm with a 0.5 mm increment. For CT angiography, a total of 50ml of iodinated contrast material (Visipaque 320 mm iodine/mL) was administered intravenously, and scans were captured at the end of an inhalation during a single breath-hold. Two radiologists with 14 and 17 years of experience in interpreting thoracic CT scans evaluated the images. These radiologists evaluated the images without access to the patient's medical history, ensuring impartial assessment.

For patients diagnosed with pulmonary embolism (PE), the pulmonary artery obstructive index (Qanadli index) was calculated based on the degree of involvement of pulmonary arterial branches.

The primary objective of the study was to identify cases of pulmonary embolism within the initial 48 hours of admission. Diagnosis of pulmonary embolism was confirmed by detecting the presence of acute thrombosis within the lumen of the pulmonary arterial tree using computed tomographic pulmonary angiography.

A significant secondary outcome concentrated on observing instances of pulmonary embolism during the 3-month tracking period in patients who were initially determined to be free of venous thromboembolism within the first 48 hours of hospital admission.

Statistical Analysis

Descriptive statistics were presented as mean ± SD for continuous variables and as numbers (percentages) for categorical variables. Comparisons between means of continuous variables were conducted using either an independent group *t*-test or the Mann–Whitney U-test. The chi-square test was employed to compare the proportions of categorical variables. The association between quantitative variables was examined using either Pearson's or Spearman's correlation tests. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 22.0 software (IBM Corp., Armonk, NY, USA), with a significance level set at $P < .05$.

Main Points

- The clinical manifestations of acute pulmonary embolism and chronic obstructive pulmonary disease (COPD) exacerbation exhibit similarities, complicating the decision of whether pulmonary embolism should be considered in this specific clinical scenario.
- A total of 5.6% of the patients with the symptoms of COPD exacerbation were diagnosed with pulmonary embolism.
- Mean main pulmonary artery diameter was higher in patients with COPD and pulmonary embolism in the mortality group compared to the survivors.

RESULTS

In the present study, a total of 286 patients with COPD and acutely worsened respiratory symptoms were admitted to the hospital and screened for potential participation. However, 21 patients were excluded from the study due to being on long-term anticoagulation therapy and 17 patients were excluded because of being unable to provide informed consent. Finally, 248 patients entered the study.

The baseline characteristics of the patients are summarized in Table 1. These patients had a mean age of 67.3 years (SD of 10.4 years), and among them, 93 were women (34.0% of the total sample). Based on the Geneva score, out of the 248 patients analyzed in the study, 130 patients (52%) had a low score. Additionally, 112 patients (45%) had an intermediate score, while 6 patients (2%) had a high score (Table 1).

Table 1. Basic Characteristics of Patients

Variables	n (%) (n = 248)
Age, mean (SD), years	67.3 (10.4)
Women	93 (34.0%)
FEV1, % predicted	0.59 (0.95)
FEV1/FVC, %	54 (16.9)
Active tobacco use	223 (89%)
Geneva score	
Low	130 (52%)
Intermediate	112 (45%)
High	6 (2%)
Heart rate >110/min	52 (21%)
Use of accessory inspiratory muscles	49 (20%)
Neurological impairment	10 (4%)
Cyanosis	37 (15%)
Bilateral lower limb edema	69 (27.8%)
Oxygen therapy required	119 (47.9%)

Primary Outcome

Among the 248 patients included in the study, 6 patients (2.4%) were classified as having a high pretest clinical probability according to the Geneva score. Among these 6 patients, pulmonary embolism was confirmed in 4 patients through spiral computed tomographic pulmonary angiography.

For the remaining 242 patients with a low or moderate pretest clinical probability, a D-dimer assay was conducted. Among these patients, 173 individuals had D-dimer levels lower than 500 µg/mL, and pulmonary embolism was considered excluded without further diagnostic work-up. Among the 69 patients with positive D-dimer test results, 68 patients underwent spiral computed tomographic pulmonary angiography. Out of these 68 patients, 10 were confirmed to have pulmonary embolism. In total, among the 248 included patients, pulmonary embolism was confirmed in 14 patients, resulting in a prevalence of 5.6% (95% CI, 4.2%-8.1%) (Figure 1).

Three-Month Follow-up

During the 3-month follow-up period, among the initial 234 patients who were determined to be free of pulmonary embolism, 2 patients were lost to follow-up, leaving a total of 232 patients available for further evaluation. Over the course of the follow-up, 3 out of the remaining 232 patients were diagnosed with pulmonary embolism. The study also disclosed mortality rates for patients with venous thromboembolism (VTE) at admission and those diagnosed with pulmonary embolism during the 3-month follow-up. Among the patients with VTE at admission, the mortality rate was 3 out of 14 patients (25.1%). In contrast, among those patients diagnosed with pulmonary embolism during the follow-up period, 1 out of 3 patients (5.1%) experienced mortality.

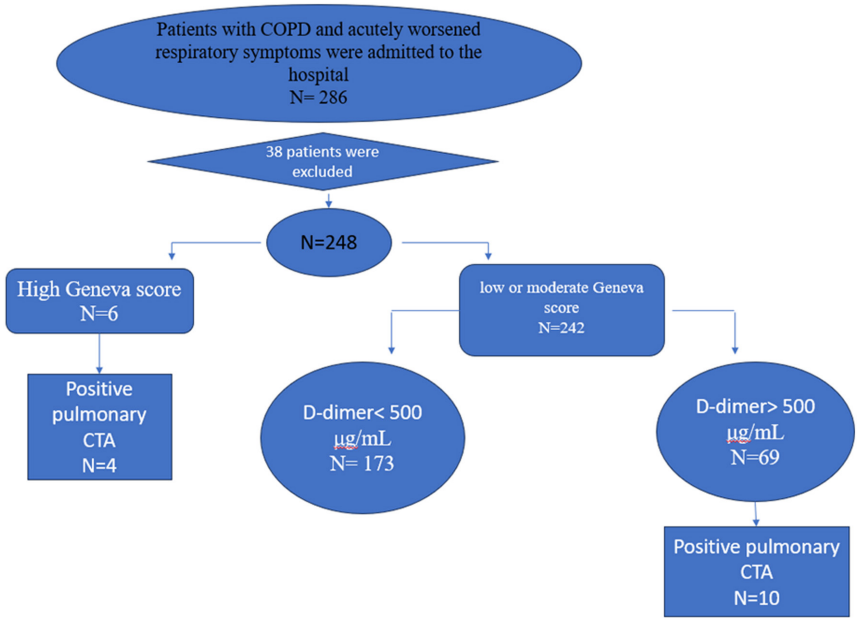


Figure 1. Flowchart showing the patients' entry into the study and their investigation results.

Table 2. Comparison of Quantitative and Qualitative Characteristics of Patients with Pulmonary Embolism Among Subgroups of Mortality and Survivors in Patients with Chronic Obstructive Pulmonary Disease

Object	Mortality Group (n = 4)	COPD Patients with PE Who Survived (n = 13)	*P*
Age, years, median (25-75th percentiles)	64 (61-75)	58 (46-73)	.300
Gender (Male)	2 (50%)	7 (54%)	.484
PAOI	13 (9-24)	4 (2-13)	.002
MPA diameter (mm)	30.5 ± 3.4	26.6 ± 2.6	.003
Aorta diameter (mm)	32.4 ± 3.5	31.3 ± 3.3	.078
MPA/aorta ratio	0.91 ± 0.13	0.65 ± 0.14	.039
Level of thrombosis			
MPA	1 (33%)	0 (0%)	.651
RPA	1 (33%)	0 (0%)	.655
LPA	0 (0%)	0 (0%)	N/A
Lobar artery	2 (66%)	5 (38%)	.093
Segmental artery	3 (100%)	6 (46%)	.225
Subsegmental artery	3 (100%)	2 (15%)	.06

COPD, chronic obstructive pulmonary disease; LPA, left pulmonary artery; MPA, main pulmonary artery; N/A, not applicable; PAOI, pulmonary artery obstruction index; PE, pulmonary embolism; RPA, right pulmonary artery.

Furthermore, the investigation assessed the average pulmonary artery obstruction index (PAOI) based on the Qanadli score in patients with pulmonary embolism. In the patients who suffered mortality, the mean PAOI was 13, while among the survivors, the mean PAOI was 4. This discrepancy was found to have statistical significance, with a *P*-value of 0.002. Similarly, the mean diameter of the main pulmonary artery (MPA) in the mortality group measured 30.5 ± 3.4 mm, which was higher than that of the survivors (26.6 ± 2.6 mm). This difference also exhibited statistical significance, with a *P*-value of 0.003, as indicated in Table 2.

DISCUSSION

This cohort study observed 248 patients with COPD who were hospitalized due to COPD exacerbation. Within 48 hours of their admission, an evaluation was conducted to detect the presence of pulmonary embolism. The findings demonstrated that 5.6% of the patients were diagnosed with pulmonary embolism. Among the initial 234 patients identified as not having venous thromboembolism at the outset of the study, 1.2% of them eventually developed pulmonary embolism.

The prevalence of pulmonary embolism in this specific study (5.6%), focusing on COPD patients admitted to the hospital, was observed to be lower in comparison to a meta-analysis that reported a higher prevalence of 16.1%.[13] This discrepancy could be attributed to the diversity observed across various studies. These variations encompass differences in diagnostic approaches for pulmonary embolism, methodologies used for COPD assessment, and disparities within the study populations.[3]

The utilization of imaging for the assessment of various medical conditions is widely recognized.[14-19] This study stands apart from preceding research due to its distinctive investigation involving pulmonary CT angiography to evaluate clot burden in COPD patients. To the best of our knowledge, this study constitutes the largest cohort analysis aimed at appraising the PAOI in documented COPD patients concurrently affected by PE. A notable strength of this study is its meticulous process for validating instances of pulmonary embolism.[20] The study provides a dependable approximation of pulmonary embolism prevalence within the particular context under scrutiny. The observed prevalence of pulmonary embolism among patients with suspected cases upon admission aligns with rates seen in recent studies encompassing a broader spectrum of outpatients with suspected pulmonary embolism. This concurrence in prevalence implies that the study's findings harmonize with outcomes from earlier investigations conducted among distinct patient groups, thereby fortifying the credibility of the prevalence estimation rendered by this study.[21,22] The study reveals a 4% prevalence of venous thromboembolism (VTE) for patients initially lacking clinical suspicion of pulmonary embolism. This finding underscores the significance of not overlooking VTE as insignificant within this subgroup. As a result, the study prompts a pertinent question concerning the necessity for systematic screening for pulmonary embolism even in patients initially lacking suspicion.[7,23-25] This study has some limitations. First of all, the study has been conducted in only 1 center. Secondly, while the study comprises a large cohort and holds value, it is important to note that generalizations cannot be made. Therefore, it is necessary to conduct a clinical study that would yield higher levels of evidence.

The results of this study show the importance of screening for PE in patients with COPD presenting with dyspnea. Not all of them are due to COPD exacerbation; a small minority of them can be due to PE, which needs prompt screening, confirmation, and therapy. However, further research with larger

cohorts is required to understand better the potential benefits and implications of systematic screening for pulmonary embolism in this specific patient population.

Ethics Committee Approval: The study was approved by the medical ethics committee of IAU (Approval No: 97169716, Date: July 25, 2017). This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.A., Z.N.; Design – Z.N., M.A.; Supervision – M.A., M.G.; Resources – M.A., Z.N.; Materials – M.A., M.G.; Data Collection and or Processing – M.A., M.G.; Analysis and/or Interpretation – A.S.; Literature Search – M.A., M.G.; Writing – N.A., Z.N.; Critical Review – M.A., M.G.

Declaration of Interests: The authors have no conflict of interest to declare.

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Original Article

Tocilizumab Reduces Lung Injury in a Rat Lung Ischemia and Reperfusion Model

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Abstract

OBJECTIVE: In this study, the effect of tocilizumab (TCZ) on lung tissue in lung ischemia–reperfusion (I/R) injury in rats was investigated.

MATERIAL AND METHODS: A total of 24 Wistar rats were divided into 4 equal groups, with 6 rats in each group: Left lung I/R was applied to I/R groups. In the I/R groups, the left lung hilum was clamped for 45 minutes, and then the clamp was removed and reperfused for 120 minutes. In the TCZ groups, 4 mg/kg and 8 mg/kg of TCZ were administered intraperitoneally to the rats 30 minutes before surgery.

RESULTS: The tumor necrosis factor-alpha mean value was not statistically significant between the groups (P = .091). Statistically significant results were observed between group I/R-TCZ (8 mg/kg) and group I/R for catalase. (P = .005). Statistically significant results were observed between group I/R-TCZ (8 mg/kg) and group I/R for malondialdehyde. (P = .009). The difference in total ischemia score between group I/R-TCZ (4 mg/kg) and group I/R-TCZ (8 mg/kg) and group I/R was statistically significant (P < .001). In terms of alveolar hemorrhage, there was a statistically significant difference between group I/R-TCZ (4 mg/kg) and group I/R-TCZ (8 mg/kg) and group I/R (P = .01 and P = .002, respectively). There was a statistically significant difference between group I/R-TCZ (8 mg/kg) and group I/R in terms of neutrophil accumulation (P = .01). In terms of interstitial edema, there was a statistically significant difference between group I/R-TCZ (4 mg/kg) and group I/R-TCZ (8 mg/kg) and group I/R (P = .006 and P = .001, respectively). In terms of pulmonary edema, there was a statistically significant difference between group I/R-TCZ (4 mg/kg) and group I/R-TCZ (8 mg/kg) and group I/R (P = .01 and P = .009, respectively).

CONCLUSION: Lung tissue may be affected by I/R injury and this damage can be reversed with the use of TCZ.

KEYWORDS: Ischemia/reperfusion, interleukin 6 blocker, lung, rat, tocilizumab

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INTRODUCTION

Ischemia–reperfusion (I/R) injury in the lung occurs frequently in cardiopulmonary bypass, pulmonary thromboendarterectomy, lung cancer operations, and lung transplantation. Various signs of damage occur in the tissue during the reperfusion period, which occurs with blood supply in the tissue after ischemia.[1-3] This process is called "reperfusion injury." The concept of reperfusion injury was first introduced by Buckberg and later by Braunwald et al.[4] Pulmonary edema after reperfusion, changes in vascular balance due to the exposure of endothelial cells to ischemia–reperfusion, decreased nitric oxide during reperfusion, vascular dysfunction due to cyclic guanosine monophosphate levels, impaired coagulation, vascular permeability, vasomotor tone, leukocyte adhesion, and aggregation increase in function is the most important problem encountered.[4-9]

Tocilizumab (TCZ) is an agent that acts as an interleukin 6 (IL-6) monoclonal antagonist and is used in some autoimmune diseases such as rheumatoid arthritis, juvenile idiopathic arthritis, and giant cell arteritis.[7] Interleukin 6 induces the proliferation and differentiation of T cells as well as terminal differentiation of B cells, including autoantibody-producing cells. Increased IL-6 production also increases autoimmune reactions. Transforming growth factor beta (TGF-β), in the presence of IL-6, was reported to induce the differentiation of pathogenic T helper cells.[8] Tocilizumab has recently emerged as a drug with significant benefits in clinical recovery in severe coronavirus disease 2019 (COVID-19) pneumonia. A study conducted in China on 21 patients with severe COVID-19 pneumonia reported that TCZ treatment had significant clinical benefits. The pathogenesis of severe respiratory failure associated with coronavirus, elevated serum proinflammatory cytokines and chemokines [interleukins 1, 6, 8, and 12 (IL-1, IL-6, IL-8, IL-12), tumor necrosis factor alpha (TNF-α), and interferon gamma] is associated with a cytokine storm. The treatment dose can start with 4 mg/kg and be increased up to 8 mg/kg.[10-12]

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This study aimed to investigate the effectiveness of TCZ in reducing oxidative damage due to lung I/R injury.

MATERIAL AND METHODS

Twenty-four Wistar albino male rats (250 mg ± 25 mg) were used in the study. This experimental study was conducted at İstanbul Bezmialem Foundation University Experimental Medicine Research and Application Center Experimental Animals Laboratory on December 15, 2021. Approval was obtained from the İstanbul Bezmialem Foundation University Experimental Medicine Research and Application Center Experimental Animals Ethics Committee (2021/240). All rats were cared for in accordance with the Principles of Care for Experimental Animals as formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals, prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health.

Groups

The subjects were divided into 4 groups, each of which had 6 rats. In group Sham, only thoracotomy was performed. In group I/R, thoracotomy was performed and an I/R period was performed. Tocilizumab was applied before ischemia–reperfusion in group I/R/4 mg/kg TCZ and group I/R/8 mg/kg TCZ groups. The rats underwent 45 minutes of ischemia and 120 minutes of reperfusion. Tocilizumab (Actemra) was given intraperitoneally (i.p.) 30 minutes before ischemia. After ischemia, the thorax was closed with sutures. At the end of the experiment, the experimental animals were sacrificed by administering a high dose (150 mg/kg ketamine/30 mg/kg xylazine) of anesthetic substance i.p. The left lung tissue was fixed in 10% formaldehyde and subjected to pathological examination. A blood sample was taken from the heart for biochemical study.

Anesthesia and Surgery

All procedures were performed under sterile conditions. The animals were kept in standard laboratory cages under standard conditions (12 hour light–12 hour darkness cycle). Anesthesia was provided intraperitoneally with 50 mg/kg ketamine (Ketalar vial, Pfizer Pharma GMBH, Germany) and 10 mg/kg xylazine hydrochloride (Alfazyne 2%, Alfasan International, Holland). When necessary, ketamine (half dose, 25 mg/kg) was repeated in order to keep the depth of anesthesia constant, by looking at reflex responses (painful stimulus to the foot with forceps-pedal reflex). Heparin (50 IU) and 0.01 mg atropine were given by IP to the rats before thoracotomy. After the tracheostomy was opened, the patient was mechanically ventilated with a tidal volume of 10 mL/kg, a respiratory frequency of 70 respirations/minute, a peep pressure of 2 cm H_2O, and 100% O_2. Arterial monitoring was performed from the right carotid artery. Drugs were administered i.p. 30 minutes before ischemia. After thoracotomy, the thorax was explored and the inferior ligament was freed by cutting, and the left lung was laterally retracted to expose the left hilar structures. Hilar ischemia was applied.

Main Points

- Ischemia–reperfusion (I/R) injury in the lung occurs frequently in cardiopulmonary bypass, pulmonary thromboendarterectomy, lung cancer operations, and lung transplantation.
- Tocilizumab (TCZ) is an agent that acts as an IL-6 monoclonal antagonist and has recently come to the fore as a drug with significant benefits in clinical recovery in severe coronavirus disease-19 pneumonia.
- Histopathologically poor results due to increased inflammation and oxidative stress after I/R were significantly reversed with TCZ.
- A statistically significant decrease was observed in the blood biochemically measured malondialdehyde and catalase levels in the 8 mg/kg group compared to the I/R group.

Histopathological Examination

After blood samples were taken, samples were taken from the lung tissue.[4-6] Samples were evaluated blindly under a light microscope by a pathologist experienced in cytology. Left lung samples taken from all groups were fixed in 10% formol and underwent routine follow-up procedures. Serial sections of 4 µm thickness were taken from the tissues embedded in paraffin blocks. Sections taken were deparaffinized, stained with hematoxylin–eosin (H-E), and evaluated under a light microscope. The scoring system previously used by Tassiopoulos and Zhou et al was modified to determine the amount of damage in the lungs. Accordingly, 0 points indicate no change; 1 point indicate focal slight changes; 2 points indicate multifocal moderate changes; 3 points indicate diffuse marked changes; 4 points indicate very heavy changes. The tissue damage score was calculated by summing the scores of 4 indexes (perivascular edema, interstitial edema, neutrophil infiltration, and intra-alveolar hemorrhage).

Biochemical Examination

Blood samples from the rats were taken from the heart just before sacrificing.[4-6] Blood samples stored at −80°C were homogenized in phosphate buffer (PBS, 0.01 M, pH 7.4). The homogenate was centrifuged at 1600 *g* for 10 minutes. Malondialdehyde (MDA) and thiobarbituric acid (TBA) composition levels (nmol/milliliter) (µmol), which show lipid peroxidation, were measured by colorimetric method using TBARS Assay kit (Cayman Chemical, Item No: 10009055). Tumor necrosis factor alpha levels (pg/mL) were measured by sandwich ELISA principle using rat TNF-α ELISA Kit (Elabscience Biotechnology Inc., Catalog No: E-EL-R0019). Results are nmol/min catalase (CAT) per milligram (mg) protein (nmol/mg) and nmol MDA composition per milligram (mg) protein (nmol/mg), picogram per milligram (mg) protein (pg) TNF-α (pg/mg). Again, with the measurement methods and kits mentioned above, CAT activity (nmol/mL), MDA (nmol/mL), and TNF-α levels (pg/mL) were measured.

Statistical Analysis

The effect size was taken as 0.0755 and the sample size required to determine the difference between the 4 groups with the help of G-Power 3.1.9.7, was determined by taking a total of 24 rats with .05 type 1 error and a power of 0.70. The data obtained in the experiment were analyzed using the Statistical Package for the Social Sciences 20.0 program for

Windows (IBM Corp., Armonk, NY, USA). One-way ANOVA was used for parameters where the data met the normality assumption for multiple analyses. When the assumption of normality was not met, the Kruskal–Wallis test was used and values with $P < 0.05$ were considered statistically significant. In cases where there was a statistically significant difference between the groups, TUKEY, one of the Post Hoc analyses for normal distribution data, and Tammahane's T2 analysis for non-normally distributed data, were used to examine which group caused the difference between the groups. The Shapiro–Wilk test was analyzed because the sample size was less than 30. Since the CAT and MDA values followed a normal distribution, parametric analyses were performed for these data, while nonparametric analyses were performed for other data that did not normally distributed.

RESULTS

Tumor necrosis factor alpha mean value in the blood was higher in group I/R than in group Sham ($P = < .001$). The mean value for TNF-α in group Sham was 8.6 pg/mL. TNF-α mean value was decreased in group I/R-TCZ 4 mg/kg (57.5 pg/mL) and group I/R-TCZ 8 mg/kg (55.2 pg/mL) compared to group I/R (65.2 pg/mL). However, the difference in TNF-α value was not statistically significant between the groups ($P = 0.091$). Box plot for TNF-α is shown in Figure 1.

Catalase mean value in the blood was higher in group I/R (7.39 nmol/mL) than in group Sham (3.82 nmol/mL). Catalase mean value was decreased in group I/R-TCZ 4 mg/kg (6.50 nmol/mL) and group I/R-TCZ 8 mg/kg (5.54 nmol/mL) compared to group I/R.Statistically significant results were also observed between group I/R-TCZ 8 mg/kg and group I/R for CAT ($P = .005$). There was a statistically significant difference between group Sham and group I/R ($P < .001$). No statistically significant result was observed between group I/R-TCZ 4 mg/kg and group I/R ($P = .268$). The box plot for CAT is shown in Figure 2.

The blood MDA level was higher in group I/R (5.60 nmol/mL) than group S (3.09 nmol/mL). MDA mean value was decreased in group I/R-TCZ 4 mg/kg (4.78 nmol/mL) and group I/R-TCZ 8 mg/kg (4.15 nmol/mL) compared to group I/R (5.60 nmol/mL). Statistically significant results were also observed between group I/R-TCZ 8 mg/kg and group I/R for

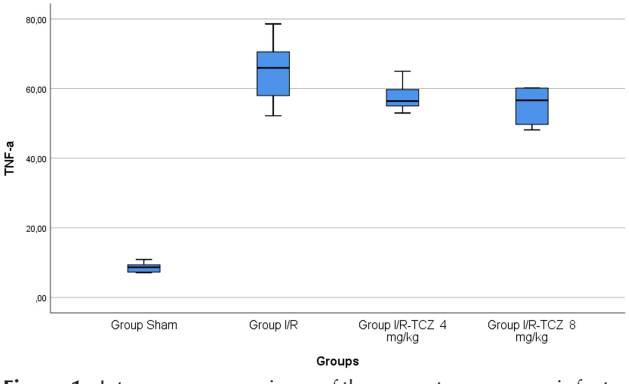


Figure 1. Intergroup comparisons of the serum tumor necrosis factor alpha (TNF-α) levels. Mann–Whitney *U*-test was used to determine statistical differences between groups and $P < .05$ was considered significant. The difference in TNF-α value was not statistically significant between the groups ($P = .091$).

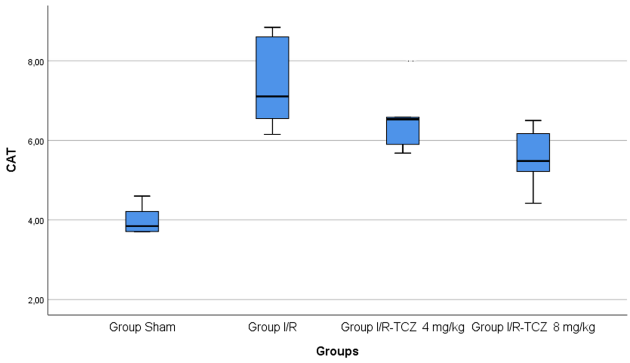


Figure 2. Intergroup comparisons of the serum catalase (CAT) levels. The Mann–Whitney *U*-test was used to determine statistical differences between groups and $P < .05$ was considered significant. Statistically significant results were also observed between group I/R-TZM 8 mg/kg and group I/R for CAT ($P = .005$).

MDA ($P = .009$). There was a statistically significant difference between group Sham and group I/R ($P < .001$). No statistically significant result was observed between group I/R-TCZ 4 mg/kg and group I/R ($P = .217$). The box plot for MDA is shown in Figure 3.

The difference in total ischemia score between group I/R-TCZ 4 mg/kg and group I/R-TCZ 8 mg/kg and group I/R was statistically significant ($P < .001$). In terms of alveolar hemorrhage, there was a statistically significant difference between group I/R-TCZ 4 mg/kg and group I/R-TCZ 8 mg/kg and group I/R ($P = .01$ and $P = .002$, respectively). There was a statistically significant difference between group I/R-TCZ 8 mg/kg and group I/R in terms of neutrophil accumulation ($P = 0.01$). In terms of interstitial edema, there was a statistically significant difference between group I/R-TCZ 4 mg/kg and group I/R-TCZ 8 mg/kg and group I/R ($P = .006$ and $P = .001$, respectively). In terms of pulmonary edema, there was a statistically significant difference between group I/R-TCZ 4 mg/kg and group I/R-TCZ 8 mg/kg and group I/R ($P = .01$ and $P = .009$, respectively).

Histopathological changes of the lung tissue are shown in Figure 4. Lung sections of group Sham stained with H-E showed a normal alveolar histological structure. No infiltration was observed, and alveolar structure was normal

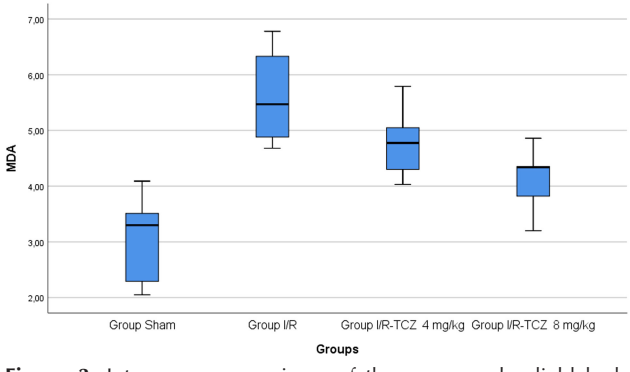


Figure 3. Intergroup comparisons of the serum malondialdehyde (MDA) levels were determined using the Mann–Whitney *U*-test was used to determine statistical differences between groups and $P < .05$ was considered significant. Statistically significant results were also observed between group I/R-TZM 8 mg/kg and group I/R for MDA ($P = .009$).

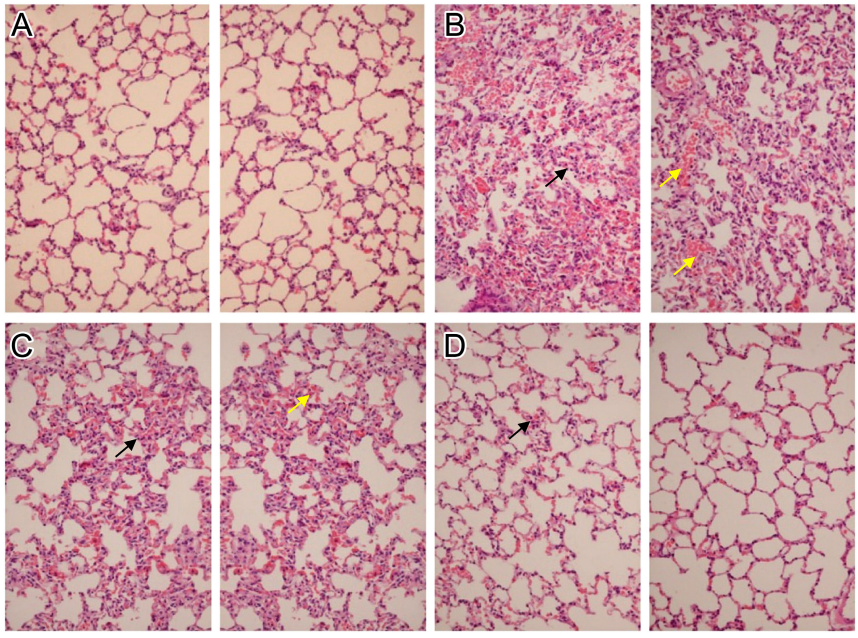


Figure 4. Lung tissue preparations, hematoxylin–eosin (×40; ×100; ×400): (A) Normal lung tissue parenchyma; group Sham; (B) Intense neutrophil infiltration and alveolar hemorrhage, alveolar edema in lung tissue, group I/R (black arrow: neutrophils, yellow arrow: erythrocytes); (C) Neutrophil infiltration, alveolar hemorrhage, alveolar edema, and hemorrhage in group I/R-4 mg/kg TZM (black arrow: neutrophils, yellow arrow: erythrocytes); (D) Neutrophil infiltration, alveolar hemorrhage, alveolar edema, and decreased hemorrhage in group I/R-8 mg/kg TZM (black arrow: neutrophils).

(Figure 4A). However, neutrophil infiltration, alveolar edema, and hemorrhage were present in lung sections on I/R (Figure 4B). Dense neutrophil infiltrates were shown, and alveolar edema, and hemorrhage were severely increased. A decrease in histological changes was observed in group I/R-TCZ 4 mg/kg and group I/R-TCZ 8 mg/kg compared to group I/R (Figure 4C and Figure 4D).

DISCUSSION

In this study, we investigated the extent to which TCZ applied before lung IR prevented histopathological changes in lung tissue. In our study, we observed a significant improvement in I/R-related damage in rats using TCZ, depending on the dose, at the histopathological level.

I/R injury is characterized by the accumulation of free oxygen radicals [Reactive oxygen species (ROS)], endothelial cell damage, increased vascular permeability, activation of the cytokine and complement system in parallel with the increase in neutrophil and platelet cell accumulation.[7,9,13] Acute lung injury in critically ill patients can occur after cardiopulmonary bypass and lung transplantation. Tissue damage occurs especially during the reperfusion period, and it has been observed that this period causes more damage than ischemia. This condition is called I/R or reperfusion injury. This process is a complex pathophysiological process in which vascular, humoral, and cellular factors interact. In the I/R period, microcirculation is also damaged, blood flow homogeneity is impaired, and local tissue damage may occur. Many studies are carried out to prevent the increase in mortality and morbidity resulting from I/R injury.[14-17]

Tocilizumab is a monoclonal IL-6 membrane receptor antagonist that competes selectively and blocks the dimerization of the glycoprotein 130 molecule in the cell membrane and IL-6 signal transmission into the cell. In vivo, the maximum (>90%) saturation saturation of the IL-6 receptor is reached at a serum TCZ concentration >1 µg/mL. At a dose of 4 ug/mL, complete inhibition of the receptors occurs.[11] Its half-life varies depending on the murine antibodies present in the human body and can be up to 240 hours after 3 doses of 8 mg/kg TCZ. Tocilizumab is dose-dependent, has nonlinear pharmacokinetics, and has a long half-life. Free TCZ can be detected in the blood.[10] It has clinical use at doses of 4 and 8 mg/kg. In our study, we used the same doses of drugs that are used clinically. There is a dose-dependent relationship between TCZ therapy and a decrease in neutrophil levels.[11] Interleukin 6 is associated with the pathogenesis of inflammatory diseases such as rheumatoid arthritis and induces the production of some mediators such as CRP. Interleukin 6 is produced from various types of cells in immunological, traumatic, and infection conditions. Interleukin 6 has pro-inflammatory and anti-inflammatory properties in the disease process.[11,12] By accelerating the transformation of T cells and B cells, it provides the expansion and activation of inflammation. Inhibition of the IL-6 receptor results in suppression of cytokine signaling. Inhibition of the IL-6 receptor complex inhibits cytokine generation from B and T lymphocytes via IL-6.

Karataş et al[15] found that 4 mg/kg TCZ administered in spinal cord ischemia had a neuroprotective effect, and the levels of TNF-α, IL-6, IL-10, whose levels were increased in the IR group, decreased significantly in rats given TCZ. They showed that the scores of histopathological symptoms such as neutrophil vacuolization, Nissl bodies, and tissue loss in the ischemia group were significantly lower in those who received TCZ.[15] Wang et al[9] showed that 8 mg/kg TCZ inhibited neuronal cell apoptosis in the hippocampus and cortex

in a rat model of cerebral infarction. In this study, antioxidant enzyme levels such as MDA, TNF-α, and CAT, which are indicators of reperfusion injury, were found to be lower in the I/R + TCZ group than in the I/R group, indicating the free radical scavenging effect of TCZ. Additionally, the decrease in inflammation and degeneration of the lung tissue in the histopathological examination of the lung tissue in the I/R + TCZ group supports the protective effect of TCZ against the reperfusion injury caused by I/R in the lung tissue. In our study, supporting these 2 studies, MDA and CAT levels showed a statistically significant decrease in group I/R-TCZ 8 mg/kg compared to the I/R group.

The release of cytokines and chemokines such as IL-6, IL-1, granulocyte–macrophage colony stimulating factor, and TNF-α from pneumocytes and other cells increases due to COVID-19 increases. Due to the release of these cytokines and chemokines, acute respiratory distress and respiratory failure occur due to increased vascular permeability and exudation in the lung alveoli.[11] Proinflammatory cytokines and IL-6 play a pivotal role in the development of many COVID-19-related complications. A 2.9 times higher concentration of IL-6 was observed in severe COVID-19 patients than in uncomplicated patients.[11] Therefore, a decrease was observed in the length of hospital stay and mortality rates after the use of TCZ in COVID-19 patients. Tocilizumab has been increasingly used in COVID-19 patients. Although the TNF-α level was not statistically significant in our study, it showed a decrease in the mean value depending on the dose in the groups given TCZ compared to group I/R.

Enzymes such as superoxide dismutase, CAT, and glutathione peroxidase play an important role in preventing tissue damage due to ROS, which is important in the pathophysiology of I/R injury. The antioxidant enzyme group, oxidoreductases, plays an important role in scavenging of free radicals and maintaining the cellular structure.[2,13,16] Catalase is one of these enzymes. Studies have shown an increase in I/R groups due to the oxidant mechanism compared to the control group. In the study by Orhan et al,[2] a decrease in the CAT level was observed in the I/R group compared to the control group, and this decrease was more prominent than in the amantadine group.[2] In our study, the CAT level was statistically significantly decreased in the group given 8 mg/kg TCZ compared to group I/R.

In IR, free oxygen radicals appear after lipid peroxidation as a result of high activity in the cell membrane. These radicals cause damage to the cell's deoxyribonucleic acid, protein, and cellular lipid structure. Malondialdehyde level is thought to be an indicator of lipid peroxidation of radicals.[17,18] In previous studies, it was shown that MDA level increased after IR and decreased in cases where agents were administered.[7,18] Orhan et al[2] found that the lung tissue MDA level, which increased in the lower extremity IR, decreased in their group in rats given amantadine. Malondialdehyde is a product of lipid peroxidation and its production increases in parallel with the formation of free oxygen radicals. Malondialdehyde levels are a very good indicator of the level of oxidative stress.[17,19] In our study, the MDA level was statistically significantly decreased in the group given 8 mg/kg TCZ compared to group I/R.

Lung IR can occur as a result of trauma, atherosclerosis, pulmonary embolism, surgery, and cardiopulmonary bypass. The mechanism of I/R damage in the pulmonary parenchyma is similar to the damage in other organs. The ROS system is activated, intracellular calcium increases, endothelial cell damage occurs, leukocyte accumulation increases in the pulmonary circulation, and as a result, the complement system is activated and arachidonic acid metabolites are released into the circulation. Basically, hydrostatic pressure increases in postcapillary venules, and edema formation occurs with increased capillary permeability due to endothelial damage. ROS and other free radicals play a key role in the development of pulmonary damage. Intracellular ROS accumulation has been demonstrated in lung endothelial cells, alveolar type 2, Clara cell, ciliated epithelial cells, and alveolar macrophage cells and alveolar macrophage cells.[13,14,18] Histopathological indicators of lung injury are alveolar wall thickening, interstitial edema, neutrophil, and lymphocyte infiltration. An increase in extravascular albumin accumulation was observed after 30 and 45 minutes of ischemia.[7] Vascular abnormality causes pulmonary hypertension, vascular reality variability, vascular obstruction, intrapulmonary shunt, increased vascular permeability, and ventilation/perfusion change.[17] In our study, an increase in perivascular edema, interstitial edema, and alveolar hemorrhage was observed in group I/R compared to the control group. In these parameters, a dose-related improvement was found in the TCZ groups.

In the study of Eppinger et al,[12] lung reperfusion injury showed a biphasic picture at 30 minutes and 4 hours.[9] In this study, 30 minutes, 1 hour, 2 hours, and 4 hours reperfusion periods were compared after 90 minutes of Lung IR. After 2 hours of reperfusion, an increase was observed in MPO, complement activity, TNF-α mRNA level, and lung permeability.[16] In our study, an increase in lung permeability and TNF-α levels was observed as a result of a 2-hour reperfusion in parallel with the results of Eppinger et al.[12]

Due to the direct contact of the lung with the external environment, it is in the largest reservoir of macrophages, monocytes, and leukocytes. As a result of reperfusion and reexpansion, lipid mediators, polypeptide mediators, and immune complexes increase in the environment. Due to these increased mediators, dysfunction occurs in endothelial cells and monocytes, PNL and macrophages enter the alveolar–capillary membrane. These blood cells that come to the environment initiate a series of reactions that cause the formation of superoxide radical.[9,14] In our study, leukocyte accumulation, which was clearly observed in the tissue in group I/R, showed a dose-dependent decrease in the TCZ groups.

The limited number of animals and our application of clamping not only to the pulmonary artery but also to the hilum in the lung are the limitations of our study. This can limit your statistical power.

In this study, we showed for the first time in the literature that the antioxidant activity of TCZ in lung I/R is particularly evident in histopathological improvement. Histopathologically poor results due to increased inflammation and oxidative stress after I/R were significantly reversed with TCZ. A statistically significant decrease was observed in the blood

biochemically measured MDA and CAT levels in the 8 mg/kg group compared to the I/R group. Future studies will add to the possibility of clinical use of the drug.

Ethics Committee Approval: This study was approved by the İstanbul Bezmialem Experimental Medicine Research and Application Center Experimental Animals Ethics Committee (2021/240).

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Author Contributions: Concept – Y.Ö.; Design – Y.Ö.; Supervision – Y.Ö.; Resources – Y.Ö.; Materials – Y.Ö., R.I., B.O., B.B.İ., T.Ö., Ş.A., B.Ö.; Data Collection and/or Processing – Y.Ö., R.I., B.O., B.B.İ., T.Ö., Ş.A., B.Ö.; Analysis and/or Interpretation – Y.Ö., R.I., B.O., B.B.İ., Ş.A., B.Ö.; Literature Search – Y.Ö.; Writing – Y.Ö.; Critical Review – Y.Ö.

Declaration of Interests: The authors have no conflict of interest to declare.

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Original Article

Influential Factors of Tuberculosis Notification Rates in Turkey: A Provincial-Level Spatial Analysis

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Abstract

OBJECTIVE: The total annual count of reported tuberculosis (TB) cases continues to decline throughout Turkey. Recognizing the regions with high and low burdens and revealing the factors affecting TB notification rates may play a role in guiding national control programs. This study aimed to analyze the spatial distribution of TB notification rates from 2005 to 2018 and evaluate the factors contributing to TB rates.

MATERIAL AND METHODS: In this ecological study, we used freely available open data from the Internet. We employed global and local spatial autocorrelation analysis to identify the spatial distribution and the clusters with low and high burdens. We conducted an ordinary least square regression model, spatial lag model, and spatial error model. The best-fitting model was selected via model parameters.

RESULTS: Throughout the study period, the provinces in West Marmara Region (Edirne, Kırklareli, Tekirdağ, Çanakkale) were consistently in a high-burden cluster. In univariate ordinary least square regression, population density, the proportion of contacts screened for TB, the proportion of TB contacts who received prophylaxis, TB dispensary count, mean particulate matter 10 levels, and gross domestic product were found to be positively associated with TB notification rate. The best-fitting multivariate spatial lag model revealed that the proportion of contacts screened for TB (β, *z*-value: 0.89, 2.21) positively affected TB notification rate.

CONCLUSION: The high TB burden in West Marmara Region should warn policymakers to maintain a focused approach to controlling TB in this area. This study showed the importance of contact tracing efforts to prevent the underdetection of TB cases.

KEYWORDS: Tuberculosis, Turkey, spatial analysis, epidemiology, contact tracing

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INTRODUCTION

Mycobacterium tuberculosis is primarily a pulmonary pathogen, but it can infect nearly any part of the body, including lymph nodes, kidneys, bones, and joints.[1] Although one-fourth of the world's population is estimated to be infected with tuberculosis (TB) bacillus, active TB disease develops in 5%-15% of these people.[2] The progression to active TB disease depends on the immune system's response to the bacillus. Risk factors that compromise the immune system, such as human immunodeficiency virus (HIV), immunosuppressive drugs, and diabetes, may precipitate active disease.[3]

According to the World Health Organization (WHO) Global TB Report 2022, it has been stated that 1.6 million people died from TB, and 10.6 million people had TB in 2021, with 98% of these cases originating from low- and middle-income countries.[4] National TB incidences are strongly associated with social and economic determinants,[5,6] driven by global socioeconomic inequalities, population mobility, urbanization, immigration, and population growth. These factors exacerbate malnutrition, inadequate housing, limited access to health care, and food insecurity.[7] Effective TB control necessitates comprehensive social and economic policies, targeting poverty reduction, improved living conditions, and addressing health and socioeconomic issues, particularly among immigrants.

Turkey has committed to reducing the TB burden by adopting the End TB Strategy and the Sustainable Development Goals in 2014-2015.[8] According to national TB surveillance data, the TB incidence (per 100 000 persons) was reported to have declined from 29.4 in 2005 to 14.1 in 2018.[9] Despite the lowering incidence rates, Turkey remains one of the 18 high-priority TB countries in the WHO European Region.[10] According to national reports, the provincial distribution of TB burden differs.[9] Identification of high-incidence regions and exploration of the spatial relationship between TB rates and demographic and socioeconomic factors will guide the national tuberculosis control programs and contribute to the development of tailored disease control strategies by health administrators and policymakers.

This study aimed to analyze the provincial-level spatial distribution of TB incidence between 2005 and 2018 in Turkey and identify the factors influencing TB notification rate.

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MATERIAL AND METHODS

This ecological study contains open data related to Turkey, which is publicly accessible and freely available via the Internet. Turkey, with a population of approximately 85 million, is a transcontinental country located mainly on Anatolian in West Asia, with a small portion on the Balkan Peninsula in Southeastern Europe. Turkey comprises a total of 81 provinces from among 12 NUTS-1 (Nomenclature of Territorial Units for Statistics) regions. For this study, ethical approval was obtained from the Ethical Committee of Dokuz Eylül University, İzmir, Turkey (No.: 2022/13-13).

Data Sources and Explanation

Provincial-level data sources used in the study include:

1. Tuberculosis data: We obtained the total number of TB cases, the total number of contacts screened for TB, the total number of TB contacts who received prophylaxis, and TB dispensary counts from the Health General Directorate of Public Health Tuberculosis Department's TB War reports covering the years 2007-2020. Due to a 2-year lag in data reporting, we analyzed data from 2005 to 2018.
2. Population and socioeconomic data: Data on population, population density, gross domestic product (GDP), average household size, the total number of foreign national populations, and foreign national immigrants were sourced from the Turkish Statistical Institute's website (https://data.tuik.gov.tr/).
3. Air quality data: Mean inhalable particulate matter 10 (PM10) levels were obtained from The Union of Chambers of Turkish Engineers and Architects' Air Pollution Report (2018).
4. Income and wealth index: The income and wealth index is a composite measure that accesses people's ability to meet their basic needs and protect themselves against economic and personal risks. It ranges from 0 to 1 and includes 3 key indicators: saving deposits per capita, the proportion of households in the middle and higher income groups, and the proportion of households declaring that they cannot meet their basic needs. Given the historical association between TB and poverty, we incorporated the income and wealth index as a provincial predictor for TB notification rates.
5. Syrian population data: Data on total Syrian population under temporary protection was sourced from Republic of Turkey Ministry of Interior Presidency of Migration Management, Migration Report for the year 2016.
6. Turkey spatial data: Spatial data for Turkey were retrieved from GADM (Database of Global Administrative Areas), version 3.6, available at https://gadm.org/download_country_v3.html.

Main Points

- This study analyzed the spatial distribution of tuberculosis notification rates from 2005 to 2018.
- Provinces in the West Marmara Region (Edirne, Kırklareli, Tekirdağ, Çanakkale) consistently exhibited a high-burden cluster.
- The findings of the multivariate spatial lag model demonstrated a positive association between the proportion of contacts screened for tuberculosis and tuberculosis notification rates.
- The study emphasizes the critical role of contact tracing efforts, particularly for individuals with known exposure to tuberculosis patients.

Data Preparation and Statistical Analysis

Due to the dynamic nature of infectious diseases, there would be a spatial dependency between the geographic neighborhood areas in terms of both disease burden and associated factors.[11] Spatial econometric models have been used to evaluate spillover effects, recognizing that neighboring units share common economic and social infrastructures. The integration of spatial statistics makes it possible to detect disease clusters and allows us to analyze disease occurrence associated with socioeconomic and environmental factors of the geographic units. In this study, we used global and local autocorrelation analyses and estimated univariate and multivariate ordinary least squares (OLS) regression and spatial econometric models.

We calculated TB notification rates by dividing the total number of reported TB cases (including both new and previously treated cases and all the cases regardless of anatomic region) by the provincial population. To investigate the spatial distribution of TB rates, we performed global and local autocorrelation analyses. Initially, we established an 81 × 81 provincial neighborhood matrix based on the queen (a piece in the game of chess) contiguity using Turkey geospatial data. Then, we weighted these provinces according to their neighborhood relationship, creating a weighted neighborhood matrix. To assess the presence of global spatial autocorrelation for each year, we employed the empirical Bayes index modified Moran's *I* permutation test (EBI Moran's *I*).[12] The Moran's *I* statistic allows for the analysis of the spatial dependence of the data. Similar to the correlation coefficient, values range from −1 to +1. Negative values closer to −1 indicate strong negative autocorrelation, suggesting that observation values in adjacent areas are dissimilar. Conversely, values approaching +1 indicate strong positive autocorrelation, suggesting the presence of clustering.

For the local autocorrelation analysis, we identified both cold (low–low) and hot (high–high) clusters in TB incidence using the Getis–Ord *Gi* local spatial autocorrelation method.[13] This method evaluates provinces and their neighbors collectively and calculates *z*-scores for each province. Statistically significant positive *z*-scores ($Z > 1.96$) indicate hot clusters with high TB incidence, while statistically significant negative *z*-scores ($Z < -1.96$) denote cold clusters with lower TB incidence.

In regression analysis, we initially conducted univariate and multivariate OLS (linear) regression using provincial TB notification rates from the year 2018 as the dependent variable. The provincial-level explanatory variables were categorized as follows: TB surveillance variables (contacts screened for TB, TB contacts who received prophylaxis, and TB dispensary count), demographic variables (population density,

average household size, foreign nationals, foreign national immigrants, and Syrian population under temporary protection), air quality (mean PM10 levels), and economic variables [gross domestic product (GDP), income and wealth index). We transformed certain variables, including the total number of contacts screened for TB, the total number of TB contacts who received prophylaxis, the total number of foreign national populations, foreign national immigrants, and total Syrian population under temporary protection, into proportions (%) by dividing them by the total provincial population. To ensure the normality, we logarithmically transformed the TB rates, mean PM10 levels, and GDP. Also, multicollinearity among explanatory variables was checked. Model outputs was expressed as β coefficients along with their 95% confidence intervals. To assess the presence of spatial autocorrelation in the residuals from the estimated multivariate OLS model, we employed Moran's *I* test. The detection of spatial autocorrelation in the OLS model residuals shows that there would be unaccounted spatial patterns in the model, and spatial models could be used alternatively to apply unbiased model parameters.

Upon confirming the presence of spatial dependency in the residuals, we proceeded with spatial lag model (SLM) and spatial error model (SEM) to account for this spatial dependency. Spatial lag model is an econometric model used to analyze spatial data when there is evidence of spatial autocorrelation. Spatial lag model introduces a lag variable which represents the weighted average of the dependent variable (TB notification rates) in neighboring provinces accounting for spatial spillover effects. Spatial error model is another spatial econometric model that assumes the spatial autocorrelation arises from an error term rather than a spatially lagged dependent variable. Details of the 2 models can be read more in-depth in the paper by Bivand and Piras.[14] Model outputs was expressed as β coefficients, standard errors (SE), and *z*-values. To select the best-fitting model, we compared model parameters using Bayesian information criterion (BIC) and log-likelihood values. The best model was chosen based on a lower BIC value and a higher log-likelihood. We used R (A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https ://www.R-project.org/) version 4.3.1 for data analysis and visualization.

RESULTS

Between 2005 and 2018, Türkiye reported a total of 219 338 cases. The highest number of notified cases was concentrated in İstanbul (n = 69 018, 31.5%), İzmir (n = 10 969, 5%), and Bursa (n = 9745, 4.4%). In contrast, Ardahan (n = 177, 0.08%), Bayburt (n = 128, 0.06%), and Tunceli (n = 86, 0.04%) reported the lowest numbers of cases. Figure 1 illustrates TB notification rates in these provinces by years. Over the 14-year period, provincial-level TB notification rates generally exhibited a decreasing trend with occasional yearly fluctuations.

Table 1 presents the results of the global spatial autocorrelation analysis for the annual TB rates spanning from 2005 to 2018. EBI-Moran's *I* values (median: 0.47, minimum–maximum: 0.43-0.59) were found to be statistically significant (*P* = .001), indicative of positive spatial autocorrelation.

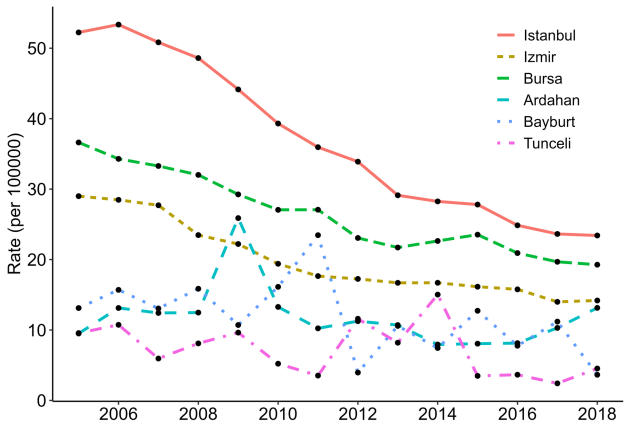


Figure 1. Tuberculosis notification rates (per 100 000) in İstanbul, İzmir, Bursa, Ardahan, Bayburt, and Tunceli (2005-2018).

We conducted local spatial autocorrelation analysis to detect localized patterns in the distribution of TB notification rates. Throughout the study period (2005-2018), the provinces in the West Marmara Region (Edirne, Kırklareli, Tekirdağ, Çanakkale) and Kocaeli were consistently exhibited in high–high clusters. İstanbul was part of a high–high cluster in all years except 2016, and Bursa was in a high–high cluster for 8 years out of 14 years ($P < 0.05$). Although low–low burden clusters were not stable over time, they were generally formed covering Western Anatolia (Ankara, Konya, Karaman), Central Anatolia (Kırıkkale, Aksaray, Niğde, Nevşehir, Kırşehir, Kayseri), and Mediterranean region (Antalya, Isparta, Burdur) provinces in most of the period. In 2018, a high–high cluster included Edirne, Kırklareli, Tekirdağ, Çanakkale, Balıkesir, Bursa, İstanbul, Kocaeli, Sakarya, Düzce, Zonguldak, and

Table 1. Global Spatial Autocorreleation Analysis Results for Tuberculosis Notification Rates in Turkey from 2005 to 2018

Year	Empirical Bayes Index Moran's *I*	*P*
2005	0.44	.001
2006	0.44	.001
2007	0.51	.001
2008	0.59	.001
2009	0.49	.001
2010	0.45	.001
2011	0.47	.001
2012	0.48	.001
2013	0.43	.001
2014	0.51	.001
2015	0.49	.001
2016	0.44	.001
2017	0.43	.001
2018	0.46	.001

Bartın provinces, while a cold cluster were detected including Van, Şırnak, and Siirt (Figure 2).

With the provincial-level variables, we initially conducted univariate and multivariate OLS regression (Table 2). In univariate analysis; TB surveillance variables [proportion of contacts screened for TB (β, 95% CI: 1.42, 0.56- 2.27), proportion of TB contacts who received prophylaxis (β, 95% CI: 7.29, 2.58-12.00), and TB dispensary count (β, 95% CI: 0.04, 0.01-0.06)], population density (β, 95% CI: 0.40, 0.10-0.70), GDP (β, 95% CI: 0.30, 0.02-0.58), and mean PM10 levels (β, 95% CI: 0.25, 0.03-0.47) were found to be positively associated with TB notification rates. In the multivariate analysis, only the proportion of contacts screened for TB retained statistical significance (β, 95% CI: 1.03, 0.09-1.97). Moran's *I* test on the residuals of the multivariate regression model indicated a significant positive spatial autocorrelation in the residuals (Moran *I* statistic standard deviate: 2.80, *P* = .003).

After observing the presence of spatial autocorrelation, we employed both SLM and SEM with all explanatory variables (Table 3). Spatial lag model (BIC: 120.5, log-likelihood: −29.5) demonstrated a better fit compared to SEM (BIC: 123.2, log-likelihood: −30.9). Spatial lag model revealed a spatial lag coefficient of 0.43 (*z*-value: 3.5, $P < 0.0001$) indicating the presence of spatial dependence whereas SEM suggested the existence of a spatially correlated error structure (lambda : 0.47, $P < 0.001$). In the SLM, contacts screened for TB (%) was positively associated with a TB notification rate (β: 0.89, SE: 0.40). However, in SEM, no significant provincial-level variables were found.

DISCUSSION

Tuberculosis surveillance has been one of the meticulously implemented and systematically reported infectious disease surveillance programs in Turkey. Reporting of TB cases is mandatory in Turkey. Prior to 2005, TB department was receiving aggregated data calculated monthly by TB dispensaries. In 2006, with the introduction of the Directly Observed Treatment Strategy (DOTS), individual data collection was initiated, enhancing the data quality. This study period spans from 2005 to 2018, during which significant improvements in data quality occurred with the introduction of the DOTS in 2006.

This study revealed disparities in TB rates across Turkey, with a notable aggregation of high TB burden observed in the West Marmara Region provinces (Edirne, Kırklareli, Tekirdağ, Çanakkale), Kocaeli, and İstanbul. A systematic review of 79 geospatial studies found that 39% of them reported high-burden spots associated with poor socioeconomic conditions.[15] However, this situation may not align with Turkey's context, as West Marmara Region provinces boast relatively high economic status, ranking in the top 25 in GDP and within the top 50 according to the income and wealth index. The high TB burden in these regions may be attributable to their healthcare and surveillance capacity. As a densely populated metropolitan city, İstanbul offers extensive diagnostic and

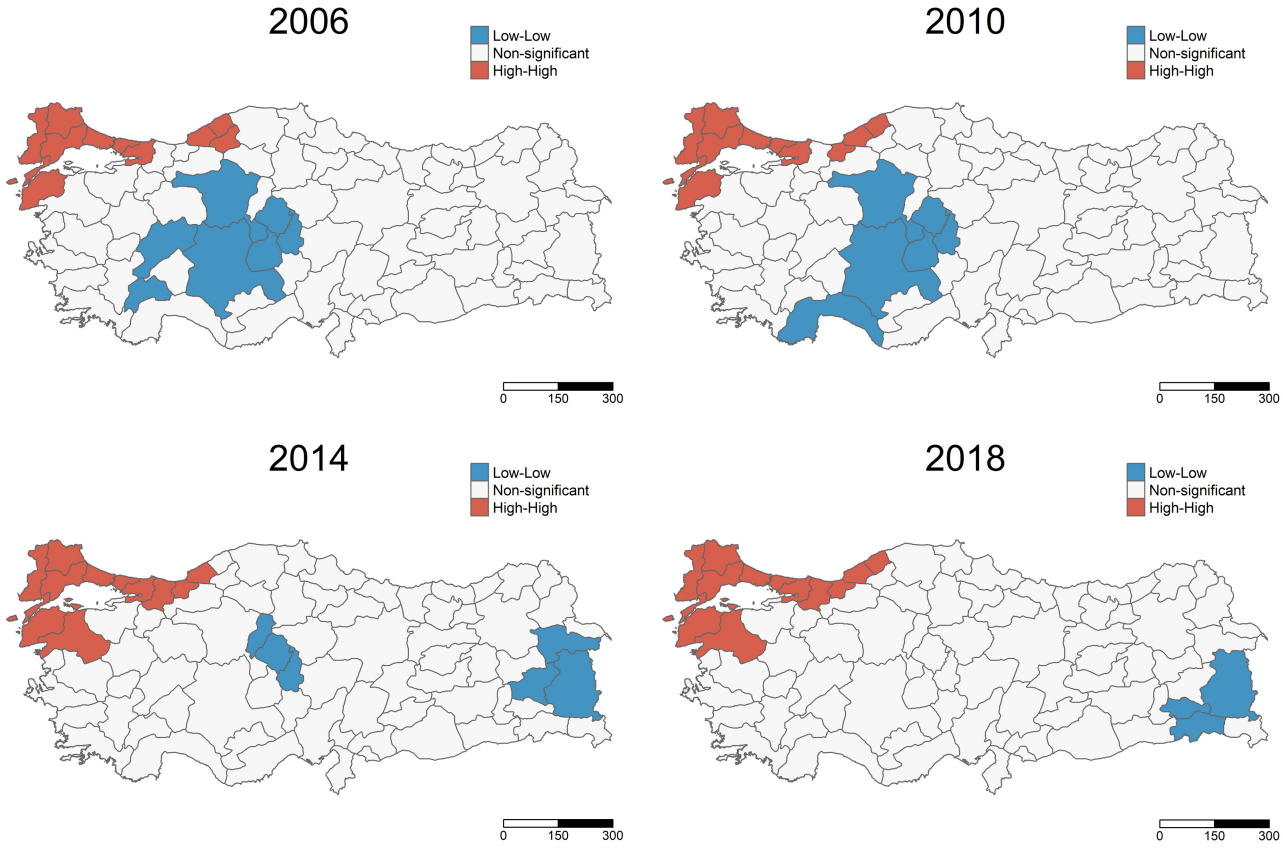


Figure 2. Local autocorrelation analysis of tuberculosis notification rates in Turkey for the years 2006, 2010, 2014, and 2018. Provinces in red indicate high incidence clusters while those in blue colors indicate low incidence clusters. White areas represent nonsignificant aggregations.

Table 2. Results of Univariate and Multivariate Ordinary Least Squares Regression for the Factors Effecting Tuberculosis Notification Rate at Provincial Level in Turkey, 2018

	Ordinary Least Regression			
	Univariate		Multivariate	
	β	95% CI	β	95% CI
TB surveillance variables				
Contacts screened for TB (%)	1.42	0.56-2.27*	1.03	0.09-1.97*
Contacts who received prophylaxis (%)	7.29	2.58-12.00*	2.49	−2.90 to 7.88
TB dispensary count	0.04	0.01-0.06*	0.004	−0.07 to 0.08
Demographic variables				
Population density (per 1000 km^2)	0.40	0.10-0.70*	0.19	−0.64 to 1.03
Average household size	−0.09	−0.21 to 0.03	−0.12	−0.31 to 0.08
Foreign nationals (%)	−0.00	−0.11 to 0.10	−0.27	−0.76 to 0.23
Foreign national immigrants (%)	0.05	−0.22 to 0.31	0.63	−0.55 to 1.82
Syrian population under temporary protection (%)	0.004	−0.005 to 0.01	0.004	−0.005 to 0.01
Economic variables				
Gross domestic product (log)	0.30	0.02-0.58*	0.18	−0.32 to 0.68
Income and wealth index	0.46	−0.09 to 1.02	-0.47	−1.64 to 0.71
Air quality				
Mean PM10 levels (log)	0.25	0.03-0.47*	0.16	−0.09 to 4.40

Multivariate ordinary least squares model parameters: BIC : 125.2; log-likelihood: −34.04.
*$P < 0.05$.

Table 3. Results of Spatial Lag Model and Spatial Error Model for the Factors Effecting Tuberculosis Notification Rate at Provincial Level in Turkey, 2018

	Spatial Lag Model			Spatial Error Model		
	β	SE	*z*-Value	β	SE	*z*-Value
Model intercept	1.43	1.98	0.72	2.99	2.18	1.37
TB surveillance variables						
Contacts screened for TB (%)	0.89	0.40	2.21*	0.71	0.39	1.82
Contacts who received prophylaxis (%)	1.55	2.32	0.67	1.41	2.26	0.62
TB dispensary count	0.02	0.03	0.49	0.01	0.03	0.36
Demographic variables						
Population density (per 1000 km^2)	0.004	0.36	0.01	0.02	0.40	0.04
Average household size	−0.07	0.08	−0.81	−0.07	0.10	−0.68
Foreign nationals (%)	−0.18	0.21	−0.83	−0.12	0.20	−0.63
Foreign national immigrants (%)	0.47	0.51	0.92	0.36	0.48	0.75
Syrian population under temporary protection (%)	0.003	0.004	0.90	0.003	0.004	0.72
Economic variables						
Gross domestic product (log)	0.08	0.21	0.38	0.12	0.24	0.51
Income and wealth index	−0.37	0.50	−0.74	−0.49	0.53	−0.94
Air quality						
Mean PM10 levels (log)	0.17	0.10	1.67	0.21	0.11	1.89

Spatial lag model parameters: BIC: 120.5, log-likelihood: −29.5; spatial error model parameters: BIC: 123.2, log-likelihood: −30.9.
*$P < 0.05$.

treatment services. Notably, 2 out of 4 of Turkey's largest reference hospitals are located in İstanbul, contributing significantly to TB diagnosis and treatment services. It is also worth emphasizing that Edirne and Kırklareli are border provinces.

Human immunodeficiency virus coinfection has a substantial impact on TB incidence. The Global TB Report 2022 highlighted that the rate of HIV-positive TB cases was on the rise in the European Region.[4] A study by Dye et al[5] investigating TB incidence trends in 134 countries found that the rates were falling more quickly in countries with lower HIV infection rates. Another study from Brazil used spatial analysis to identify high-risk areas for pulmonary TB and found a higher proportion of people living with HIV in high-risk areas compared to low-risk areas.[16] Unfortunately, we had no provincial data on HIV. Therefore, it is crucial to investigate the impact of HIV coinfection on high-burden regions in Turkey in future studies.

In this study, univariate analysis revealed positive associations between TB incidence and TB surveillance variables. However, in the multivariate SLM, only the proportion of contacts screened for TB was a statistically significant determinant of TB incidence. Efficient and reliable surveillance systems are vital for monitoring TB cases. In Turkey, TB dispensaries serve as the primary operational units of the TB Control Programme, responsible for screening, diagnosis, treatment, follow-up, notification, and registration. Contact tracing carried out by the TB dispensaries identifies contacts of the patients and screens them. A local study conducted in the capital city of Turkey demonstrated that the initiation of active surveillance activities led to a substantial increase in new cases.[17] Moreover, notifications may be limited by underascertainment due to not all cases seeking healthcare or by underreporting due to the failure of reporting cases.[18-20] Standardizing and strengthening contact tracing procedures at the provincial level would enhance case finding and thus TB notifications. Targeted interventions, especially in low–low burden regions, such as replacing the personnel shortage and providing an optimal number of TB dispensaries per population, may contribute to better surveillance activities.

Despite the consistent decline in TB notification rates year by year, foreign-born cases are increasing in Turkey.[9] The migration flow to Turkey has increased over the past years due to the Syrian conflict that began in 2011. The total number of Syrians under temporary protection was 2 834 441 in 2016, and has risen to 3 288 755 in 2023.[21] Syrian migrants comprise an increasing proportion of foreign-born TB patients in Turkey.[22] Within the temporary shelters; active screening, referral, physician presumption, and consecutive examination have led to the diagnosis and treatment of a total of 1022 cases of active tuberculosis among Syrian refugees between 2012 and 2015.[23] When comparing the burden of TB between Syria and Turkey, the 2 countries exhibit a similar baseline rate, although this claim is debatable due to Syria's fragmented and disrupted surveillance activities.[23] Additionally, migrants may experience poor and overcrowded living conditions. While our study did not provide spatial evidence of the impact of foreign-born or Syrian populations on TB notification rates, it is essential that control measures continue to focus on foreign-born individuals and immigrants.

Tuberculosis has historically been linked to poverty due to its association with factors such as limited access to health services, delayed diagnosis, living and working in overcrowded and poorly ventilated environments, as well as malnutrition.[7,24] In the study of Janssens and Rieder, a negative correlation was identified between GDP and TB incidence at the country level.[25] However, in our study, we observed a positive association between GDP and TB notification rates, which contradicts the conventional understanding that TB is a disease of the poor. Similarly, in a study by He et al,[26] GDP was found to be positively associated with pulmonary TB rates. They attributed this unexpected finding to internal migration patterns, with individuals from rural areas moving to economically prosperous regions for physical labor opportunities.[26] Given their attractiveness for informal employment, this argument could also be relevant for high GDP areas in Turkey. Moreover, in this study, the association between GDP and TB rate may also be linked to the availability of diagnostic facilities, health-care experience, and a more favorable health system in high GDP regions.

The study has a few limitations. First, the spatial level used in this study (provinces) may remain relatively large for the spatial modeling of TB. Conducting spatial analyses on smaller levels, such as districts within a province, with available data, might yield more precise and reliable results. Nonetheless, this study is the first to analyze spatial distribution in Turkey that provided a valuable overview of the distribution of TB notification rate. More detailed spatial studies on smaller scales are needed with updated data. Secondly, the practical application of this study is not easy because implementing real-life interventions or policies on provincial level would be challenging. Thirdly, while the univariate analysis showed an association between PM10 levels and TB rates, the reliance on PM10 levels is limited by the fact that 38% of monitoring stations lacked reliable data reception in 2018.[27] Lastly, it is important to note that we were unable to investigate the impact of HIV coinfection and immunosuppression factors, such as malignancy and the use of immunosuppressive drugs, due to the unavailability of provincial-level data on these variables.

In conclusion, this study underscores the importance of contact tracing efforts, particularly among individuals with known exposure to TB. While implementing such provincial-level measures may present challenges, it is imperative for policymakers to adopt a targeted approach in TB control programs that takes into account regional variations in TB incidence.

Ethics Committee Approval: This study was approved by Ethics Committee of Dokuz Eylül University (Approval number: 2022/13-13, Date: 2022).

Peer-review: Externally peer-reviewed.

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Original Article

Effectiveness of a Program to Raise Awareness About Pneumococcal Vaccination Among Physicians and Patients with Chronic Respiratory Diseases: A Multicenter Cohort Study

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Abstract

OBJECTIVE: There is a need to increase patient and clinician awareness on the effectiveness of pneumococcal vaccination in at-risk groups. The aim of the study was to evaluate the effect of reminders for physicians and patients using the vaccination tracking system created in the hospital information management system (HIMS) on the vaccination rate, and the effect of pneumococcal vaccination on pneumonia-related hospitalization and mortality over a 12-month period.

MATERIAL AND METHODS: This prospective observational cohort study was undertaken during a 2-year period in 3 tertiary care centers. Patients were followed up for 12 months following vaccination, and hospital admissions and mortality were recorded via HIMS. During the campaign, HIMS transmitted pneumococcal immunization reminder messages in accordance with guideline recommendations to physicians' computers and patients' mobile phones. Educational posters on pneumococcal vaccination were posted in outpatient clinics. Regular seminars on the evidence for pneumococcal vaccination were organized. All patients who were hospitalized during the follow-up period for chronic obstructive pulmonary disease (COPD), asthma, lung cancer, or pneumonia were analyzed in relation to their vaccination history regarding clinical outcomes.

RESULTS: A total of 29 530 patients were included in the study. During the study period, the annual vaccination rate increased by 74.4% and reached 4.8% in 3 hospitals ($P = .001$). The rates were 3.9% in patients older than 65 years without comorbidities and 5.2% in those with COPD and asthma ($P = .002$). In pneumococcal vaccine recipients, pneumonia-related hospital mortality was lower (relative risk (RR) = 0.19, CI 0.09-0.35, $P < .001$).

CONCLUSION: It is possible to raise the rate of pneumococcal vaccination through awareness campaigns. Individuals with COPD and asthma are more willing to receive pneumococcal vaccination. Among patients hospitalized for pneumonia, prior pneumococcal vaccination is associated with lower mortality.

KEYWORDS: 65-year-old, chronic obstructive pulmonary disease, mortality, pneumonia, pneumococcal vaccination
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INTRODUCTION

Streptococcus pneumoniae is the leading bacterial cause of community-acquired pneumonia (CAP) worldwide and in Turkey.[1-5] Advanced age, chronic disorders (diabetes, chronic lung, heart, liver, kidney, and nervous system diseases), malignancies, and immunosuppressive conditions are associated with an increased incidence of pneumococcal infection and a worse prognosis.[2-6] For these reasons, national and international guidelines advocate vaccination against pneumococcal infections for the at-risk groups. Comprehensive studies on pneumococcal vaccination rates in Turkey are lacking, but estimates remain well below the targets. The coverage rate in risk categories was around 1% until recently when the Ministry of Health adopted policies encouraging adult vaccination and initiated the free rollout of conjugate vaccines to family physicians.[7] In Western nations, this rate ranges from 13% to 69%.[8] The main obstacles to adult vaccination are that health authorities and professional organizations do not make clear recommendations on this subject, physicians do not have enough knowledge about the efficacy and safety of vaccines, and this issue is not a primary concern during the limited time they spend with the patient because of their heavy workload, whereas patients expect clear guidance from their

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physicians and health authorities regarding vaccination.[9-12] In Turkey, the Ministry of Health and professional organizations such as the Turkish Thoracic Society and the Infectious Diseases and Clinical Microbiology Society have developed guidelines recommending pneumococcal immunization for those in at-risk groups. However, these recommendations hardly reach any physician–patient encounter because of the time constraint imposed by the adopted health policies. In such brief patient contacts, simple reminders may be of help to the physicians in recommending vaccination to their at-risk patients. Besides, physician training programs and goal setting for vaccination coverage can boost the adult immunization rate, as shown in a study from Denizli, Turkey.[13] Another questionnaire-based study showed that patients had knowledge gaps and misperceptions regarding adult vaccination.[14]

This study was planned and implemented in 3 large tertiary chest disease training and research hospitals to improve the pneumococcal conjugate vaccination (PCV-13) rates of adults in high-risk groups. The project included reminder mechanisms for both patients and physicians, and training programs to raise physicians' awareness of the impacts of pneumococcal vaccine on adult health and health economy. This study aimed to assess whether these interventions had any effect on adult vaccination rates and any impact on pneumonia-related hospital mortality during a 12-month period.

MATERIAL AND METHODS

This was a prospective observational cohort study and included all patients who presented to the outpatient clinics of 3 tertiary care centers for respiratory diseases in 2 major cities of the country.

Patients

During the study period, all patients with pneumococcal vaccine indications were retrieved from the hospital information management system (HIMS) and included in the study. Thus, patients who were older than 65 years and those previously diagnosed and/or followed up with chronic conditions were included in the study (Figure 1).

The diagnosis of patients was based on the International Classification of Diseases, Tenth Revision (ICD-10), which was used for the eligible study population, and all study-related diseases and their ICD-10 coding were obtained from the hospital electronic system. International Classification of Diseases, Tenth Revision coding J44.0-J44.9 were accepted as COPD, J45.0-J45.9 were accepted as asthma, and C00.0-C97.0 were accepted as malignancy. However, patient-specific age, gender, and comorbidities were not obtained from the hospital electronic system. In this study, total numbers of patients were recorded and given for COPD, asthma, and malignancy. The region and the type of malignancy were not classified. Pneumonia (J13.0-J18.9) cases were recorded. Besides, pneumonia-related in-hospital mortality was derived from patients whose diagnosis of hospitalization was pneumonia (J13.0-J18.9). However, we were not able to obtain the data on these patients' characteristics.

Main Points

- This study found that programs aimed at raising awareness of pneumococcal vaccination through messages and reminder posters to physicians and patients could produce a nearly 75% increase in the annual pneumococcal vaccination rate.
- The study also discovered that adults over the age of 65 with COPD and asthma have greater rates of pneumococcal vaccination than those in the same age group who do not have such comorbidities.
- The pneumonia vaccinations have shown protective effect in-hospital mortality for pneumonia patients with risky comorbid diseases.

Individuals with contraindications to the pneumococcal vaccine, patients who had previously (within 1 year) received the pneumococcal vaccine, pregnant or breastfeeding patients, and those lost to follow-up were excluded from the study.[2] Patients who received a 13-valent pneumococcal conjugate vaccine (PCV13 [Prevenar 13, Pfizer, Inc.]) but who moved to another location during the 1-year follow-up period were also not included (see Figure 1) The intervention period was between November 15, 2018 and November 15, 2019. All participants were followed up for at least 1 year until November 15, 2020.

Clinical Endpoints

The primary endpoint was the rate of vaccination during the 1-year follow-up period. The study population was divided into 2 groups, namely those who were vaccinated and those who were not vaccinated, despite the interventions. The secondary endpoint was in-hospital mortality in hospitalized patients with pneumonia.

Patients who were and who were not administered the 13-valent pneumococcal conjugate vaccine were identified from the data registry. The patients were monitored for a duration of 1 year, regardless of whether they were admitted to the hospitals in the study centers. If these individuals were admitted to the hospital because of pneumonia (ICD-10 J13.0-J18.9), any deaths that occurred during their hospital stay (including in the emergency department or intensive care unit) were recorded as "mortality with pneumonia."

Interventions

Mobile phone messages were sent to patients who had made an appointment at the hospital to raise their awareness about pneumococcal vaccination. These messages were sent 1 hour prior to the hospital appointment time to all patients for whom the 13-valent conjugate vaccine was indicated.[2-4] The message read: "If you have not been vaccinated against pneumonia, please ask your doctor whether you could benefit from one such vaccine. Best wishes." In addition, pneumococcal vaccine reminder pop-ups were also prepared for physicians when the patient's electronic records were opened on the doctor's computer. These messages only appeared for patients 65 years and older and/or with a previous diagnosis of a disease listed as an indication for pneumococcal vaccination. The pop-up message read: "This patient may be at increased risk for pneumococcal infections. If you think he/she qualifies for pneumococcal vaccination, please refer him/her to the vaccination unit".

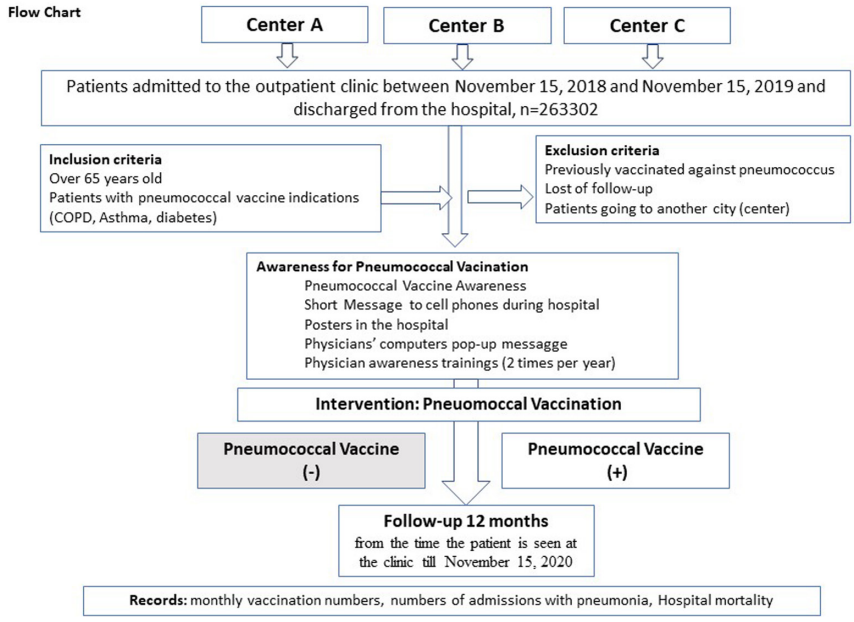


Figure 1. Flow chart of patients' enrollment.

Posters were posted on outpatient clinic doors for patient and physician awareness. For patients, a 50 × 70 cm poster with the following information was displayed on the outer side of the clinic door facing the waiting hall. The poster read, "Dear Patients, if you are 65 or older or if you have respiratory conditions such as COPD, asthma, bronchiectasis, or other chronic conditions like diabetes, please consult your physician about pneumococcal vaccine. We wish you well." For physicians, a 50 × 70 cm poster containing the following information was posted on the inner side of the clinic door facing the doctor's table. The poster contained information about the pneumococcal vaccination indications and schedule.

Modifications to the Program Serving as the HIMS: A large room was designed for and dedicated to adult vaccination (according to standards set by the Ministry of Health). Nurses were appointed to serve during work hours. A HIMS-programmed computer was installed in the vaccination room. This enabled the nurses in charge of the vaccination to see online the list of patients referred by the physicians and to make sure they were all called and immunized. The vaccine section on the HIMS page was updated with the vaccine's name, type, and vaccination date/time. This allowed all physicians taking care of the patient to be informed about his/her vaccination status. This study was approved by the Ethics Committee of the University of Health Sciences Süreyyapaşa Chest Diseases and Thoracic Surgery Teaching and Research Hospital (032-01.11.2018), and it was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Signed informed consent was obtained from all participants.

Statistical Analysis

The statistical analysis was done by the Statistical Package for Social Sciences version 20.0 package program (IBM Corp.; Armonk, NY, USA). The age and gender of the patients were determined through descriptive analysis of additional disorders. Dichotomous values are shown as numbers and percentages. For continuous variables with a normal distribution, the mean values and standard deviation (SD) are used. For variables with nonnormal distribution, the median values and interquartile ratio (IQR) are used. The vaccinated and nonvaccinated groups were compared using Student's *t*-test for continuous numerical data, with a normal distribution, or Mann–Whitney *U*-test when there was a nonnormal distribution, and with chi-square test for dichotomous. The significant *P* value was accepted if below .05.

RESULTS

In the study period, a total of 263 302 patients were evaluated. Table 1 shows the summary of monthly vaccination data for all and individual hospitals during the study period. Between November 2018 and October 2019, the administration of the 13-valent conjugate vaccine increased by 74.4% compared to the previous year at the 3 chest disease hospitals ($P < .001$).

The numbers of inpatients and outpatients classified according to their vaccination status are shown in Table 2. In the follow-up period, unvaccinated patients with COPD or asthma who were 65 years and older had 18.3-fold (8077/442); patients without COPD and asthma who were 65 years and older had 24.9-fold (3506/141); patients with COPD irrespective of age had 16.4-fold (9005/549); patients with asthma irrespective of age had 12.5-fold (2044/163); patients with pneumonia had 21.7-fold (8751/404); and patients with malignancy had 28.4-fold (4798/169) increased risk of hospitalization (Table 2).

Among the risk groups, the rate of hospitalization in the vaccinated individuals compared with the unvaccinated ones (Table 3).

Pneumonia-related hospital mortality rates in vaccinated and unvaccinated groups were 2.5% and 13.6%, respectively (relative risk (RR) = 0.19, CI 0.09-0.35, $P < .001$), pointing to a 81% decrease in the risk of pneumonia-related mortality.

Table 1. Monthly Pneumococcal Vaccination Numbers and Percent Changes in the 3 Centers

	All Centers*			Center A			Center B			Center C		
Months	**Preintervention**	**Postintervention**	**Change %**	**Preintervention**	**Post-intervention**	**Change %**	**Preintervention**	**Postintervention**	**Change %**	**Preintervention**	**Postintervention**	**Change %**
November	481	680	141	140	166	119	162	186	115	179	328	183
December	421	591	140	161	131	81	162	180	111	98	280	286
January	281	534	190	92	137	149	98	137	140	91	260	286
February	198	526	266	61	127	208	73	198	271	64	201	314
March	225	475	211	59	115	195	112	192	171	54	168	311
April	344	524	152	158	112	71	108	271	251	78	141	181
May	671	883	132	460	441	96	118	312	264	93	130	140
June	240	519	216	55	103	187	116	314	271	69	102	148
July	264	535	203	72	99	138	78	336	431	114	100	88
August	149	409	274	45	67	149	56	260	464	48	82	171
September	458	867	189	142	226	159	133	527	396	183	114	62
October	709	1203	170	220	263	120	160	832	520	329	108	33
Total	4441	7746	174	1665	1987	119	1214	3559	293	1400	2014	144

Pre-awareness period: November 15, 2017-November 14, 2018; Awareness period: November 15, 2018-November 14, 2019.
*All center difference.

Table 2. Vaccination Numbers Among Outpatients and Hospitalized Patients During the Study Follow-Up Period

	Vaccinated			Unvaccinated			General Total (Row, n)
3 Centers	Hospitalized	Outpatients	Total (Row%)	Hospitalized	Outpatients	Total (Row%)	
65-year older people with COPD or asthma, n (%)	442 (16.5)	2235 (83.5)	2677 (100)	8072 (6.3)	120625 (93.7)	128697 (100)	131374
65-year older people without COPD and asthma, n (%)	141 (10.9)	1149 (89.1)	1290 (100)	3506 (4.1)	81571 (95.9)	85077 (100)	86367*
COPD, n (%)	549 (21.2)	2022 (78.8)	2571 (100)	9005 (12.7)	61788 (87.3)	70793 (100)	73364*
Asthma, n (%)	163 (8.7)	1700 (91.3)	1863 (100)	2044 (2.5)	78878 (97.5)	80922 (100)	82785*
Pneumonia, n (%)	404 (30.1)	940 (69.9)	1344 (100)	8751 (16)	45954 (84)	54705 (100)	56049
Malignancy, n (%)	169 (22.7)	576 (77.3)	745 (100)	4798 (23.9)	15243 (76.1)	20041 (100)	20786*

(%) Row. Total of these cases 263302.
COPD, chronic obstructive pulmonary disease. *Total number of cases in vaccinated and unvaccinated group in row.

The group over 65 with COPD and asthma received 3 times more vaccinations than the group over 65 without COPD or asthma. Among the individuals older than 65 years without comorbidities, the pneumococcal vaccination rate was 3.9%, as compared to 5.2% among individuals with COPD and asthma in the same age group (RR =1.34, P = .002).

DISCUSSION

This study shows that a nearly 75% increase in the annual pneumococcal vaccination rate can be achieved with programs aiming to raise awareness through messages and reminder posters to physicians and patients. The study also reveales that adults older than 65 years with COPD and asthma have higher rates of pneumococcal vaccination than individuals without such comorbidities in the same age group. Finally, vaccination with pneumococcal conjugate vaccine is associated with an 81% decrease in hospital mortality.

Awareness of Pneumococcal Vaccination

Stoffel et al[15] examined Swiss general practitioners' (GPs) knowledge of pneumococcal vaccination guidelines for adult risk categories. In this study, 4607 GPs were invited to complete a survey by email, and 300 GPs responded. They indicated that they prescribed pneumococcal vaccine for at-risk people, they concluded that GP awareness could increase immunization rates and protect at-risk people.[15] A randomized controlled trial was conducted in Brazil to investigate whether contacting diabetes patients via phone (intervention group) to update their vaccinations would be an effective method of intervention.[16] Significant improvements in vaccination rates were found among the intervention group subjects following a phone call, showing it to be an easy and successful method. The authors indicated that a professional was required for the phone calls.[16] The present study aimed to improve both the physicians' and patients' awareness about pneumococcal vaccination.

Artificial intelligence can be used to raise awareness about vaccination. Hospital information management systems are easily adaptable to inform physicians about the possibility of pneumococcal vaccination when it is indicated. In this study, HIMS of the 3 centers followed similar algorithms to draw the attention of physicians and patients on pneumococcal vaccination. This was an easy and cost-effective method both to raise awareness and for follow-up of the vaccinated patients. Monthly pneumococcal vaccination reports showed significant increases.

Pneumococcal Vaccination in 65-Year-Old and Older

Ates Bulut et al[17] aimed to evaluate whether specialists know about older people's vaccination schedules and how often the defined vaccines are recommended to patients in daily practice. In 2021, they used a questionnaire and sent a link to the doctors via email, social media, and text message. In

Table 3. Number and Percentages of Hospitalized Patients in the Vaccinated and Unvaccinated Groups

	Vaccinated (n = 1426)	Unvaccinated (n = 28104)	% Difference (95% CI)	*P*
COPD, n (%)	549 (38)	9005 (32)	5.6 [3.06-8.21]	0.001*
Asthma, n (%)	163 (11)	2044 (7)	4.16 [2.58-5.94]	0.001*
Pneumonia, n (%)	404 (28)	8751 (31)	2.8 [0.39-5.18]	0.024*
Malignancy, n (%)	169 (12)	4798 (17)	5.22 [3.39-6.86]	0,001*
65-year older people without COPD and asthma, n (%)	141 (%10)	3506 (%13)	2.59 [0.89-4.08]	0.004*

COPD, chronic obstructive pulmonary disease.
*Significant value P = .05; chi-square test.

that study, it was emphasized that vaccines, including inactivated or recombinant influenza, PPSV23, PCV13, and other vaccines, were recommended for older people in the guidelines. There were a total of 435 physicians who took part, and 94.5% (411) of the doctors said they had told their patients to get vaccinated. However, 20% of the physicians chose the correct vaccination and 33.8% had not asked the patients about their vaccination background. Doctors who had not looked at the "National Adult Vaccination Scheme," were younger and had less experience, and had not asked patients about their vaccination history. They concluded that physicians should be more aware of routine vaccination regimens, periodic reminders for immunization should be given in each health-care environment and novel methods should be put into practice to improve physicians' attitudes on immunization.[17]

In this study, older patients without comorbidities were less frequently vaccinated than the same age group with COPD and asthma. The tendency to receive pneumococcal vaccination was lower in healthy elderly individuals than in those with pulmonary comorbidities. PCV-13 vaccine has been recommended for persons aged ≥65 years who do not have an immunocompromising condition, CSF leak, or cochlear implant and who have not previously received PCV13.[18,19] Very recently, in 2022, PCV-20 was developed, and pneumococcal vaccination programs have been revised.[20] In the CAPITA study, PCV-13 was found to lower the incidence of invasive pneumococcal illness by 75% and the need for hospital care owing to vaccine-type strains of CAP by 45.6% in the 84 496 senior participants.[21] This study showed that an easy and pragmatic multidimensional awareness approach significantly contributed to the vaccine uptake in the elderly patients with chronic lung diseases. There will hopefully be further increases in the percentage of healthy adults over 65 who receive vaccinations as publications and awareness of the benefits increase. Physician and individual awareness-raising efforts should keep growing in this regard.

Pneumococcal Vaccination and Mortality in Patients Hospitalized due to Pneumonia

This study showed that the mortality was lower in PCV-13 vaccinated patients if they were hospitalized for pneumonia. Similar observations were made in other studies. Kolditz et al[22] identified a significant reduction in 30-day all-cause mortality after pneumonia. They found that the number needed to vaccinate was 1722 to prevent one death due to pneumonia. In that population-based cohort of people over 60 years of age, PPV13 immunization was linked to a slight decrease in all-cause pneumonia, which was only found in women, and a decrease in all-cause mortality after pneumonia, which was only seen in patients between the ages of 60 and 79. This effect on mortality following pneumonia may be explained by either a shortened course of pneumococcal pneumonia or a switch to less virulent pneumococci.[22] Beatty et al[23] conducted a prospective, population-based clinical registry of 1636 hospitalized adult patients (18 years and above) with bacteremic pneumococcal pneumonia between 2000 and 2010. The study showed that the pneumococcal vaccination rate was less than 5% and all-cause hospital mortality was 14% (226/1636).[23] The pneumococcal vaccination was associated with reduced in-hospital mortality (adjusted odds ratio, 0.2; 95% CI, 0.05-0.9, $P = .033$). Vaccination was not associated with any decrease in the rate of major complications ($P = .2$).[23] In a recent retrospective study from Japan, Naito and colleagues aimed to evaluate whether prior pneumococcal vaccination (with 23-valent polysaccharide vaccine) contributed to better clinical outcomes, as well as the cost related to all-cause hospital admissions in people 65 years old and above.[24] In this study, a total of 1355 patients were enrolled, including 310 (22.9%) patients who had received pneumococcal vaccine.[24] The percentages of patients with pneumonia were similar in vaccinated and unvaccinated groups (n = 35, 11.3% and n = 119, 11.4%, respectively, $P > .99$), but vaccinated patients had lower all-cause in-hospital mortality rate than unvaccinated patients (3.9% vs 8.2%, $P = .008$).[24]

The main strengths of the study were that it was a multicenter, prospective study which included a big population, that several interventions directed to both physicians and patients were used and that all vaccinated and unvaccinated participants were followed up for 1 year.

This study had some limitations that should be noted. First, the number of hospital admissions due to pneumonia during the study period may have been higher than that observed in the study. Because the follow-up period partly coincided with the pandemic's first year (November 2019-November 2020), curfews, mask wearing, and precautions to keep distance from others may have prevented pneumonia, especially in people 65 and older. However, the lower mortality in patients hospitalized for pneumonia is a relevant finding, independent from the prevalence of serious pneumonia in the general population. Secondly, mortality risk analysis could not be carried out by comparing the comorbidities of people who had and had not been vaccinated. We did not have access to the individual data (age, gender, and comorbid diseases) of the patients followed by the 3 tertiary care centers. We were only able to report the total number of patients with age over 65, COPD, asthma, and malignancy. Thirdly, the fact that this study was performed in 3 large teaching institutions for chest diseases possibly prevents generalizability of the findings to other hospitals. These referral centers mostly deal with more severe and complicated cases, and the outcomes may be different in health-care centers dealing with less severe patients. Finally, mortality that was reported was crude mortality and the causes of death were not precisely determined.

In summary, activities to improve awareness of pneumococcal vaccination, including delivering messages to physicians and patients and placing reminder posters in hospitals, can increase vaccination rates. The presence of comorbidities appears to influence the physicians' attitudes more than older age. Pneumococcal vaccination is associated with lower mortality in patients hospitalized for CAP. Continued efforts are needed to further improve awareness among physicians and patients.

Ethics Committee Approval: This study was approved by Ethics Committee of University of Health Sciences Süreyyapaşa Chest Diseases and Thoracic Surgery Teaching and Research Hospital (032-01.11.2018), and it was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Original Article

The Prevalence of Tobacco Product Use Among Students in the Faculty of Medicine at Pamukkale University and Their Views on the Smoke-Free Campus Implementation

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Abstract

OBJECTIVE: Tobacco use is an important risk factor for more than 20 types of cancer, especially cardiovascular and respiratory diseases, and many other health problems. Cigarettes are one of the most commonly used tobacco products in the world, and they can cause both physical and mental addiction. Adolescence is known to be the highest-risk period in terms of addiction among all age groups. As a result, smoke-free campus practices have become even more important in universities. This study investigates the prevalence of smoking among Pamukkale Medical School students and their views and behaviors regarding smoke-free campus practices.

MATERIAL AND METHODS: This cross-sectional study was conducted with 548 medical students at Pamukkale Universıty Faculty of Medicine during the academic year 2021-2022, between April 1-29, 2022. A face-to-face interview was conducted. Students' smoking status and their views about a smoke-free campus were assessed. In the questionnaire, the independent variables were socio-demographic characteristics, duration of staying in a smoke-free environment, smoking status in the place of residence, areas where smoking is most common, Fagerström nicotine dependence level, knowledge about smoke-free campus applications and campuses with the smoke-free application. The Statistical Package for the Social Sciences version 21.0 package program was used to analyze the data. Descriptive statistics are presented with numbers and percentages for categorical variables, while the arithmetic mean and standard deviation are used for continuous variables. The chi-square test was used to compare categorical variables,and the Kolmogorov-Smirnov analysis was used to test the compatibility of data to normal distribution.

RESULTS: The student smoking rate increased significantly as the number of semesters increased ($P = .021$). The smoking rate of male students was higher than that of female students ($P = .001$). The smoking rate of students living with their family or relatives was lower ($P = .020$). Smokers (14.7%) were more likely to have heard about the introduction of smoke-free zones on campus than nonsmokers (11%) ($P = .280$). 81.4% of students affirmed the statement, "The number of smoke-free rooms should be increased," and 84.3% responded, "I support the existence of smoke-free spaces." Nonsmoking students (90.8%) are more likely to agree that smoke-free spaces should be increased than those who smoke (57.7%) ($P < .001$). Among the students, 17.6% of nonsmokers and 37.8% of smokers find the information about smoke-free spaces sufficient ($P < .001$). The rate of those who consider smoke-free space inspections to be sufficient is lower for nonsmoking students than for nonsmokers ($P = .017$). Nonsmokers (89.5%) support the existence of smoke-free spaces to a higher degree than smokers (71.2%) ($P < .001$).

CONCLUSION: One-third of Pamukkale University Faculty of Medicine students smoke, and smoking rates are higher among men and those who do not live with family or relatives. All participants strongly support the existence of smoke-free zones (84.3%), while a proportion of tobacco users (31.4%) support the implementation of a smoke-free campus. Student opinions of the smoke-free zones and the smoke-free campus application are more positive among nonsmokers than smokers.

KEYWORDS: Smoke-free campus application, fighting tobacco, smoke-free zone
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INTRODUCTION

The nicotine found in tobacco is addictive, and the use of these products causes many negative health problems, including cardiovascular disease, respiratory disease, and more than 20 different types of cancer. More than 8 million people die every year as a result of tobacco use. Cigarettes are the most widely consumed tobacco product in the world. It causes physical and psychological addiction.[1,2] Globally, 942 million men and 175 million women aged 15 years and older smoke.[3] According to Turkish Statistical Institute (TUIK, 2019), the proportion of people aged 15 years and older who use tobacco daily is 28%. Adolescence is considered the riskiest time among other age groups in addiction.[4,5] The Global Youth and Tobacco Survey (2017) reported the rate of current smokers as 17.9% and the rate of those who have tried smoking at least once as 40.2%.[6] The World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) attaches great importance to the prevention of tobacco use among young people.[7,8] In our country, the Tobacco Control Strategy Paper and Action Plan emphasize the prevention of tobacco use among youth.[9] This has made advocacy for smoke-free campuses even more important. Tobacco-free college/campus practices are pioneering work in different

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parts of the world. Their recognized goal is to ensure protection from all types of harmful effects of tobacco in the college environment.[10]

The practice of tobacco-free universities includes the most important goals, such as eliminating tobacco use in indoor and outdoor areas, prohibiting tobacco sales on campus, supporting those who want to quit smoking, and spreading healthy lifestyle habits in universities.[11] University of Michigan (2012)[12] for the first time in the world. The request for a smoke-free campus accepted by the Ministry of Health and the Council of Higher Education in our country is also included in Circular No. 2015/6 of the Presidency of the Public Health Institution of Turkey (Article 3).[13] It is still applied by Bilkent, Hacettepe, and Başkent Universities.[10]

In this study, we aimed to investigate the prevalence of smoking among Pamukkale University Faculty of Medicine students and their views and behaviors regarding smoke-free practices on campus.

MATERIAL AND METHODS

The population of this cross-sectional study consists of 1463 students enrolled in the Faculty of Medicine at Pamukkale University during the academic year 2021-2022. The study was conducted between April 1 and 29, 2022, at the Faculty of Medicine. The study's sample size was calculated to be 454 individuals with a confidence interval of 95%, a precision rate of 3%, and a known prevalence value of 19.6% using the Open Epi program. A questionnaire was implemented in person in the study, and a total of 548 students were reached.

The dependent variables of the study are the smoking status of the medical students and their views about requesting a smoke-free campus, while the independent variables include sociodemographic characteristics, the time they spend smoking indoors, the smoking status in their place of residence, the place where they smoke the most, and their knowledge about the request for a smoke-free campus.

The questionnaire, which was created based on a literature review, contains 8 questions on sociodemographic characteristics, 5 questions on smoking habits, 6 questions on the Fagerström nicotine addiction test, 2 questions on the request for a smoke-free campus, and 20 questions about the opinions and behaviors related to smoke-free zone. The questionnaire consists of 41 questions in total.

Main Points

- The unstoppable rise in smoking frequency in Turkey necessitates strong public health measures.
- Anti-smoking measures targeting higher education youth are urgently needed.
- It is seen that non-smoking physician candidates (89.5%) support the practice of smoke-free areas more than smokers (71.2%) on campus ($P < .001$).
- National determination is important in the transition to "Smoke-Free Campus Practices" initiated by World Health Organization.

The Fagerstrom Test for Nicotine Dependence

Fagerstrom and Schneider[14] developed the Fagerstrom Test for Nicotine Dependence (FTND) to detect nicotine dependence due to smoking. It is a 6-item scale that includes questions about the time of the first cigarette smoked after waking up, challenges in places where smoking is prohibited, an indispensable smoking time during the day, number of cigarettes smoked per day, amount of cigarettes smoked in the morning, and smoking status when ill. In Turkey, the validity and reliability study was conducted by Uysal et al[15] (Cronbach alpha 0.56). Each item on the scale is scored 0, 1, 2, or 3, and the range of scores obtained with the scale is 0-10. The higher the score on the scale, the more severe the cigarette addiction is. 0-2 points are classified as very low, 3-4 points as low, 5 points as medium, 6-7 points as high, and 8-10 points as very high.

Statistical Analysis

The Statistical Package of the Social Sciences® version 21.0 package program (IBM Corp., Armonk, NY, USA) was used to analyze the data. Descriptive statistics are presented with numbers and percentages for categorical variables, while the arithmetic mean and standard deviation are used for continuous variables. The chi-square test was used to compare categorical variables. Whether the responses given in the test conformed to the normal distribution was tested using the Kolmogorov-Smirnov method. The significance level was set as $P < .05$. Twelve views (3, 4, 6, 7, 13, 14, 15, 16, 17, 18, 19, 20) from opinions and behavioral suggestions related to smoke-free zones were selected, and the chi-square test was applied according to smoking status.

Ethics Committee Approval

Ethical approval was obtained for the study from the Pamukkale University Ethics Committee for Non-Interventional Clinical Research, dated March 31, 2022, and with the number E-60116787-020-193171. Verbal informed consent was obtained from the patients who agreed to take part in the study.

RESULTS

Sociodemographic Characteristics and Smoking Behavior

The mean age of participants in the study is 21.72 years. 20.1% of the participants are 2nd semester students, and 10.9% are 5th semester students. 52.9% of our participants are women. 98.2% of students are single, and 46.0% live alone. Those who live at home with their families constitute 20.3% of the participants. 36.7% of mothers and 52.9% of fathers are university graduates. The income of 54.2% of the students is equal to their expenses (Table 1). 54.2% of participants have never smoked in their lives. 31.9% have smoked more than 5 packs of cigarettes. Current smokers are 28.5% of the participants. While 41.7% of smokers reported that they could go without smoking for more than 5 hours, only 9.6% reported that they could not smoke for more than half an hour. 73.7% of participants smoke in their homes. The most common places to smoke are school (45.5%) and home (32.1%). The mean score of smoker students on the

Table 1. Sociodemographic Characteristics of Participants

Age (Mean SD)	**21.72 ± 2.28**	
Variables	**n**	**%**
Term		
Term 1	103	18.8
Term 2	110	20.1
Term 3	97	17.7
Term 4	87	15.9
Term 5	60	10.9
Term 6	91	16.6
Gender		
Female	290	52.9
Male	258	47.1
Marital status		
Married	7	1.3
Single	538	98.2
Divorced	–	–
Other	3	0.5
Place of residence		
At home with his family	111	20.3
At home with a friend	87	15.9
At home with relatives	3	0.5
Living alone	252	46
Dormitory	95	17.3
Mother's Educational Status		
Illiterate	9	1.6
Literate	16	2.9
Primary school graduate	102	18.6
Secondary school graduate	54	9.9
High School Graduate	166	30.3
University graduate/master/doctorate	201	36.7
Father's education status		
Illiterate	3	0.5
Literate	12	2.2
Primary school graduate	61	11.1
Secondary school graduate	38	6.9
High School graduate	144	26.3
University graduate/master/doctorate	290	52.9
Income rate		
Income less than expenditure	72	13.1
Income equal to expenditure	297	54.2
Income more than expenditure	179	32.7
Lifetime Cigarette Smoking		
Never smoked	297	54.2
Smoked less than 100 (5 packs) and quit	76	13.9
Smoked more than 100 (5 packs)	175	31.9
Current smoking status		
Yes	156	28.5
No	392	71.5
Some features belonging to the smoking group		
Duration that they can stay indoors without smoking	15	9.6
Half an hour	43	27.6
30 min-2 h	33	21.2
2-5 h	65	41.7
More than 5 h		
Smoking at place of residence		
Yes	115	73.7
No	41	26.3
The place where they smoke the most		
School	71	45.5
Home	50	32.1
Dorm	8	5.1
Other	27	17.3
Dependency level of smoking students (*FTND Total score is 2.19 ± 1.35, the range of scores obtained from* the scale *varies between 0 and 10.)*		
Very slightly dependent	69	45.7
Slightly dependent	29	19.2
Moderately dependent	19	12.6
Highly dependent	23	15.2
Very highly dependent	11	7.3

Fagerstrom scale for nicotine addiction was 2.19, and the addiction level of smoker students was 45.7% (Table 1). The smoking rate of university students increased significantly as the number of semesters increased (P = .021). The smoking rate of male students was higher than that of female students (P = .001). The smoking rate of students living with their family or relatives is lower (P = .020) (Table 2). Although there is no statistical significance, smokers (14.7%) were more likely than nonsmokers (11%) to report that they had heard of a smoke-free campus (P = .280). Smokers (4.5%) were more likely to know of smoke-free campuses than nonsmokers (2%) (P = .145) (Table 3).

Use of Smoke-Free Zones and Smoke-Free Campuses

About 81.4% of participants agreed with the statements, "There should be more smoke-free rooms." 84.3% said, "I support the existence of smoke-free rooms," and 74.5% said, "There should be smoking cessation studies (training/seminars) at universities." The percentages of the answers "no" or "I don't have an opinion" are as follows: 85% for the statement, "It is difficult for you not to smoke in places where smoking is prohibited (libraries, theaters, hospitals, etc.)," 76.6% to "Information about smoke-free zones is sufficient," 87.4% for the statement, "Controls of smoke-free zones are sufficient," 77.6% to the statement, "It is difficult to go out alone to smoke during class breaks or recesses," and 79% to the statement, "The smoking ban is an attack on the individual's rights" (Table 4). A higher percentage of nonsmokers (90.8%) than those who smoke (57.7%) believe that the number of smoke-free rooms should be increased (P < .001). While 17.6% of nonsmoking students found information about smoke-free zone adequate, 37.8% of smoking students found it sufficient (P < .001). Non-smokers find their smoke-free zone information sufficient (P = .017). Nonsmokers (89.5%) are more supportive of smoke-free areas than smokers (71.2%) (P < .001). Students who smoke think the smoking ban is complicated to implement and that the smoking ban is an attack on individuals' rights to a greater extent compared to nonsmokers (P < .001). About 54.6% of nonsmokers and 44.2% of smokers reported that the university smoking ban encourage students to smoke (P = .029). In addition, 46.9%

Table 2. Smoking Status of the Participants According to Their Socio-demographic Characteristics

Variables	Smoker		Nonsmoker		*P*
	n	%	n	%	
Term					.021
Term 1	17	16.5	86	83.5	
Term 2	30	27.3	80	72.7	
Term 3	36	37.1	61	62.9	
Term 4	23	26.4	64	73.6	
Term 5	22	36.7	38	63.3	
Term 6	28	30.8	63	69.2	
Gender					<.001
Female	59	20.3	231	79.7	
Male	97	37.6	161	62.4	
Marital status					1.000
Married	2	28.6	5	71.4	
Other (single, divorced)	154	28.5	387	71.5	
Place of residence					.020
Next of kin or family	22	19.3	92	80.7	
Other	134	30.9	300	69.1	
Education level of mother					.924
Secondary school graduate and below	52	28.7	129	71.3	
High school graduate and above	104	28.3	263	71.7	
Education level of father					.203
Secondary school graduate and below	27	23.7	87	76.3	
High school graduate and above	129	29.7	305	70.3	
Family income level					.616
Income less than expenditure	24	33.3	48	66.7	
Income equal to expenditure	82	27.6	215	72.4	
Income more than expenditure	50	27.9	129	72.1	

of nonsmokers and 25.6% of smokers indicated that the smoking ban would lead to an increase in smoking as a result of the smoking ban ($P < .001$). While 79.6% of nonsmoking students indicated that activities on smoking cessation (training/seminars) should be conducted at universities, 61.5% of smokers affirmed this statement ($P < .001$). Nonsmoking students affirmed the statements "Universities should establish a smoke-free campus," "If there is a smoke-free campus, the rate of smoking cessation will increase," and "If a smoke-free campus is established, it will be easy to adapt to this process" to a greater extent than nonsmokers ($P < .001$) (Table 5).

Table 3. Information Status of Participants on Smoke-Free Campus Application by Smoking Status

Variables	Smokers n (%)	Nonsmokers n (%)	*P*
Knowledge about the smoke-free campus policy			.280
Yes	23 (14.7)	43 (11.0)	
No	133 (85.3)	349 (89.0)	
Knowledge of campuses with smoke-free campus policy			.145
Yes	7 (4.5)	8 (2.0)	
No	149 (95.5)	384 (98.0)	

DISCUSSION

In our study, about one-third of students smoke, 84.3% support smoke-free zones, and 62.8% support a smoke-free campus.

In a study conducted in 2016 at Pamukkale University Faculty of Medicine, smoking prevalence was found to be 18.8%.[16] A study conducted between 2016 and 2017 among first- and sixth-year students at Katip Çelebi University Faculty of Medicine in İzmir revealed that smoking prevalence was 16.6%.[17] In other studies conducted in 2017-2018 among first- and sixth-year medical students in Zonguldak and Konya, smoking prevalence was 33% and 11.57%, respectively.[18,19] In another study conducted in 2019 with medical school students in Kahramanmaraş, smoking prevalence was 22.9%.[20]

In studies investigating tobacco dependence among medical students in Turkey, the smoking rate varied between 17.6-52.6%.[21]. In a cross-sectional study among medical students in Pakistan, the prevalence of smoking among medical students was 13.4%, which was lower than our study.[22] A joint study conducted at the medical schools of Brown University in the United States and the University of Bologna in Italy concluded that the prevalence of smoking at the University of Bologna (29.5%) was significantly higher than at Brown University (6.1%).[23] In the study, in contrast to other studies, it was found that the prevalence of smoking was significantly higher in the third year (37.1%) compared to the other years. It was found that the frequency of smoking in the 3rd year was twice as high as in the 1st year. This could be due to the influence of peers. Other studies on medical students show that the frequency of smoking increases during medical school.[17,18,24] This difference could be due to the different study environments and time differences.

In this study, smoking prevalence was higher in males than females. The reason could be the strong influence of traditional and cultural structures in Turkey and the fact that the society does not approve of women smoking. Similar results were found in studies by Babar et al[22], Emiroğlu et al[25], Dağtekin et al[26] and La Torre et al.[27] This study found that

Table 4. Distribution of Views and Behaviors of the Participants Regarding Smoke-free Zones

	n (%)	
Propositions	**Yes**	**No—No Idea**
It is difficult for you not to smoke in places where smoking is prohibited (libraries, theaters, hospitals, etc.).	82 (15)	466 (85)
Not smoking indoors is a factor for quitting smoking.	244 (44.5)	304 (55.5)
Smoke-free zones should be increased.	446 (81.4)	102 (18.6)
Information about smoke-free zones is sufficient.	128 (23.4)	420 (76.6)
Smoke-free zone inspections are sufficient.	69 (12.6)	479 (87.4)
I support the existence of smoke-free zones.	462 (84.3)	86 (15.7)
It is difficult to go out alone to smoke during class breaks or recesses	123 (22.4)	425 (77.6)
The increase in nonsmoking areas affects you.	297 (54.2)	251 (45.8)
Long lesson times/long breaks increase the desire to smoke.	217 (39.6)	331 (60.4)
Smoke-free zones affect the frequency of my visits to these places.	284 (51.8)	264 (48.2)
The prohibition of smoking is a complex and difficult regulation to implement.	221 (40.3)	327 (59.7)
Prohibition of smoking is an attack on the rights of individuals.	115 (21)	433 (79)
Smoking in universities encourages students to smoke.	283 (51.6)	265 (48.4)
As a result of the smoking ban, there will be an increase in smoking cessation.	224 (40.9)	324 (59.1)
Studies on smoking cessation (trainings/seminars) should be conducted in universities.	408 (74.5)	140 (25.5)
There should be a smoke-free campus policy at universities.	344 (62.8)	204 (37.2)
If there is a smoke-free campus policy, the rate of smoking cessation increases.	289 (52.7)	259 (47.3)
If a smoke-free campus policy is implemented, it will be easy to adapt to this process.	240 (43.8)	308 (56.2)

smoking frequency was higher among those who lived alone with their friends at home, in their apartment, or in a dormitory than among those who lived with their family and relatives. This finding, consistent with the literature,[25,28-30] could be because they were with friends who smoked and were separated from their families. This suggests that peer

Table 5. Distribution of Some of the Participant Views on Smoke-free Zones According to Smoking Use

	Smokers n (%)		Nonsmokers n (%)		
Propositions	**Yes**	**No—No Idea**	**Yes**	**No—No Idea**	***P***
Smoke-free zones should be increased.	90 (57.7)	66 (42.3)	356 (90.8)	36 (9.2)	**<.001**
Information about smoke-free zones is sufficient.	59 (37.8)	97 (62.2)	69 (17.6)	323 (82.4)	**<.001**
Smoke-free zone inspections are sufficient.	28 (17.9)	128 (82.1)	41 (10.5)	351 (89.5)	**.017**
I support the existence of smoke-free zones.	111 (71.2)	45 (28.8)	351 (89.5)	41 (10.5)	**<.001**
The prohibition of smoking is a complex and difficult regulation to implement.	80 (51.3)	76 (48.7)	141 (36)	251 (64)	**.001**
Prohibition of smoking is an attack on the rights of individuals.	54 (34.6)	102 (65.4)	61 (15.6)	331 (84.4)	**<.001**
Smoking in universities encourages students to smoke.	69 (44.2)	87 (55.8)	214 (54.6)	178 (45.4)	**.029**
As a result of the smoking ban, there will be an increase in smoking cessation.	40 (25.6)	116 (74.4)	184 (46.9)	208 (53.1)	**<.001**
Studies on smoking cessation (trainings/seminars) should be conducted in universities.	96 (61.5)	60 (38.5)	312 (79.6)	80 (20.4)	**<.001**
There should be smoke-free campus policies at universities.	49 (31.4)	107 (68.6)	295 (75.3)	97 (24.7)	**<.001**
If there is a smoke-free campus policy, the rate of smoking cessation increases.	50 (32.1)	106 (67.9)	239 (61)	153 (39)	**<.001**
If a smoke-free campus policy is implemented, it will be easy to adapt to this process.	45 (28.8)	111 (71.2)	195 (49.7)	197 (50.3)	**<.001**

Values in bold indicate statistical significance.

influence was still important in increasing smoking frequency during the study period. The WHO indicates that factors associated with smoking include being away from family and the presence of smokers around the individual.[31] Smoking students stated that they agreed with the view that the smoking ban restricts the individual rights of individuals with a higher frequency than nonsmoking students. Similar results were found in studies by Baştürk et al[17] and Baykan et al.[32]

It was found that the frequency of agreement on the statement, "Universities should apply for a smoke-free campus" was higher among nonsmokers than smokers. A similar result was found in a study by Kekliktepe,[33] which evaluated university students' views on the application of a smoke-free campus. The higher support for a smoke-free campus policy among nonsmokers might be related to their addiction habits. When we look at the responses to the propositions, "Universities should have a smoke-free campus policy," "If there is a smoke-free campus policy, the rate of smoking cessation will increase," and "If there is a smoke-free campus policy, it will be easy to adapt to this process," it shows that smokers find it less suitable. At the same time, nonsmokers support the smoke-free zone in the campus environment, with a significant difference. In this study, nonsmokers were found to agree more often than smokers with the view that smoking cessation will increase due to the smoking ban. This result is consistent with the study of Keklitepe[33] on Üsküdar University students. In the study, 1 out of 10 people responded "yes" to the statement, "Smoke-free zone controls are sufficient." The study by Demir et al[34] in 2016 on employees in tobacco control facilities found that only 37% of the participants thought adequate monitoring was being conducted. It is noteworthy that tobacco control staff also believe that adequate control is not conducted.

Although there are many studies on the reasons for smoking among university students and the factors associated with smoking, the studies on the practice of smoke-free campuses are limited. This study, which focuses on smoke-free zones and smoke-free campuses, is very important. Since it is a cross-sectional study, causality between variables is weak.

One-third of medical school students at Pamukkale University smoke, with a higher proportion among males and those who do not live with family or relatives. All participants strongly support the existence of a smoke-free zone (84.3%), while some (31.4%) tobacco users support the use of a smoke-free campus. Student opinions of smoke-free zones and smoke-free campus applications are more positive among nonsmokers than smokers. We provide training programs to raise awareness among physician candidates who will play a key role in the fight against tobacco products concerning smoke-free zones and campuses. Young people at universities should be encouraged never to start smoking and to quit permanently if they still smoke. We recommend that university senates support the fight against tobacco through smoking cessation polyclinics and smoke-free campus practices.

Ethics Committee Approval: This study was approved by the Ethics Committee of Pamukkale University (Approval No: E-60116787-020-193171, , Date: March 31, 2022).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

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Review

Impact of Earthquakes on Lung Health

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Abstract

Earthquakes are catastrophic natural disasters that cause extensive damage to infrastructure and disrupt the lives of millions worldwide. Beyond the immediate physical and psychological damage caused by earthquakes, these events can significantly impact respiratory health. The inhalation of dust, smoke, particulates, toxic gases, and asbestos exposure can lead to various respiratory health pathologies. These include respiratory infections, exacerbations of pre-existing respiratory diseases, chest traumas, and pulmonary and venous thromboembolism. Longitudinal studies are necessary to assess the long-term respiratory health effects in affected populations. By addressing these knowledge gaps, future mitigation strategies and preparedness measures can be developed to minimize the respiratory health impacts of earthquakes and improve the well-being of affected communities. Robust building infrastructure and comprehensive earthquake preparedness are emerging as the most important determinants for not only mitigating building collapse but also significantly reducing the potential health impacts that follow. This comprehensive review aims to provide a systematic overview of the lung health impacts of earthquakes. It highlights the need for further research to identify specific pollutants, air contaminants, and environmental factors contributing to respiratory health issues following earthquakes.

KEYWORDS: Earthquake, dust, exacerbation, respiratory diseases, asbestos, respiratory infections, trauma

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INTRODUCTION

Earthquakes are one of the most devastating natural disasters, causing extensive damage to infrastructure and disrupting the lives of millions worldwide.[1,2] Earthquakes are linked to the movement of tectonic plates and can be influenced by several factors, such as plate boundaries, geological structures, and volcanic activity.[3,4] These seismic phenomena are often destructive and can result in significant loss of life and property damage. Globally, seismic events surpass 1 million annually, implying a frequency of approximately 2 earthquakes per minute.[5,6] According to the U.S. Geological Survey (USGS), on average, around 18 earthquakes with magnitudes between 7.0 and 7.9 on the Richter scale have occurred annually since 1900, while earthquakes with magnitudes of 8.0 and above happen only once a year on average. Recently, a decrease in the frequency of earthquakes with magnitudes of 7.0 and above has been observed.[7]

On February 6, 2023, the 7.8 and 7.6 magnitude earthquakes hit Southeastern Turkey in about 78 500 km^2 and the north-western territories of Syria, causing widespread damage in both countries. The earthquakes have resulted in more than 50 000 deaths and 120 000 injuries, with 448 healthcare providers, including 101 physicians, losing their lives. The affected area had approximately 15 million people, including 2 million Syrian refugees.[8]

Apart from the immediate physical and psychological harm caused by earthquakes, these events can also significantly impact individuals' respiratory health. These impacts include the inhalation of dust, smoke, particulates, and other toxic gases; exposure to asbestos; respiratory infections; exacerbation of respiratory diseases; chest traumas; and venous thromboembolism (Table 1, Figure 1).[9-12] In nations where the building infrastructure boasts a high standard of quality, a considerable reduction is observed both in the number of individuals affected by the mentioned health effects and in the intensity of their impact. Consequently, it becomes evident that factors such as the quality of the building stock and the level of earthquake preparedness exert a more substantial influence on the emergence of health effects than the sheer magnitude of the seismic event itself. This review aims to provide a comprehensive and systematic overview of the lung health impacts of earthquakes.

INHALED IRRITANTS AND RESPIRATORY IMPACTS

Particulate Matters: Dust and Silica Particles

Airborne particulate matter (PM) is a heterogeneous mixture comprising of various chemical components rather than a single pollutant. It encompasses a complex blend of solid particles, liquid-coated solid cores, and minuscule liquid droplets in the form of aerosols. These particles can encompass inorganic ions, metallic compounds, elemental carbon, organic

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Table 1. Main Impacts of an Earthquake on Lung Health

- Respiratory problems due to inhalation of dust, smoke, particulates, radioactive, and toxic gases
- Respiratory infections (bacterial, viral, fungal infections, and tuberculosis)
- Chest traumas (pneumothorax, rib fracture, hemothorax, diaphragmatic tear, etc.)
- Exacerbation of respiratory diseases (chronic obstructive pulmonary disease and asthma)
- Asbestos-related lung diseases
- Venous thromboembolism

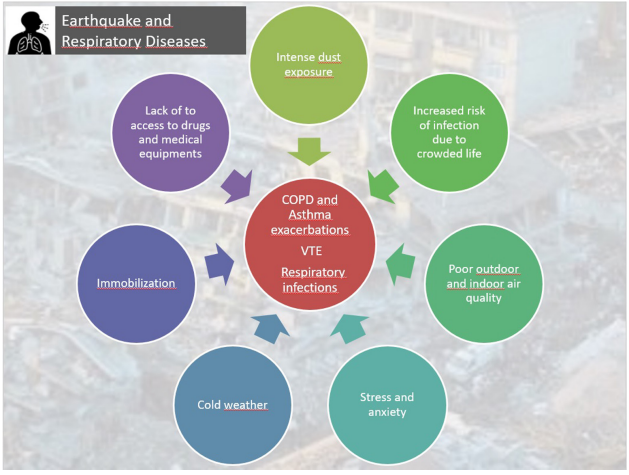


Figure 1. Effects of an earthquake on respiratory diseases.

compounds, and substances originating from the Earth's crust.[13] They exhibit significant variations in size, shape, and chemical composition. To regulate air quality, particle diameter is a crucial metric, with particles that measure 10 µm or smaller (PM_{10}) being inhalable and capable of negatively impacting human health. On the other hand, fine PM ($PM_{2.5}$) refers to particles with a diameter of 2.5 µm or less.

During earthquakes, releasing particulate pollution containing dust and silica particles from collapsed buildings into the air severely threatens respiratory health. Inhaling these particles, particularly the $PM_{2.5}$ particles, can facilitate deep penetration into the respiratory system. General sources of these particles include car exhaust, in particular diesel exhaust, industrial processes, construction activities, and environmental dust and pollen. Prolonged exposure to such particles can exacerbate preexisting lung conditions, cause respiratory disorders, and elevate the risk of respiratory infections.[8,9]

Main Points

- Earthquakes pose significant respiratory health risks due to environmental and occupational exposures like particulates, asbestos, mold, and hazardous chemicals.
- Addressing these risks requires: training healthcare professionals, monitoring exposure levels, and constructing resilient buildings.
- Longitudinal studies are necessary to assess the long-term respiratory health effects in affected populations.
- Interdisciplinary collaboration among public health experts, geologists, engineers, and policymakers is essential for holistic approaches to mitigate immediate and long-term respiratory health impacts.

Among those most exposed to PM following earthquakes are victims and search-and-rescue teams, who are exposed to dust particles in the debris during and immediately after the seismic event. Demolition teams engaged in dismantling buildings are severely affected by the earthquake, and teams involved in rubble removal also face substantial exposure. Furthermore, the concentrated presence of airborne dust particles during debris clearance poses a significant risk of acute and chronic respiratory diseases for individuals residing near the debris and those living in nearby tent cities.[14-16]

On January 17, 1995, a significant earthquake, known as the Hanshin earthquake, struck the city of Hyogo, Japan. Within a year after the earthquake, the demolition of damaged buildings commenced. An air quality assessment conducted in the earthquake-affected regions revealed high total suspended particulate levels in heavily damaged areas, with a maximum concentration of 150 µg/m^3 measured at 5 locations. Additionally, 8 concrete, mortar, and soil dust samples were collected and analyzed using the elemental x-ray fluorescence method. The concrete and mortar samples exhibited calcium (Ca) and sulfur (S) elements. In contrast, the soil samples contained heavy metals such as titanium (Ti), iron (Fe), and zirconium (Zi).[17] Another study conducted after the Hanshin earthquake disclosed that the concentration of inhalable dust particles in the demolition area exceeded the recommended threshold limit value of 2 mg/m^3 set by the Japan Society for Occupational Health.[18] In 2011, a significant earthquake of approximately 9 hit the city of Tohoku, Japan, followed by a subsequent tsunami 6 minutes later, resulting in many casualties and injuries.[19] Three weeks after the earthquake, a case of pulmonary alveolar proteinosis was reported due to the intense inhalation of fine dust particles.[14] Following an earthquake in central Italy in 2009, the affected region witnessed thousands of construction sites over the course of 10 years. Mastrantonio et al[20] determined that workers engaged in manual demolition activities were exposed to inhalable dust particles exceeding the threshold limit value of 10 mg/m^3.

In 2002, a 6-magnitude earthquake in Sultandagi, Afyon, Turkey, resulted in 39 deaths and 325 injured individuals. This study showed that one of the leading causes of death was respiratory failure resulting from inhaling dust particles associated with the traditional architecture of rural areas.[21] Research on the increased dust density in earthquake-affected areas after seismic events and the specific PM species contributing to this increase is limited. Identifying such data immediately after and in the days following an earthquake, during rescue and demolition activities, would contribute to raising awareness and implementing measures to safeguard the lung health of survivors and aid teams.

Radon, Carbon Dioxide, and Carbon Monoxide Gases

Radon and carbon dioxide (CO_2) can be released during and after an earthquake.[22] Radon is a naturally occurring

radioactive gas produced by the decay of uranium in soil and rocks and can seep into buildings through cracks and other openings.[23,24] Carbon dioxide is a colorless and odorless gas that is also naturally occurring but can be released from underground sources during seismic activity.[25] These radon offspring are thought to be the primary cause of human exposure to alpha radiation, which damages DNA and causes cellular harm to the respiratory system. Lung cancer and radon-induced lung illnesses eventually develop because of these alterations in the respiratory epithelium.[26] Studies show that exposure to radon gas can increase the risk of lung cancer, particularly for those exposed to high gas levels over a long period of time. Exposure to high radon levels can cause symptoms such as headaches, dizziness, and nausea.[27] Exposure to CO_2 can also be dangerous, particularly in sealed spaces with poor ventilation. High concentrations of CO_2 can cause symptoms such as headaches, dizziness, and shortness of breath. In extreme cases, exposure to high levels of CO_2 can lead to unconsciousness and even death.

During and after an earthquake, secondary effects can potentially lead to the release of carbon monoxide (CO). For example, if there is damage to gas lines or heating systems, CO can be released. Appliances linked to CO poisoning in disasters are furnaces, boilers, gas stoves, water heaters, portable generators, automobiles, vans and trucks, portable heaters, chainsaws, pressure washers, and petroleum or diesel-powered tools. Taking CO safety seriously is crucial, and ensuring appropriate precautions are in place. Fuel-burning equipment should be checked regularly to minimize the risk of CO leakage. On the other hand, survivors may use enclosed spaces and vehicles for shelter in cold conditions, especially during the winter. Such areas with insufficient ventilation can lead to the accumulation of CO, which can cause CO poisoning.[28-31]

RESPIRATORY INFECTIONS

Bacterial, Viral and Fungal Infections

Victims of earthquakes, volunteers involved in rescue operations, and survivors are exposed to microbiological threats during and after the earthquake. Following the 1999 Marmara earthquake in Turkey, Keven et al[32] examined the clinical and laboratory results of 639 patients admitted to 35 hospitals and reported infections in 223 patients. Sepsis was found in more than half of these patients, while wound infections were observed in half of the remaining patients and lung infections in the other half. Furthermore, the analysis revealed that most of these infections were caused by gram-negative aerobic bacteria and *Staphylococcus* spp.

Wang et al[33] conducted a bacteriological evaluation on patients with crush syndrome admitted to Sichuan University, West China Hospital after the Wenchuan earthquake and identified 210 different bacterial isolates from 42 out of 66 earthquake victims. Most of these isolates were gram-negative bacilli, followed by gram-positive bacteria and fungi. The main isolates obtained from the wounds were *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

In another study published in 2012, pathogenic bacteria were investigated in 91 patients rescued alive from under the rubble during the same earthquake. In 43.3% of the patients, infections were detected in the wound areas, and in 37.1%, infections were detected in the airways. The report stated that 62 patients had gram-negative bacilli, 23 had gram-positive rods, 9 had fungi, and 3 had *Clostridium perfringens*, an anaerobic bacterium. Additionally, these patients had different isolates from the microbiological isolates obtained from non-earthquake trauma patients in the hospital. The most frequently observed pathogenic isolates were *Escherichia coli*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *Burkholderia cepacia*, and *Enterococcus* sp.[34]

Furthermore, Zhang et al[35] demonstrated that wound infection, lung infection, and sepsis were common complications in 112 out of 147 crush syndrome patients admitted to the hospital due to infection after the Wenchuan earthquake (75.7% of the patients). Mainly, lung infections were observed in 24 patients, and sputum examinations showed that the bacterial isolates responsible for lung infection were *A. baumannii* (11/24), *Klebsiella pneumonia* (5/24), *S. aureus* (4/24), *E. coli* (2/24), and *P. aeruginosa* (2/24).

Another microbial threat from earthquakes is the contamination of water sources with bacteria, viruses, fungi, and parasites due to damage to water distribution systems and sanitation units or direct earthquake-induced soil liquefaction and tsunamis.[36,37] These contaminations can lead to various waterborne diseases and respiratory infections. Moreover, this risk is particularly high for survivors pulled from the debris, those involved in rescue operations, and people living in tent cities, making it an issue that requires careful attention. Inadequate sanitation and improper waste disposal can contribute to the spread of infectious microorganisms.[38] Urgent measures such as water quality assessment, sanitation promotion, and emergency medical services are necessary to mitigate the impact of these hazards on lung health.

Earthquakes often result in population displacement, with people seeking temporary shelter in crowded spaces such as evacuation centers or makeshift camps. These crowded living conditions can facilitate the spread of viral respiratory infections, particularly those transmitted through respiratory droplets. Earthquakes and their subsequent aftermath can lead to increased stress levels that could lead to post-traumatic stress disorder syndrome among individuals. Stress has been associated with immune system dysfunction, potentially making individuals more susceptible to viral respiratory infections and worsening outcomes.[9]

The study conducted by Kun et al[39] highlights an essential point regarding the increased risk of acute respiratory infections among rescuers and healthcare workers in the aftermath of earthquakes. The study focused on rescue teams living in shelters in Beichuan after the 2008 China earthquake and found that acute upper respiratory tract infections were the most common disease reported among these individuals, accounting for 13.2% of cases.

Following seismic events, compromised and damp structures can create favorable conditions for the proliferation and dissemination of molds, fungi, and organic PM. Water infiltration into buildings also provides an optimal environment for

these microorganisms' growth; when their spores become airborne, they can lead to respiratory pathologies, including allergies. Additionally, inhalation of high concentrations of organic dust derived from soil, debris, and decaying organic matter poses respiratory risks.

In the aftermath of the 1994 Northridge earthquake in Ventura County, California, a significant outbreak of coccidioidomycosis, a respiratory disease caused by inhaling airborne spores of the dimorphic fungus *Coccidiodes immitis, was* experienced. This fungus primarily grows in the upper layers of grand soil, around 10-30 cm below the surface, in limited semi-arid regions of the western hemisphere, including the southwestern United States, Mexico, and parts of Central and South America. Approximately 60% of infected individuals remain asymptomatic, while others may exhibit symptoms resembling influenza-like respiratory illness or other clinical manifestations.[40]

The Santa Susana Mountains, located north of Simi Valley, California, experienced landslides triggered by the earthquake and its strong aftershocks. These landslides generated dust clouds dispersed into nearby valleys by north-easterly winds. Consequently, the number of coccidioidomycosis cases in the region dramatically increased 2 weeks after the earthquake. Out of the 203 identified cases, 56% occurred in Simi Valley. Individuals physically present in the dust clouds were 3 times more likely to be diagnosed with acute coccidioidomycosis than those not exposed. The risk of acute coccidioidomycosis diagnosis increased with a longer duration of exposure and a prolonged stay within the dust clouds.[41] These reports strongly suggest that the outbreak of coccidioidomycosis in Ventura County was linked to the dissemination of *C. immitis* arthrospores through dust clouds caused by the landslides triggered by the 1994 Northridge earthquake.

The geographical distribution of respiratory tract infection agents can vary due to a variety of factors, including climate, population density, healthcare infrastructure, and cultural practices. Establishing a robust disease surveillance system is crucial for early detection and effective management of infectious diseases after disasters.[5]

Conducting prompt assessments and developing remediation and prevention strategies to address these hazards and protect lung health is important. Moreover, it should be noted that no studies have been published regarding cases of coccidioidomycosis or other respiratory fungal infections following earthquakes in Turkey. However, it is plausible to expect that in the aftermath of earthquakes, damaged buildings, debris areas, and moistened rubble provide favorable conditions for mold and fungal growth and dissemination. To mitigate these risks and safeguard lung health, regular and rapid evaluation of disease-causing microorganisms, as well as the implementation of effective cleaning and prevention strategies, is essential.

Tuberculosis

The relationship between earthquakes and tuberculosis (TB) primarily revolves around the potential impact of earthquakes on TB control programs and the living conditions that can facilitate the transmission of TB. Earthquakes can cause damage to healthcare infrastructure, disrupt healthcare services, and lead to the displacement of populations. This can hamper the diagnosis, treatment, and follow-up of individuals with TB and interrupt the supply of medications.

Following an earthquake, displaced populations may be forced to live in crowded temporary shelters or communal areas. Overcrowding and poor ventilation can increase the risk of TB transmission among individuals, particularly in settings with a high TB burden. Earthquakes often result in economic hardships and social disruptions. Poverty and a lack of access to healthcare services can contribute to delays in TB diagnosis and treatment, leading to increased transmission and poorer treatment outcomes.[5]

The psychological stress caused by earthquakes can weaken individuals' immune systems and make them more susceptible to TB infection. Stress and trauma can also contribute to the reactivation of latent TB infections.[42]

In a study assessing the risk of TB after earthquakes, 5746 children in earthquake-affected areas were tested for *Mycobacterium tuberculosis* in the 2013 Bohol earthquake in the Philippines. Of these, 355 tested positive for the tuberculin skin test, indicating latent TB, and 16 were found to have active TB.[43] Tuberculosis incidence increased in individuals in the earthquake-affected region after the 2010 Haiti earthquake.[44] Similarly, an increase in TB cases was found during the 2008 Wenchuan earthquake compared to the same period in the previous year.

Balbay et al[45] investigated the effects of 2 consecutive earthquakes on TB patients' sociodemographic and disease-related characteristics in Düzce, a rural area in northwest Turkey. Although the study did not specifically focus on factors influencing patient adherence to TB therapy, no major changes were observed in the socioeconomic parameters that could impact the outcome of TB. In the pre-earthquake period, patients were frequently hospitalized, while in the peri- and post-earthquake periods, patients received ambulatory care. In the peri-earthquake period, patients were significantly monitored every month. Furthermore, patients were mainly followed by the same doctor in the post-earthquake period. Their findings suggested that the earthquakes had a minimal impact on TB incidence and control during and after the earthquakes in Düzce. Another study from Turkey aimed to investigate the adherence to TB treatment. Although the adherence rate for patients who initiated anti-TB therapy before the earthquake tended to be higher than that for those who initiated treatment immediately after the earthquake, this was not significant.[46]

It is important to note that the relationship between earthquakes and TB is complex, and the specific impact may vary depending on the magnitude of the earthquake, the local TB epidemiology, and the existing healthcare infrastructure. Efforts to mitigate the impact of earthquakes on TB control may include maintaining and strengthening healthcare services, ensuring access to medications, implementing infection control measures in crowded settings, and conducting active case-finding activities in post-disaster situations.

CHEST TRAUMAS

Trauma is a significant cause of morbidity and mortality in earthquake situations, and it is often the primary reason for hospital admissions in the immediate aftermath of an earthquake, particularly within the first 24 hours.[12] Bulut et al[47] conducted a retrospective analysis of the medical records of 645 earthquake victims in Türkiye following the 1999 Marmara earthquake. Most patients (77%) were hospitalized within the first 3 days after the earthquake, and approximately 10% of the individuals who sought medical attention at the hospital during the earthquake had chest traumas. Chest traumas can occur in earthquake situations for various reasons, including collapsing buildings or constructions, falling debris, or being struck by objects.[48] The forceful compression or impaction on the chest during an earthquake can lead to rib fractures, which can cause significant pain, difficulty breathing, and an increased risk of lung injury. Pneumothorax may be caused by rib fractures or other trauma to the chest during an earthquake. Crushing injuries to the chest may occur when individuals are trapped under collapsed structures. These injuries can cause severe damage to the chest wall and internal organs and may result in various complications, including respiratory distress.[49,50] It is important to note that the severity and prevalence of these chest injuries can vary depending on the earthquake's magnitude, the proximity to the epicenter, and the level of destruction.

The initial hours after an earthquake pose significant challenges for emergency medical services and hospitals, as they must rapidly assess, triage, and treat many trauma patients. The severity of injuries and the immediate need for medical intervention often determine the priorities in such situations. Prompt and effective management of trauma victims, i.e., timely triage, stabilization, and surgical interventions, can substantially reduce morbidity and mortality rates.[47]

In the 1999 Marmara earthquake, Toker et al[51] evaluated 19 patients with chest trauma, and pneumothorax was observed in 37% of the patients. Rib fractures, hemothorax, and hemopneumothorax were present in 26% and 11% of the patients, respectively. Diaphragmatic tears, subcutaneous emphysema, and cervical tracheal damage were observed in 11%, 11%, and 5% of the injuries, respectively. In their study on hospitalized patients in the Düzce and İzmit earthquakes, Ozdoğan et al[48] found that pneumothorax was the most frequent pathology, accounting for 50% of the injuries, and rib fractures were the second most common finding, accounting for 33.3% of the injuries. These findings provide valuable insights into the types and frequencies of chest trauma observed in earthquake situations, and pneumothorax and rib fractures appear to be the most common injuries in such conditions.

Healthcare systems and emergency responders must be well-prepared and equipped to handle the surge in trauma cases following an earthquake. This includes having sufficient medical personnel, supplies, and facilities in place and establishing effective communication and coordination systems to ensure a timely and organized response.

EXACERBATION OF RESPIRATORY DISEASES

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) patients can experience exacerbations or worsening of symptoms during and after an earthquake. The environmental conditions and interruptions associated with earthquakes can lead to COPD exacerbations. The damage and collapse of buildings can lead to the release of dust and other airborne particles. These particles can irritate the airways of individuals and induce symptoms such as coughing, wheezing, and shortness of breath.[52] The sudden and unexpected nature of earthquakes can also induce stress and anxiety, worsening COPD symptoms and leading to increased breathing difficulties and exacerbating respiratory symptoms.[53] Earthquakes can disrupt infrastructure, including power outages, damage to air filtration systems, or contamination of water sources. These factors can deteriorate indoor and outdoor air quality, adversely affecting COPD patients.[52]

Ma et al[54] investigated the major risk factors for acute exacerbations of COPD in patients who survived the Wenchuan earthquake in Sichuan, China. The study utilized a questionnaire survey conducted at multiple time points (1 month, 3 months, and 12 months) after the earthquake. The study included 301 COPD patients from both earthquake-affected and non-earthquake areas. Patients from the earthquake zone had a significantly higher incidence of acute exacerbations of COPD compared to those from the non-earthquake zone at 3 months and 12 months following the earthquake. Furthermore, patients from the earthquake area had a significantly higher prevalence of post-traumatic stress disorder (PTSD) and higher scores on the Self-Rating Anxiety Scale and Self-Rating Depression Scale within 1 month and 3 months after the earthquake. The difference in PTSD prevalence remained significant even 12 months after the earthquake. The identified risk factors, including older age, worse pulmonary functions, psychological disorders, and poor living environment, were associated with an increased risk of acute exacerbations of COPD. The study suggested that COPD patients should receive psychotherapy and better living arrangements as early as possible after such severe disasters to minimize the risk of exacerbations.

A retrospective cohort analysis from Ishinomaki, a region severely affected by the Great East Japan Earthquake in 2011, investigated the impact of the disaster on patients with COPD. The findings of the study revealed several important observations. Firstly, in the immediate aftermath of the disaster, patients who required oxygen therapy at home visited the hospital to receive oxygen. This suggests that the disruption caused by the earthquake led to a lack of access to essential medical equipment and supplies necessary for managing COPD at home. Furthermore, during the subacute phase, which encompassed the third to fifth weeks after the earthquake, there was a significant increase in the number of hospitalizations due to COPD exacerbations compared to the prior period. This suggests that the disaster had a detrimental effect on the respiratory health of COPD patients, potentially due to various factors such as increased stress, exposure to

environmental hazards, or limited access to medical care. The incidence of exacerbated COPD cases returned to normal levels 6 weeks after the earthquake, suggesting that although the disaster initially had a significant negative impact on COPD patients, the situation gradually improved over time, possibly due to the restoration of healthcare services and the overall recovery efforts in the region.[55]

Asthma

Dust particles resulting from the crashed buildings and debris may irritate the airways of individuals with asthma, triggering symptoms such as coughing, wheezing, and shortness of breath.[56]

The sudden and unexpected nature of earthquakes can also induce stress and anxiety, which are known to be potential triggers for asthma symptoms. Emotional stress can lead to increased sensitivity of the airways and bronchoconstriction, making asthma symptoms more likely to occur.[57] Earthquakes may disrupt access to essential medications or medical care, making it challenging for asthma patients to manage their condition effectively. Inadequate access to rescue inhalers or maintenance medications can increase the risk of an asthma attack.

Tomita et al[56] conducted a retrospective cohort involving 156 asthmatic outpatients of Tottori University Hospital, aged 18-89. They documented the asthmatic symptoms and monitored patients' peak expiratory flow (PEF) rates for more than 1 year before the Tottori-Ken Seibu earthquake and 1 year after the earthquake. Among the study participants, 17 patients (11%) experienced an exacerbation of asthma within 1 month after the earthquake. The researchers compared the diurnal variability of PEF during the month following the earthquake to values recorded during a matched month 1 year prior to the earthquake. They also reviewed the medical case noted to identify factors associated with the exacerbation and used the multivariate analysis to determine the contribution of these factors. The results indicated that airflow limitation was independently associated with asthma exacerbations after the earthquake.

Furthermore, acute asthma attacks were more likely to occur within the first week following the earthquake, even without diurnal PEF variability. The study highlights the importance of identifying individuals with asthma who have the risk of exacerbations after earthquakes. Factors such as preexisting airflow limitations may increase susceptibility to exacerbations. The early post-earthquake period, particularly the first week, appears to be critical for monitoring and managing asthma symptoms in at-risk individuals.[56]

Following the major earthquake in Eastern Japan (March 11, 2011), the indoor fungal contamination in prefabricated temporary housing, private residences, and rental apartments during the winter season and rainy days was significantly higher than the recommended indoor fungal contamination level of 1000 colony-forming units (cfu)/m^3. The contaminant identified was *Aspergillus*, a known allergenic species.[58,59] In February 2012, a 66-year-old male ex-smoker diagnosed with bronchial asthma since the age of 5 presented to the hospital with symptoms of chest tightness, coughing, and wheezing following the earthquake. A skin prick test on the patient revealed a positive reaction to the reproductive stage form of *Aspergillus glaucus*, known as *Eurotium herbarium (E. herbarium)*. Air sampling from the patient's home revealed a significantly high count of *E. herbarium* at 163 200 colony-forming units per cubic meter (CFU/m^3). Further clinical evaluations confirmed the patient's diagnosis of bronchial asthma.[60]

Individuals with asthma must consult their healthcare provider for personalized guidance on managing asthma during earthquakes.

ASBESTOS-RELATED LUNG DISEASES

Among other particles that affect the respiratory system following earthquakes are asbestos fibers. Asbestos is a well-established carcinogen known to cause pulmonary fibrosis (asbestosis), lung cancer, and mesothelioma. The International Agency for Research on Cancer has classified asbestos as a group 1 carcinogen, indicating that there is sufficient evidence to support its carcinogenicity in humans. Also, studies have demonstrated a causal relationship between asbestos exposure and various cancers, including larynx carcinoma, nasopharynx carcinoma, gastrointestinal system cancers, and ovarian cancers.[61]

The extensive collapse of buildings during earthquakes is believed to disperse asbestos fibers into the air, thereby exposing rescue workers and disaster victims to inhalation risks. The adverse health effects of asbestos fibers have been observed in low-dose ambient exposure and high-dose occupational exposure cases. Asbestos has been strictly prohibited since 2006 in Japan and 2010 in Turkey. However, major natural disasters like earthquakes and tsunamis can lead to the release of asbestos due to damage to numerous buildings and homes constructed before the implementation of the asbestos ban. In Turkey, it was reported that 1.2 million tons of asbestos were used as a construction material between 1900 and 2003, before the ban.[62-64]

Van Orden et al[65] analyzed the air samples from buildings following the 1989 earthquake in central coastal California. Their results showed that, in general, asbestos levels in the sampled buildings did not significantly differ from outdoor levels, even immediately after the earthquake. However, there were exceptions to this finding, and samples collected near debris clean-up areas and in buildings undergoing asbestos abatement showed slightly higher concentrations than indoor and outdoor samples. These findings suggest that while there were some localized areas with higher asbestos levels due to debris clean-up and ongoing abatement, the overall risk of asbestos exposure in the sampled buildings was relatively low and within regulatory limits.

Following 2 major earthquakes that occurred on February 6 in Southeastern Turkey, there is an ongoing potential risk of asbestos dissemination in areas characterized by extensive pre-2010 construction. Therefore, it is crucial to analyze ambient PM and surrounding debris from buildings for the presence of asbestos and to compile reports addressing the consequences of such exposure in earthquake-prone areas.

Additionally, taking precautions to minimize asbestos exposure during demolition activities is paramount. It is essential to inform and educate the public, including residents and workers in affected areas, about the risks of asbestos exposure and the proper precautions to take during post-earthquake activities. Also, the implementation of a specific surveillance program focusing on the incidence of cancer among people exposed to asbestos or workers engaged in post-earthquake activities in earthquake-affected areas is of great importance.

VENOUS THROMBOEMBOLISM

There is no direct relationship between earthquakes and venous thromboembolism (VTE). However, it is important to note that in the aftermath of a major earthquake, secondary effects may be indirectly contributing to an increased risk of VTE. In areas affected by earthquakes, medical infrastructure may be damaged or overwhelmed, leading to delays in accessing appropriate medical care. This delay in treatment or lack of access to anticoagulant medications could potentially increase the risk of VTE in individuals who are already susceptible. Earthquakes can cause structural damage, requiring individuals to remain confined to shelters or temporary accommodations for extended periods. Prolonged immobility can be a risk factor for VTE, especially if people cannot move around.[66]

Earthquakes can cause injuries that require immobilization, such as fractures or crush injuries. Immobilization of a limb due to trauma can increase the risk of developing blood clots in the veins of the affected limb.[67] Sakuma et al[68] investigated the occurrence of acute pulmonary embolism (APE) following the 2004 Mid-Niigata Prefecture earthquake in Japan and assessed the associated risk factors. The study found a higher relative risk of APE in the high evacuee rate area compared to the low evacuee rate area. Additionally, the risk of APE was higher in women. All patients in the high evacuee rate area had stayed in their automobiles for long periods, whereas none of the patients in the low evacuee rate area had done so. This suggests a potential link between prolonged immobilization in automobiles and the occurrence of APE. Staying in automobiles for extended periods was identified as a potential risk factor for APE in the high evacuee rate area. Also, Watanabe et al[69] investigated the impact of the earthquake in Niigata, Japan, on the occurrence of pulmonary embolism (PE) and sudden death. The researchers observed an increase in PE cases following the earthquake compared to pre-earthquake periods and previous years. The first case of PE occurred 2 days after the initial earthquake, and new cases continued to be reported for 27 days after that. Six out of the 9 patients (67%) with PE had taken refuge in their automobiles before experiencing symptoms, suggesting a potential association between prolonged immobilization in automobiles and the risk of PE. The study also observed an increase in sudden death cases after the earthquake. Of the 22 cases, 7 (32%) had spent 1 or more nights in automobiles. Based on these findings, the study suggests that PE should be considered and attended to after disasters. It also highlights the potential risk of prolonged immobilization in automobiles as a contributing factor to the increased occurrence of PE and sudden death following earthquakes.

Maintaining mobility, staying hydrated, and seeking medical attention are crucial steps to reduce the risk of VTE, especially in situations where movement might be restricted due to the aftermath of an earthquake. In addition to these measures, individuals in earthquake-affected areas should also be mindful of other risk factors that might exacerbate the risk of VTE, such as preexisting medical conditions, certain medications, and genetic predisposition. Following medical advice and guidance is paramount, as healthcare professionals can provide tailored recommendations based on individual health status and the specific circumstances of the earthquake aftermath. Emergency response and medical personnel play a critical role in providing appropriate care and support to those in earthquake-affected areas.

CONCLUSION

Earthquakes cause various environmental and occupational exposures that can significantly impact lung health. Understanding and addressing the risks associated with PM, asbestos, mineral fibers, metallic particles, molds, fungi, organic dust, and microbiological hazards are crucial for protecting individuals and implementing effective mitigation strategies. By prioritizing appropriate measures and ensuring proper handling and protective measures, the adverse effects of earthquakes on lung health can be minimized, and this can also facilitate a healthier recovery. Training healthcare professionals in disaster management and implementing disaster response plans can further enhance the readiness and effectiveness of healthcare systems in managing earthquake-related trauma.

Measuring occupational and environmental exposure levels to factors such as dust, particulates, toxic gases, and hazardous chemicals requires a combination of technical methods and strategic planning. Monitoring changes in these exposure levels over time involves a systematic approach to data collection, analysis, and interpretation.

It is clear that robust building infrastructure and effective earthquake preparedness play a pivotal role in minimizing the cascading effects of earthquakes, including their impact on respiratory health. By focusing on constructing resilient buildings and bolstering preparedness efforts, communities can not only mitigate building collapses but also significantly reduce the potential health consequences that follow. Such measures should be seen as integral parts of overall disaster management strategies.

As a result, this comprehensive review underscores the urgent need for further research into the specific pollutants, air contaminants, and environmental factors that contribute to respiratory health issues following earthquakes. Identifying these factors will enable more targeted interventions and policies that can safeguard respiratory health during and after seismic events. Furthermore, collaboration among interdisciplinary teams, including public health professionals, geologists,

engineers, and policymakers, is crucial to developing holistic approaches that account for both immediate- and long-term health impacts.

FUTURE RESEARCH

Although the existing literature suggests an association between earthquakes and increased threats to respiratory health, gaps and unmet needs still require further investigation. To address these gaps, future research should concentrate on the following areas.

Identifying Specific Pollutants and Environmental Factors

Earthquakes can release various pollutants into the air, such as PM, gases, and toxic substances. Determining the specific pollutants, toxicants, and irritants responsible for the respiratory health impacts observed during and after earthquakes is important. This knowledge can help in developing targeted mitigation strategies and interventions.

Assessing Exposure Levels and Patterns

Understanding the exposure levels and patterns of affected populations is crucial for evaluating respiratory health impacts and implementing effective protective measures. Future research should focus on assessing the duration, frequency, and intensity of exposure to various pollutants and environmental factors resulting from earthquakes. This information can also provide insights into the potential mechanisms through which earthquakes affect respiratory health.

Longitudinal Studies for Long-Term Impacts

While the immediate respiratory health effects of earthquakes are well documented, there is a need for more longitudinal studies to assess the middle- and long-term impacts. These studies should follow the cohorts and individuals over an extended period, allowing researchers to investigate the persistence or development of respiratory conditions such as asthma, pulmonary fibrosis, COPD, malign mesothelioma, and other respiratory diseases associated with earthquakes.

Vulnerable Populations and Susceptibility Factors

Research should focus on identifying vulnerable populations and factors that increase susceptibility to the respiratory health impacts of earthquakes. Factors such as age, preexisting respiratory conditions, socioeconomic status, and access to healthcare can influence the severity and duration of respiratory pathologies. Understanding these factors can help target interventions and support services for those most in need.

Mitigation Strategies and Preparedness

Future research should also explore effective mitigation strategies and preparedness measures to reduce the respiratory health impacts of earthquakes. This could involve studying the effectiveness of engineering solutions, building codes, urban planning approaches, and early warning systems in minimizing exposure to harmful pollutants and improving respiratory health outcomes.

By addressing these research areas, we can enhance our understanding of the relationship between earthquakes and respiratory health and develop evidence-based strategies to mitigate the impacts on affected populations.

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Erratum

In the original article authored by Güngör et al, titled "Evaluation of Patients with COVID-19 Followed Up in Intensive Care Units in the Second Year of the Pandemic: A Multicenter Point Prevalence Study" (Thorac Res Pract. 2024;25(1):11-16. DOI: 10.5152/ThoracResPract.2023.23024) published in the January 2024 issue of Thoracic Research and Practice, the name of one of the co-authors was written incorrectly (Nilgün Kavruk) by an oversight. Subsequently, the name is corrected (Nilgün Kavrut Öztürk) and the online version of the original article has been updated accordingly. You can access the revised version of this original article via the following link: https://thoracrespract.org/en/evaluation-of-patients-with-covid-19-followed-up-in-intensive-care-units-in-the-second-year-of-the-pandemic-a-multicenter-point-prevalence-study-132252.

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