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ABOUT

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Editorial



Exposome and the Prevention of Lung Diseases: A New Paradigm for Lung Health and Prevention

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In recent years, the concept of the exposome—the totality of environmental exposures across the lifespan—has gained traction in respiratory medicine. Lung diseases are now increasingly recognized not as the consequence of a single risk factor or genetics alone, but as complex outcomes of lifelong interactions between genes and environment.¹ The exposome framework encompasses chemical, physical, biological, and social exposures, providing a holistic lens for prevention. This is especially timely: fine particulate matter (PM_{2.5}) is recognized as the leading environmental health risk worldwide, acutely exacerbating asthma and chronic obstructive pulmonary disease (COPD) and contributing to lung cancer, cardiovascular disease, and dementia over the long term.² Globally, pollution is linked to 9 million premature deaths annually, with respiratory illnesses representing a substantial share.³ Against this backdrop, the exposome paradigm offers an urgently needed foundation for prevention.

Chemical exposures remain central drivers of respiratory disease. Beyond smoking, outdoor air pollution has been classified as a group 1 lung carcinogen by the International Agency for Research on Cancer. Recent mechanistic data demonstrate that PM_{2.5} can act as a tumor promoter, awakening preexisting oncogenic mutations through macrophage-derived interleukin-1 β signaling.⁴ In experimental models, IL-1 β blockade prevented tumor outgrowth, underscoring that modifying exposures or targeting inflammation could reduce cancer risk.⁴ Physical exposures add to the burden. Occupational inhalants such as silica and coal dust cause progressive fibrotic lung disease, while radon remains a leading cause of lung cancer in never-smokers. Climate-related exposures are emerging threats: wildfire smoke episodes are associated with surges in hospitalizations for asthma and COPD, and evidence suggests wildfire-derived PM_{2.5} may be more toxic per unit than urban pollution.⁵ Extreme heat further stresses vulnerable patients, increasing the risk of exacerbations and mortality.⁶ Biological exposures are equally important. Early-life contact with microbial diversity, as seen in farm environments, can lower asthma risk by modulating immune development.⁷ By contrast, mold exposure is increasingly recognized as a cause of hypersensitivity pneumonitis, with improvements in lung function reported after remediation.⁸ Recurrent respiratory infections across the life course, including influenza and Coronavirus disease-2019, can accelerate declines in lung function.⁹ The airway microbiome has emerged as an interface of the exposome, with microbial composition shown to mediate the respiratory effects of pollution.¹⁰ Finally, the social environment shapes exposure risk and vulnerability. A 2024 analysis estimated that more than half of the excess all-cause mortality among Black populations in the United States compared with White populations was attributable to higher PM_{2.5} exposure and greater susceptibility.¹¹

Advances in technology are transforming how exposures are measured. Wearable sensors now track personal exposure to air pollutants, volatile organic compounds, and allergens in real time. One innovation, a smart mask, was shown

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capable of continuously harvesting exhaled breath condensate and analyzing inflammatory biomarkers in daily life, offering a noninvasive early warning system.¹² At the molecular level, untargeted exposomics using high-resolution mass spectrometry allows simultaneous detection of thousands of exogenous compounds in biospecimens.¹³ This approach has uncovered a previously unmeasured dark matter of exposures, broadening the biomonitoring landscape. Complementary multi-omics approaches reveal the biological imprints of exposures: DNA methylation at loci such as AHRR remains a durable marker of smoking and pollution, while proteomic signatures of inflammation and oxidative stress predict COPD progression.^{14,15}

Exposome data are inherently high-dimensional and require advanced analytic methods. Machine learning can model dozens of exposures and their biological interactions simultaneously. A recent European analysis applied an urban exposome risk score to nearly 350,000 participants across 14 cohorts. The score strongly predicted asthma incidence, and simulations suggested that coordinated urban planning interventions could prevent up to 11.6% of new cases.¹⁶ These findings illustrate the potential of exposome-informed precision prevention: tailoring interventions to individuals and communities based on exposure profiles. Clinically, this may mean expanding eligibility for lung cancer screening to include non-smokers with high cumulative pollution exposure or targeting early interventions for children living in polluted neighborhoods at greater asthma risk.

Perhaps the exposome's greatest contribution lies in reframing policy as prevention. By quantifying cumulative exposures and linking them to disparities, exposome research underscores that reducing pollution is a form of disease interception. Lowering PM_{2.5} levels is projected to yield disproportionate benefits for disadvantaged communities, narrowing mortality gaps.¹¹ Globally, pollution remains a preventable pandemic of noncommunicable disease, still responsible for about 9 million deaths annually.³ Urban design—integrating green spaces, reducing traffic emissions, and curbing nighttime light pollution—represents an evidence-based strategy to reduce asthma risk.¹⁶

The exposome era is reshaping prevention in respiratory health. Clinically, it strengthens early detection, risk stratification, and precision public health. At the population level, it provides quantitative evidence to support equitable environmental policies. Technological innovations, from wearable sensors to multi-omics platforms, enable real-time monitoring of exposures and early intervention. By integrating these advances, medicine can move from treating downstream disease to intercepting upstream exposures. Ultimately, the exposome underscores that

lung disease is not inevitable but a modifiable outcome of our environments.

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Original Article



The Value of Inverted Images for Pulmonary Nodule Detection

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Abstract

OBJECTIVE: Chest X-ray (CXR) is the most commonly used initial modality for most lung diseases, including pulmonary nodules. In diseases such as lung cancer, tuberculosis, and fungal infections, detecting a single nodule in the early stages will facilitate treatment. One of the most important obstacles to searching for a single pulmonary nodule on a CXR is peripheral background contrast enhancement, and density differences. The aim of this study was to demonstrate the superiority of inverted gray scale to the standard image of CXR in the detection of a single pulmonary nodule.

MATERIAL AND METHODS: The design of the study included the evaluations of two radiologists unaware of each other, and past computed tomography reports. They randomly evaluated standard and inverted gray scale images of posteroanterior CXRs of both nodule-containing and non-nodule-containing patients, totaling 100 in total. Each evaluation was graded from one to three as one stood for nodule negative, two was for doubtful and three was for nodule positive ones.

RESULTS: The percentage of the patients who were correctly identified as having the nodule [sensitivity (inverted 68.15% - standard 57.14%)] and not having [specificity (inverted 87.56% - standard 88.71%)] showed a statistically significant difference in inverted gray scale (negative) image compared to the standard image ($P \leq 0.001$).

CONCLUSION: Inverted chest radiogram is significantly exposing the nodule presence over the white background so that should be highlighted and considered as a part of useful scanning. So that in terms of functional benefit and additionally cost effectiveness, we advice this technique in part of routine CXR evaluation.

KEYWORDS: Inverted gray-scale, standard image, pulmonary nodule, chest X-ray

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INTRODUCTION

Lung cancer, tuberculosis, fungal infections, and pneumonia are common lung diseases for public health, so that their correct diagnosis and good differentiation is important.¹

Detecting a single (solitary) nodule in the early stages would certainly facilitate the treatment.²⁻⁵ However, a solitary pulmonary nodule is detected in only 1/500 chest X-ray (CXR) scans, and most of these nodules, approximately 90%, exist without distinct clinical findings. The CXR alone is not sufficient imaging method as well as for diseases work-up and progress.

The literature already stated that the margin of error in diagnosis by CXR is between 20 and 50%.^{2,4,6,7} The standard images of CXR define lung nodule as a small round or oval-shaped radiopacity that is smaller than three centimeters in diameter. While searching for a single pulmonary nodule in the CXR, one of the main obstacles is the involvement of environmental (background) contrast and density differences. Today's new digital applications advanced the image

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quality and increased the local contrast. The perception of contrast difference by the human visual system has also been studied, and it has been proven that better perception can be achieved when a dark object is presented over a light background.⁸ The digital X-ray machine has a software program which could provide this so-called perceptual phenomenon by changing the standard (positive image) into the inverted (negative image). The main change here is that a subtle pulmonary nodule would appear as a dark spot over the white background. So we questioned in this study whether negative images would be more effective to catch an average sized solitary pulmonary nodule.

MATERIAL AND METHODS

Study Design

This study is a case-control study planned with a cross-over design. Computed tomography (CT) and CXR were obtained from the hospital picture archiving and communication system (PACS). This study was approved by the University of Health Sciences Türkiye Hamidiye Faculty of Medicine Ethics Committee (IRB: 20-39, date: 19.05.2020). Informed written consent was obtained for each patient who underwent CXR and CT, and the Declaration of Helsinki was fully adhered to during measurement and writing.

Inclusion and Exclusion Criteria

A total of four hundred patients who were referred for posteroanterior (PA) CXR from the chest diseases outpatient clinic and were subsequently sent to the radiology unit were chosen in the study. Our study included patients over eighteen years. The patients were suspected to have nodules before diagnosis. We established study groups in two categories: fifty patients with a single pulmonary nodule and fifty people in the control group (without nodule). The presence of nodules in the patients had been confirmed by a previous CT reports (Figure 1). The patients were chosen from those whose nodule size was between 5 and 10 mm. Patients aged <18 years, with multiple pulmonary nodules, a history of thoracic surgery, pneumothorax, or chest trauma were excluded from the study.

Main Points

- The aim of this study was to demonstrate the superiority of inverted gray scale compared to the standard chest X-ray image in the detection of a single pulmonary nodule.
- The design of study included the evaluations of two radiologists unaware of each other and past computed tomography reports.
- The percentage of the patients who were correctly identified as having the nodule (sensitivity) and not having (specificity) was showing statistically meaningful difference in inverted gray scale (negative) image comparing to the standard image ($P \leq 0.001$).
- An inverted chest radiogram significantly exposes the presence of nodules over the white background, which should be highlighted and considered as a part of the diagnostic process.

Imaging Evaluate and Data Collection

The CXRs of these two groups were taken from the system and stored in a random order. All CXRs of the patients and the control group were evaluated at different times by two different radiologists, independently of the physician who created the data collection. These two radiologists had at least 4 years of experience in thoracic radiology. The radiologists were not informed about each other's participation, and the images were shown separately in a random sequence. The images were screened on the monitor that is 1280x1024 pixels of resolution. The CXR of patients and the control group with their standard and the gray scale (negative) images (Figure 2a, 2b) made a total of 100 images and took 4 days of radiologists' who viewed each image 15 minutes duration long. The statistical work up based on the total of 400 evaluation. The study randomization was supplied by director of the study. During the evaluation of the images zooming like operations were not interfered with. However, the use of contrast and coloring processes has been restricted.

Each radiologist gave a score between one and three for each image. The score one meant there was no nodule, two was standing for undetermined or suspicious cases and three indicated a nodule (Figure 3).



Figure 1. Coronal computed tomography image right inferosuperior segment 4 mm peripherally located non-calcifying nodule

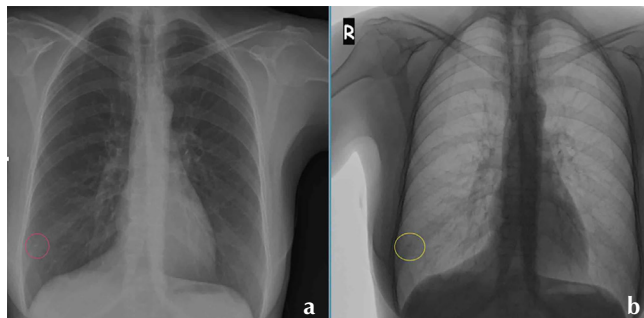


Figure 2. (a) Postero-anterior chest X-ray of right inferosuperior nodule. b) Negative (gray-scale inverted) image of right inferosuperior nodule

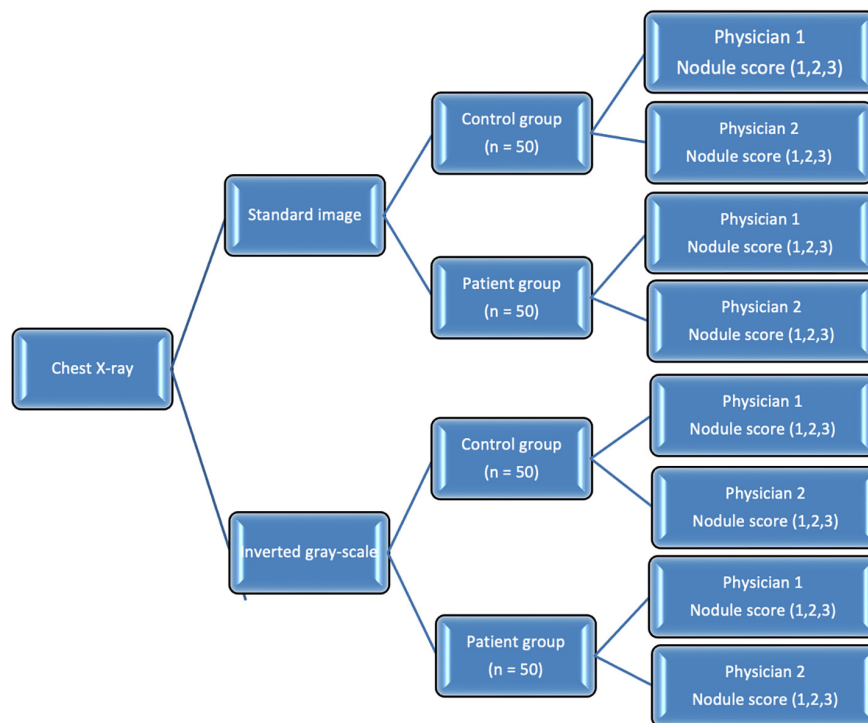


Figure 3. Evaluation of pulmonary nodules on chest X-ray

Statistical Analysis

All analyses of the data were made using Statistical Package for the Social Sciences version 22, (IBM, Armonk, NY, USA). All numerical variables were defined as median, minimum, maximum, and categorical variables were defined as frequency and percentages. Spearman's Rho, Pearson chi-square, and Fisher's exact test were used to evaluate interpersonal correlation. According to Spearman's coefficient values (P), <0.3 represents a weak relationship, $0.3-0.7$ represents a moderate relationship, and >0.7 represents a strong relationship. Statistical significance was obtained at $P < 0.01$ level. Since the data did not show a normal distribution, all analyses were performed with non-parametric methods.

RESULTS

The study included 56 female and 44 male patients over the age of 18 (minimum 21-maximum 93), and median age was 39.50. The twenty nodule positive (+) patients were female and thirty nodule positive (+) patients were male; the minimum age of nodule positive patients was 22, maximum 93, and the median age was 53. The thirty-six nodule negative (-) patients were male, and fourteen nodule negative (-) patients were female; the minimum age of nodule negative patients was 21 years, maximum 50 years; the median age was 29.

Two radiology physicians evaluated the images, and their assessments were compared using Spearman's correlation. All of the radiology physicians' X-ray image assessments were positively correlated with each other; the lowest positive correlation was $P < 0.04$ ($P = 0.29$), and the highest was $P < 0.0001$ ($P = 0.62$). All of the radiology physicians' inverted image assessments were positively correlated with each other. The lowest positive correlation within the physicians was $P < 0.0001$, ($P = 0.42$), and the highest was $P < 0.0001$, ($P = 0.66$).

Fifty X-ray control (nodule negative) lung images and fifty inverted control lung images were evaluated by the radiologists. The results of their evaluations were categorized as 1: I did not diagnose any nodules, 2: I am not sure, 3: I did diagnose nodules. Fifty X-ray positive (nodule positive) lung images and fifty inverted positive lung images were also evaluated by the same radiologists. The results of their evaluations were categorized as described above.

In the 100 X-ray control lung image evaluations (50 images, 2 radiology physicians, 100 evaluations), 82 evaluations were 1 (right answer); 11 evaluations were 3 (wrong-positive answer); and 7 evaluations were 2 (not sure). Seven evaluations in category 2 were included in category 3, because the radiology physicians reported those as "Nodule". Therefore, there were 18 false-positive evaluations in the X-ray control lung images.

In the 100 inverted control lung image evaluations (50 images, 2 radiology physicians, 100 evaluations), 84 evaluations were rated as 1 (right answer), 12 evaluations were rated as 3 (wrong-positive answer) and 4 evaluations were rated as 2 (not sure). Four evaluations in category 2 were included in category 3, because the radiology physicians reported those as "Nodule (?)". Therefore, there were 16 false-positive evaluations in the inverted control lung images.

According to the evaluations of the control lung images, inverted images provided more accurate evaluations than X-ray images. The higher number of the true-negative evaluations of the inverted control lung images was statistically significant ($P = 0.0001$), and the lower number of the wrong-positive evaluations was statistically significant ($P = 0.002$) as shown in Table 1.

In the 100 X-ray positive lung images evaluations, (50 images, 2 radiology physicians, 100 evaluations), 48 evaluations were 3 (correct-positive response), 36 evaluations were 1 (incorrect-negative response), and 16 evaluations were 2 (uncertain). Sixteen evaluations in category 2 were included in category 3 because the radiology physicians reported them as “Nodule (?)”. Therefore, there were 64 true positive evaluations and 36 false negative evaluations in the X-ray positive lung images.

In the evaluations of 100 inverted positive lung images (50 images, 2 radiology physicians, 100 evaluations), 61 evaluations were 3 (right answer), 28 evaluations were 1 (wrong-negative answer), and 11 evaluations were 2 (not sure). Eleven evaluations in category 2 were included in category 3 because the radiologists reported them as “Nodule (?)”. Therefore, there were 72 right-positive and 28 wrong-negative evaluations in the inverted positive lung images.

According to the evaluations of the nodule positive lung images, inverted images were evaluated more accurately than X-ray images. The higher number of the true-positive evaluations of the inverted positive lung images was statistically significant ($P = 0.0001$), and the fewer number of the wrong-negative evaluations of the inverted positive lung images was statistically significant ($P = 0.0001$) as shown in Table 2. For routine CXR images, sensitivity was calculated as 57.14% and specificity as 88.71%. In inverted roentgenogram, sensitivity was found to be 68.15% and specificity 87.56%.

DISCUSSION

In our study we aimed to see is there any advantage of the inverted image so that the common sized and shaped nodules

are better visible in the most frequently used method? For this, we set out from physiological studies on vision which indicated the dark-coloured images on a bright background were more easily discernible than bright images on a dark background.⁸ In the literature, first, MacMahon et al.⁹ studied 60 PA and anteroposterior chest radiograms diagnosed as hemithoraces with non-calcified pulmonary nodules, pneumothorax, interstitial infiltrate, and bone lesion, which were evaluated by twelve radiologists. There were no significant differences between positive and negative images in nonlinear and true gray scale inversion.⁹ However they mentioned in case if negative mode was chosen for image presentation, true gray scale reversal was necessary for adequate contrast resolution. Differently, our aim was to address one specific diagnosis, and based on the physiological study, the finding that black density was clear on white was observed. In their study, there were four diagnoses and four different densities which were not all black and white. Lungren et al.¹⁰ later reported that gray scale inversion and choice display sessions resulted in significantly higher nodule detection specificity and decreased sensitivity, thereby reducing false positivity. They interpreted 144 chest radiograms (72 normal and 72 with pulmonary nodules) with a 6-segment distribution. Three radiologists evaluated a different number of nodules, reporting them as three, two, or one.¹⁰ In our study there was only one nodule which should be diagnosed, and we limited the contrast arrangements on machine. Sheline et al.¹¹ compared standard and inverse-intensity images to determine their ability to identify pathologically confirmed malignant pulmonary nodules and suggested that inverted images may have some advantages in the detection of pulmonary nodules. Instead of malignant lesions, in our study, we focused on the function of inverted images for ordinary sized and shaped

Table 1. Assessment of the evaluations according to the control (nodule-negative) lung images

Categorized control lung image evaluations (Total n = 100)	The imaging technique		Diagnosis evaluations	P
	X-ray	Inverted		
1. Did not diagnose nodules (n)	82 (%)	84 (%)	True-negative	0.0001***c
2. Not sure “Nodule (?)” (n)	7 (%)	4 (%)	Wrong-positive	0.002**c
3. Did diagnose nodules (n)	11 (%)	12 (%)		
Wrong-positive (n)	18 (%)	16 (%)		

n: number of evaluations.
c: chi-square-Fisher's exact test, *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.0001$

Table 2. Assessment of the evaluations according to the positive (nodule-positive) lung images

Categorized control lung image evaluations (Total n = 100)	The imaging technique		Diagnosis evaluations	P
	X-ray	Inverted		
1. Did not diagnose nodules (n)	36 (%)	28 (%)	Wrong-negative	0.0001***c
2. Not sure “Nodule (?)” (n)	16 (%)	11 (%)	True-positive	0.0001***c
3. Did diagnose nodules (n)	48 (%)	61 (%)		
Wrong-negative (n)	36 (%)	28 (%)		

n: number of evaluations.
c: chi-square-Fisher's exact test, *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.0001$

single nodule detection and its contribution to the early diagnosis, that would inevitably contribute to the treatment. In some other studies pneumothorax, pulmonary nodule, rib fractures, proximal dental problems and bullous lung diseases were studied.¹²⁻¹⁴

Musalar et al.¹⁵ studied pneumothorax on anterior CXR images of a total of 268 patients (106 patients with spontaneous pneumothorax and 162 patients of control groups) with ten non-radiologists. The study was carried out by nonradiologists and was aimed at searching for non-nodular pathology. In our study, we based our analysis on the physiological principles of the human visual system, which claim the density would be discreet on the white background, as is done in negative imaging. In the case of pneumothorax, the opposite was true; their study found that negative imaging was not prioritized for diagnosing pneumothorax.¹⁵

De Boo et al.¹⁶ evaluated the efficacy of gray-scale using the PACS on 74 patients and 54 nodule-negative controls. There were a total of 129 solid pulmonary nodules in these patients, and the nodule diameter range was 5-30 mm (mean: 13 mm). Six radiologists with varying levels of experience evaluated the gray-scale inversion and the standard CXR images in two separate reading sessions. Five radiologists showed a slight increase in sensitivity with the use of gray-scale reversal, but on average, the difference was not significant ($P > 0.05$).¹⁶ Schalekamp et al.¹⁷ investigated the effect of bone suppression imaging (BSI) on the performance of observers in the detection lung nodules on CXR, compared to standard gray-scale. PA and lateral digital CXR of 111 patients with a CT proven solitary nodule (median diameter: 15 mm), and 189 controls were read by 5 radiologists and 3 residents. The prominence of nodules on radiographs was classified into four groups: marked ($n = 32$), moderate ($n = 32$), mild ($n = 29$), and very mild ($n = 18$). Observers read the PA and lateral CXRs without, then with an additional PA BSI (ClearRead Bone Suppression 2.4, Riverain Technologies) within one reading session. Nodules were better detected using BSI than with standard CXR, with the increase in detection performance being greatest for moderately and mildly prominent nodules ($P = 0.02-0.03$).¹⁷

This study had a few limitations. First, the relatively small number of cases ($n = 100$) evaluated was compared to other studies,^{10,15-17} which limits the generalizability of the results. Secondly, the number of physicians (two radiologists) performing CXR evaluation was lower compared to some studies.^{9,10,15-17} The third is that only CXRs taken in the PA plane were evaluated.⁹ The fourth limitation is that only a single pulmonary nodule is evaluated.¹⁷ Another limitation is the lack of a similar study using a similar nodule scoring (1,2,3) with which we can make a comparison.^{10,11}

CONCLUSION

As a result, CXRs are the most common first methods for most lung pathologies, including pulmonary nodules. Predicting existing physiological facts, we wanted to see whether the diagnostic capability of the most commonly used technique would be enhanced by inverting standard images to negative images for the usual sized solitary lung nodule, which in turn

inevitably contributes to early diagnosis and better treatment choice. We have obtained positive results supporting our hypothesis, so that in terms of functional benefit and additionally cost effectiveness, we advice this technique in part of routine CXR evaluation.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye Hamidiye Faculty of Medicine Ethics Committee (IRB: 20-39, date: 19.05.2020).

Informed Consent: Informed written consent was obtained for each patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: All authors contributed equally to all contribution sections.

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

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Original Article



Comparative Long-term Effects of Nintedanib and Pirfenidone in Idiopathic Pulmonary Fibrosis: A Real-life Study with Five-year Follow-up

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Abstract

OBJECTIVE: This study aimed to compare the clinical, radiological, and functional outcomes of idiopathic pulmonary fibrosis (IPF) patients treated with nintedanib or pirfenidone, focusing on long-term efficacy, safety, and survival.

MATERIAL AND METHODS: A retrospective cross-sectional real-life study was conducted at a tertiary healthcare center between 2016 and 2021, including 93 IPF patients treated with either nintedanib (n = 41) or pirfenidone (n = 52). Data on demographics, pulmonary function tests [forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and diffusing capacity for carbon monoxide], radiological assessments, exacerbations, mortality, and side effects were analyzed using appropriate statistical methods.

RESULTS: Both groups were comparable in age (nintedanib: 68.6 years; pirfenidone: 71.3 years) and gender distribution. Patients on pirfenidone had a higher body mass index (27.7 vs. 26.0 kg/m², *P* = 0.049) and more radiological involvement (*P* = 0.034). Baseline: Gender, Age, Physiology scores were lower in the nintedanib group (3.39 vs. 4.21, *P* = 0.007). Lung function (FVC, FEV1) was significantly better in the nintedanib group at two years; though differences were not sustained over five years. Side effects were more frequent with nintedanib (73.2% vs. 46.2%, *P* = 0.009), particularly affecting the gastrointestinal system. At five years after follow-up, mortality was higher in the pirfenidone group (53.4% vs. 17.5%, *P* = 0.02), although time from diagnosis to death was longer (33.8 vs. 19.0 months, *P* = 0.020).

CONCLUSION: Pirfenidone may prolong survival in patients with severe disease and greater radiological involvement, while nintedanib showed lower mortality in milder disease. Treatment outcomes appear influenced by baseline characteristics, highlighting the need for individualized therapeutic strategies. Comprehensive studies involving more homogeneous patient groups are needed to clarify the comparative efficacy of these treatments.

KEYWORDS: Idiopathic pulmonary fibrosis, nintedanib, pirfenidone, lung function, long-term outcomes, real-life data

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a severe and progressive interstitial lung disease characterized by irreversible scarring of lung tissue, leading to significant impairment in respiratory function and quality of life.¹ It primarily affects older adults, presenting with symptoms such as progressive dyspnea and chronic cough. Although the exact etiology remains unclear, genetic predisposition and environmental factors, including smoking and potential viral infections, are considered key contributors. IPF is relatively rare, with a global incidence of 2.8 to 9.3 per 100,000, but it carries a high burden of morbidity and mortality. Without treatment, the median survival is 3-5 years post-diagnosis.^{2,3} Over the past decade, the introduction of antifibrotic therapies has significantly advanced IPF management, offering hope for slowing disease progression.

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Two key antifibrotic agents, nintedanib and pirfenidone, have become central in IPF treatment. Nintedanib, a tyrosine kinase inhibitor, targets fibrosis-related pathways activated by growth factors such as platelet-derived growth factor and transforming growth factor-beta (TGF- β).² The INPULSIS trials demonstrated its efficacy in significantly reducing forced vital capacity (FVC) decline over one year.⁴ Pirfenidone, on the other hand, has both anti-inflammatory and antifibrotic properties, primarily through its inhibition of TGF- β -induced collagen production and fibroblast proliferation. Clinical trials like CAPACITY and ASCEND have shown that pirfenidone slows FVC decline and may improve progression-free survival.^{2,5-8} Both drugs have been shown to reduce acute exacerbations and prolong survival, though side effect profiles often guide treatment selection.^{9,10}

This study aimed to directly compare the clinical, radiological, and functional outcomes of nintedanib and pirfenidone in patients with IPF. By evaluating long-term efficacy, safety, and survival outcomes, the study seeks to provide valuable insights into optimizing therapeutic strategies for IPF management.

MATERIAL AND METHODS

Patients with IPF followed at the pulmonology clinics of a tertiary healthcare center between 2016 and 2021 were included in this retrospective study. A total of 118 patients with a confirmed diagnosis of IPF were initially screened. Of these, 25 were excluded due to either a disease duration of less than one year at the time of data collection or incomplete medical records, in accordance with the study's exclusion criteria. Consequently, 93 patients were included in the final analysis. The inclusion criteria were adults aged 18 years or older with an IPF diagnosis confirmed by radiological or histopathological criteria. The patient selection process and follow-up scheme are summarized in Figure 1. Data were collected using a standardized case report form designed by the researchers. This form included demographic information, clinical symptoms, physical examination findings, radiological features, treatment details, observed side effects, and outcomes, such as acute exacerbations and mortality.

Main Points

- This five-year, real-life retrospective study compared the clinical, radiological, and functional outcomes of idiopathic pulmonary fibrosis (IPF) patients treated with nintedanib or pirfenidone.
- Despite similar functional outcomes, long-term mortality was significantly lower in the nintedanib group, which included patients with lower baseline the Gender, Age, Physiology scores and milder disease severity.
- Gastrointestinal side effects were more common with nintedanib, while photosensitivity occurred in both groups with similar frequency.
- Patients treated with pirfenidone, despite having more severe baseline radiological involvement, experienced a longer time from diagnosis to death, suggesting a potential survival benefit in advanced disease.
- The findings emphasize the influence of baseline disease severity on treatment outcomes and support the need for personalized antifibrotic therapy decisions in IPF management.

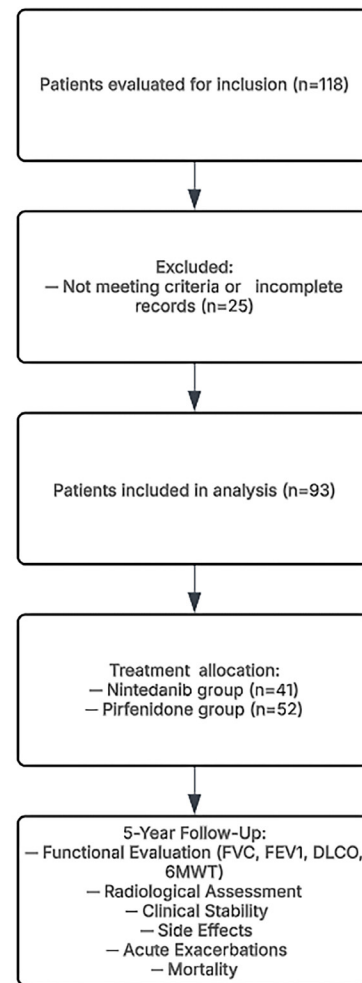


Figure 1. Flowchart of patient inclusion, treatment allocation, follow-up, and outcome assessment in the study

FVC: Forced vital capacity, FEV1: Ratio of forced expiratory volume in the first second, DLCO: Diffusing capacity for carbon monoxide, 6MWT: 6 minute walk test

Radiological disease extent was evaluated based on the anatomical lobe distribution of fibrotic changes observed in high-resolution computed tomography scans, categorized as involvement of lower lobes only, middle and lower lobes, or upper, middle, and lower lobes. The categorization was performed by experienced radiologists as part of routine clinical reporting at the time of diagnosis.

The Gender, Age, Physiology (GAP) index was recorded at diagnosis, while clinical, radiological, and functional parameters were evaluated both at baseline and during follow-up (at 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years). Patients were categorized based on the antifibrotic treatment regimen received: either nintedanib or pirfenidone. Detailed records of treatment dosage, duration, and any adjustments due to side effects or disease progression were maintained. Pulmonary function tests were conducted in the pulmonary laboratory of the healthcare center, using a Jaeger Master Scope spirometer. Tests were performed with the patient in a seated position and followed the American Thoracic Society/European Respiratory Society criteria.¹¹ A certified technician conducted all tests. Forced expiratory volume in 1 second (FEV1), FVC,

and the FEV1/FVC ratio were measured. Bronchodilation tests were performed 15 minutes after salbutamol inhalation (4 puffs, 400 µg). Results were recorded as percentages of the predicted values. The 6 minute walk test (6MWT) was utilized to evaluate the functional capacity of the patients. Each test was conducted on a flat surface, and patients were instructed to walk at their maximum speed for 6 minutes. Oxygen saturation (SpO₂) was measured using pulse oximetry before and after the test. Dyspnea and fatigue levels were assessed and recorded pretest and posttest. The primary outcome measures were changes in FVC, radiological progression, and survival rates. Secondary outcomes included the incidence of acute exacerbations and an assessment of treatment-related side effects. The study was approved by the Aydın Adnan Menderes University Local Ethics Committee and conducted, following the principles of the 1964 Declaration of Helsinki and its later amendments (approval no: 2022/108, date: 04.08.2022).

Patient Follow-up and Missing Data Handling

During the five-year follow-up period, some patients missed scheduled visits or discontinued regular clinical follow-up. However, vital status, (alive or deceased) of all patients was verified through the national electronic health record system, allowing complete and accurate mortality data collection for all patients regardless of clinic attendance.

For other outcome variables [e.g., pulmonary function tests, diffusing capacity for carbon monoxide (DLCO), 6MWT, radiological and clinical assessments], only data from patients who attended follow-up visits at each timepoint were included in the analyses. Missing data were not imputed, and an available-case analysis was used for each parameter at each timepoint.

A total of 10 patients (24.4%) in the nintedanib group switched to pirfenidone, and 9 patients (17.3%) in the pirfenidone group switched to nintedanib. Patients who were lost to follow-up or switched treatments, did not significantly differ in baseline characteristics [age, sex, body mass index (BMI), GAP index, and extent of radiologic involvement] compared to those who remained on their original treatment.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 22.0 (IBM SPSS, Chicago, IL). The normality of continuous variables was assessed with the Kolmogorov-Smirnov test. Descriptive statistics, including means, standard deviations, and percentages, were used to summarize the data. Chi-square tests were applied to categorical variables, while t-tests or Mann-Whitney U tests were used for continuous variables based on their distribution. Statistical significance was defined as $P < 0.05$.

RESULTS

The study included 41 patients in the nintedanib group and 52 patients in the pirfenidone group. In the comparative analysis of demographic and clinical characteristics between the two treatment groups, both groups had similar age distributions, with nintedanib-treated patients having a mean age of

68.67±7.98 years and pirfenidone-treated patients having a mean age of 71.33±7.63 years ($P = 0.098$). The sex distribution was also comparable, with no statistically significant difference ($P = 0.061$). However, a significant difference was observed in BMI between the treatments, with Pirfenidone-treated patients having a higher mean BMI (27.65±3.68 kg/m) compared to nintedanib-treated patients (26.00±4.30 kg/m, $P = 0.049$). No significant differences were found between the groups regarding education level, residence, smoking history, or the presence of comorbidities, indicating similar demographic and clinical profiles across treatments. The follow-up duration was also comparable between the nintedanib and pirfenidone groups (35.48±20.22 vs. 35.19±19.90 months, $P = 0.814$). In terms of diagnostic methods, clinical and radiological diagnosis was predominant in both groups, though histopathological diagnosis was more frequently observed in the pirfenidone group (13.5%) compared to the nintedanib group (2.4%, $P = 0.074$). In the analysis of radiological findings, lower lobe involvement was significantly higher in nintedanib-treated patients (41.5%) compared to those treated with pirfenidone (25.0%), whereas combined middle and lower lobe involvement was more pronounced in the pirfenidone group. Detailed results of this comparison are presented in Table 1.

In the comparative analysis of laboratory and functional parameters between the nintedanib and pirfenidone groups, no significant differences were observed in arterial blood gas measurements, including pH, pO₂, and pCO₂ levels ($P > 0.05$). Pulmonary function tests also showed comparable results between the groups, with no statistically significant differences in FVC, FEV1, FEV1/FVC ratio, or DLCO levels ($P > 0.05$). Similarly, functional capacity as assessed by the 6MWT revealed no significant differences, with both groups achieving comparable distances ($P = 0.565$). However, GAP scores, a composite measure of disease severity, were significantly lower in the nintedanib group (3.39±1.61) compared to the pirfenidone group (4.21±1.14, $P = 0.007$), indicating that patients in the nintedanib group had less severe disease at baseline. Detailed results are presented in Table 2.

In the analysis of treatment characteristics between the nintedanib and pirfenidone groups, significantly, more patients in the nintedanib group reported experiencing side effects compared to the pirfenidone group (73.2% vs. 46.2%, $P = 0.009$). Among those with reported side effects, skin-related issues were observed in 14.6% of nintedanib patients and 11.5% of pirfenidone patients, while gastrointestinal side effects were more common in the nintedanib group (58.5%) compared to the pirfenidone group (30.8%). Additionally, other side effects were only observed in the pirfenidone group (3.9%). Detailed results of the comparison of treatment side effects are presented in Table 3.

This study involves a five-year longitudinal evaluation of functional, clinical, and radiological outcomes in patients with IPF with nintedanib or pirfenidone. Throughout the follow-up period, radiological and clinical progression rates were comparable between the two treatment groups, with no significant differences observed overall. Notably, during the second year of follow-up, patients receiving nintedanib showed significantly better lung function outcomes, with

higher FVC (88.95 ± 26.99 vs. 73.45 ± 20.37 , $P = 0.026$) and FEV1 (94.05 ± 28.21 vs. 79.32 ± 20.93 , $P = 0.040$) compared to those treated with pirfenidone. However, this difference in lung function parameters did not persist in subsequent years, as no significant variations were observed between the groups in later follow-ups (Table 4).

In the comprehensive five-year evaluation of treatment dynamics and outcomes between the nintedanib and pirfenidone groups, the mean follow-up duration was comparable at 35.48 ± 20.22 months for nintedanib and 35.19 ± 19.90 months for pirfenidone ($P = 0.814$). Radiological stability was observed in 48.0% of nintedanib-treated patients compared to 38.7% in the pirfenidone group, though this difference was not

statistically significant ($P = 0.368$). Similarly, clinical stability was reported in 48.0% of nintedanib patients and 38.7% of pirfenidone patients ($P = 0.401$). Acute exacerbations were slightly more frequent in the nintedanib group (44.0%) than in the pirfenidone group (40.9%), but this difference was not statistically significant ($P = 0.777$). Most exacerbations were due to infections, with a smaller proportion being idiopathic, again with no significant difference between the groups. Lung cancer incidence was low and similar across both groups, at 2.4% for nintedanib and 1.9% for pirfenidone ($P = 1.000$). In terms of clinical endpoints, mortality was significantly higher in the pirfenidone group (53.4%) compared to the nintedanib group (17.5%) ($P = 0.002$) (Table 5).

Table 1. Comparison of demographic, clinical, and diagnostic characteristics between nintedanib and pirfenidone treatment groups in IPF patients

Parameter	Nintedanib (n = 41)	Pirfenidone (n = 52)	P
Age, (years)	68.67 ± 9.78	71.33 ± 7.65	0.098
Gender, n (%)			0.061
- Male	29 (70.7%)	45 (86.5%)	
- Female	12 (29.3%)	7 (13.5%)	
BMI, (kg/m ²)	26.00 ± 4.30	27.65 ± 3.68	0.049
Education level, n (%)			0.103
- Less than high school	19 (22.6%)	10 (19.2%)	
- High school	36 (42.9%)	20 (38.5%)	
- University or higher	29 (34.5%)	22 (42.3%)	
Residence, n (%)			0.099
- Urban	19 (46.3%)	33 (63.5%)	
- Rural	22 (53.7%)	19 (36.5%)	
Smoking history, n (%)			0.335
- Yes	27 (65.9%)	39 (75.0%)	
- No	14 (34.1%)	13 (25.0%)	
Average smoking duration (years)	37.26 ± 15.76	30.71 ± 12.90	0.069
Comorbidities, n (%)			
- Yes	32 (78)	38 (73.1)	0.581
- No	9 (22)	14 (26.9)	
sPAP, (mmHg)	33.65 ± 8.46	38.64 ± 19.17	0.781
Radiological involvement, n (%)			0.034
- Lower lobe	41.5%	25.0%	
- Middle and lower lobes	48.8%	44.2%	
- Upper, middle, and lower lobes	9.08%	30.08%	
PA/Ao	0.90 ± 0.13	0.87 ± 0.15	0.304
Follow-up duration, (months)	35.48 ± 20.22	35.19 ± 19.90	0.814
Diagnosis method, n (%)			0.074
- Histopathological	1 (2.4%)	7 (13.5%)	
- Clinical and radiological	40 (97.6%)	45 (86.5%)	

IPF: idiopathic pulmonary fibrosis, SPAP: systolic pulmonary artery pressure, PA/Ao: pulmonary artery/aorta ratio, BMI: body mass index

Table 2. Comparison of laboratory and functional parameters between nintedanib and pirfenidone treatment groups in IPF patients

Parameter	Nintedanib (n = 41)	Pirfenidone (n = 52)	P
Arterial blood gas measurements			
- pH	7.41±0.04	7.42±0.04	0.361
- pO ₂ (mmHg)	71.65±5.85	75.47±6.15	0.734
- pCO ₂ (mmHg)	34.85±3.94	36.13±3.92	0.391
Pulmonary function tests			
- FVC (%)	77.37±18.68	72.00±17.67	0.160
- FEV1 (%)	82.63±19.46	77.15±16.93	0.150
- FEV1/FVC (%)	86.02±7.98	83.54±11.84	0.219
- DLCO (%)	55.21±16.64	54.06±16.70	0.493
6 minute walk test, (m)	359.89±42.23	347.91±41.47	0.565
6 minute walk test, %	65.92±14.60	65.08±15.20	0.805
GAP score	3.39±1.61	4.21±1.14	0.007
IPF: idiopathic pulmonary fibrosis, PFT: pulmonary function tests, FVC: forced vital capacity, FEV1/FVC: ratio of forced expiratory volume in the first second to forced vital capacity, DLCO: diffusing capacity for carbon monoxide, m: meter			

Table 3. Comparison of treatment characteristics between nintedanib and pirfenidone groups

Parameter	Nintedanib (n = 41)	Pirfenidone (n = 52)	P
Antifibrotic drug side effects			
- Yes	30 (73.2%)	24 (46.2%)	0.009
- No	11 (26.8%)	28 (53.8%)	
Side effects type			
- Skin	6 (14.63%)	6 (11.54%)	0.227
- GIS	24 (58.54%)	16 (30.77%)	
- Other	0 (0%)	2 (3.85%)	
GIS: gastrointestinal			

Table 4. Longitudinal comparison of functional, clinical, and radiological outcomes between nintedanib and pirfenidone treatment groups over five years

Year	Parameter	Nintedanib (n = 41)	Pirfenidone (n = 52)	P
6 months	Mortality (%)	7.89% (3/38)	0% (0/50)	0.077
	FVC (%)	79.97±20.86	75.00±15.71	0.179
	FEV1 (%)	84.64±20.64	80.92±17.85	0.375
	FEV1/FVC (%)	86.75±9.14	83.86±10.01	0.163
	DLCO (%)	61.88±51.40	54.70±14.37	0.972
	6MWT (m)	363.82±97.78	372.68±132.17	0.803
	Radiology, n (%)			
	Stable	35 (94.6)	49 (98.0)	0.572
	Progression	2 (5.4)	1 (2.0)	
	Clinical n (%)			
	Stable	34 (91.9%)	49 (98.0%)	0.308
	Progression	3 (8.1%)	1 (2.0%)	

Table 4. Continued

Year	Parameter	Nintedanib (n = 41)	Pirfenidone (n = 52)	P
1 year	Mortality (%)	0% (0/32)	0% (0/47)	-
	SpO ₂	95.59±2.30	93.81±4.56	0.155
	FVC (%)	82.06±26.64	72.53±16.52	0.061
	FEV1 (%)	86.03±24.47	78.02±16.87	0.114
	FEV1/FVC (%)	86.56±10.31	84.98±10.73	0.656
	DLCO (%)	52.55±17.22	51.40±14.24	0.755
	6MWT (m)	369.83±103.27	362.17±108.03	0.788
	sPAP	41.60±17.90	55.80±22.54	0.353
	Radiology, n (%)			
	Stable	24 (75.0%)	36 (76.6%)	
	Progression	8 (25.0%)	11 (23.4%)	0.871
	Clinical, n (%)			
	Stable	22 (68.8%)	34 (72.3%)	
	Progression	10 (31.3%)	13 (27.7%)	0.730
2 year	Mortality (%)	7.1% (2/28)	20.5% (9/44)	0.183
	SpO ₂	95.16±2.17	92.68±5.55	0.266
	FVC (%)	88.95±26.99	73.45±20.37	0.026
	FEV1 (%)	94.05±28.21	79.32±20.93	0.040
	FEV1/FVC (%)	86.11±8.24	85.46±9.65	0.920
	DLCO (%)	46.92±15.75	55.08±13.06	0.257
	6MWT (m)	368.44±69.69	353.75±114.94	0.479
	Radiology, n (%)			
	Stable	13 (68.4%)	17 (54.8%)	
	Progression	6 (31.6%)	14 (45.2%)	0.341
	Clinical, n (%)			
	Stable	14 (73.7%)	16 (51.6%)	
	Progression	5 (26.3%)	15 (48.4%)	0.122
	Mortality (%)	3.85% (1/26)	14.71% (5/34)	0.377
3 year	SpO ₂	95.00±2.55	93.81±5.24	0.857
	FVC (%)	96.11±28.03	78.44±21.58	0.074
	FEV1 (%)	97.89±26.83	83.94±20.80	0.165
	FEV1/FVC (%)	84.56±12.22	85.25±8.55	0.609
	DLCO (%)	50.29±8.67	53.36±12.31	0.765
	6MWT (m)	406.67±20.82	381.36±121.32	0.696
	Radiology n (%)			
	Stable	7 (77.8%)	10 (62.5%)	
	Progression	2 (22.2%)	6 (37.5%)	0.661
	Clinical n (%)			
	Stable	7 (77.8%)	10 (62.5%)	
	Progression	2 (22.2%)	6 (37.5%)	0.661

Table 4. Continued

Year	Parameter	Nintedanib (n = 41)	Pirfenidone (n = 52)	P
4 year	Mortality (%)	0% (0/25)	20.69% (6/29)	0.129
	SpO ₂ (%)	95.8±0.84	95.5±2.07	0.747
	FVC (%)	107.0±15.22	85.2±33.30	0.111
	FEV1 (%)	107.0±19.84	93.2±35.67	0.220
	FEV1/FVC (%)	79.2±9.83	87.3±6.04	0.121
	DLCO (%)	45.5±3.54	48.5±14.83	1.000
	6MWT (m)	Not provided	Not provided	
	Radiology n (%)			
	Stable	3 (60.0%)	7 (70.0%)	1.000
	Progression	2 (40.0%)	3 (30.0%)	
5 year	Clinical n (%)			
	Stable	3 (60.0%)	8 (80.0%)	0.560
	Progression	2 (40.0%)	2 (20.0%)	
	Mortality (%)	4% (1/25)	13.04% (3/23)	1.000
	Radiology n (%)			
	Stable	1 (100.0%)	1 (25.0%)	0.400
	Progression	0 (0.0%)	3 (75.0%)	
	Clinical n (%)			
	Stable	1 (100.0%)	2 (50.0%)	1.000
	Progression	1 (0.0%)	2 (50.0%)	

SpO₂: peripheral oxygen saturation, FVC: forced vital capacity, FEV1/FVC: ratio of forced expiratory volume in the first second to forced vital capacity, DLCO: diffusing capacity for carbon monoxide, GAP: Gender, Age, Physiology Score, sPAP: systolic pulmonary artery pressure

Table 5. Outcomes and treatment dynamics between nintedanib and pirfenidone treatment groups over a five-year period

Parameter	Nintedanib (n = 41)	Pirfenidone (n = 52)	P
Follow-up duration, (months)	35.48±20.22	35.19±19.90	0.814
Radiological stability rate, % (rate)	51.6% (16/31)	37.2% (16/43)	0.217
Clinical stability rate, % (rate)	48.4% (15/31)	34.9% (15/43)	0.243
Incidence of acute exacerbations, % (rate)	44.1% (15/34)	61.2% (30/49)	0.124
Idiopathic cause	13.3% (2/15)	10.0% (3/30)	1.000
Infection-related	100% (13/13)	96.3% (26/27)	1.000
Lung cancer development rate, % (rate)	2.4% (1/41)	1.9% (1/52)	1.000
Mortality rate, % (rate)	17.5% (7/31)	53.4.0% (23/43)	0.002
Time from diagnosis to mortality (month)	19.00±16.15	33.83±12.69	0.020
Cause of death % (rate)			
IPF-associated causes	71.4% (5/7)	58.3% (14/24)	0.676
Non-IPF causes	28.6% (2/7)	41.7% (10/24)	
Switched treatments (%)			
From pirfenidone to nintedanib	-	17.3% (9/52)	
From nintedanib to pirfenidone	24.4% (10/41)	-	
IPF: idiopathic pulmonary fibrosis			

IPF: idiopathic pulmonary fibrosis

DISCUSSION

This study provides valuable insights into the comparative efficacy and safety profiles of nintedanib and pirfenidone in the management of IPF. Below, the key findings and their implications are discussed:

The baseline characteristics of the two treatment groups, including age, sex, smoking history, comorbidities, SpO₂ levels, mean pulmonary artery pressure, and pulmonary function parameters (FVC and DLCO), were comparable, enhancing the reliability of the study outcomes. However, a notable difference was BMI, which was higher in the pirfenidone group. This difference may reflect potential disparities in the metabolic processing or side effect profiles of the drugs, given the influence of BMI on drug pharmacokinetics and pharmacodynamics.¹² Further studies are needed to explore the clinical implications of this finding, particularly in antifibrotic therapies, where data remain limited.

The side effect profiles differed between the two groups. Drug-related side effects were more frequently observed in the nintedanib group (73.2% vs. 46.2%; $P = 0.009$). Gastrointestinal side effects, particularly diarrhea, were significantly more common in patients treated with nintedanib, consistent with previous studies, including those by Bargagli et al.¹³ and Hughes et al.¹⁴ On the other hand, photosensitivity and rash were more frequent in the pirfenidone group in earlier studies, such as the CAPACITY and ASCEND studies.^{7,8} However, our study found a lower incidence of skin-related side effects in pirfenidone-treated patients, which may be attributed to lifestyle factors and patient adherence to preventive measures such as sunscreen use and sun avoidance. In the literature, the incidence of photosensitivity associated with nintedanib use has generally been reported as low.¹⁵⁻¹⁷ However, in our study, the incidence of photosensitivity in patients treated with nintedanib (14.63%) was higher compared to those treated with pirfenidone (11.54%). We believe this may be related to factors specific to our patient population, such as genetic predisposition, comorbid conditions, or concomitant medications. Although the mechanisms underlying the development of photosensitivity in patients treated with nintedanib are not fully understood, this finding warrants further investigation in future studies. In this context, careful monitoring of dermatological side effects during nintedanib treatment and providing patients with appropriate information on this matter appears to be crucial.

Functional parameters, including FVC, FEV1, DLCO, 6MWT, and SpO₂, showed similar trends in both groups during the 5-year follow-up. However, at the 2-year mark, significantly lower FVC and FEV1 values were observed in the pirfenidone group, which could be due to the exclusion of some patients for reasons such as treatment changes or mortality. Despite this, the long-term trends were consistent between the two groups, aligning with previous studies showing comparable efficacy of both drugs in maintaining pulmonary function.^{6,10,18}

At the end of the 5-year follow-up in our study, both groups demonstrated similar clinical and radiological courses. These findings align with broader clinical studies, such as INPULSIS and ASCEND, which have shown that both treatments effectively slow radiological progression.^{4,8} The lack of a significant

difference in clinical stability and progression rates supports the notion that both drugs exhibit comparable long-term efficacy in the management of IPF.

In our study, the rates of acute exacerbations were similar between the two treatment groups, supporting the efficacy of both antifibrotic agents in reducing exacerbation risk. This finding aligns with previous studies evaluating antifibrotic therapies in IPF. Notably, the TOMORROW and INPULSIS trials demonstrated that nintedanib significantly reduces the frequency of acute exacerbations.^{19,20} However, in the INSTAGE trial, this effect was not observed in patients with more advanced disease.²¹ For pirfenidone, the CAPACITY and ASCEND trials reported a reduction in exacerbation rates among patients treated with pirfenidone, but these reductions did not reach statistical significance.^{7,8} A meta-analysis by Petnak et al.²² compared the risk of acute exacerbations between IPF patients receiving antifibrotic therapy and those who did not. The analysis, which included 26 studies (8 randomized controlled trials and 18 cohort studies) and a total of 12,956 patients, found that antifibrotic therapies effectively reduce exacerbation risk. The effect was more consistent with nintedanib than with pirfenidone, which showed less consistency. Furthermore, real-world data from the Belgian Health System records indicated a trend toward fewer acute exacerbations in the nintedanib group compared to the pirfenidone group, although this difference was not statistically significant.²³ A 2019 meta-analysis of 10 randomized controlled trials also reported no significant difference between nintedanib and pirfenidone in their effects on acute exacerbations.²⁴ Increased radiological extent is a well-established risk factor for acute exacerbations in IPF.²⁵ Despite the pirfenidone group in our study showing more extensive radiological involvement at baseline, the frequency of acute exacerbations remained comparable between the two groups. This observation suggests that pirfenidone may provide additional protection against exacerbations. However, further studies involving patient groups with similar baseline radiological characteristics are required to validate this finding.

Mortality outcomes in our study revealed notable patterns. A higher mortality rate was observed in patients treated with pirfenidone. However, previous studies comparing the effects of pirfenidone and nintedanib on mortality have generally reported similar all-cause mortality rates for both drugs.^{10,26,27} This discrepancy in our findings may be attributed to differences in baseline characteristics, particularly the more extensive radiological involvement in the pirfenidone group, which is a well-established risk factor for mortality in IPF.^{25,28}

In our study, the GAP index, a multidimensional tool integrating factors such as sex, age, and pulmonary function, was significantly higher in the pirfenidone group compared to the nintedanib group ($P = 0.007$). While the two groups were comparable in terms of baseline age, sex, and pulmonary function parameters, the higher GAP index in the pirfenidone group correlates with the increased mortality rate observed in this cohort. These findings highlight the critical importance of using integrated assessment methods like the GAP index in predicting mortality, as they provide a more comprehensive evaluation than individual parameters alone.

Studies in the literature have shown that in patients with IPF treated with pirfenidone or nintedanib, the time from diagnosis to mortality is generally similar for both drugs.^{29,30} However, in our study, this duration was significantly longer in the pirfenidone group than the nintedanib group. Interestingly, despite the more extensive baseline radiological involvement in the pirfenidone group - a known risk factor for mortality - the longer time from diagnosis to mortality suggests that pirfenidone may have a more pronounced effect on prolonging survival, despite this risk factor. Further studies with patient groups matched for radiological involvement are needed to validate these findings and clarify the comparative impacts of these antifibrotic agents.

The limitations of our study include its retrospective design, which relies on the accuracy and completeness of patient records, potentially limiting the generalizability of the findings. Additionally, significant baseline differences between the nintedanib and pirfenidone groups, such as GAP index and radiological involvement, may reduce the reliability of conclusions regarding treatment efficacy. Furthermore, the exclusion of some patients during the 5-year follow-up due to treatment changes or mortality limits the ability to comprehensively assess long-term outcomes. In addition, due to incomplete longitudinal FVC data in absolute values, we were unable to calculate yearly FVC change in milliliters or percentage from baseline, which limits the precision of treatment effect comparisons.

CONCLUSION

In this study, we evaluated the comparative efficacy and safety of nintedanib and pirfenidone in IPF, providing insights that contribute to clinical decision-making. We believe that antifibrotic therapies have a positive impact on mortality. The incidence of mortality was found to be higher in patients treated with pirfenidone compared to those treated with nintedanib, a finding that aligns with the lower GAP index observed in the nintedanib group. However, this finding should be interpreted cautiously due to the more extensive baseline radiological involvement in the pirfenidone group. Despite the higher baseline radiological involvement in the pirfenidone group, the longer time from diagnosis to mortality, compared to the nintedanib group, suggests that pirfenidone may have the potential to extend this period. Furthermore, the similar frequency of acute exacerbations between the two groups, despite the greater radiological burden in the pirfenidone group, suggests a potential protective effect of pirfenidone. To better understand the efficacy of antifibrotic agents in the treatment of IPF and to compare these therapies, more comprehensive studies are needed that include patients with similar demographic and functional characteristics and comparable radiological involvement.

Ethics

Ethics Committee Approval: The study protocol was approved by the Aydın Adnan Menderes University Local Ethics Committee (approval no: 2022/108, date: 04.08.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Y., O.Y., Concept: A.Y., O.Y., Design: A.Y., O.Y., Data Collection or Processing: A.Y., O.Y., Analysis or Interpretation: O.Y., Literature Search: A.Y., O.Y., Writing: A.Y., O.Y.

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

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Original Article



Assessment of Inspiratory Muscle Endurance in Healthy Adults by Recording Breathing Characteristics

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Abstract

OBJECTIVE: Respiratory muscle function is considered as strength and endurance. Since respiratory muscles are used a submaximally in daily life, measurement of respiratory muscle endurance rather than respiratory muscle strength is a more functional assessment. Measurement of respiratory muscle endurance is recommended to be performed by controlling the respiratory frequency and recording the breathing parameters. The purpose of this study was to evaluate respiratory muscle endurance with the incremental threshold loading (ITL) test in healthy adults by recording breathing parameters.

MATERIAL AND METHODS: This observational, cross-sectional study included 112 healthy adult subjects aged between 18 to 35 years. The anthropometric characteristics (weight and height), pulmonary function testing including forced expiratory volume (FEV1), forced vital capacity (FVC), and maximal voluntary ventilation (MVV), maximum inspiratory pressure (MIP), and physical activity level [International Physical Activity Questionnaire-Short Form (IPAQ-SF)] were evaluated. Inspiratory muscle endurance is assessed with ITL.

RESULTS: The inspiratory muscle endurance (P_{Imax}) was 54.08 ± 21.62 cmH₂O. Correlations between the P_{Imax} showed weak positive results with height ($r=0.392$, $P < 0.001$), weight ($r=0.382$, $P < 0.001$), and FEV1 ($r=0.386$, $P < 0.001$), moderate positive results with FVC ($r=0.446$, $P < 0.001$) and MVV (%) ($r=0.541$, $P < 0.001$), while strong positive results with MIP ($r=0.796$, $P < 0.001$). According to the regression analysis results, the MIP and MVV% values explained 63% of P_{Imax} .

CONCLUSION: Inspiratory muscle endurance in healthy adults can be explained with MIP and MVV. The ITL testing that is performed by recording respiratory mechanics, such as the inspiratory volume, inspiratory flow and work of breathing, can guide the determination of respiratory muscle training intensity.

KEYWORDS: Muscle endurance test, respiratory muscles, respiratory mechanics, inspiratory volume, inspiratory flow, inspiratory pressure

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INTRODUCTION

A comprehensive respiratory system assessment includes information on history, symptoms if present, physical examination, respiratory function, and respiratory muscle performance. The respiratory muscle performance, which is assessed as strength (maximum power generation capacity) and endurance (ability to continue a given task for a long time), should be part of a detailed and complete evaluation process. Measuring the strength of the respiratory muscles alone does not provide sufficient information regarding respiratory muscle function. The functional importance of respiratory muscle strength is controversial because maximal pressure is not reached often during the day. Moreover, in pathological conditions, respiratory muscles usually begin to weaken before clinical symptoms appear. Assessing the respiratory muscle strength alone may mask this weakness.^{1,2} Even if the inspiratory muscles are of sufficient strength, a loss of endurance may have started in stages where such pathological conditions do not progress much. In other

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words, the measurement of respiratory muscle endurance also provides predictive information regarding respiratory function. Comprehensive assessment of respiratory muscle performance is essential before starting respiratory muscle training on time. For these reasons, the endurance of the respiratory muscles (especially the inspiratory muscles) also needs to be evaluated. However, the effect of the respiratory pattern on the outcome measurements, and the fact that a standardized measurement method has not been developed yet, prevent the routine measurement of inspiratory muscle endurance in the clinic.³⁻⁶

There are several methods of assessing respiratory muscle endurance (Figure 1). The incremental threshold loading (ITL) test is one of the most frequently used to determine inspiratory muscle endurance.⁴ This measures a person's ability to sustain increased inspiratory load at regular intervals.^{7,8} Gradually increasing the test, which starts with a low load, allows participants to develop strategies to tolerate high loads. However, as high loads increase, decreased inspiratory volume and inspiratory time make maintaining ventilation throughout the step difficult. This situation, which causes the participants to terminate the test early with a feeling of suffocation, can be prevented by measuring devices that provide conic flow resistive loading.⁹⁻¹¹

The European Respiratory Society recommends evaluating the control of respiratory frequency and the recording of breathing parameters during the ITL test.¹⁰ Conic flow resistive loading devices allow these recordings separately for each breath.¹² To the best of our knowledge, there has been no study generating prediction models with this recommendation in young adults. Therefore, the aim of the study is to evaluate respiratory muscle endurance with the ITL test in healthy adults by recording breathing parameters.

MATERIAL AND METHODS

For this cross-sectional observational study, healthy adults were recruited from June 2020 to July 2022. Since the study data were collected during the Coronavirus disease-2019 (COVID-19) pandemic period, triage was applied to each patient for COVID-19 before the test, considering the "Recommendations for Pulmonary Function Tests During and After the COVID-19 Pandemic" published according to the Expert Opinion Report of the Turkish Thoracic Society, to avoid any risk of transmission. According to the answers given to the screening questions in the triage form, the participants who were not considered at risk for the measurements were evaluated. After the measurements, the equipment and laboratory room were disinfected, and the room was ventilated. During the tests, a filtered mouthpiece was used to prevent bacterial and viral cross-contamination.¹³ The study was approved by the Non-interventional Clinical Research Ethics Committee of Kütahya Health Sciences University (approval number: 2020/04-11, date: 25.02.2020). The study was conducted in accordance with the Declaration of Helsinki.

Participants

Participants between the ages of 18 and 35 years, who did not have any disease, did not regularly exercise, and did not smoke were included in the study. Adults with respiratory tract disease, heart disease, neuromuscular disease, scoliosis, previous thoracic surgery, and those who previously underwent a respiratory muscle endurance protocol were not included in the study.^{14,15} Volunteer participants who met the inclusion criteria were randomly selected. Informed consent was obtained from all participants.

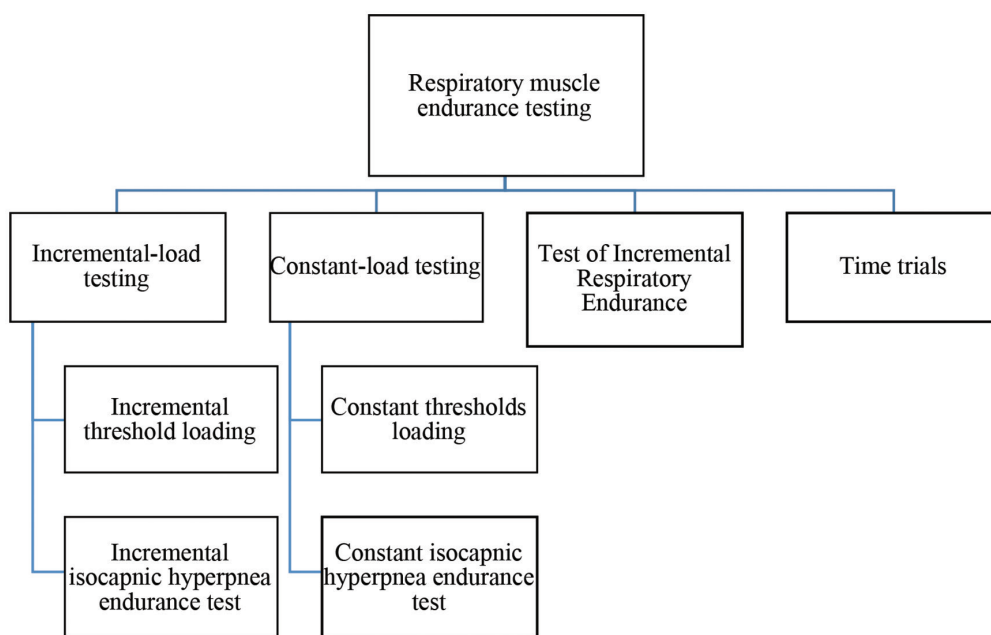


Figure 1. Respiratory muscle endurance assessment methods

Assessments

Firstly, anthropometric measurements of the participants were evaluated. Pulmonary function testing (PFT) measurements were then performed. After the inspiratory muscle strength measurement, participants took a rest break of 15 to 20 minutes. Then the inspiratory muscle endurance test was performed. Finally, the participants were asked to complete the International Physical Activity Questionnaire-Short Form (IPAQ-SF).

Experimental Design

The weight and height of the participants were evaluated. Weight was assessed using a digital scale in the orthostatic position, without shoes, with minimal clothing¹⁶ (Tanita BC 730, Tokyo, Japan). Height was measured with the feet parallel and adjacent to each other, the arms extended by the body, and the head in a neutral position¹⁷ (Seca 213, Hamburg, Germany).

PFT was performed using a spirometer (Cosmed Pony FX, Inc, Italy). Forced vital capacity (FVC), and forced expiratory volume (FEV1), were recorded.¹⁸ For maximal voluntary ventilation (MVV) measurements, the participant was asked to breathe deeply and rapidly (90-110 breaths/min) for twelve seconds. The highest value from at least three technically acceptable maneuvers was expressed as the percentage of the predicted values in each test.¹⁹

IPAQ-SF was used to measure the physical activity level of the subjects. The physical activity score is calculated by converting the questionnaire score to the metabolic equivalent of task (MET) (MET-min/week, 1 MET=3.5 mL/kg/min). Levels of moderate and intense physical activity, as well as the duration of walking and sitting, in the previous seven days were evaluated with the IPAQ-SF. The physical activity level was classified as 'inactive' for values lower than 600 MET-min/week, 'minimally active' for values of 600-3000 MET-min/week, and 'active' for values over 3000 MET-min/week.²⁰

The inspiratory muscle strength was assessed with maximum inspiratory pressure (MIP), formed at the mouth (POWERbreathe KH2, POWERbreathe International Ltd., UK). The participants

were asked to perform maximal inspiratory efforts; starting from the residual volume and sustaining it for at least one and a half seconds. The measurements were repeated nine times, at one-minute intervals, showing no more than a 10 cmH₂O or 10% difference between the results. The highest MIP value was used for inspiratory muscle endurance.^{10,21}

The inspiratory muscle endurance was evaluated with the ITL test. In a preliminary study, the reproducibility of the test was evaluated with thirty of the participants. The test-retest reliability of the ITL was found to be excellent (intraclass correlation coefficient: 0.979; $P < 0.001$). There was no significant difference between the breathing parameters, rate of perceived exertion (RPE), or the duty cycle of the test and retest.²² An eight-step test was started with 30% of the MIP, and the pressure was increased by 10% at one-minute intervals. Breathing frequency was fixed at fifteen breaths per minute by metronome. In the last ten seconds of each load level, the subjects were requested to RPE using the modified Borg Scale.²³ This scale is used to assess the severity of perceived fatigue, with a scoring range from 0 to 10. The individual indicates a value between 0-10 according to their perceived fatigue. It means "0: None" and "10: Most severe. The test was terminated when the participant was too tired to continue or was unable to open the valve three consecutive times. The outcome measure, called sustained maximal inspiratory pressure (P_{Imax}), was defined as the highest load in percentage of MIP sustained for a full minute. The parameters of work of breathing (WOB), inspiratory volume, inspiratory pressure, and inspiratory flow rate were recorded for each step. In addition, the ratio of the inspiratory time to the total respiration time (duty cycle) was calculated for each breath.^{10,24}

Statistical Analysis

Data analysis and calculations were performed using the IBM Statistical Package for the Social Sciences (SPSS) statistics 26.0 software package (IBM SPSS statistics for Windows, version 26.0; IBM, Armonk, New York). Data were expressed as frequency, percentages, and mean±standard deviation. The normality of the data was checked using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare the continuous data of the paired groups determined by measurement. A comparison of the parameters in the first and last steps of the test was performed with the Wilcoxon paired-sample test. Correlations between the ITL and variables were evaluated using Spearman correlation analysis. In the correlation analysis, the correlation coefficient (ρ) 0.00-0.19 was considered as indicating no relationship or an insignificantly weak relationship; 0.20-0.39 as a weak relationship; 0.40-0.69 as a moderate relationship; 0.70-0.89 as a strong relationship; and 0.90-1.00 as a very strong relationship.²⁵ Multiple linear regression analysis was applied to determine the variables predicting the P_{Imax} , and the stepwise method was preferred. A priori power analysis using G-power (a G-power 3.1.9 package program) demonstrated a minimum sample size of 109 with a medium effect size and power of 80% according to eight predictors. The level of significance was $P < 0.05$.

Main Points

- This paper provides objective data from the evaluation of inspiratory muscle endurance (IME) with the incremental threshold loading test recording breathing characteristics in healthy subjects.
- IME in healthy adults can be explained by maximal inspiratory pressure and maximal voluntary ventilation.
- Respiratory mechanics recorded during testing can be helpful in determining respiratory muscle exercise intensity.
- The pressure threshold at which work of breathing, inspiratory volume, and flow are high may help to increase the benefits of training.

RESULTS

One hundred sixteen healthy non-smoking adult subjects aged between 18 and 35 years participated in the study. Three of the participants declared their cold, flu, and cough complaints in the 'COVID-19 Screening Form before the Respiratory Function Test'. One participant was excluded from the study due to a lack of cooperation during the test. Data from 112 participants were analyzed.

The physical and demographic characteristics of the subjects are given in Table 1. According to the ITL test results, P_{max} was 54.08 ± 21.62 cmH₂O. The duty cycle was 0.52 ± 0.06 . The mean respiratory muscle endurance value was $60.64 \pm 14.97\%$ of MIP. The RPE was 6.55 ± 2.22 according to the modified Borg Scale. No subject completed all the steps of the test.

Table 1. Characteristics of the subjects

	n = 112 (mean±SD)
Age (years)	24.92±5.3
Gender (M/F)	56/56
Height (cm)	168.92±9.19
Weight (kg)	70.63±16.20
Body mass index (kg/m ²)	24.60±4.56
Pulmonary function testing	
FEV1 (L)	3.56±0.76
(% predicted)	93.94±9.39
FVC (L)	4.17±0.90
(% predicted)	95.59±9.51
MVV (L/min)	111.86±29.26
(% predicted)	84.35±16.89
Respiratory muscle strength	
MIP (cmH ₂ O)	88.91±26.49
(% predicted)	108.02±17.89

M: male, F: female, FEV1: forced expiratory volume, FVC: forced vital capacity, MVV: maximal voluntary ventilation, MIP: maximal inspiratory pressure, SD: standard deviation

The weekly energy consumption of the participants was calculated in MET-min and classified into physically inactive, low physical activity level, and adequate physical activity level according to the IPAQ-SF. There was no significant difference in the values of respiratory muscle strength and endurance according to the physical activity levels of the participants ($P > 0.05$) (Table 2).

Breathing parameters, such as inspiratory volume, inspiratory pressure, inspiratory flow, and WOB, recorded during the ITL test are shown in Table 3. The mean of inspiratory volume, inspiratory flow and WOB reached during the test was 1.26 ± 0.4 , 0.73 ± 0.34 and 58.05 ± 33.4 , respectively. The difference between the breathing parameters in the first step and in the last step was statistically significant. In the last step of the test, the inspiratory volume and inspiratory flow decreased, while the inspiratory pressure and WOB increased ($P < 0.05$). The highest inspiratory volume, inspiratory flow, and WOB reached during the test were 43.7%, 46.12%, and 48.67% of MIP, respectively.

The difference between the P_{max} values, RPE levels, and breathing parameters of the female and male participants was statistically significant ($P < 0.05$). There was no significant difference between the physical activity levels of the women and men according to the IPAQ-SF results ($P = 0.22$) (Table 4).

Correlations of the inspiratory muscle endurance with descriptive variables are shown in Table 5. A stepwise model was used in multiple regression analysis to identify possible predictors of the respiratory muscle endurance value. Gender did not influence the model. MIP and MVV % values explained 63% of P_{max} .

$$P_{\text{max}} = -15.991 + 0.586*(\text{MIP}) + 0.213*\text{MVV} (\%)$$

$$R^2=0.629.$$

A strong positive correlation was demonstrated ($\rho = 0.80$; $P < 0.001$) when correlating the values predicted by the proposed equation with the absolute values of the ITL (Figure 2).

Table 2. Inspiratory muscle performance according to physical activity level

Inspiratory muscle strength and endurance	Physical activity level			χ^2	P
	Inactive (n = 42) Mean±SD	Minimally active (n = 60) Mean±SD	Active (n = 10) Mean±SD		
MIP (cmH ₂ O)	82.21±3.82	92.58±3.56	95.06±7.38	4.700	0.095
P_{max} (cmH ₂ O)	49.04±3.39	57.18±2.79	56.66±5.59	4.722	0.094
Perceived exertion (modified Borg Scale)	6.10±0.30	6.75±0.28	7.30±1.03	4.291	0.117
i/i+e	0.52±0.01	0.51±0.01	0.51±0.02	0.149	0.928

SD: standard deviation, χ^2 : Kruskal-Wallis test chi-square value, P_{max} : inspiratory muscle endurance value, MIP: maximal inspiratory pressure, i/i+e: inspiration time/inspiration and expiration time

Table 3. Breathing characteristics

	First step of test Mean±SD	Last step of test Mean±SD	z	P
Breathing parameters				
Inspiratory volume (L)	1.33±0.55	1.09±0.51	-4.839	<0.001*
Inspiratory pressure (cmH ₂ O)	16.95±5.20	33.35±12.23	-9.103	<0.001*
Inspiratory flow (L/s)	0.72±0.37	0.63±0.33	-3.004	0.003*
WOB (Joules)	43.19±24.43	57.52±42.94	-3.883	<0.001*

*P < 0.05, z: Wilcoxon paired two-sample test value, WOB: work of breathing, SD: standard deviation

Table 4. Respiratory muscle endurance value, test parameters and physical activity level according to gender

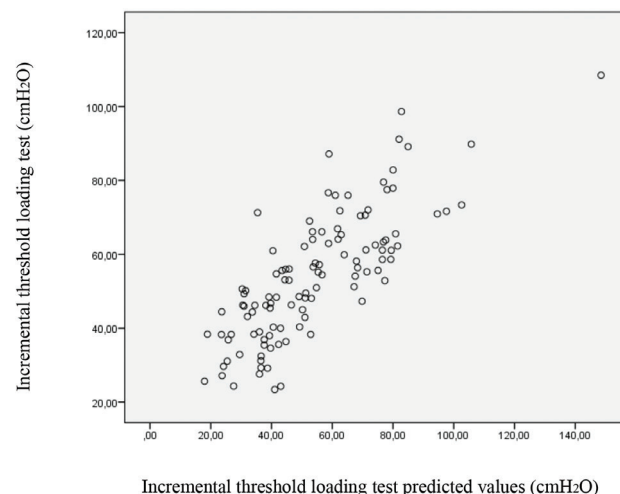
	Gender		z	P
	Female (n = 56) Mean±SD	Male (n = 56) Mean±SD		
Variables				
Plmax (cmH ₂ O)	45.31±2.42	62.85±2.86	-4.606	<0.001*
RPE (modified Borg Scale)	7.29±0.28	5.82±0.28	-3.414	<0.001*
i/i+e	0.51±0.01	0.52±0.01	-0.869	0.385
Inspiratory volume (L)	1.51±0.07	1.01±0.04	-5.418	<0.001*
Inspiratory pressure (cmH ₂ O)	22.31±0.91	28.70±1.13	-3.945	<0.001*
Inspiratory flow (L/s)	0.56±0.03	0.89±0.045	-5.562	<0.001*
WOB (Joules)	36.34±2.72	73.75±4.48	-6.133	<0.001*
IPAQ-SF (METs/min/week)	995.71±941.80	1274.16±1227.89	-1.237	0.216

z: Mann-Whitney U test value, *P < 0.05, Plmax: respiratory muscle endurance, i/i+e: duty cycle, WOB: work of breathing, IPAQ-SF: International Physical Activity Questionnaire Short Form, RPE: rate of perceived exertion

Table 5. The relationship between the ITL test and descriptive data

		Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)	FVC (L)	FEV1 (L)	MVV (L)	MIP (cmH ₂ O)
P_{lmax}	P	-0.024	0.392	0.382	0.247	0.446	0.386	0.541	0.796
	ρ	0.801	<0.001*	<0.001*	0.009	<0.001*	<0.001*	<0.001*	<0.001*

*P < 0.05, ρ: Spearman correlation analysis value (rho), P_{lmax}: respiratory muscle endurance, MIP: maximal inspiratory pressure

**Figure 2.** Correlations between the absolute values of ITL with the values predicted by the proposed equations

DISCUSSION

This study presents the multiple linear regression model for the ITL, examining the relationship between the main independent variables and inspiratory muscle endurance prediction. As a result of regression analysis, MIP and MVV values were the variables that best explained P_{Imax} . In fact, one of the factors reflecting respiratory muscle performance is inspiratory muscle strength and the other is inspiratory muscle endurance. Therefore, it is possible to predict this relationship. The MVV is used for the evaluation of respiratory muscle endurance in both athletes and patients where the airway is affected.^{26,27} The MVV is not recommended as a respiratory muscle endurance assessment method because the test period is not long enough to evaluate endurance. In addition, since it is affected by the airways, it does not provide precise information whether the test result reflects only the endurance of the respiratory muscles. Therefore, it is recommended not to use the MVV as a respiratory muscle endurance assessment method.¹⁰ In line with the results obtained in the current study, it was concluded that the MVV is related to the respiratory muscles and should be evaluated with alternative methods.

The independent variables differ in studies that create a regression model for respiratory muscle endurance in the literature. Woszezenki et al.¹⁴ in their study with healthy children aged 4-18 years, 66% of the P_{Imax} value was explained in the regression model with the MIP and age variables for the ITL. Neder et al.²⁸ included one hundred healthy participants aged 20-80 years in their study. Age and anthropometric measurements explained 56% of the MVV. Fiz et al.²⁹ found a significant relationship between the P_{Imax} value and FEV1, MIP, age and height in their study with ninety-nine healthy individuals aged 20-70 years. Variation in independent factors associated with respiratory muscle endurance between studies may be due to the population participating in the study, the age range of the subjects, sample size, and test type. While age and SFT were among the possible factors predicting respiratory muscle endurance value in studies with a wide age range, the MIP value was included in the regression formula in studies where the test procedure was determined using the MIP measurement.

It has been reported that for a well-controlled endurance test to contribute to a standardized evaluation program, it is not only sufficient to keep the respiratory frequency constant during the test but also to control the respiratory parameters. Several authors have reported that using a device that continuously records flow, volume, and pressure variables during measurement makes respiratory muscle endurance assessment more standardized.^{9,10} A device that can record respiratory parameters was used in this study, whose validity and reliability studies were performed working with the principle of conic flow resistive loading.^{9,12} The flow, volume, pressure, and WOB parameters recorded for each breath of each step of the test were analyzed. The inspiratory volume was found to be higher in the first steps of the test. The inspiratory flow increased as the pressure increased, but reached its peak before the end of the test. It is one of the strategies used to increase the flow rate by reducing the inspiratory volume during the test, to meet the threshold pressure load and create greater power. In this

case, considering the incremental nature of the test, increasing the inspiratory pressure causes the volume to decrease and the flow rate to increase at each step.^{11,30} In the current study, the inspiratory volume did not decrease enough to cause an increase in the flow rate. The use of a conical flow resistance device and fixation of inspiration and expiration times may have contributed to this result. Devices working with the principle of conic flow resistive loading allow inspiratory flow after the pressure threshold is exceeded and therefore prevent the tidal volume from falling.³¹ In the systematic review and meta-analysis of Beaumont et al.³² it was reported that optimal settings should be adjusted in respiratory muscle training to have a positive effect on dyspnea. The studies included in this meta-analysis use a classical inspiratory muscle training device. The advantage of devices working with the principle of conic flow resistive loading over classical muscle training devices is that they allow inspiratory flow after the pressure threshold is exceeded, and thereby increase tidal volume and vital capacity.¹² For this reason, determining the appropriate exercise intensity by considering the volume and flow values together with the inspiratory pressure may enhance the effect of respiratory muscle training and reduce dyspnea. The ITL performed with a device that measures respiratory parameters can be used to determine the appropriate training intensity.

In this study, the mean value of the WOB was greater than the values in both the first and the last steps. It has been suggested that the WOB value may be the most important determinant of respiratory muscle endurance, independent of the breathing pattern. The peak WOB reached during the test may be an indicator of the dynamic capacity of the respiratory muscles. It has been reported in the literature that the WOB during ITL reaches its peak in the first steps and decreases rapidly before reaching the last step of the test. This indicates that the ability to generate inspiratory flow and inspiratory volume is also high during the high WOB stage.¹⁰ The current study shows that, in parallel with the literature, the respiratory workload reached its peak value before reaching the last step of the test. At the same time, the peak steps of the volume, flow, and WOB were close and were in the range of 40-50% of the MIP. This value corresponded to the second and third steps of the test. In the literature, the intensity of respiratory muscle training varies between 30-80% of the MIP. After an individual evaluation, choosing the level with a high WOB, and inspiratory volume and flow as the training intensity can help increase the benefits of training.

In the present study, both inspiratory muscle strength and endurance of male participants were significantly higher than those of female participants. The perceived exertion level of women at the end of the test was also significantly higher than that of men. The difference in respiratory muscle performance may be due to the lower muscle mass of women compared to men.³³ Although there was a difference between the respiratory muscle strength of men and women, no difference was found in respiratory muscle endurance. The authors stated that this situation was due to insufficient sample size, high variability of outcome measurements and unknown factors.^{29,34,35} In this study, the number of groups was equal, the sample size was sufficient to show sex differences, the respiratory frequency

was fixed during the measurement, and the standardization provided by controlling the respiratory parameters made the test more sensitive in showing the change between the groups. With the combination of these factors, the current study, unlike other studies in the literature, showed the change in respiratory muscle strength and endurance according to gender.

This study has some limitations. The age range of the participants included in the study is limited. Conducting the study in a wider age range may explain the age-related changes in respiratory muscle endurance. In the present study, a self-report scale is used to measure the level of physical activity. None of the participants included in the study had regular physical activity habits. However, according to the scale results, 8.92% of the participants seem to have sufficient physical activity levels. Evaluating the physical activity level using a more objective method, such as accelerometers and pedometers rather than self-reported activity, will contribute to a more accurate interpretation of the results. There is also a need for studies evaluating the response of the ITL to respiratory muscle training with a device operating based on the principle of conical flow resistive loading.

CONCLUSION

Respiratory muscle function is evaluated as strength (maximum power generation capacity) and endurance (ability to continue a given task for a long time). Respiratory muscle strength provides information about respiratory muscle function. However, evaluation of respiratory muscle strength and endurance is more effective in determining respiratory muscle dysfunction. As a result of the regression analysis, the analysis showed that the variables that best explained the P_{max} value were the values of MIP and MVV (%). MIP and MVV could account for 63% of the P_{max} value. Anthropometric values, gender, FEV1, and FVC values were other independent variables that were related to the ITL but were not included in the regression formula. Respiratory workload and inspiratory flow parameters peaked during the test and decreased before reaching the last step of the test. Considering that the effect of standard respiratory muscle training in increasing ventilation has not been demonstrated, evaluating these parameters may enhance respiratory muscle training. In a measurement where respiratory muscle endurance is evaluated by ITL, the pressure where the inspiratory volume, inspiratory flow, and WOB (considered an indicator of the dynamic capacity of the respiratory muscles) are high can guide the determination of the intensity of respiratory muscle training.

Ethics

Ethics Committee Approval: The study was approved by the Non-interventional Clinical Research Ethics Committee of Kütahya Health Sciences University (approval number: 2020/04-11, date: 25.02.2020).

Informed Consent: Informed consent was obtained from all participants.

*The study has clinical trial registration (ClinicalTrials.gov identifier: NCT05237427).

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Footnotes

Authorship Contributions

Surgical and Medical Practices: S.O-G., Concept: S.O-G., Ö.A., Design: S.O-G., Data Collection or Processing: S.O-G., Analysis or Interpretation: S.O-G., Ö.A., Literature Search: S.O-G., Ö.A., Writing: S.O-G.

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

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Original Article



E-cigarette Attitude and Belief Scale in Adolescents: A Validity and Reliability Study

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Abstract

OBJECTIVE: Electronic cigarette (e-cigarette) use has increased significantly since its appearance on the global market in the mid-2000s. International studies have indicated that substance use among children is as prevalent as 7.8% worldwide and 15.4% among high school students in Türkiye. To prevent this public health problem, it is necessary to understand why adolescents use e-cigarettes. This study aimed to develop an attitude and belief scale about adolescent e-cigarette use.

MATERIAL AND METHODS: Chronic disease-free adolescents aged 14-18 who applied to pediatric outpatient clinics were invited to the study. Three hundred forty eligible participants were recruited. The scale on e-cigarette use was developed in light of the existing literature and comprises a total of 31 questions, including 20 assessing beliefs and 11 assessing attitudes.

RESULTS: Following specialist reviews, the following exploratory factor analysis, internal consistency analysis, criterion validity analysis, discriminant validity analysis, confirmatory factor analysis, test-retest reliability analysis, and internal validity tests were conducted. The 18-item scale, which has been proven to measure attitudes and beliefs toward e-cigarettes, is sufficient, valid, and reliable.

CONCLUSION: The developed “E-cigarette Attitude and Belief Scale in Adolescents” scale can be a critical tool for future studies. Gaining insight into adolescents’ attitudes and beliefs toward e-cigarettes can contribute to creating targeted educational and awareness initiatives on this issue.

KEYWORDS: Electronic cigarette, adolescents, scale, validation, reliability

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INTRODUCTION

In response to the declining market share of conventional tobacco products, the tobacco industry introduced alternatives such as heated tobacco and electronic cigarettes (e-cigarettes), often targeting children and adolescents.¹⁻³ As a result, the consumption of e-cigarettes increased, posing a severe public health concern globally.²

E-cigarettes entered the global market in the mid-2000s. The industry has employed diverse marketing strategies to promote these products, including targeted media advertising, sponsorships, and film collaborations.¹ The National Youth Tobacco Survey reports that the prevalence of e-cigarette use among high school students in the United States (US) increased from 9.3% in 2014 to 27.5% in 2019.⁴ According to the analysis of national survey data obtained from 3,925 participants aged 8-20 in 69 countries and regions, the prevalence of electronic and non-electronic nicotine-carrying device use among children was 17.2%; and the prevalence of e-cigarette use in the last 30 days was 7.8%.⁵ E-cigarette sales are prohibited in Türkiye.⁶ However, these products remain accessible through online platforms and direct marketing channels.⁶ This ease of access poses a significant challenge to regulatory enforcement and contributes to the increasing prevalence of e-cigarette use, particularly among adolescents. Although no nationally representative

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study assesses the prevalence of e-cigarette use in Türkiye, a local survey of high school students reported a prevalence of 15.4%.⁷

The rationale for understanding adolescents' beliefs and attitudes toward e-cigarettes stems from well-established behavioral theories, such as the Theory of Planned Behavior and the Health Belief Model, which suggest that an individual's beliefs significantly influence health-related behaviors.^{8,9} Exploring adolescents' beliefs and attitudes allows us to identify cognitive and emotional factors that may predict or explain e-cigarette use. Behavior and expectancy scales regarding e-cigarette use have been developed and validated for adolescents.^{10,11} However, to date, only one such scale has been tailored to a specific racial or ethnic group.¹²

To address this gap, we aimed to develop a comprehensive and culturally adaptable tool - the "E-cigarette Attitude and Belief Scale in Adolescents (ECABA)". Our goal was to create a reliable and valid instrument capable of capturing the complex beliefs and perceptions that underlie adolescent e-cigarette use. Such a scale would not only provide insight into current attitudes but also serve as a valuable metric to evaluate the long-term effectiveness of preventive interventions.

MATERIAL AND METHODS

Study Design

The validation study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Before commencing the study, it was approved by the the Ethics Committee of Koşuyolu High Specialization Training and Research Hospital (İstanbul, Türkiye) (decision no: 2024/16/920, approval date: 17.09.2024).

Participants and Settings

The participants were adolescents aged 14-18 who applied to the three pediatric outpatient clinics of İstanbul Medeniyet University Faculty of Medicine, between October and December 2024. All adolescents without chronic diseases who applied to the outpatient clinic were invited to participate in the study.

As this study involved both the development and validation of a new scale, the sample size was determined based on general recommendations suggesting a participant-to-item ratio of at least 5:1 to 10:1 for exploratory factor analysis.^{13,14} Since the initial draft scale had 31 items, we calculated the sample size

to be 310 participants. However, considering the possibility of non-respondents and missing data, it was decided to include 400 participants (Figure 1).

Demographic Information Form: To determine the demographic characteristics of the participants, information was collected regarding their ages, genders, parents' education levels, and whether they or others in their surrounding environment used packaged cigarettes or e-cigarettes. It consists of 16 questions.

Lifetime Substance Use: Participants' lifetime use of e-cigarettes and smoking was assessed (yes/no). The frequency of e-cigarette use or smoking in the last 1 month was also investigated.

Missing Data: Sixty participants, who either incompletely filled out the questionnaire or had no knowledge of e-cigarettes or tobacco, were excluded. Regarding demographic characteristics, participants with missing ECABA data did not differ significantly from participants with available ECABA data.

Smoking Decision Balance Scale: Youth Form

Initially developed by Velicer et al.,¹⁵ this scale assesses perceptions of the harms and benefits of smoking. Pallonen et al.¹⁶ adapted a 12-item version for children, later validated in Turkish by Bektaş et al.¹⁷ The five-point Likert scale comprises benefit and harm subscales. This scale is used with permission from the author.

Scale Development

The items in the initial draft scale, which measure attitude and belief regarding e-cigarette use, were developed in light of the existing literature.¹⁸⁻²¹

This initial scale comprised 31 items (20 belief questions and 11 attitude questions). Four specialists (three professors of pediatric pulmonology working on tobacco prevention and a psychologist working with adolescents with addiction) reviewed and revised the initial draft scale, and two items were excluded. The scale items were scored on a five-point Likert-type scale: "strongly disagree" (1), "disagree" (2), "undecided" (3), "agree" (4), and "strongly agree" (5).

Variables and Data Collection

Before beginning the questionnaire, participants and one of their parents read and reviewed the consent and were provided with comprehensive information about the study. The researcher provided adolescents with printed questionnaires, and an outpatient clinic room was designated for them to complete the questionnaires anonymously.

Validation and Reliability

Exploratory factor analysis with Varimax rotation, criterion validity analysis, discriminative validity analysis, confirmatory factor analysis, and test-retest reliability were conducted (Figure 2). The scale was reduced to 18 items in the final version.

Statistical Analysis

After collecting the data, all statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS)

Main Points

- A novel scale was developed to assess adolescents' attitudes and beliefs regarding e-cigarette use.
- Comprehensive psychometric analyses, including factor analysis and reliability testing, validated an 18-item version of the scale.
- This validated scale can facilitate future research and targeted interventions aimed at preventing e-cigarette use among adolescents.

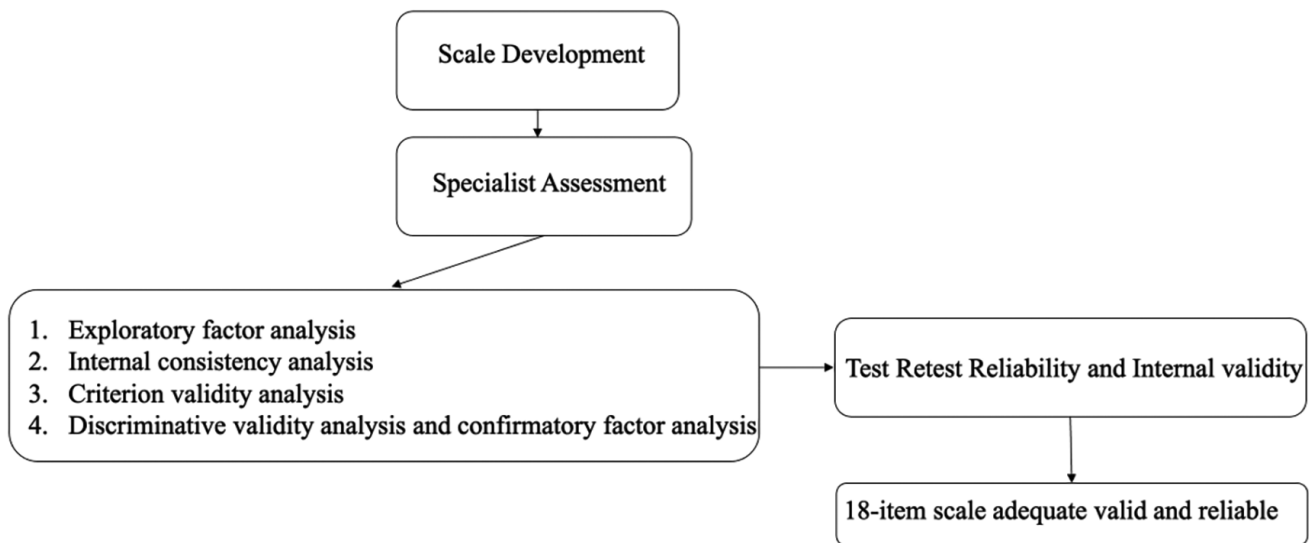


Figure 1. Flowchart

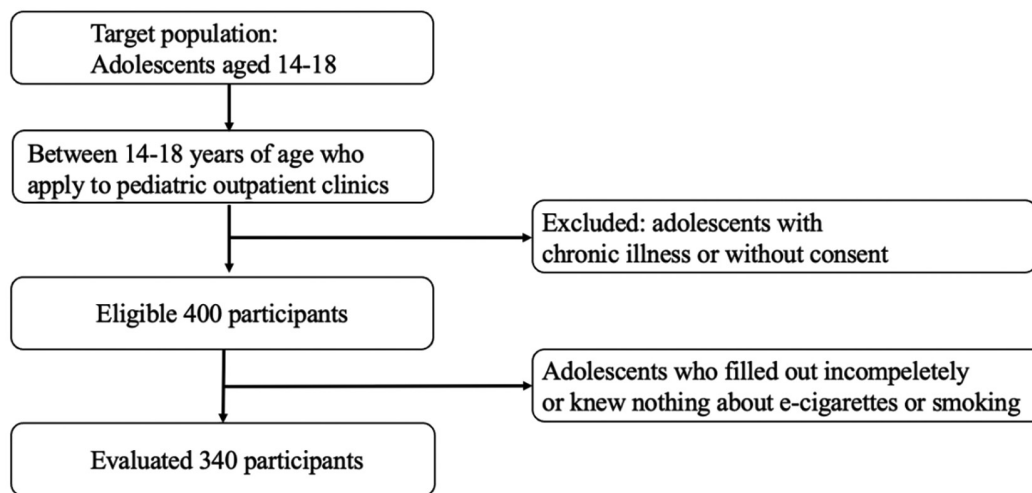


Figure 2. Flow diagram of the participants

statistics and IBM SPSS Amos, both for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) to assess the validity and reliability of the ECABA scale. Exploratory factor analysis with Varimax rotation, internal consistency analysis, criterion validity analysis, discriminative validity analysis, and confirmatory factor analysis were conducted.

In the exploratory factor analysis, sampling adequacy and sphericity were assessed for the scale, as suggested by Kaiser. The Kaiser-Meyer-Olkin (KMO) sampling adequacy and Bartlett's test for sphericity were evaluated and reported accordingly.^{22,23} Principal component analysis was used as the extraction method. At the same time, Varimax with Kaiser normalization was applied as the rotation method.

Internal consistency analysis, a commonly used reliability measure, effectively assesses the homogeneity of the questions designed to evaluate a specific area, determining whether the questions appropriately target and measure only the intended concept.¹³

Cronbach's alpha coefficient is a reliability coefficient found by dividing the sum of the covariances of the k items in the scale by the overall variance.²⁴ Cronbach's alpha values were evaluated with a tiered approach: ≥ 0.90 excellent, ≥ 0.80 good, ≥ 0.70 acceptable, ≥ 0.60 questionable, ≥ 0.50 poor, and ≤ 0.50 unacceptable.²⁵

The internal consistency of the final version of the scale was analyzed by calculating Cronbach's alpha values.

The difference between the mean scores of the 27% lower-upper groups is expected to be significant, measuring the scale's discriminative validity. To evaluate the significance of the difference in mean scores between the groups with the highest and lowest 27% of total scale scores, an independent samples t-test was conducted.

Correlation coefficients between the scale and the 'Child Decision Balance Scale' were calculated to test the scale's criterion validity. Confirmatory factor analysis is a type of

structural equation model application. It is used to test whether there is a significant relationship between the factors; whether the factors are independent of each other; which variables are related to which factors; and whether they are adequate to explain the model.¹⁴ First-level confirmatory factor analysis was conducted to determine whether the scale met the goodness-of-fit indices reported in the literature.²⁶

Test-retest Reliability and Internal Validity

The same baseline scale was administered to 30 participants at 2-week intervals. Table 1 shows the results of the paired sample t-test for the difference between the scale's test-retest averages. The mean scores obtained in the first test were compared with those obtained in the retest, which occurred fifteen days later.

Figure 1 presents the analysis algorithm.

RESULTS

Demographic Variables

Our study included 400 adolescents aged 14-18, however, after excluding those who provided incomplete responses, the final sample consisted of 340 adolescents aged 14-18 [mean age = 15.79; standard deviation (SD) = 1.204] (Figure 2), with 53.8% females (n = 183; mean age = 15.78; SD = 1.216) and 46.2% males (n = 157; mean age = 15.79; SD = 1.193) participants. Sixty adolescents were unaware of e-cigarettes and had never

been exposed to environments where e-cigarettes or smoking were used. They were excluded from the study to prevent potential bias and ensure the accuracy of the results. Of the participants, 19.4% had tried or used e-cigarettes, and 22.4% had tried or used packaged cigarettes.

Validity and Reliability of the E-cigarette Attitude and Belief Scale

Exploratory Factor Analysis

Factor analysis is a construct validity technique used to determine whether there is a particular order among participants' responses to the items in the measurement tool being developed.¹³ As a result of exploratory factor analysis, sub-dimensions, related to the concept to be measured by the scale, may be formed.¹³

In the exploratory factor analysis, all 29 items of the ECABA scale were subjected to principal component analysis with Varimax rotation (KMO = 0.875; Bartlett test₍₁₅₃₎ = 2681.429; $P < 0.001$). As a result of the study, a structure with 18 items and five factors was identified, each factor having an eigenvalue above one, explaining 66.63% of the variance (Table 2).

Internal Consistency Analysis

After conducting an exploratory factor analysis, internal consistency coefficients were calculated based on the factor

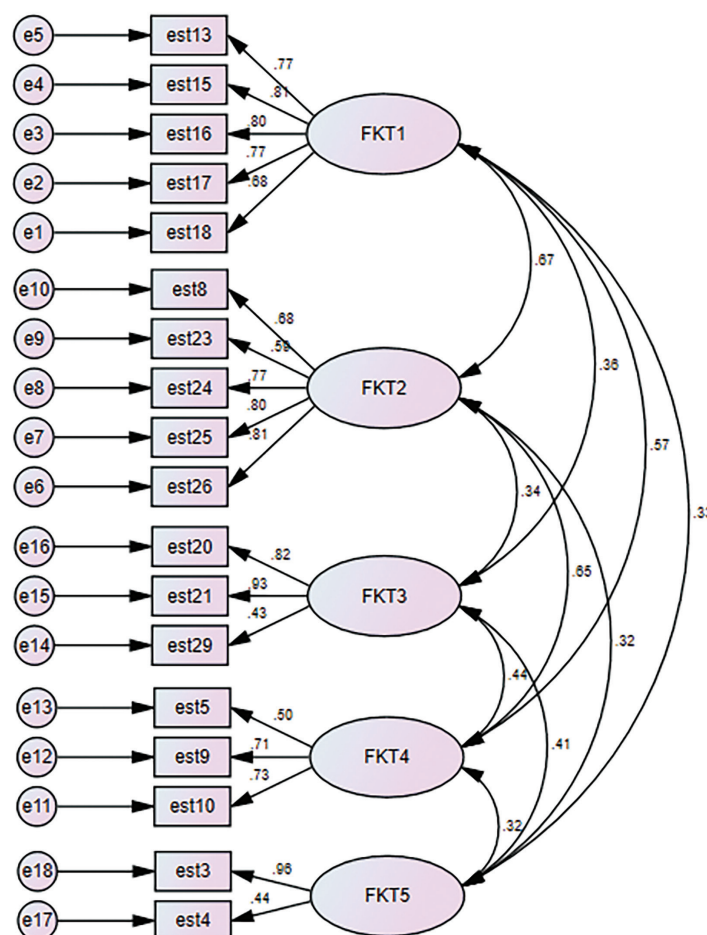


Figure 3. The five-dimensional latent structure established by the confirmatory factor analysis

distributions of the 18 items that formed the scale. As a result of the internal consistency analysis, $\alpha=0.888$ for the total item, $\alpha=0.877$ for F1, $\alpha=0.847$ for F2, $\alpha=0.747$ for F3, $\alpha=0.657$ for F4, and $\alpha=0.591$ for F5 were found to be (Supplementary Table 1).

Criterion Validity

To determine the scale's criterion validity, the correlation coefficients between the scores obtained from the scale and

its subscales, and the scores obtained from the "Benefits of smoking" and "Harms of smoking" subscales of the Decisional Balance Scale for Children were calculated. The calculation was done using Pearson correlation analysis, as detailed in Supplementary Table 2.

There was a positive and significant relationship at a medium effect level between the total scores obtained from the ECABA Scale and the "Benefits of Smoking" subscale of the Child Decisional Balance Scale ($r = 0.477$; $P = 0.000$), while there

Table 1. Paired sample t-test findings regarding the difference between the test-retest averages of the scale

	Test		Re-test		t	P
	Mean	SD	Mean	SD		
Total	34.94	10.904	34.88	10.444	0.387	0.701
Physical consequences of e-cigarette	10.09	4.129	9.97	3.786	0.941	0.353
E-cigarettes versus packs of cigarettes	10.47	3.871	10.44	3.735	0.329	0.744
Identification	5.03	2.747	4.97	2.634	1.436	0.160
E-cigarette addiction	6.12	2.422	6.21	2.384	-1.787	0.083
Socialization	3.24	1.458	3.29	1.508	-1.436	0.160

$P < 0.05$.

SD: standard deviation

Table 2. Exploratory factor analysis results

	F1	F2	F3	F4	F5
Physical consequences of e-cigarette: eigenvalue 6.511; variance explained: 36.171%					
18. E-cigarettes do not cause infertility (inability to have children).	0.796				
16. E-cigarettes do not cause loss of concentration.	0.789				
17. E-cigarettes do not cause nausea.	0.759				
15. E-cigarettes do not cause stroke.	0.752				
13. E-cigarettes do not cause headache.	0.713				
E-cigarette vs. packed cigarettes: eigenvalue 1.848; explained variance: 10.266%					
24. E-cigarettes are less harmful than packed cigarettes.		0.801			
26. E-cigarette use is less harmful than packed cigarette smoke.		0.785			
25. E-cigarettes are less addictive than packed cigarettes.		0.782			
8. E-cigarettes are less harmful and safer than packed cigarettes.		0.658			
23. E-cigarettes are tools that helps people quit smoking.		0.617			
Establishing identification: eigenvalue 1.450; explained variance: 8.057%					
20. Influencers using e-cigarettes makes me think positively about e-cigarettes.			0.899		
21. Celebrities/athletes using e-cigarettes makes me think positively about e-cigarettes.			0.896		
29. There is no problem in using e-cigarettes to avoid being excluded from your circle of friends.			0.451		
E-cigarette addiction: eigenvalue 1.134; explained variance: 6.300%					
10. E-cigarettes do not contain harmful or addictive substances.				0.786	
5. E-cigarette use is not addictive.				0.696	
9. E-cigarettes do not contain nicotine, unlike classic cigarettes.				0.628	
Socialization: eigenvalue 1.050; variance explained: 5.835%					
4. Refusing an e-cigarette when offered causes social exclusion.					0.850
3. E-cigarettes contribute to socialization.					0.744

was a negative and significant relationship at a low effect level between the “Harms of Smoking” subscale and the “Harms of Smoking” subscale ($r = -0.130$; $P = 0.017$).

When the relationships of the ECABA subscales with the benefits of smoking and the harms of smoking subscales are examined, it is revealed that there is a significant positive small effect between the psychological consequences of smoking subscale and the benefits of smoking subscale ($r = 0.275$; $P = 0.000$). There was a significant positive small effect between findings that e-cigarettes are less harmful than classical cigarettes and the benefits of smoking subscale ($r = 0.333$; $P < 0.001$); significant adverse small effect between the identification subscale and the benefits of smoking subscale ($r = 0.481$; $P = 0.000$) and harms of smoking subscale ($r = -0.216$; $P = 0.000$); significant positive small effect between the e-cigarette addiction subscale and the benefits of smoking subscale ($r = 0.288$; $P = 0.000$); There is a significant positive medium effect between the socialization subscale and the benefits of smoking subscale ($r = 0.477$; $P < 0.001$) and a significant adverse small effect between the socialization subscale and the harms of smoking subscale ($r = -0.130$; $P = 0.017$).

Discriminative Validity Analysis

A 27% lower vs. upper group comparison was conducted to measure the discriminative validity of the E-cigarette Attitude and Belief Scale. An independent sample t-test was conducted to determine whether there is a statistically significant difference between the mean scores of the lower 27% group (lowest scores) and the upper 27% group (highest scores) (Supplementary Table 3). As a result of the independent sample t-test, the differences between the mean scores of the 27% lower and upper groups from the scale and subscales were statistically significant ($P < 0.001$). Thus, it was determined that the scale had discriminative validity.

Confirmatory Factor Analysis

Confirmatory factor analysis was conducted for the five-factor structure of the ECABA Scale. According to the standard goodness-of-fit measures reported by Schermelleh-Engel et al.²⁶ (2003) (Supplementary Table 4).

When the obtained fit values were compared with the goodness-of-fit indexes accepted in the literature, the model for the five-factor structure of the ECABA Scale provided acceptable fit values (Figure 3).

Test Re-test Reliability and Internal Validity

The same baseline scale was administered at 2-week intervals to 30 participants. No significant difference was found between the mean scores of the first test and the retest conducted at 15-day intervals. Therefore, the scale was concluded to have retest reliability. Internal validity was evaluated with Cronbach's alpha (Table 1).

Supplementary Table 5 comprehensively presents the reasons for the retention or removal of all items initially evaluated in the statistical process. The complete, finalized version of the “Adolescent E-cigarette Attitude and Belief Scale (ECABA)” is

available as Supplementary Tables 6 and 7 in both English and Turkish.

DISCUSSION

It is essential to understand why adolescents use e-cigarettes. The validated scale holds strong potential to serve as a key instrument in future research exploring adolescent perspectives on e-cigarette use. A thorough understanding of these beliefs and attitude systems is crucial for designing impactful, evidence-based, educational and policy interventions to curb both the initiation and persistence of e-cigarette use among youth. Therefore, we need concrete measurement tools to assess young people's attitudes and beliefs towards e-cigarette use. Behavior and expectancy scales about e-cigarette use have been developed and validated for adolescents.²⁷ To our knowledge, only one e-cigarette attitude scale has been developed for a specific group based on race/ethnicity.¹²

This study aims to develop a scale for measuring the attitudes and beliefs of adolescents related to e-cigarettes. It measures attitudes and beliefs about the Physical Consequences of E-cigarettes, E-cigarettes vs. Pack Cigarettes, Establishing Identification, E-cigarette Addiction, and Socialization. A valid and reliable attitude and belief scale can help assess the effectiveness of prevention studies and changes in them over time.

During the scale development process, several items were removed based on specialist review, semantic coherence, and statistical criteria. Initially, two items were excluded following specialist assessment as they reflected either self-assessed knowledge or external observations rather than personal attitudes. Subsequently, EFA led to the removal of additional items that either cross-loaded on multiple factors or did not logically fit within the emerging factor structure. Many of these items addressed misconceptions or general statements about the harms of e-cigarettes, suggesting they constitute a distinct dimension unrelated to the intended attitude construct. A final EFA, conducted after removing semantically inconsistent items, yielded a five-factor structure comprising 18 items, all demonstrating satisfactory factor loadings (>0.50) and strong internal consistency (Cronbach's $\alpha=0.88$). Detailed item-level decisions and exclusion criteria are provided in Supplementary Table 5.

Upon examining the results of the internal consistency analysis, it was observed that the values generally aligned with those reported in the literature. The internal consistency coefficients for the subscales of e-cigarette addiction and socialization were found to be low but within acceptable limits. It was suggested that increasing the number of items loading on the subscales of socialization and e-cigarette addiction could enhance internal consistency. To test the criterion validity of the scale, its correlation with the reference test was assessed.¹⁷ As a result, it was found that as positive attitudes towards e-cigarettes increased, scores for these attitudes regarding the benefits of smoking also rose moderately. In contrast, negative attitude scores towards the harms of tobacco decreased slightly. The correlation of the attitude and belief scale towards e-cigarettes, with the benefits of smoking subscale, demonstrated that

the assumption of criterion validity was met. In contrast, the correlation between the initial scale and the harms of smoking subscale was low.

The scale's discriminant validity analysis revealed that it could distinguish between individuals with positive and negative attitudes and beliefs toward e-cigarettes. Therefore, the scale was assessed to measure participants' self-assessments in a way that differentiates them based on their attitudes and beliefs. A confirmatory factor analysis was conducted to test the model obtained from the exploratory factor analysis of the scale, and it was observed that the model met the goodness-of-fit values reported in the literature.²⁶ When evaluating the validity and reliability results of the E-cigarette Attitude and Belief Scale, it was evident that the scale items measured the intended characteristic and distinguished between individuals with and without the targeted attitude and belief. Expert opinions were utilized to determine the content validity of the scale. Exploratory and confirmatory factor analyses were used to assess the scale's construct validity. The scale's high and acceptable internal consistency coefficients indicate that the items within the subdimensions are consistent.

This study makes a significant contribution to the literature, but it also has some limitations. Although the study focuses on adolescents, the primary target group of the e-cigarette industry, conducting it in a hospital setting may have influenced responses due to social desirability bias. While previous studies and guidelines on e-cigarettes were utilized for item development, cognitive testing was not conducted with adolescents to ensure the items were meaningful and appropriate for this age group. Additionally, apart from pediatric pulmonology specialists specializing in e-cigarettes, and a psychologist specializing in substance abuse, no revision was obtained from other experts.

Although the study population was drawn from pediatric outpatient clinics, the sample demonstrated comparable socioeconomic, educational, and geographic diversity with that reported in national data by the Turkish Statistical Institute. This supports the generalisability of our findings to the broader Turkish adolescent population.

Despite these limitations, the current study offers a scientifically robust and original tool for measuring adolescents' attitudes and beliefs about e-cigarettes. By providing a reliable and valid scale to assess these attitudes and beliefs quantitatively, this study lays a strong foundation for future research and intervention programs. The responses can provide valuable insights for developing targeted educational initiatives and policy regulations to prevent e-cigarette use among adolescents.

CONCLUSION

In conclusion, e-cigarette use among adolescents represents a pressing public health concern that demands immediate attention. The ECABA Scale provides a valid and reliable tool for assessing adolescents' attitudes and beliefs, offering a foundation for identifying both risk factors that compromise health and protective factors that support healthy behaviors. It can also inform the design of targeted educational and

awareness programs to prevent e-cigarette use in this vulnerable population.

Ethics

Ethics Committee Approval: The Ethics Committee of Koşuyolu High Specialization Training and Research Hospital (İstanbul, Türkiye) (decision no: 2024/16/920, date: 17.09.2024) approved the application.

Informed Consent: Before beginning the questionnaire, participants and one of their parents read and reviewed the consent and were provided with comprehensive information about the study.

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I would like to thank my daughter, Deniz Oksay, for her valuable contribution to the preparation of the visual materials.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.C.O., Concept: S.C.O., G.B., S.G., Design: S.C.O., G.B., Z.R.O., E.D., Data Collection or Processing: S.C.O., G.A., G.B., D.M.T., Z.R.O., E.G., S.G., Analysis or Interpretation: S.C.O., G.A., G.B., E.D., S.G., Literature Search: S.C.O., G.A., S.G., Writing: S.C.O., G.A.

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Original Article



Diagnostic Success of Non-contrast Computed Tomography Findings in Central Acute Pulmonary Thromboembolism: A Case Control Study

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Abstract

OBJECTIVE: Computed tomography pulmonary angiography (CTPA) is the gold standard in the diagnosis of pulmonary thromboembolism (PTE) but it cannot be used safely in conditions such as renal failure and contrast allergy. Therefore, recognition of emboli with non-contrast thoracic CT can be useful in the management of PTE. The aim of our study was to determine the diagnostic success of non-contrast thoracic CT findings in the diagnosis of PTE.

MATERIAL AND METHODS: Patients who had both non-contrast thorax CT and CTPA imaging within 24 hours and were diagnosed with PTE were analyzed. A control group was formed by randomization in a 1:1 ratio (n = 55). CTPA images of the patients in both groups were evaluated blindly by two expert radiologists and demographic and clinical characteristics were recorded.

RESULTS: Fifty-five patients had embolism. The mean age was 68.5±15.2. Mortality rates were 36.4% in the embolism group and 40.0% in the control group. The main pulmonary artery diameter was significantly higher in the PTE group (32.0 mm vs. 29.4 mm, $P = 0.007$). The mean attenuation of the pulmonary blood pool in the PTE group was higher than that of the control group [46.2 Hounsfield units (HU) (29.4-63.9) vs. 41.1 HU (32.5-62.4)] ($P = 0.025$).

CONCLUSION: Direct and indirect findings obtained from non-contrast thoracic CT can help the diagnosis, in patients in whom CTPA cannot be performed. Diagnostic utility may increase when the presence of these findings is evaluated together with clinical and laboratory findings. Validation studies should be performed in larger populations.

KEYWORDS: Non-contrast computed tomography, pulmonary thromboembolism, diagnosis, pulmonary artery

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INTRODUCTION

Pulmonary thromboembolism (PTE) is a disease that occurs when the pulmonary arteries (PA) and their branches are occluded by fragments of thrombi from various veins. It usually occurs together with deep vein thrombosis. The two are called venous thromboembolism.¹ It is the third most common acute cardiovascular syndrome after myocardial infarction and stroke.² In epidemiological studies, the annual incidence of PTE varies between 39 and 115 per 100,000 population.^{1,3} Mortality rates of up to 30% are observed in untreated patients.⁴ Early diagnosis is particularly important to prevent mortality and morbidity.

The widespread use of non-invasive imaging methods and increased awareness of PTE have led to an increase in its incidence. Computed tomography pulmonary angiography (CTPA) is the gold standard imaging modality in patients with suspected PTE. Thanks to its multi-detector scanners, the medical imaging system can reliably detect emboli

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even at the subsegmental level.⁴⁻⁶ It has been shown that as the number of sections increases, the diagnostic success increases in segmental and subsegmental embolism.^{7,8} CTPA also allows simultaneous assessment of other structures, such as the mediastinum, lung parenchyma, and aorta (Ao).⁴

Although CTPA is a gold standard method in diagnosis, it cannot be used safely in conditions such as renal failure, contrast allergy, pregnancy, and breastfeeding.⁹ Due to the excessive cost of the device, CTPA is not accessible in many centers. In addition, renal function tests have to be completed before CTPA, which delays the diagnosis of the disease. Therefore, in recent years, researchers have started to research the recognition of emboli, especially in the proximal branches of the PA. They have used non-contrast thoracic CT. These studies often focus on the hyperdense lumen finding observed in the area where the embolus is located.^{4,5,10,11} However, the incidence of hyperdense lumen finding is approximately 35%.¹⁰ In addition to this finding, measuring the mean attenuation of the pulmonary blood pool the diameters of the PAs and their branches, and detecting indirect signs of PTE may help in the early diagnosis of acute PTE in patients who cannot use contrast agents.

The aim of our study was to determine the diagnostic success of non-contrast thorax CT findings for PTE using CTPA as the gold standard.

MATERIAL AND METHODS

Study Population

Our study was planned as a retrospective case-control study. The study was approved by the Ethics Committee of the İzmir Bakırçay University on the 5th of January 2022 (decision no: 478). Patients aged 18-80 years who applied to the emergency department of a tertiary hospital between January 2016 and December 2021 and had both non-contrast thoracic CT and CTPA imaging within 24 hours were analyzed. The rationale for performing two CT scans within a 24-hour period was that, in most cases, an initial non-contrast thoracic CT was performed in the emergency department to assess non-specific

symptoms such as chest pain, dyspnea, or hemoptysis. This scan served as a general screening tool to evaluate alternative thoracic pathologies. When PTE was subsequently suspected based on clinical evolution and pulmonology consultation, CTPA was performed within the same 24-hour interval. Patients with segmental and subsegmental embolism, pulmonary hypertension (HT), chronic PTE, inadequate contrast enhancement preventing CTPA evaluation, hemoglobin (Hb) levels <7 g/dL, and data loss were excluded from the study. A total of 47 patients met these exclusion criteria. CTPA reports of the remaining eligible patients were then analyzed. CTPA images of the patients were evaluated blindly by two expert radiologists working in our hospital and the diagnoses were confirmed. The case group included patients with thromboembolism involving the main, right or left PAs, or lobar branches (n = 55). Among the control population, CT scans of 529 patients were independently reviewed in a double-blinded manner by two radiologists. Patients with additional radiologic abnormalities that could potentially confound vascular assessment were excluded, including those with vascular anomalies (n = 5), PA-invasive masses (n = 11), and congenital cardiac anomalies (n = 1). After these exclusions, 512 patients remained eligible. To achieve a 1:1 ratio with the case group, 55 control patients were selected from this cohort using systematic random sampling.

Demographic data, comorbid diseases, laboratory, non-contrast CT findings, echocardiography findings, and outcome status of all patients in the case and control groups were documented. The groups were compared in terms of these variables, especially non-contrast CT findings, and the data were analyzed (Figure 1).

Main Points

- Diagnosing pulmonary embolism (PTE) can be challenging due to its non-specific clinical presentation.
- Computed tomography pulmonary angiography (CTPA) is the gold standard for PTE diagnosis, but it may not be feasible in patients with contrast allergy or renal impairment.
- In this study, patients who underwent non-contrast thoracic CT followed by CTPA within 24 hours were retrospectively compared with a control group that had only non-contrast thoracic CT.
- Pulmonary artery enlargement and increased attenuation in the pulmonary blood pool on non-contrast thoracic CT are notable indicators of PTE.
- In cases where CTPA is not possible, non-contrast thoracic CT findings, when evaluated alongside clinical and laboratory data, may enhance diagnostic accuracy.

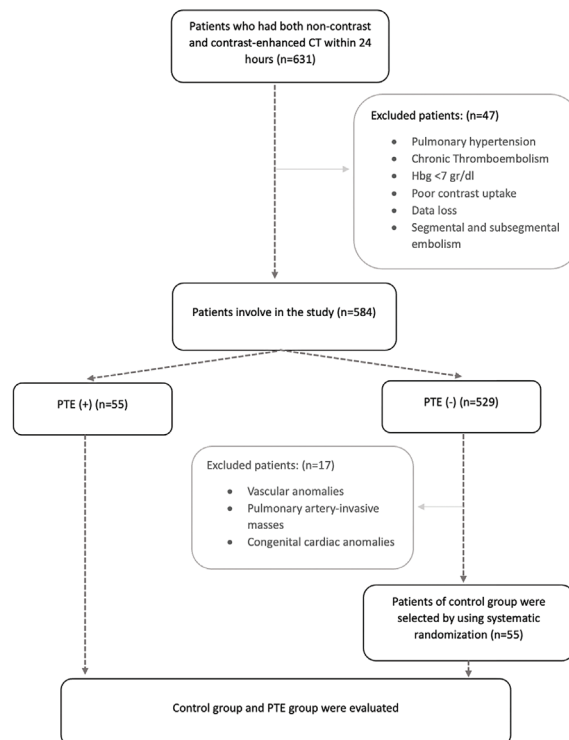


Figure 1. Patient selection and study design of research

CT: computed tomograph, Hbg: hemoglobin, PTE: pulmonary thromboembolism

Computed Tomography Protocol

Non-contrast thoracic CT and CTPA were performed in all patients using a 128-detector spiral CT scanner (GE Optima CT660®, USA). In CTPA, 50 mL of contrast material (iohexol) was administered intravenously through the antecubital vein as a bolus injection, followed by a saline chaser at a rate of 4.5 mL/sec. Image acquisition was performed in the PA phase. On non-contrast thoracic CT, images were reconstructed with a slice thickness of 3 mm, whereas the axial images from CTPA were reconstructed with a slice thickness of 0.625 mm. All images were interpreted on a standard PACS workstation by two experienced radiologists blinded to the clinical data. The evaluations were performed blindly by two experienced radiologists at the hospital workstation. For cardio-vascular diameter and density measurements, mediastinal window settings were used [window width: 350 Hounsfield units (HU); window level: 40 HU], while lung parenchymal findings and indirect signs (e.g., pleural effusion, consolidation, and wedge-shaped opacity) were evaluated using lung window settings (window width: 1500 HU; window level: -600 HU). On non-contrast CT, the diameters of the main PA and ascending Ao were measured at the level of the bifurcation in axial sections, and the PA-to-Ao ratio was calculated. The diameters of the

right main PA and the left main PA were measured at the widest point. For attenuation measurements, four circular regions of interest (ROIs), each measuring 1-1.5 mm², were placed in the main PA, right main PA, and left main PA, making a total of 12 ROIs (Figure 2). Additionally, one ROI was placed in each of the three right lobar arteries and in each of the two left lobar arteries (5 ROIs in total). This resulted in a total of 17 pulmonary vascular locations for density evaluation. All attenuation values were recorded in HU. Pleural and parenchymal changes, and cardiomegaly findings on CT were also noted (Figure 3).

Statistical Analysis

Statistical analysis was performed using IBM SPSS for Windows® 26.0 software (IBM Corp., Armonk, NY, USA). Demographic data, comorbid diseases, and laboratory findings were presented as descriptive statistics. In descriptive statistics, categorical variables were expressed as numbers and frequency. Continuous variables were presented as mean±standard deviation.

Intraclass correlation analysis was used to measure the agreement between the evaluators in terms of continuous variables when evaluating non-contrast CT. A two-way

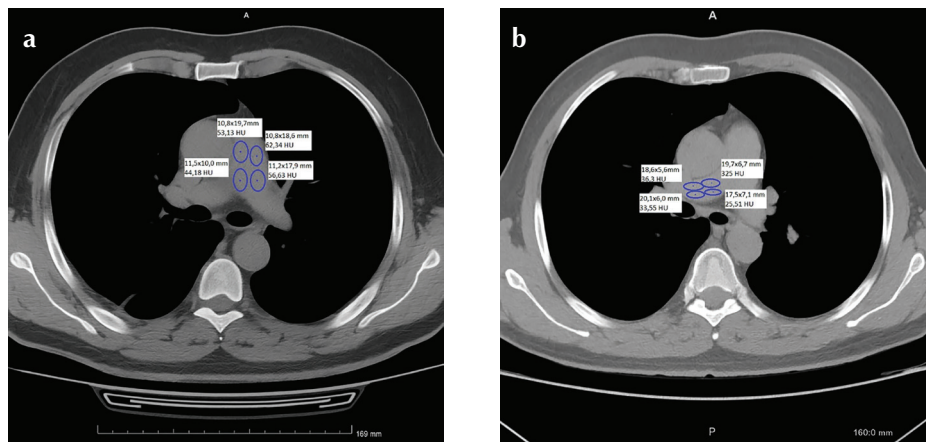


Figure 2. Pulmonary truncus on axial non-contrast thoracic CT image (a) and density measurement with four ROIs placed in the right main pulmonary artery (b)

CT: computed tomography, ROI: regions of interest

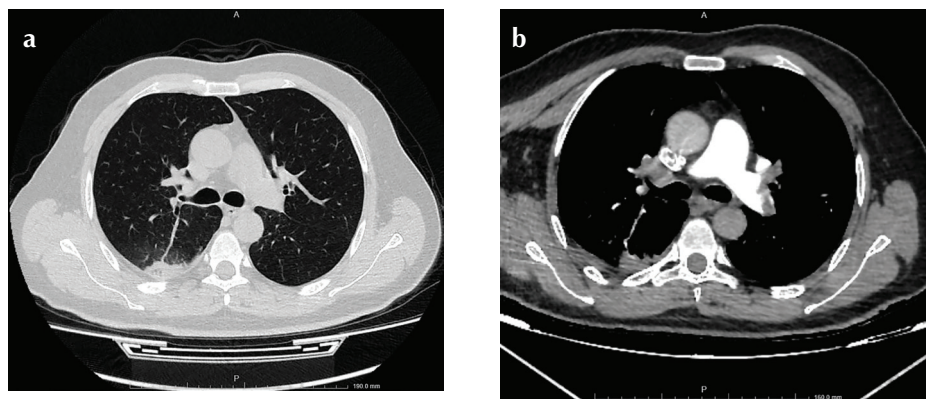


Figure 3. Subpleural consolidation in the right upper lobe posterior segment that suggests pulmonary infarct is shown in axial CT image (a) CTPA image of the same patient, near complete occlusion of the right upper lobe artery (b)

CT: computed tomography, CTPA: computed tomography pulmonary angiography

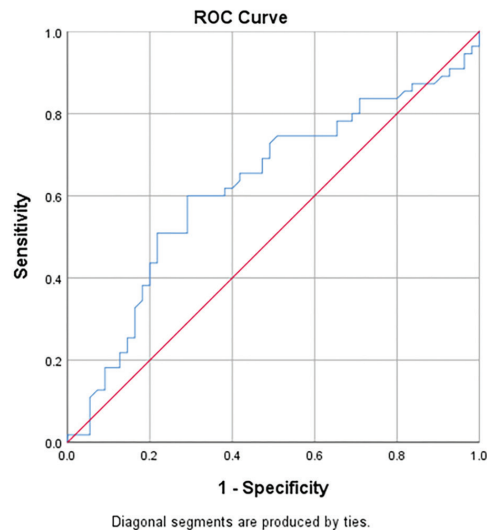


Figure 4. ROC curve for pulmonary blood pool mean attenuation

ROC: receiver operating characteristic

random model was used for these calculations. Agreement in categorical variables was measured by Cohen's Kappa analysis. The agreement between the two reviewers was good for the mean attenuation measurements of the PA pool ($P = 0.850$). This agreement was also good for ascending Ao main PA right main PA, and left main PA diameters. Moderate agreement was obtained in the evaluation of parenchymal findings (Table 1). Because of the good agreement between the reviewers, the data of the more experienced reviewer was used as the basis for statistical analysis.

Before comparing the two groups, the continuous data were analyzed with the Kolmogorov-Smirnov test to determine whether they conformed to the normal distribution. Independent t-test analysis was used for the comparison of data conforming to a normal distribution. Mann-Whitney U analysis was used for the comparison of data not conforming to normal distribution. Chi-square analysis was used to compare categorical variables. $P < 0.05$ was considered statistically significant.

RESULTS

Prevalence and Distribution of Pulmonary Embolism

A total of 631 patients underwent both non-contrast thoracic CT and CTPA within 24 hours of admission. After applying the inclusion and exclusion criteria, 584 patients were deemed eligible for the study. Among these, 55 patients (9.4%) were diagnosed with PTE based on the presence of contrast-filling defects in the main PA and/or lobar branches. Saddle emboli involving the main PA were identified in 10 patients (18.2%), whereas 31 patients (56.3%) had emboli located in the right or left main PAs. In 14 patients (25.5%), emboli were confined to lobar branches. Most emboli were bilateral (70.9%).

Demographic and Clinical Characteristics

The mean age of the study population was 68.5 ± 15.2 years, with no statistically significant difference between the PTE and control groups. Among all patients, 64 were women and 46 were men. The proportion of female patients was significantly

higher in the PTE group ($P = 0.02$). HT was the most common comorbidity observed in both groups, followed by diabetes mellitus and chronic obstructive pulmonary disease. However, HT and malignancy were significantly more prevalent in patients with PTE ($P = 0.008$ and $P = 0.028$, respectively). Troponin and D-dimer levels were also significantly higher in the PTE group ($P < 0.001$), whereas other laboratory parameters did not differ significantly. The overall in-hospital mortality rate was 38.2%, with 36.4% in the PTE group and 40.0% in the control group ($P > 0.05$). Further demographic and clinical data are summarized in Table 2.

Quantitative Vascular and Indirect Signs on Non-contrast Computed Tomography

Quantitative assessment of vascular structures showed that the main PA diameter was significantly higher in the PTE group compared to the control group (32.0 mm vs. 29.4 mm, $P = 0.007$). Similarly, the right PA diameter and the PA-to-Ao ratio were significantly greater in the PTE group ($P = 0.025$ and $P = 0.004$, respectively). In contrast, the left PA diameter showed only borderline significance ($P = 0.053$), and the diameter of the ascending Ao did not differ between groups ($P = 1.00$).

The mean attenuation of the pulmonary blood pool was significantly higher in the PTE group (46.2 HU; range: 29.4-63.9) compared to the control group (41.1 HU; range: 32.5-62.4), ($P = 0.025$). Receiver operating characteristic (ROC) curve analysis identified a threshold of 42.2 HU for predicting the presence of embolism, with a sensitivity of 61.8%, an area under the curve (AUC) of 0.623 [95% confidence interval (CI): 0.51-0.73], and statistical significance ($P = 0.026$). Additional attenuation and diameter measurements are presented in Table 3.

Indirect signs of PTE were present in 65.4% of patients in the embolism group and in 61.8% of those in the control group. Cardiomegaly was the most frequent indirect finding in the PTE group (47.3%), while pleural effusion was more common in the control group (25.5%). Statistically significant differences

Table 1. Inter-rater agreement in non-contrast thoracic CT

Variable	P	95% CI
Ascending aorta diameter	0.873	0.787-0.921
Main pulmonary artery diameter	0.814	0.740-0.869
Right main pulmonary artery diameter	0.845	0.782-0.891
Left main pulmonary artery diameter	0.834	0.767-0.883
Pulmonary blood pool attenuation	0.850	0.785-0.896
Indirect PTE findings*	0.417	0.250-0.584

*: Cohen's Kappa analysis was used, PTE: pulmonary thromboembolism, CI: confidence interval, CT: computed tomography

Table 2. Descriptive statistics and comparison of statistics between groups

	Total (n = 110)	PTE (+) (n = 55)	PTE (-) (n = 55)	P
Age (mean±SD) [‡]	68.5±15.2	70.27±16.81	65.63±13.55	0.07
Gender* (n, %)				0.020
Female	64 (58.2)	38 (69.1)	26 (47.3)	
Male	46 (41.8)	17 (30.9)	29 (52.7)	
Laboratory[‡] (mean±SD)				
Hemoglobin (g/dL)	12.37±1.82	12.32±1.82	12.42±1.85	0.78
Platelets (/uL)	257536±99110	266873±100396	248200±97830	0.33
D-dimer (ng/mL)	3303.00±1382.59	3912±970	2740±1473	<0.001
Troponin (ng/L)	55.34±78.16	80.2±92.5	30.0±49.3	0.001
Comorbidities* (n, %)				
Coronary artery disease	22 (20%)	13 (23.6%)	9 (16.3%)	0.34
Diabetes mellitus	32 (29.1%)	17 (30.9%)	15 (27.2%)	0.63
Interstitial lung disease	0 (0%)	0 (0%)	0 (0%)	1.000
COPD	23 (20.9%)	10 (18.1%)	13 (23.6%)	0.41
Cerebrovascular disease	6 (5.5%)	4 (7.2%)	2 (3.6%)	0.40
Malignancy	8 (7.3%)	7 (12.7%)	1 (1.8%)	0.028
Heart failure	12 (10.9%)	8 (14.5%)	4 (7.3%)	0.22
Hypertension	56 (50.9%)	35 (63.6%)	21 (38.2%)	0.008
Other diseases	36 (32.7%)	16 (29.1%)	20 (36.4%)	0.42
Location of PTE		n = 55		
Saddle		10 (18.2)		
Left and right main pulmonary artery		31 (56.3)		
Lobar		14 (25.5)		

[‡]: independent sample t-test, *: chi-square test, COPD: chronic obstructive lung disease, SD: standard deviation

were observed between the groups in terms of cardiomegaly ($P = 0.010$) and peripheral consolidation or ground-glass opacities ($P = 0.001$). A detailed comparison of indirect findings is provided in Table 4.

Multivariate Analysis of Diagnostic Predictors

Binary logistic regression analysis was performed using the following independent variables: mean HU of the pulmonary blood pool, main PA diameter, right PA diameter, PA/Ao ratio, presence of indirect signs on thorax CT, and D-dimer levels. Prior to the analysis, an outlier assessment was conducted, and

no significant outliers were identified. The model demonstrated an overall prediction accuracy of 73% in distinguishing between case and control groups. According to the analysis, the PA/Ao ratio [$P = 0.034$, odds ratio (OR): 4.886, 95% CI: 1.124-21.240] and D-dimer level ($P < 0.001$, OR: 1.001, 95% CI: 1.000-1.001) were found to be statistically significant independent predictors of PTE. Other variables—including main and right PA diameter, mean HU values, and the presence of indirect signs on non-contrast thoracic CT—did not show a statistically significant contribution to the model ($P > 0.05$ for all) (Table 5).

Table 3. Comparison of non-contrast CT measurements between groups

Variables (mean±SD)	PTE (+) (n = 55)	PTE (-) (n = 55)	P
Diameters (mm)			
Main pulmonary artery	32.04±4.49	29.47±5.20	0.007
Ascending aorta	35.98±4.05	35.98±4.56	1.000
PA/Ao ratio	0.897±0.128	0.824±0.132	0.004
Left main pulmonary artery*	26.00 (19-35)	25.00 (17-30)	0.05
Right main pulmonary artery	25.95±3.71	24.35±3.69	0.025
PA/Ao ratio categorized (n, %)			
Normal (≤0.9)	27 (49.1%)	39 (70.9%)	0.020
High (>0.9)	28 (50.9%)	16 (29.1%)	
Attenuation (HU)			
Mean pulmonary blood pool *	46.2 (29.4-63.9)	41.1 (32.5-62.4)	0.025
Main pulmonary artery	43.70±8.26	43.42±8.66	0.09
Right pulmonary artery	44.13±8.72	43.71±9.40	0.08
Left pulmonary artery*	43.00 (28.2-83.2)	41.75 (28.5-63.2)	0.28

*: Mann-Whitney U test was applied to variables that did not fit the normal distribution. Data are presented as median (min-max), PA/Ao: pulmonary artery diameter/ascenden aort diamater, SD: standard deviation, PTE: pulmonary thromboembolism, CT: computed tomography, HU: Hounsfield units

Table 4. Comparison of indirect signs on non-contrast thoracic CT between groups

Indirect findings	PE (+) (n = 55)	PE (-) (n = 55)	P
Atelectasis	12 (21.8)	7 (12.7)	0.22
Pleural effusion	13 (23.6)	14 (25.5)	0.83
Peripheral consolidation/ground glass	22 (40)	7 (12.7)	0.001
Cardiomegaly	26 (47.3)	13 (23.6)	0.01
Fibrotic bands	1 (1.8)	5 (9.1)	0.09
Mosaic attenuation	2 (3.6)	1 (1.8)	0.56
Others	4 (7.3)	4 (7.3)	1.000

PTE: pulmonary thromboembolism, CT: computed tomography

Table 5. Binary logistic regression analysis results

Variable	OR	95% CI	P
Main pulmonary artery diameter	0.951	0.791-1.143	0.591
Right pulmonary artery diameter	1.091	0.912-1.304	0.342
PA/Ao (categorized)	4.886	1.124-21.240	0.034
Mean pulmonary blood pool HU	1.051	0.983-1.123	0.146
Indirect signs on thoracic CT	2.216	0.696-7.058	0.178
D-Dimer (ng/mL)	1.001	1.000-1.001	<0.001

PA/Ao: pulmonary artery diameter/ascenden aort diamater, CT: computer tomography, CI: confidence interval, HU: Hounsfield units, OR: odds ratio

DISCUSSION

In this retrospective case-control study, we investigated the diagnostic utility of non-contrast thoracic CT findings in detecting central PTE, using CTPA as the reference standard. Our analysis demonstrated that patients with confirmed PTE, had significantly larger main and right PA diameters, higher PA/Ao ratio, and greater mean attenuation values in the pulmonary blood pool compared to control subjects. Additionally, certain indirect signs—such as cardiomegaly and peripheral consolidation/ground-glass opacities—were more frequently observed in the PTE group. In multivariate analysis, PA/Ao ratio and D-dimer levels emerged as independent predictors of PTE, while other imaging markers did not retain statistical significance. These findings suggest that selected non-contrast CT parameters, when interpreted alongside laboratory data, may assist in the diagnosis of central PTE, particularly, in patients for whom CTPA is contraindicated.

Previous studies on this subject show that the hyperdense lumen sign may help the diagnosis in the presence of central PTE.^{4,10,11} However, the small number of cases presented in these studies and insufficient validation studies reduce the reliability.^{11,12} In studies, the diagnostic value of the sign is lost as we move towards segmental and subsegmental branches.¹⁰ In contrast to these studies, Cobelli et al.¹² reported that in some cases of central PTE, hypoattenuation findings may be observed alongside the hyperattenuation sign.

Studies have shown that high attenuation values in the blood pool are caused by an excess of protein in the concentrated red blood cells. As the water content of the thrombus decreases over time, Hb becomes more concentrated, and attenuation values increase.¹³ This suggests that increased thrombus burden, and/or a period after the event, may be required for the appearance of hyperdense lumen sign on non-contrast thoracic CT. In addition, slowing of pulmonary blood flow after PTE has also been reported to cause increased attenuation. The fact that the hyperdense lumen finding occurs after the thrombus is organized, and is observed at low rates in the acute period led us to investigate the diagnostic success of findings, other than hyperdense lumen, on non-contrast thoracic CT. In our study, increased mean pulmonary blood pool attenuation was associated with PTE.¹⁰ Our data suggest that increased attenuation of the pulmonary blood pool caused by slowed pulmonary blood flow after thrombus may be another diagnostic finding in addition to hyperdense lumen sign.

The mean attenuation in the pulmonary blood pool outside the embolus area was 36.3 HU in the study by Kanne et al.¹¹ and 38.3 HU in the study by Tatco and Piedad.¹⁰ In these studies, the attenuation of embolism areas varied between 60-65 HU.^{10,11} In our study, the predictive value for the mean attenuation of the pulmonary blood pool including the embolus areas was found to be 42.2 HU.

Although ROC curve analysis demonstrated that increased mean pulmonary blood pool attenuation was significantly associated with the presence of pulmonary embolism, the AUC value of 0.623 indicates only modest diagnostic performance. This relatively low AUC suggests that blood pool attenuation alone may not be sufficient for reliable diagnosis and should

not be used in isolation. Instead, it should be interpreted in conjunction with other imaging features (e.g., PA/Ao ratio, parenchymal findings) and clinical parameters. Our findings emphasize that while pulmonary blood pool attenuation may serve as a supportive radiological clue, its diagnostic utility is limited, and should be further validated through larger studies with more robust predictive modeling.

Truong et al.¹⁴ found a main PA diameter of 25.1 ± 2.8 mm in the normal population; a cut-off value of 28.9 mm in men and 26.9 mm in women was associated with dyspnea. The PA/Ao ratio was reported as 0.77 ± 0.09 in that same cohort.¹⁴ In the study by Edwards et al.¹⁵, the mean diameter of the main PA was measured as 27.2 ± 3.0 mm, with the upper limit defined at 33.2 mm. Based on these and similar studies, an upper reference value of 29 mm for main PA diameter and a PA/Ao ratio of 0.9-1 is generally accepted as thresholds in thoracic CT evaluation. In a separate comparative study between acute PTE patients and healthy individuals, significantly increased values for main, left, and right PA diameters, and PA/Ao ratios were found in the PTE group.¹⁶ Consistent with these data, our study also demonstrated that increased PA diameter and elevated PA/Ao ratio were significantly associated with PTE. These findings suggest that measurement of PA diameters and PA/Ao ratio on non-contrast thoracic CT may serve as valuable indicators in patients with suspected PTE, particularly in those without known conditions that elevate PA pressure.

Studies have shown that indirect parenchymal findings may guide in the diagnosis of PTE. In the study by Coche et al.¹⁸, pleural-based consolidations and fibrotic band findings were found to be associated with PTE. Only wedge-shaped consolidation was found to be associated with PTE in the Pfeil et al.¹⁷ study. In our study, the presence of parenchymal consolidation/ground-glass and cardiomegaly was found to be associated with PTE. The finding of peripheral consolidation/ground glass and cardiomegaly on non-contrast thoracic CT may indicate the need for further investigation for PTE.

The interpretation of non-contrast thoracic CT findings may be influenced by several potential confounding factors. One of the most important factors is the patient's Hb level at the time of imaging, which directly affects blood attenuation values on CT scans. Higher Hb levels are associated with increased attenuation, independent of the presence of thrombus, potentially mimicking the hyperdense lumen sign or elevating mean blood pool HU values.¹³ Furthermore, cardiopulmonary conditions such as chronic pulmonary HT, left heart failure, or fluid overload can lead to vascular remodeling or enlargement, thereby influencing PA diameters and the PA/Ao ratio.¹⁴ Additionally, concurrent pulmonary infections, neoplastic processes, or interstitial lung diseases may produce parenchymal changes (e.g., ground-glass opacities or consolidations) that mimic or obscure indirect signs of PTE.¹⁸ In our study, although patients with known confounding conditions such as chronic thromboembolism, PA-invasive masses, or severe anemia (Hb <7 g/dL) were excluded, the presence of unrecorded or subclinical factors cannot be ruled out entirely. This limitation underscores the need for comprehensive clinical correlation and, ideally, prospective studies that can better control for such confounding variables.

In the multivariate logistic regression analysis, only the PA/Ao ratio and D-dimer levels emerged as statistically significant independent predictors of PTE. The PA/Ao ratio was strongly associated with the presence of PTE, with a remarkably high OR, although the wide CI suggests a degree of imprecision, likely due to the limited sample size. Similarly, elevated D-dimer levels were independently associated with PTE, consistent with their established role in thromboembolic risk stratification. Other imaging parameters, including mean HU values of the pulmonary blood pool, main PA diameter, and the presence of indirect signs on non-contrast thoracic CT, did not retain statistical significance in the multivariate model. These findings imply that while certain non-contrast thoracic CT features may appear relevant in univariate analyses, their predictive utility may diminish when adjusted for other factors. This underscores the importance of combining radiologic indicators with laboratory and clinical data to enhance diagnostic accuracy.

In our study, agreement between radiologists was good in terms of attenuation and diameter measurements. Agreement rates decreased when lobar branches were included in the analysis. Our data show that higher agreement rates were achieved than in similar studies in the literature.^{4,10}

This study has several limitations that should be acknowledged. First, the relatively small sample size (n = 110) may limit the statistical power and generalizability of the findings. Second, the single-center design may introduce selection bias and limit the applicability of the results to broader clinical settings. Due to the retrospective nature of the analysis, complete clinical parameters and standardized risk scores (e.g., Wells, Geneva) were not consistently recorded, precluding their integration into the analysis. We acknowledge that integrating imaging findings with established clinical scoring systems such as the Wells or Geneva criteria could potentially enhance the diagnostic accuracy and clinical applicability of our results. However, due to the retrospective design of our study and the absence of complete clinical data required to calculate these scores, such an analysis could not be performed. Future prospective studies that include standardized clinical probability assessments in conjunction with imaging parameters may better elucidate the complementary role of non-contrast thoracic CT findings in the diagnostic algorithm of pulmonary embolism.

CONCLUSION

Non-contrast thoracic CT provides valuable direct and indirect radiological markers that may aid in the diagnosis of PTE, particularly in settings where CTPA is contraindicated or unavailable, such as in patients at risk for contrast-induced nephropathy. Our findings demonstrate that increased PA diameters, elevated PA/Ao ratios, and higher attenuation values of the pulmonary blood pool are significantly associated with the presence of PTE. Additionally, the presence of indirect findings further supports the radiological suspicion of embolism.

Diagnostic success may increase when the presence of these findings is evaluated together with clinical and laboratory findings. Validation studies to be performed in a larger population are needed for the findings to be used in the clinic,

obtained in our study.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the İzmir Bakırçay University on the 5th of January 2022 (decision no: 478).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: M.O.G., A.A., Ö.S.U., Design: M.O.G., S.Ö., D.S.U., Data Collection or Processing: Z.A.Ö., A.A., D.S.U., Analysis or Interpretation: M.O.G., Z.A.Ö., Ö.S.U., Literature Search: M.O.G., S.Ö., Writing: M.O.G., Z.A.Ö., D.S.U.

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Original Article



Impact of Inspiratory Muscle Strength and Lung Function on Functional Exercise Capacity in Post-myocardial Infarction Patients: A Cross-sectional Study

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Abstract

OBJECTIVE: This study aims to investigate the contribution of lung function and respiratory muscle strength in predicting functional exercise capacity in post-myocardial infarction (MI) subjects.

MATERIAL AND METHODS: This cross-sectional study included 56 stable post-MI subjects. Lung function was assessed using a digital spirometer, and respiratory muscle strength was measured using an intraoral pressure meter. The 6-minute walk distance (6MWD) was conducted to assess functional exercise capacity. Correlations and multiple regression analyses were performed to evaluate predictors of 6MWD, considering demographic factors, lung function, and respiratory muscle strength. The Bland-Altman plot was used to investigate the agreement between observed and predicted 6MWDs.

RESULTS: Significant positive correlations were found between 6MWD and forced vital capacity (FVC)_{%predicted} ($r = 0.528$, $P = 0.022$) and maximum inspiratory pressure (MIP)_{%predicted} ($r = 0.640$, $P = 0.022$). Age ($r = -0.350$, $P = 0.008$) and body mass index (BMI) ($r = -0.561$, $P < 0.001$) were negatively correlated with 6MWD. The best regression model included MIP_{%predicted} ($\beta = 0.332$, $P = 0.002$), BMI ($\beta = -0.264$, $P = 0.012$), being male ($\beta = 0.262$, $P = 0.003$), age ($\beta = -0.210$, $P = 0.020$), and FVC_{%predicted} ($\beta = 0.219$, $P = 0.026$) as significant unique contributors. The final multiple linear regression model was significant [$F(5, 50) = 19.08$, $P < 0.001$] and explained 65.6% of the variance ($R^2 = 0.656$) in the 6MWD.

CONCLUSION: Lung function and respiratory muscle strength significantly contribute to functional exercise capacity in post-MI. This study emphasizes the importance of comprehensive respiratory function assessments in rehabilitation strategies to improve exercise capacity in patients with post-MI.

KEYWORDS: Myocardial infarction, lung function, respiratory muscle strength, functional exercise capacity, 6-minute walk test

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INTRODUCTION

Cardiovascular diseases represent a significant public health challenge, being the leading cause of mortality worldwide. Myocardial infarction (MI), commonly referred to as a heart attack, is a critical condition that contributes substantially to the overall burden of cardiovascular diseases.^{1,2} Individuals who experience MI often suffer from impaired lung function, reduced respiratory muscle strength, and decreased self-confidence, which limit functional exercise capacity and daily activities.^{3,4} These physiological changes can adversely affect the patient's ability to perform tasks and reduce functional exercise capacity.

The 6-minute walk test distance (6MWD) is an easy-to-perform, valid, and reliable submaximal exercise test to assess the functional exercise capacity of various populations, including those with cardiovascular conditions.⁵⁻⁸ It is a popular fitness-based functional exercise capacity test in which individuals are instructed to walk as far as possible within

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a set time interval.⁹ This test is widely used in the clinical management of patients with chronic lung^{6,7} and heart^{5,8} diseases. Studies indicate that assessment of 6MWD is safe for post-MI patients.⁹

Studies have shown that MI patients exhibit reduced inspiratory muscle strength, which is associated with poorer exercise tolerance.¹⁰ Improvements in maximum inspiratory pressure (MIP), an indicator of inspiratory muscle strength, have been associated with 6MWD, emphasizing the importance of respiratory muscle function in predicting functional exercise capacity.^{11,12} In addition, the interaction between respiratory muscle strength and lung function parameters such as forced vital capacity (FVC) emphasizes the importance of evaluating both parameters.^{11,13} Post-MI patients commonly experience impairments in respiratory function due to reduced cardiopulmonary reserve, deconditioning, and potential respiratory muscle weakness.¹⁰ Inspiratory muscle strength, typically measured via MIP, has been shown to be a significant determinant of functional capacity in both cardiac and pulmonary populations.^{11,12,14-16} Reduced MIP is associated with dyspnea and exercise intolerance, while improvements in MIP correlate with enhanced walking distance and daily functional status.^{11,12,14-16} Lung function, particularly FVC, is also considered a key parameter reflecting ventilatory mechanics and pulmonary reserve. Given that respiratory muscle strength and lung function are interdependent and may synergistically affect exercise capacity, incorporating both parameters into predictive models provides a more comprehensive understanding of functional limitations in post-MI patients.^{11,13} Therefore, MIP and FVC were included as independent variables in this study based on their physiological relevance and prior evidence linking them to exercise performance. Understanding the contributions of these factors to the 6MWD provides valuable insights for optimizing rehabilitation strategies. This study aims to investigate the contribution of demographic factors, respiratory muscle strength, and lung function in predicting 6MWD in post-MI patients.

MATERIAL AND METHODS

Study Design and Participants

In this cross-sectional study, a total of 56 clinically stable post-MI patients (≥18 years) were consecutively recruited from the Cardiology Department of Dokuz Eylül University Hospital between January 2024 and May 2024. Furthermore, since the main guidelines for assessment of 6MWD and lung function tests recommend a minimum of 1 month after the MI, to perform the tests, participants were recruited at least 1 month after

MI.^{9,17} Exclusion criteria were followed: not stable acute MI, acute MI with arrhythmia, atrial fibrillation, chronic obstructive pulmonary disease, asthma, class 3-4 angina pectoris according to Canadian Cardiovascular Society classification,¹⁸ exercise-induced myocardial ischemia, aortic stenosis, pericardial disease, any heart valve disease, resting heart rate (HR) more than 120, resting systolic blood pressure ≥180 mmHg, resting diastolic blood pressure ≥100 mmHg, resting peripheral O₂ saturation ≤90%, and not being in good physical condition to perform a walking test (such as having any orthopedic disease that may affect walking performance).

The study was conducted following the Declaration of Helsinki and its later amendments or comparable ethical standards and was approved by the Institutional Ethical Board of Dokuz Eylül University (approval number: 2023/29-04, date: 20.09.2023). All participants gave informed consent before the study. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guideline for reporting this study.¹⁹

Assessments

Once the demographic and clinical parameters were recorded, lung functions, respiratory muscle testing, and 6MWD were assessed.

According to the guidelines of the American Thoracic Society (ATS) and the European Respiratory Society, lung function and respiratory muscle strength were measured using standardized methods, using a digital spirometer and an intraoral pressure meter device (CosmedR Pony FX, Italy).^{20,21} Lung function tests were repeated with three satisfactory maneuvers by measuring the total volume of air exhaled from total lung capacity to maximal expiration, and the highest values were recorded.²⁰ Peak expiratory flow (PEF) and FVC were measured in lung function tests. Respiratory muscle strength tests, including MIP and maximal expiratory pressure (MEP), were measured from residual volume and total lung capacity. The highest value of three maneuvers, varying by less than 10%, was recorded.^{21,22} All tests were performed in a seated position, with participants wearing nose clips and using a standard mouthpiece during the maneuver.^{20,21} All parameters are presented as percentages (%) of predicted values.

The 6MWD was performed in a covered, flat, 30-m corridor marked with cones in the cardiology department, according the ATS guidelines.⁹ The test was performed by a physiotherapist in a setting where the unit's medical staff could be called upon if necessary. HR, blood pressure, peripheral oxygen saturation (SpO₂), and the modified Borg scale for perceived exertion were measured at baseline and post-test, respectively. HR and SpO₂ were also monitored during the test performance using a pulse oximeter. Signs and symptoms of exertional intolerance (chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance) were used as criteria to interrupt the test.²³ In this case, patients were initially excluded, then immediately assessed by medical staff, and, if necessary, provided with additional tests and medication.

Main Points

- Lung function contributes to functional exercise capacity in post-myocardial infarction (MI) patients.
- Respiratory muscle strength is a highly predictive factor of functional capacity in post-MI patients.
- Respiratory muscle strength assessments in rehabilitation can optimize outcomes by addressing individual functional limitations in post-MI patients.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 (SPSS Inc., Chicago, IL, USA). Data were checked for distribution and presented as means±standard deviation. Categorical variables were presented in percentages. The relationship between 6MWD and other parameters was analyzed using the Pearson correlation coefficient (*r*), and a stepwise regression analysis was carried out to evaluate independent parameters explaining the variance in the 6MWD. Sex was assigned a dummy value (0 = female; 1 = male). The variance inflation factor (VIF) was used to assess multicollinearity, with a VIF value below 5 indicating that the independent variables did not demonstrate multicollinearity.

We extracted a reference equation (based on the final model) to check how the regression model explains contributions of parameters. First, we used regression lines displaying the slope and intercept to confirm the calibration of observed 6MWD vs. predicted 6MWD (calculated from the regression equation). In the next stage, we investigated the agreement between observed and predicted 6MWDs using the Bland-Altman method. $P < 0.05$ was considered statistically significant for all analyses.

We calculated an estimated required sample size for this study using G*Power software version 3.1.9.2, based on the correlation between MIP and 6MWD in a relevant study in the literature.²⁴ We found an estimated required sample size of at least 50 participants with an expected correlation of at least $r = 0.4$, assuming a 5% margin of error ($\alpha = 0.05$) and 85% power ($1-\beta = 0.85$). We invited a total of 60 subjects to participate in the study, estimating a ~20% non-participation rate.²⁵

RESULTS

A total of 102 subjects were screened for eligibility to participate in the study. Of these, 42 were excluded for not meeting the inclusion criteria. In total, 60 subjects were invited to the study and 4 of them declined to participate. Therefore, the study was completed with the 56 subjects who agreed to participate.

The mean age of the patients was 56.9 ± 10.2 years, and their body mass index (BMI) was 25.6 ± 3.3 kg/m². The mean 6MWD was 487.2 ± 82.8 meters. Demographic and clinical characteristics of patients are presented in Table 1.

There were significant positive correlations between 6MWD and height ($r = 0.305$, $P = 0.022$), $FVC_{\%predicted}$ ($r = 0.528$, $P = 0.022$), $PEF_{\%predicted}$ ($r = 0.376$, $P = 0.022$), $MIP_{\%predicted}$ ($r = 0.640$, $P = 0.022$), and $MEP_{\%predicted}$ ($r = 0.425$, $P = 0.022$). There were significant negative correlations between 6MWD and age ($r = -0.350$, $P = 0.008$), weight ($r = -0.370$, $P = 0.002$), and BMI ($r = -0.561$, $P < 0.0001$) (Figure 1, Table 2).

The best model included $MIP_{\%predicted}$ ($\beta = 0.332$, $P = 0.002$), BMI ($\beta = -0.264$, $P = 0.012$), being male ($\beta = 0.262$, $P = 0.003$), age ($\beta = -0.210$, $P = 0.02$), and $FVC_{\%predicted}$ ($\beta = 0.219$, $P = 0.026$), as significant unique contributors. The final multiple linear regression model was significant [$F(5, 50) = 19.08$,

$P < 0.001$, Table 3] and explained 65.6% of the variance ($R^2 = 0.656$) in the 6MWD (Table 2).

Therefore, the reference equation including respiratory functions (final model) was as follows: $6MWD(m) = 534.311 + (52.412 \times \text{sex}) - (6.546 \times \text{BMI kg/m}^2) - (1.702 \times \text{age years}) + (1.078 \times FVC_{\%predicted}) + (0.909 \times MIP_{\%predicted})$. In the equation, sex is 1 if male and 0 if female.

When comparing the observed values to the predicted values of 6MWD in relation to the regression model's calibration, there was no correlation between the differences (bias) and the mean, and the fitted line was less sloped compared to the main diagonal (observed and predicted 6MWDs correlation: $r = 0.810$, $P < 0.001$) (Figure 2).

In Figure 3, the Bland-Altman plot illustrated a good level of agreement between observed and predicted 6MWD, with no evidence of systematic bias. Although a slight bias was observed for high and low values of distance covered, most of the differences were within the limits of agreement.

Table 1. Demographic and clinical characteristics of patients

Variables	
Demographic and anthropometric data	
Sex	
Male, n (%)	44 (78.6)
Female, n (%)	12 (21.4)
Age (years)	56.9 ± 10.2
Height (m)	1.72 ± 0.07
Weight (kg)	75.3 ± 10.1
BMI (kg/m ²)	25.6 ± 3.3
Angina classification	
Class 1, n (%)	40 (71.4)
Class 2, n (%)	16 (28.6)
Class 3, n (%)	-
Class 4, n (%)	-
Smoking status	
Current smokers, n (%)	19 (33.9)
Ex-smokers, n (%)	22 (39.3)
Non-smokers, n (%)	15 (26.8)
Lung function	
$FVC_{(\%predicted)}$	89.5 ± 16.8
$PEF_{(\%predicted)}$	63.9 ± 18.8
$MIP_{(\%predicted)}$	87.3 ± 30.3
$MEP_{(\%predicted)}$	73.8 ± 21
6-minute walk distance (m)	487.2 ± 82.8

Data are presented as mean±SD or n (%).

SD: standard deviation, BMI: body mass index, FVC: forced vital capacity, PEF: peak expiratory flow, MIP: maximal inspiratory pressure, MEP: maximal expiratory pressure

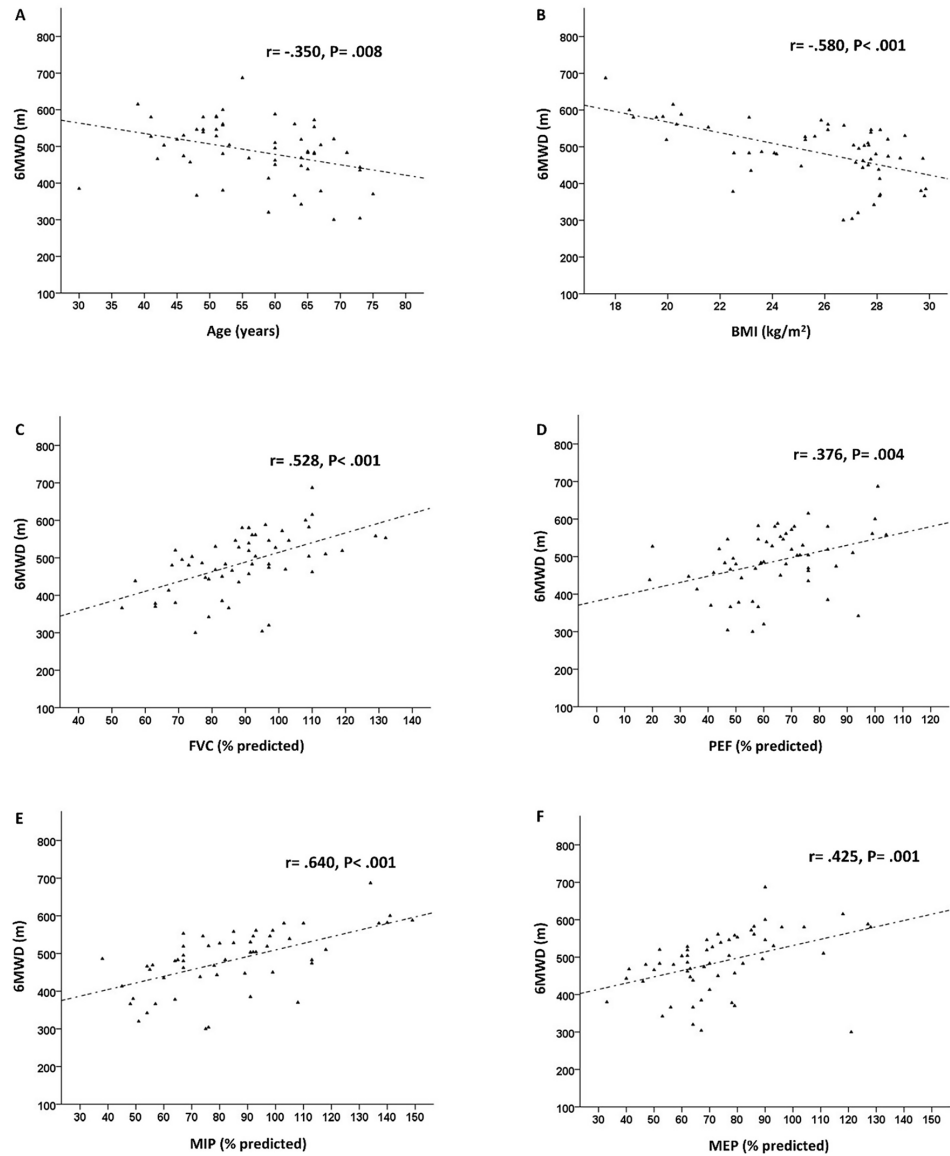


Figure 1. Relationship of the 6MWD with (A) age, (B) BMI, (C) FVC_{%predicted}, (D) PEF_{%predicted}, (E) MIP_{%predicted}, (F) MEP_{%predicted}. 6MWD: 6-minute walk distance, BMI: body mass index, FVC: forced vital capacity, PEF: peak expiratory flow, MIP: maximal inspiratory pressure, MEP: maximal expiratory pressure

Table 2. Correlations for the 6MWD with demographic parameters and respiratory function		
Variables	6MWD	
	r	P
Age (years)	-0.350	0.008
Height (m)	0.305	0.022
Weight (kg)	-0.401	0.002
BMI (kg/m²)	-0.580	<0.001
FVC (%predicted)	0.528	<0.001
PEF (%predicted)	0.376	0.004
MIP (%predicted)	0.640	<0.001
MEP (%predicted)	0.425	0.001

BMI: body mass index, FVC: forced vital capacity, PEF: peak expiratory flow, MIP: maximal inspiratory pressure, MEP: maximal expiratory pressure, 6MWD: 6-minute walk distance

Table 3. Linear regression analysis between 6-minute walk distance and maximal inspiratory pressure, body mass index, gender, age, and forced vital capacity

	B	SE	β	VIF	t	P
Constant	534.311	111.907			4.775	0.000
MIP (%predicted)	0.909	0.276	0.332	1.477	3.298	0.002
BMI (kg/m ²)	-6.546	2.508	-0.264	1.482	-2.610	0.012
Male	52.412	17.001	0.262	1.050	3.083	0.003
Age (years)	-1.702	0.707	-0.110	1.103	-2.408	0.020
FVC (%predicted)	1.078	0.471	0.219	1.331	2.290	0.026

Final model, dependent variable: 6-minute walk distance, $R^2 = 0.656$, $F(5, 50) = 19.08$, $P < 0.001$. * $P < 0.05$.

B: unstandardized beta, SE: standard error for B, β : standardized beta, t: Student's t-test statistic, VIF: variance inflation factor, MIP: maximal inspiratory pressure, BMI: body mass index, FVC: forced vital capacity

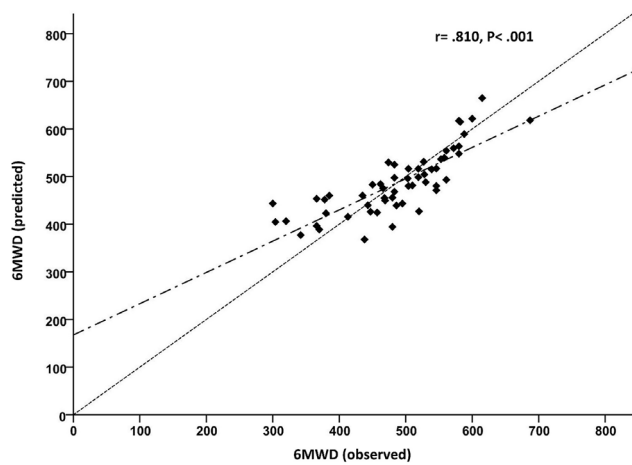


Figure 2. Calibration plot of the observed vs. predicted values for the 6MWD

6MWD: 6-minute walk distance

DISCUSSION

The current study aimed to investigate the contribution of lung function, respiratory muscle strength, and demographic factors to 6MWD in post-MI patients. The key findings of this study suggest that demographic factors (age, BMI, and sex), lung function (FVC_{%predicted}), and inspiratory muscle strength (MIP_{%predicted}) are significant predictors of 6MWD in post-MI patients.

The relationships between respiratory functions, specifically FVC and MIP, and the 6MWD in post-MI patients are a critical area of research. Understanding these relationships is important for evaluating functional exercise capacity, cardiovascular mortality, and morbidity risk, and overall prognosis in this population.²⁶⁻²⁸ Studies have demonstrated that both FVC and MIP correlate positively with functional exercise capacity, as measured by 6MWD, across different populations.²⁸⁻³⁵ Luchesa et al.³⁰ found that FVC and MIP were independent contributors to the 6MWD in obese Brazilian women. Similarly, Huzmeli et al.³⁴ reported significant correlations between pulmonary functions, including FVC and MIP, and 6MWD in patients with stable angina. Moreover, in individuals with chronic heart failure, reduced MIP has been associated with reduced exercise capacity, impaired quality of life, and increased mortality risk.²⁸

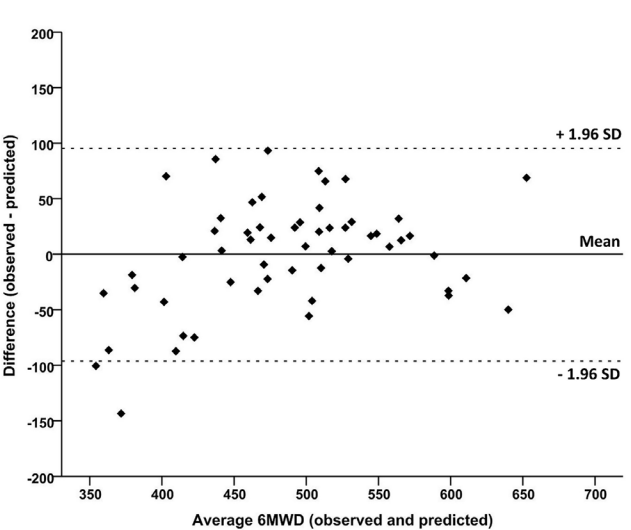


Figure 3. Bland altman plot of the averaged values and the differences (observed-predicted values) for 6MWD

6MWD: 6-minute walk distance, SD: standard deviation

In line with these findings, our results showed that FVC and MIP were independently associated with 6MWD, reinforcing the relevance of respiratory function in post-MI patients. These findings suggest that impairments in FVC and MIP may limit functional exercise capacity and highlight the value of incorporating respiratory assessments into routine clinical evaluation for patients recovering from MI.

There is also growing evidence supporting the efficacy of inspiratory muscle training (IMT) in improving respiratory muscle strength and functional capacity in the cardiac disease population. Beaujolin et al.³⁶ (2024), in a recent systematic review, demonstrated that IMT significantly increased both MIP and 6MWD in patients with cardiovascular diseases. Similarly, a meta-analysis by Azambuja et al.³⁷ (2020) concluded that isolated IMT resulted in an increase in inspiratory muscle strength, functional capacity, and quality of life in patients with heart failure. These findings lend support to our suggestion that MIP is a modifiable determinant of 6MWD and may be a viable target for cardiac rehabilitation.

In addition to physiological variables, demographic factors were also significant predictors of 6MWD in this study. Age and BMI were negatively associated with walking distance, consistent with the existing literature.^{4,30,38} Age-related declines in skeletal muscle mass, cardiovascular efficiency, and pulmonary function may collectively contribute to reductions in exercise capacity.^{39,40} Similarly, higher BMI may lead to increased effort during physical activity due to excess body weight, which can reduce functional exercise capacity.³⁰ Conversely, males were found to have positively contributed to 6MWD in our study, suggesting that men, in general, have greater walking capacity than women. This may reflect differences in muscle mass, body composition, and lung function between sexes.⁴ This result also aligns with the American Heart Association statistic, which found that men engage in more physical activity than women.¹ This is expected to further increase the 6MWD by positively affecting the muscle strength and aerobic capacity of men. Besides, men usually have greater height than women, which also affects step length and, consequently, walking distance.¹ This result is consistent with other studies conducted in different populations.^{4,41,42}

A notable strength of our study is that, to the best of our knowledge, it is the first study to present a reference equation for the 6MWD in post-MI patients that considers both lung function and respiratory muscle strength as independent variables for the predictive model. However, there are several limitations worth noting. First, the cross-sectional design of the study precludes conclusions about causality. Future longitudinal studies are needed to determine whether interventions targeting respiratory muscle strength can lead to improvements in 6MWD over time. Moreover, the study assumes linear relationships among MIP, FVC, and 6MWD without accounting for the complex physiological and behavioral interactions, such as cardiac remodeling, pharmacological influences, peripheral fatigue, and variability in patient adherence to exercise, that may mediate or moderate these associations. Although BMI was included in our regression model as an independent predictor, other potentially important confounding variables, such as hemoglobin levels, smoking status, medication use, and prior physical activity, were not adjusted for, which may influence the internal validity of the findings. Additionally, our sample size, while adequate, was relatively small and limited to patients from a single center, which may affect the generalizability of our findings. Although patients with general deconditioning or lower functional status were not excluded, the exclusion of individuals with orthopedic conditions affecting gait may have unintentionally resulted in a relatively healthier sample. This reduced the representation of frailer or mobility-limited individuals, thereby limiting the generalizability of our findings to the broader patient population.

CONCLUSION

In conclusion, our findings highlight the importance of assessing lung function, respiratory muscle strength, and demographic factors in predicting functional exercise capacity in post-MI patients. The development of a predictive equation for 6MWD may help clinicians tailor rehabilitation programs to individual patient profiles, ultimately improving outcomes and quality of life. Interventions, such as IMT, aimed at improving

these predictors of 6MWD could enhance functional exercise capacity and overall outcomes in this population. Further studies are needed to show how 6MWD, would change by improving lung function and inspiratory muscle strength in this population.

Ethics

Ethics Committee Approval: The study was conducted following the Declaration of Helsinki and its later amendments or comparable ethical standards and was approved by the Institutional Ethical Board of Dokuz Eylül University (approval number: 2023/29-04, date: 20.09.2023).

Informed Consent: All participants gave informed consent before the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.O.A, H.D., Concept: R.A., Ö.O.A, S.Ö., H.D., Design: R.A., Ö.O.A, S.Ö., H.D., Data Collection or Processing: Ö.O.A, Analysis or Interpretation: R.A., Literature Search: R.A., Ö.O.A, S.Ö., Writing: R.A., Ö.O.A, S.Ö., H.D.

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Original Article



The Causal Link Between Air Pollution and Respiratory Diseases: Evidence from Granger Causality Test

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Abstract

OBJECTIVE: Air pollution can exacerbate respiratory illnesses, such as asthma, chronic obstructive pulmonary disease (COPD), pneumonia, bronchitis, and upper respiratory tract infections (URTIs). This study investigated the causal relationship between air pollution and emergency department visits for certain respiratory illnesses, such as pneumonia, acute bronchitis, URTIs, and exacerbations of asthma and COPD.

MATERIAL AND METHODS: This study was conducted between 1 April 1 2023 and 30 March 2024. The causal relationship between the number of asthma, COPD, pneumonia, bronchitis, and URTI patients visiting the emergency department and air pollution levels was determined by conducting a Granger causality analysis.

RESULTS: It was determined that the highest number of visits to the emergency room was in January, and the highest concentrations of air pollutants were in December. According to the results of the Granger causality test, there was a one-way causal relationship between nitrogen (NO), nitrogen oxide (NO_x), and nitrogen dioxide (NO₂) levels and the numbers of patients with asthma, COPD, pneumonia, bronchitis, and URTI, as well as a relationship between particulate matter₁₀ (PM₁₀) concentrations and the numbers of patients with pneumonia and bronchitis.

CONCLUSION: There is a causal relationship between levels of air pollutants including NO, NO_x, NO₂, and PM₁₀ and the numbers of patients with respiratory diseases visiting the emergency department.

Keywords: Respiratory diseases, Granger causality, air pollutants, human exposure assessment

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INTRODUCTION

Air pollution is defined by the World Health Organization (WHO) as the pollution of the indoor or outdoor environment by any chemical, physical, or biological agent that alters the natural properties of the atmosphere.¹ The health effects of air pollution remain a public health concern worldwide. Exposure to air pollution has many substantial adverse effects on human health. Air pollution can induce the acute exacerbation of chronic obstructive pulmonary disease (COPD) and the onset of asthma, increasing respiratory morbidity and mortality rates. The health effects of air pollution depend on the components and sources of pollutants, which vary depending on countries, seasons, and time.² According to the WHO 2021 report, 99% of people breathe polluted air, and approximately 7 million deaths are caused by air pollution and related complications.³ Air pollution ranks 4th globally and 5th in Türkiye among the risks factors of deaths.^{4,5} Air pollution has severe health impacts, and it was reported that one-third of deaths from diseases such as stroke, lung cancer, and heart disease were associated with air pollution.¹

Domestic fuels, motor vehicles, industrial facilities, and wildfires are familiar sources of air pollution. Gaseous pollutants that cause air pollution and health problems include carbon monoxide (CO), ozone (O₃), NO₂, and sulfur dioxide (SO₂).¹ Particulate matter (PM) consists of micrometric substances suspended in the air and is mainly produced by industrial processes, coal-oil burning, road construction, and agricultural activities. Particles smaller than 10 microns are called PM₁₀, and those smaller than 2.5 microns are called PM_{2.5}. These PM categories are frequently used in air pollution

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studies. Inhaled into the respiratory tract, PM larger than 10 microns is retained in the nose and nasopharynx, particles smaller than 10 microns are deposited in the bronchi, particles 1-2 microns in diameter are collected in the alveoli, and particles 0.5 microns in diameter diffuse from the alveoli into the intracapillaries.⁶ While SO_2 , one of the gaseous pollutants of air, is eliminated in the nose and pharynx, O_3 and NO_2 , which are not water-soluble gases, can reach deep into the respiratory system. CO diffuses through the alveolar-capillary membrane and binds to hemoglobin.⁶ Studies conducted in Türkiye have reported a significant relationship between pollutants such as SO_2 and PM_{10} and respiratory diseases.⁷⁻⁹

In Türkiye, air quality is one of the primary concerns about environmental pollution, especially in areas with intense industrialization. People are exposed to PM emitted from vehicles at dangerous levels, and the concentrations of these pollutants are above WHO's standards. The transportation sector, the second sector after the industrial sector in terms of energy use in Türkiye, is the primary source of air pollution.¹⁰ Tuygun et al.¹⁰ (2017) reported that industrial facilities in the industrial zone cause SO_2 , nitrogen oxide (NO_x), and PM_{10} emissions, while residential heating and road traffic cause an increase in CO emissions.¹¹ The presence of brick factories, tobacco and vine leaf cultivation, and denim and dye factories in Erbaa, through which a highway with intensive truck transportation passes, changes the air pollution rate of the district. In the literature, a relationship between air pollutants and respiratory diseases has been reported, but there have not been many studies examining emergency room visits due to air pollution and respiratory diseases together. Additionally, causality in the relationship between these two factors has not been investigated in existing studies.^{12,13}

In health research, causality is defined as the occurrence of one event or situation due to another event or situation.¹⁴ The Granger causality test is generally used to determine a causality relationship. Since causality tests are econometric tests, these tests are used mainly in economics and econometrics. However, today, this test is widely used in natural sciences, engineering, and health sciences.¹⁵⁻¹⁷ By definition, a random variable X is said to be a Granger cause of Y if its history, after considering all other possible relevant factors and non-

random information, provides a better prediction of the future of another random variable Y.¹⁵ Determining whether there is a relationship between air pollutants and the number of patients presenting to emergency care for asthma, COPD, pneumonia, bronchitis, and upper respiratory tract infections (URTI) would be beneficial in managing diseases, creating care plans, and adjusting healthcare system budgets. Programs can be created by considering this causality relationship in educational practices, which are among the roles of nurses. The self-management skills of patients can be improved by considering the effects of outdoor air pollution on diseases.

This study aimed to show the causal relationship between the air quality, in relation to air pollution, and the number of visits to the emergency department at Erbaa State Hospital due to respiratory diseases including pneumonia, acute bronchitis, URTI, and exacerbations of asthma and COPD.

MATERIAL AND METHODS

This study was conducted with a retrospective design to examine the causal relationship between the daily air pollutant levels published by the Turkish Ministry of Environment and Urbanization and the number of respiratory system patients visiting the emergency department.

In this study, the data of patients with asthma, COPD, pneumonia, bronchiectasis, and URTI visiting the emergency department at Erbaa State Hospital between 1 April 2023 and 30 March 2024 were examined retrospectively.

The inclusion criteria were determined according to the International Classification of Diseases, revision 10 (for codes: J45.9-asthma; J44.0, J44.1, J44.9-COPD; J18.9-pneumonia; J20.9-acute bronchitis; J42-chronic bronchitis, and J06.8, J06.9-URTI), and data about patients diagnosed with asthma, COPD, bronchitis, pneumonia, and URTI were included. Respiratory diseases defined by other codes in the same classification system were not included in the study. Twelve months of data were collected, and the months were divided into two main groups: warm months (April, May, June, July, August, and September) and cold months (October, November, December, January, February, and March).

Data Collection

Health data: Data were collected from retrospective patient records. The data consisted of the numbers of patients diagnosed with asthma, bronchitis, pneumonia, URTI, and COPD presenting to the emergency department. Data collection started after obtaining the necessary permissions from the Erbaa Provincial Directorate of Health and informing the health professionals in the Statistics/Information Processing Units of the relevant hospital.

Air pollution data: SO_2 , NO, NO_x , NO_2 , CO, PM_{10} , and $\text{PM}_{2.5}$ were selected as air pollution indicators. Daily data on indicators were obtained from the air quality monitoring website of the Turkish Ministry of Environment and Urbanization. Data on 24-hour average SO_2 , NO, NO_x , NO_2 , CO, PM_{10} , and $\text{PM}_{2.5}$ concentrations for the days when the patients whose data we examined visited were recorded based on the website (mobil.

Main Points

- Exposure to air pollution: the air pollutants PM_{10} , NO_x , and NO levels were highest in December 2023, SO_2 was highest in February 2024, and NO_2 was highest in April 2023.
- Impact of exposure to air pollution: Hospital admissions are higher following months when air pollution is high compared to other months. Relationship of air pollution and admission emergency: increases in air pollutants such as NO, NO_x , NO_2 , and PM_{10} effectively determine the number of patients admitted to the emergency department.
- Need for targeted interventions: the findings emphasize the necessity for enhanced enforcement of policies and targeted public health interventions to reduce air pollution.

airizleme.gov.tr) in units of $\mu\text{g}/\text{m}^3$. $\text{PM}_{2.5}$ and CO data for the Erbaa/Tokat region were unavailable on the website, and analyses related to these values could not be performed.

Ethical statements

Approval was obtained from Tokat Gaziosmanpaşa University Ethics Committee for conducting the study (date/number: 21.05.2024/09.12).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL) program was used for the statistical analyses. The categorical variables are expressed as frequencies and percentages. The differences between groups of variables were analyzed using t-tests. The relationships between variables were tested by regression analysis. Granger causality analysis was performed using the Stata 15.0 program. A value of $P < 0.05$ was considered significant in the statistical analyses. In the Granger causality test, the significance level was accepted as 10%. Detailed information about the Granger causality test is presented in the additional file.

RESULTS

The results of this study, which was conducted to demonstrate the causal relationship between air pollution and the numbers of respiratory disease patients visiting the emergency department of a state hospital in the Black Sea Region of Türkiye in the last year, are presented in this section.

The numbers of patients visiting the emergency department for one year and air pollution statistics in the same period are shown in Table 1. As seen in Table 1, the total number of patients with respiratory diseases who presented to the emergency department was 727,915. The highest number of visits was due to URTI at 296,027, asthma at 21,907, and bronchitis at 14,739.

The highest number of emergency room visits for respiratory system diseases occurred in January 2024. The levels of PM_{10} , NO_x , and NO were the highest in December 2023, the levels of SO_2 were the highest in February 2024, and the levels of NO_2 were the highest in April 2023 (Table 1).

The results of the analyses performed to test whether there was a significant difference between the numbers of patients visiting the emergency department due to respiratory system diseases in warm and cold months are presented in Table 2. It was determined that the numbers of emergency department visits in cold months were higher for all respiratory diseases examined in this study, while this increase was statistically significant in patients diagnosed with pneumonia, in those with bronchitis, and in overall cases ($P < 0.05$) but not statistically significant in asthma, COPD, and URTI cases ($P > 0.05$) (Table 2).

The results of the analyses conducted to determine whether there was a significant difference between the air pollutant rates in the warm and cold months during the study period are presented in Table 3. As seen in Table 3, in cold months, NO , SO_2 and PM_{10} values reached about five times, more than two times, and almost two times their values in warm months, respectively. These increases were statistically significant ($P < 0.05$). NO_2 and NO_x values also increased in cold months compared to warm months, but this increase was not statistically significant ($P > 0.05$) (Table 3).

The Granger causality test was used to determine the direction of causality and which variable was causally determinant for another variable.¹⁸ The results of the Granger causality test conducted to determine the causal relationship between the numbers of patients with respiratory diseases visiting the emergency department and the levels of air pollutants are presented in Table 4. Accordingly, the null hypothesis was rejected for the causal relationship between NO , NO_2 , and NO_x and the number of asthmatic patients since the probability value

Table 1. Number of respiratory disease patients visiting emergency rooms and air pollutant concentrations by months

Months	Respiratory diseases						Air pollutants				
	Asthma	COPD	Pneumonia	URTI	Bronchitis	Total	PM_{10}	SO_2	NO_2	NO_x	NO
April 2023	1,672	677	567	29,331	935	56,722	27.39	4.07	79.50	85.69	6.19
May 2023	1,994	907	610	23,423	1,078	59,756	26.78	4.36	57.64	60.62	3.01
June 2023	1,783	845	410	20,684	892	53,915	25.01	4.32	35.38	38.25	2.86
July 2023	1,549	794	520	21,208	825	61,900	32.71	4.93	26.11	29.13	3.01
August 2023	1,249	624	429	15,883	825	59,687	49.78	3.17	15.26	17.98	2.71
September 2023	1,464	610	443	18,845	936	51,709	49.14	5.28	14.86	18.71	3.85
October 2023	1,720	760	581	25,164	1,357	59,118	67.12	6.95	27.94	38.09	10.15
November 2023	1,617	716	587	23,134	1,509	57,420	53.12	8.35	36.08	45.63	9.48
December 2023	1,980	687	696	34,642	1,718	68,183	86.79	8.74	67.97	95.20	27.23
January 2024	2,742	1,051	997	38,876	2,040	73,184	57.35	11.16	31.08	44.52	13.39
February 2024	2,238	963	701	20,392	1,307	63,173	63.06	11.98	37.09	50.22	13.11
March 2024	1,899	833	667	24,445	1,317	63,148	49.54	9.25	36.68	53.45	16.78
Total	21,907	9,467	7,208	296,027	14,739	727,915					

URTI: upper respiratory tract infections, NO: nitrogen, NO_x : nitrogen oxide, NO_2 : nitrogen dioxide, PM_{10} : particulate matter₁₀, SO_2 : sulfur dioxide

was smaller than 5% (0.0141, 0.0346, and 0.0272 <0.05). In the analysis of the causal relationship between PM₁₀ and SO₂ and the number of asthmatic patients, the null hypothesis could not be rejected because the probability was greater than 5% (0.3334 and 0.1080 >0.05). Accordingly, a unidirectional Granger causality relationship was detected from NO, NO₂, and NO_x to the number of patients with asthma. According to these results, NO, NO₂, and NO_x were Granger causes of asthma, while PM₁₀ and SO₂ were not Granger causes of asthma.

In the analyses of the causal relationships between NO, NO₂, and NO_x and the number of patients with COPD, the null hypothesis was rejected because the probability value was smaller than 10% (0.0930 <0.10, 0.0635 <0.10, and 0.0224 <0.05). In the analyses of the causal relationships between PM₁₀ and SO₂ and the number of patients with COPD, the null hypothesis could not be rejected because the probability was higher than 5% (0.6737 and 0.4143 >0.05). Accordingly, a unidirectional Granger causality relationship was detected from levels of NO, NO₂, and NO_x to the number of patients with COPD. According to these results, NO, NO₂, and NO_x were Granger causes of COPD, while PM₁₀ and SO₂ were not Granger causes of COPD.

In the analyses of the causal relationships between NO, NO₂, NO_x, and PM₁₀ and the number of patients with pneumonia, the null hypothesis was rejected since the probability value was smaller than 10% (0.0462, 0.0421, 0.0292 <0.05, and 0.0957 <0.10). In the analysis of the causal relationship between SO₂ and the number of patients with pneumonia, the null hypothesis could not be rejected since the probability was greater than 5% (0.2360 >0.05). Accordingly, a unidirectional Granger causality relationship was found between NO, NO₂, NO_x, and PM₁₀ levels and the number of patients with pneumonia. According to these results, NO, NO₂, NO_x, and PM₁₀ were

Granger causes of pneumonia, while SO₂ was not a Granger cause of pneumonia.

In the analyses of the causal relationships between NO, NO₂, and NO_x levels and the number of patients with URTI, the null hypothesis was rejected because the probability value was smaller than 10% (0.0773, 0.0632, and 0.0626 <0.10). In the analyses of the causal relationships between PM₁₀ and SO₂ levels and the number of patients with URTI, the null hypothesis could not be rejected because the probability value was greater than 5% (0.3089 and 0.3033 >0.05). Accordingly, a unidirectional Granger causality relationship was detected from NO, NO_x, and NO₂ to the number of patients with URTI. According to these results, NO, NO₂, and NO_x were causes of URTI, while PM₁₀ and SO₂ were not causes of URTI.

In the analyses of the causal relationships between NO, NO₂, NO_x, and PM₁₀ levels and the number of patients with bronchitis, the null hypothesis was rejected since the probability value was smaller than 10% (0.0011 and 0.0028 <0.05, 0.0616, and 0.0852 <0.10). The null hypothesis could not be rejected in the analysis of the causal relationship between SO₂ levels and the number of patients with bronchitis patients since the probability value was higher than 5% (0.6319 >0.05). Accordingly, a unidirectional Granger causality relationship was detected from NO, NO₂, and PM₁₀ to the number of patients with bronchitis. According to these results, NO, NO₂, NO_x, and PM₁₀ were causes of bronchitis, while SO₂ was not a cause of bronchitis (Table 4).

A multiple regression model was established with all four predictor variables, and the final model was created by excluding those that did not contribute statistically significantly to the model. It was determined that every unit increase in SO₂ values corresponded to 99 asthma ($P = 0.005$), 49 COPD (P

Table 2. Number of patients visiting emergency services in warm and cold months

Number of patients admitted to the emergency department (mean±SD)	Warm months	Colder months	Test value
Asthma	1618.50±259.289	2032.67±409.022	t=-2.095, $P = 0.063$
COPD	742.83±123.375	835.00±144.730	t=-1.187, $P = 0.263$
Pneumonia	496.50±81.616	704.83±152.384	t=-2.952, $P = 0.014$
URTI	21,562.33±4,568.370	27775.50±7271.062	t=-1.772, $P = 0.107$
Bronchitis	915.17±93.956	1541.33±289.876	t=-5033, $P = 0.001$
Total	57,281.5000±3,897.1590	64037.6667±5837.37937	t=-2.358, $P = 0.040$

SD: standard deviation, COPD: chronic obstructive pulmonary disease, URTI: upper respiratory tract infections

Table 3. Levels of air pollutants in warm and cold months

Air pollutant values (mean±SD)	Warm months	Cold months	Test value
PM₁₀	35.134±11.39	62.829±13.36	t=-3.862, $P = 0.003$
SO₂	4.354±0.72	9.404±1.86	t=-6.191, $P < 0.001$
NO₂	38.124±25.72	39.473±14.42	t=-0.112, $P = 0.913$
NO_x	41.731±26.66	54.521±20.609	t=-0.930, $P = 0.374$
NO	3.604±1.32	15.023±6.52	t=-4.199, $P = 0.002$

SD: standard deviation, NO: nitrogen, NO_x: nitrogen oxide, NO₂: nitrogen dioxide, PM₁₀: particulate matter₁₀, SO₂: sulfur dioxide

= 0.002), 43 pneumonia ($P = 0.002$), and 106 bronchitis ($P = 0.001$) patients visiting the emergency department. It was also determined that every unit increase in PM_{10} values predicted 5 COPD patients ($P = 0.016$), and every unit increase in NO values predicted 570 URTI ($P = 0.025$) patients visiting the emergency department (Table 5).

DISCUSSION

Respiratory tract diseases are important as they rank third in the list of diseases that cause death in the world and Türkiye.^{19,20} Since the incidence of respiratory diseases is gradually increasing worldwide, causing an increase in mortality and morbidity rates, it is important to examine the relationship between air pollution and the number of patients visiting hospitals. The results of this study showed that the highest number of visits to the emergency department by patients with respiratory diseases was in January. The number of patients visiting the emergency department increased in the cold months, and this increase was statistically significant for diseases such as pneumonia and bronchitis. The air pollutants, PM_{10} , NO_x , and NO, had the highest levels in December 2023, whereas SO_2 had the highest

levels in February 2024, and NO_2 had the highest levels in April 2023. These results were likely because individuals exposed to high concentrations of air pollutants in December presented to the emergency room the following month of January. The results of the Granger causality test also supported this conclusion.

In this study, air pollutant levels differed between warm and cold months. In the cold months, NO, SO_2 , and PM_{10} values reached about five times, more than two times, and almost two times, respectively, their levels in the warm months, and these increases were found to be statistically significant. NO levels had the highest rate of increase. The Granger causality test showed that NO was a cause of all respiratory system diseases experienced by patients visiting the emergency room that were examined in this study. Likewise, a significant increase in PM_{10} levels caused an increase in pneumonia and bronchitis cases. Similar to our findings, Cengiz et al.⁷ reported that levels of SO_2 and PM_{10} were significantly different between warm and cold months. There was a significant relationship between the number of patients visiting the hospital and air pollutants. These results may have been due to the increase in air pollutant values

Table 4. Causality relationship between respiratory diseases and air pollutants

Causality aspect/hypothesis	F-statistics	Probability	Decision
NO is not a Granger cause of asthma.	9.41834	0.0141	H_0 : Rejected
NO_2 is not a Granger cause of asthma.	6.20963	0.0346	H_0 : Rejected
NO_x is not a Granger cause of asthma.	6.97894	0.0272	H_0 : Rejected
PM_{10} is not a Granger cause of asthma.	1.32655	0.3334	H_0 : Not rejected
SO_2 is not a Granger cause of asthma.	3.29892	0.1080	H_0 : Not rejected
NO is not a Granger cause of COPD	3.62232	0.0930	H_0 : Rejected*
NO_2 is not a Granger cause of COPD	4.51844	0.0635	H_0 : Straight
NO_x is not a Granger cause of COPD	7.63512	0.0224	H_0 : Rejected
PM_{10} is not a Granger cause of COPD	0.42223	0.6737	H_0 : Not rejected
SO_2 is not a Granger cause of COPD	1.02415	0.4143	H_0 : Not rejected
NO is not a Granger cause of pneumonia	68.2776	0.0462	H_0 : Rejected
NO_2 is not a Granger cause of pneumonia	5.62250	0.0421	H_0 : Rejected
NO_x is not a Granger cause of pneumonia	6.74649	0.0292	H_0 : Rejected
PM_{10} is not a Granger cause of pneumonia	3.55909	0.0957	H_0 : Rejected*
SO_2 is not a Granger cause of pneumonia	1.85472	0.2360	H_0 : Not rejected
NO is not a Granger cause of URTI	4.04224	0.0773	H_0 : Rejected*
NO_2 is not a Granger cause of URTI	4.53137	0.0632	H_0 : Rejected*
NO_x is not a Granger cause of URTI	4.55472	0.0626	H_0 : Rejected*
PM_{10} is not a Granger cause of URTI	1.43811	0.3089	H_0 : Not rejected
SO_2 is not a Granger cause of URTI	1.46531	0.3033	H_0 : Not rejected
NO is not a Granger cause of bronchitis	4.59706	0.0616	H_0 : Rejected*
NO_2 is not a Granger cause of bronchitis	26.2474	0.0011	H_0 : Rejected
NO_x is not a Granger cause of bronchitis	18.4115	0.0028	H_0 : Rejected
PM_{10} is not a Granger cause of bronchitis	3.81740	0.0852	H_0 : Rejected*
SO_2 is not a Granger cause of bronchitis	0.49603	0.6319	H_0 : Not rejected

*Indicates statistical significance at 10% significance level.

NO: nitrogen, NO_x : nitrogen oxide, NO_2 : nitrogen dioxide, PM_{10} : particulate matter₁₀, SO_2 : sulfur dioxide, COPD: chronic obstructive pulmonary disease, URTI: upper respiratory tract infections

Table 5. Association between air pollutants and number of patients with respiratory disease-related visits

Variables	B	SE	Beta	P
Asthma				
Constant	1145.174	206.621	-	$P < 0.001$
SO ₂	98.899	27.767	0.748	0.005
COPD				
Constant	720.099	77.456	-	$P < 0.001$
PM ₁₀	-5.482	1.864	-0.748	0.016
SO ₂	49.033	11.766	1.060	0.002
Pneumonia				
Constant	306.479	76.981	-	0.003
SO ₂	42.761	10.345	0.794	0.002
URTI				
Constant	19356.372	2531.701	-	$P < 0.001$
NO	570.362	215.633	0.642	0.025
Bronchitis				
Constant	498.735	178.637	-	0.019
SO ₂	106.037	24.007	0.813	0.001

NO: nitrogen, PM₁₀: particulate matter₁₀, SO₂: sulfur dioxide, COPD: chronic obstructive pulmonary disease, URTI: upper respiratory tract infections

caused by the combustion of fossil fuels for heating during the cold months, and thus, the number of patients increases in parallel.

Checking for the existence of the Granger causality relationship between time series allows one to examine whether the dynamics of each time series determine the evolution of the other time series included in the study.¹⁷ In this study, the Granger causality test revealed a unidirectional causal relationship between NO, NO_x, and NO₂ levels and the numbers of patients with asthma, COPD, pneumonia, bronchitis, and URTI. These results meant that increased NO, NO_x, and NO₂ levels led to increased hospital visits for respiratory diseases. The United States Environmental Protection Agency (US EPA) reported that even short-term exposure to NO_x can worsen respiratory diseases such as asthma, leading to increased respiratory symptoms, hospitalizations, and emergency room visits.²¹ The US EPA also reported that prolonged exposure to high concentrations of NO₂ may contribute to a potential increase in susceptibility to respiratory infections and the development of asthma.²¹ In our study, NO, NO_x, and NO₂ values were determined to cause higher numbers of emergency department visits by patients with asthma, COPD, pneumonia, bronchitis, and URTI. NO_x is present in the air as NO, but this species is easily oxidized to NO₂ by reacting with O₃. NO₂ is a highly toxic gas that can trigger cell damage and inflammatory processes throughout the respiratory system, from the nose to the lung alveoli.²² Based on the results found in our study, it is thought that NO, NO_x, and NO₂ triggered inflammatory processes and caused emergency room visits.

PM is a mixture of extremely small particles and droplets in the air, consisting of various solid and liquid components such

as organic and inorganic substances suspended in the air. The presence of PM in the air causes increased health risks. In particular, PM with an aerodynamic diameter of 10 µm and smaller (PM₁₀) cannot be filtered through the nose, eyelashes, or mucus in the respiratory tract. Therefore, it can reach the tracheobronchial and alveolar regions of the respiratory tract, enter the circulatory system, and cause diseases.¹³ In this study, a unidirectional causal relationship was found between PM₁₀ levels and pneumonia- and bronchitis-related visits to the emergency room. Accordingly, the increase in PM₁₀ levels increases the number of patients with bronchitis and pneumonia visiting the emergency department. Similar to our findings, Slama et al.¹² (2019) reported a positive relationship between ambient air pollution and hospitalization, where PM_{2.5} and PM₁₀ had the most significant effect. Zhang et al.¹³ reported that PM exposure increased hospital visits due to arrhythmia, hypertension, cerebrovascular disease, and ischemic heart disease. These results are thought to be due to the structure of PM₁₀ that can reach the lung alveoli. In addition to the effect of air pollution on respiratory diseases, it is also thought that it triggers other health problems, and predicting that hospital admissions will increase when air pollution is intense and making plans in this direction will contribute to the management of diseases. In this study, it was concluded that there was no causal relationship between SO₂ levels and the number of emergency room visits due to respiratory diseases, and an increase in SO₂ levels was not a cause of an increased number of emergency room visits. Unlike our findings, Kara et al.²³ reported that SO₂ levels had a significant effect on asthma cases admitted to hospital. It is thought that this difference is due to the analysis performed. Kara et al.²³ investigated whether there was an effect according to their correlation analysis results. In our study, Granger causality was analyzed.

Moreover, according to the correlation analysis performed after the Granger causality test, a correlation was found between asthma and SO_2 .

In the literature, the relationship between air pollutants and respiratory tract diseases has been tested by regression and correlation analyses. In the regression/correlation relationships established in these studies, analyses have been carried out by assuming that a causality relationship between these variables. However, the establishment of regression models by examining the causality relationship between two variables provides more successful predictions. According to Granger, before moving on to the precise mathematical representation of causality, many research papers investigating cause-and-effect relationships between stochastic processes (or random processes) use correlation, partial correlation, or the mutual information function as tools to investigate causality. Although these approaches are not entirely wrong, they do not manage the concept of causality effectively and often lead to misleading results. The main difference between these techniques and Granger causality is that these measures can provide information about the correlation-independence (influence/relationship) between processes, not whether the information provided by one stochastic process can usefully contribute to the predictability of another.²⁴ In the literature, there are studies using time series, similar to our study, but these studies have usually examined correlation relationships rather than causality. In the ecological time series study carried out by Nascimento et al.²⁵ (2016), similar to our findings, it was concluded that respiratory diseases led to hospitalizations as a result of exposure to a large number of air pollutants such as NO_2 , PM_{10} , CO , and SO_2 . In another study using an ecological time series, César et al.²² estimated the relationship between air pollutants and hospitalization due to respiratory diseases. Comparing mortality associated with respiratory diseases to estimated daily levels of air pollutants over about one year, the results of their study revealed an association between exposure to NO_x and mortality from respiratory diseases. Air pollution involving O_3 , PM , diesel exhaust particles, NO_2 , and SO_2 increases the permeability of the airways, facilitates the penetration of allergens into the mucous membranes, and causes interactions with immune system cells.²⁶ As a result, air pollution is thought to play an inflammatory role in the airways of predisposed patients and is considered to be the cause of emergency visits and admissions.

In this study, a regression analysis was performed after the Granger causality tests to make more successful predictions. As a result of the analysis, it was determined that there was a significant relationship between asthma, COPD, pneumonia, and bronchitis cases involving visits to the emergency department and concentrations of SO_2 , as well as relationships between visits for COPD cases and levels of PM_{10} and between visits for URTI cases and levels of NO . SO_2 levels were a predictor of visits to the emergency department due to asthma, COPD, pneumonia, and bronchitis, PM_{10} levels were a predictor of bronchitis-related visits, and NO levels were a predictor of visits related to URTI. Slightly differently from our findings, Saygin et al.⁸ (2017) reported a strong correlation between PM_{10} and COPD, a weak correlation between PM_{10} and asthma, and a correlation between SO_2 and COPD but

not asthma. Like our results, Kara et al.²³ found a correlation between SO_2 and PM_{10} levels and asthma cases. Çapraz et al.²⁷ reported that short-term exposure to PM_{10} , $\text{PM}_{2.5}$, and NO_2 was associated with increased hospital admissions. Similar findings are thought to be associated with the usage of the same analyses and parameters.

This study had some limitations. First, the study was conducted in a single region, data from a period of one year were used, and CO and $\text{PM}_{2.5}$ data could not be obtained from the system for the examined region. Unlike other studies in the literature, the use of time series and the Granger causality test (Appendix 1) provided more substantial evidence of the cause-and-effect relationships, constituting the study's strength. Another strength of the study is that it was conducted in a region with brick, paint, and textile factories, where inhaled dust sources such as tobacco and vine leaves are grown, and a main road, which is a main truck transport route. The results of the study revealed a causal relationship between pollutants such as NO and emergency room visits for asthma and COPD. However, respiratory tract infections and air pollutants also had an increasing effect on asthma and COPD visits during the same period, which could be considered a limitation.

CONCLUSION

It was determined that there was a Granger causality relationship between increased levels of air pollutants such as NO , NO_x , NO_2 , and PM_{10} and the numbers of patients visiting the emergency department. For this reason, the values of these air pollutants should be considered while preparing emergency department shift schedules, creating maintenance plans, and budgeting. Hospital/emergency department visits due to respiratory diseases are closely related to cold weather but are also closely associated with increased outdoor air pollution rates. Since the number of inpatients is also closely related to the number of emergency department visits, knowing in which months the number of patients will increase in the coming periods would affect disease and hospital management. Therefore, understanding and analyzing the effects of air pollutants on increases in the number of patients visiting the emergency department is critical in the appropriate management of diseases, increasing the quality of health care, and preventing hospital overcrowding. It is recommended that studies involving more extended time series in a larger region should be conducted in the future. Additionally, studying the causal relationship between air pollutants and diseases other than those of the respiratory tract will contribute to the literature.

Ethics

Ethics Committee Approval: Approval was obtained from Tokat Gaziosmanpaşa University Ethics Committee for conducting the study (date/number: 21.05.2024/09.12).

Informed Consent: Retrospective study.

Footnotes

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Appendix 1. Granger causality test

This section aims to identify causal relationships between time series that are useful in forecasting.

Causality implies that the estimated future values of a time series variable are affected by the past values of another related time series variable.²⁸ According to Granger (1969), causality refers to the relationship between X and Y in the presence of two variables. If the prediction of variable X is better than the prediction based only on lagged values of X, then variable Y is a Granger cause of X.²⁹ The formulae used for the Granger causality test are given in equations 1 and 2.

$$X_t = \sum_{i=1}^m \alpha_i X_{t-i} + \sum_{j=1}^m \beta_j Y_{t-j} + \lambda_1 t + u_{1t} \quad (1)$$

$$Y_t = \sum_{i=1}^m \gamma_i Y_{t-i} + \sum_{j=1}^m \delta_j X_{t-j} + \lambda_2 t + u_{2t} \quad (2)$$

In equations 1 and 2, t is the time variable, and u_{1t} and u_{2t} are the error terms. u_{1t} and u_{2t} are assumed to be uncorrelated.

In equation 2, if δ_j is different from zero, it can be stated that there is a Granger causality relationship from X to Y. If β_j coefficients are significantly different from zero, it can be stated that there is a Granger causality relationship from Y to X. The null hypothesis in the Granger causality test is "X is not a Granger Cause of Y".³⁰

In the Granger causality test, the null hypothesis is "independent variables are not Granger causes of the dependent variable," while the alternative hypothesis is "independent variables are Granger causes of the dependent variable".²⁸ The null hypotheses for this study were as follows; "CO is not a Granger cause of asthma. SO₂ is not a Granger cause of asthma. PM₁₀ is not a Granger cause of asthma. CO is not a Granger cause of COPD. SO₂ is not a Granger cause of COPD. PM₁₀ is not a Granger cause of COPD. CO is not a Granger cause of pneumonia. SO₂ is not a Granger cause of pneumonia. PM₁₀ is not a Granger cause of pneumonia. CO is not a Granger cause of bronchitis. SO₂ is not a Granger cause of bronchitis. PM₁₀ is not a Granger cause of bronchitis. CO is not a Granger cause of URTI. SO₂ is not a Granger cause of URTI. PM₁₀ is not a Granger cause of URTI."

Original Article



Long-term Effect of Pulmonary Rehabilitation in Pulmonary Tuberculosis Patients

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Abstract

OBJECTIVE: Post-pulmonary tuberculosis (post-PTB) sequelae, including impaired lung function, reduced exercise capacity, and diminished quality of life (QoL), pose significant challenges even after successful anti-tuberculosis treatment. While pulmonary rehabilitation (PR) is an established intervention for chronic respiratory diseases, its long-term effectiveness in post-PTB patients is not well-documented. This study aimed to evaluate the long-term impact of an 8-week outpatient PR program on respiratory function, exercise performance, and QoL in post-PTB patients.

MATERIAL AND METHODS: In a randomized controlled trial, 90 post-PTB patients aged ≥ 18 years were allocated to either the PR group or a control group. The PR program included supervised endurance and resistance training, breathing exercises, and patient education, delivered over 8 weeks. Primary outcomes, including the 6-minute walk distance (6MWD), Saint George's Respiratory Questionnaire (SGRQ), and pulmonary function tests, were assessed at baseline, immediately post-intervention, and at 12 months. Data were analyzed using repeated measures ANOVA.

RESULTS: The PR group demonstrated significant and sustained improvements across all measures. The 6MWD increased by 217 meters post-PR and remained 143 meters higher at 12 months ($P < 0.05$). SGRQ scores showed a 28-point reduction post-PR and a 32-point reduction at 12 months ($P < 0.05$). FEV1 improved by 41% post-PR, and by 45% at 12 months ($P < 0.05$). No significant changes were observed in the control group.

CONCLUSION: An 8-week PR program delivers long-term benefits in respiratory function, exercise capacity, and QoL in post-PTB patients. Incorporating PR into post-PTB care is a promising strategy to mitigate chronic sequelae and enhance patient outcomes.

KEYWORDS: Post-pulmonary tuberculosis, pulmonary rehabilitation, long-term outcomes, quality of life, respiratory health, exercise capacity

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INTRODUCTION

The World Health Organization's End Tuberculosis Strategy aspires to achieve a world free of pulmonary tuberculosis (PTB) by 2035, with the ambitious goal of eradicating deaths, disease, and suffering associated with the condition. While nearly 20 million individuals globally survived PTB in 2020 due to advancements in anti-tuberculosis treatment, there is a significant gap in knowledge regarding long-term respiratory sequelae, the effects on quality of life (QoL), and the potential need for continued rehabilitation among these survivors.¹ Despite effective treatments since the 1950s, TB remains a major global health issue, with over 10 million new cases annually.² Many post-TB survivors experience long-term respiratory issues that negatively affect their QoL, leading to ongoing costs for them, their families, and healthcare

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systems. Additionally, survivors often face persistent stigma, contributing to social exclusion, unemployment, unstable housing, and limited access to healthcare.³

Regular follow-ups with post-TB survivors can help reduce hospital admissions. Yet, the primary focus of care remains to achieve a microbiological “cure,” with little attention given to patients’ health-related QoL (HRQoL).⁴ Recently, pulmonary rehabilitation (PR) has been recommended by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) to improve the mental and physical health of patients with respiratory conditions and encourage healthy lifestyle practices. However, post-treatment PTB patients are not typically assessed for impairments or provided with follow-up care.⁵ Despite effective anti-tubercular treatment, preventable mortality remains a significant issue, and the lengthy treatments result in poor adherence, worse outcomes, and ongoing pulmonary complications.⁶

Although some studies have evaluated PR in PTB, there is limited research on its long-term effects on patients with post-tuberculosis sequelae (PTS).⁷ Regardless of significant progress towards the “End PTB Strategy” goal of a 90% treatment success rate, many PTB survivors still suffer from poor HRQoL.⁸ PR has proven effective for other chronic lung diseases, including chronic obstructive pulmonary disease (COPD), but its long-term benefits for post-PTB lung disease are unknown.⁹ This study aims to assess whether a multidisciplinary outpatient PR program, including unsupervised home exercise, can help PTB patients maintain respiratory function, exercise capacity, and QoL for at least one year after an 8-week PR program.

MATERIAL AND METHODS

This randomized controlled trial received ethical approval from the Institutional Ethics Committee, SMA & R and Sharda Hospital, Sharda University approved on 26 July 2021, (approval no: SU/SM&R/76-A/2021/91) and was registered with

the Clinical Trials Registry of India (CTRI/2022/08/045006). The study design followed the CONSORT guidelines for reporting randomized controlled trials. All participants were screened for eligibility and provided with detailed information about the study protocol. Written informed consent was obtained from each participant in accordance with the ethical standards outlined in the Declaration of Helsinki (1964). To ensure full understanding and voluntary participation, participants were thoroughly briefed on the procedures before the commencement of the trial, with measures taken to address potential discomfort and foster informed engagement.

The study included PTB patients aged 18 years or older with exertional shortness of breath and limitations in daily activities; who had a documented history of smear-positive PTB, with pharmacological therapy completed at least six months before enrolment and no participation in physical activity or rehabilitation programs during that period.¹⁰ Exclusion criteria encompassed asymptomatic individuals with a history of treated PTB, patients with a known history of multidrug-resistant TB to ensure homogeneity in disease severity, and those diagnosed with cardiovascular conditions such as myocardial infarction, angina, or congestive heart failure. Patients with coexisting respiratory diseases—including COPD, asthma, or interstitial lung disease—were also excluded. Additional exclusion criteria comprised individuals with medical, surgical, cognitive, psychological, or orthopedic impairments that could hinder participation in rehabilitation, as well as patients aged over 80 years.¹¹

Sample Size Calculation

Software G*Power 3.1.9.2 (Franz F, Universitat Kiel, Kiel, Germany) was used to determine the sample size from a previous study conducted by Singh et al.,¹² using data on changes in the 6MWD. A total of ninety subjects were considered necessary, (forty-five in each group), which includes an additional 10% for dropouts, based on the effect size of 0.384, alpha level of 0.05, and power (1-beta) of 0.95.

Study Procedure

First, the therapist gathered records of the patient from the TB-DOT Centre. The patient records were analyzed, and patients were selected based on eligibility criteria derived from this analysis. Then, appointments were made at a clinic to gather data following the screening. Ninety stable patients with PTB who had finished their chemotherapy were drawn from the centers according to the inclusion criteria. The selected patients were briefed about the study. Those who declared their willingness to participate and filled out the written informed consent were included in the study. All the patients were randomly assigned in a 1:1 ratio using a computer-generated random number table and allocated into the experimental group and control group. All the outcome measures were assessed upon enrolment, on the last PR session, and at 12-month follow-up by a physiotherapist blinded to the intervention.

Patients who were allocated to the rehabilitation group had to complete a minimum of 24 sessions of an outpatient PR program over eight weeks (three sessions per week). The program was run at the outpatient TB-DOT Centers from March

Main Points

- Chronic respiratory impairments in post-pulmonary tuberculosis (post-PTB) patients are often neglected, despite their significant impact on quality of life (QoL), highlighting the need for long-term management strategies.
- An 8-week pulmonary rehabilitation (PR) program demonstrated measurable improvements in lung function, exercise capacity, and overall QoL in post-PTB patients.
- The positive outcomes of PR were sustained up to 12 months post-intervention, showcasing its potential for long-term efficacy and durability in managing post-TB respiratory issues.
- PR offers a feasible and affordable solution, making it an attractive addition to existing TB management strategies, particularly in resource-limited settings.
- The study underscores the importance of integrating PR into global TB care frameworks and calls for further research to optimize protocols, enhance accessibility, and address diverse patient populations.

2022 until July 2023. The complete exercise prescription for this PR program was implemented under the guidance of a licensed physiotherapist at the TB DOT hospital. The therapist also motivated the patients to continue all exercises at home. Moreover, all the patients were requested to contact the therapist in case of doubt regarding any exercise, and supervised follow-ups were conducted at regular intervals during the study, extending up to 12 months.

Immediately after the PR session, all the biomedical waste used in this study, such as gloves, masks, and tissue papers, were disposed of in the different colored dustbins available at the study site. Waste handlers were provided with masks and gloves, which prevent their exposure to infectious agents.

Various measures were taken to improve the adherence rate of the program, such as daily telephone calls to patients and their attendants to report to the center so that they would not skip the PR session. Transportation was also arranged for those having difficulty traveling to the center. Since patients with PTB often feel isolated because of social stigma, therefore we made a “buddy” scheme in which new patients were paired with patients who have previously completed the PR program so they get social support and enthusiasm to continue the program.¹³ Another barrier was a lack of motivation, therefore, we regularly encouraged patients not to discontinue the PR program by explaining its various benefits with no side effects. Lastly, we rescheduled the sessions for the patients who skipped them due to unavoidable reasons.

Assessment

One week before baseline testing, all participants were informed about the research procedures and potential risks. Each participant underwent a primary health examination before the initial testing. The baseline testing took place over two days. On day one, participants completed the Saint George Respiratory Questionnaire (SGRQ), a generic HRQoL assessment, followed by a dyspnea assessment using the Borg Dyspnea Scale (0-10). On day two, participants underwent a pulmonary function test (PFT) in accordance with the guidelines of the ATS/ERS. This included measurements of forced vital capacity (FVC), forced expiratory volume in the first second (FEV₁), and the FEV₁/FVC ratio. Following ATS/ERS guidelines, blood pressure, heart rate, oxygen saturation (SpO₂), and dyspnea were recorded before and after the 6-minute walk distance (6MWD). Participants were instructed to walk at their own pace, aiming to cover the maximum distance possible in six minutes. The total distance covered was recorded in meters and as a percentage, and the Enright¹⁴ equation was used to estimate the predicted 6MWD for both males and females.

After the baseline testing, participants were randomly assigned to either the PR group or the control group. Those in the control group received maximal medical care and were instructed to continue their usual routines for eight weeks. All measurements were taken at enrollment, 8 weeks after completing the PR program, and 12 months after the start of the study (Figure 1).

Pulmonary Rehabilitation Intervention

The PR sessions were customized for each patient based on their performance during the initial assessment. These sessions included supervised endurance and resistance training, stretching of the upper and lower extremity muscles, self-management, patient education, and static circuit training to improve peripheral muscle strength and general mobility with breathing exercises. Each session consists of 30 minutes of breathing exercises.¹⁵

Ground walking was used as part of the endurance workout regimen. The walking prescription primarily reflects everyday activities. It is practical, easy to use, affordable, and widely applicable.¹⁶ According to Chandrasekaran and Reddy¹⁷ (2018), the distance traveled during 6MWD was used to determine the walk speed or training intensity. For the majority of individuals, a baseline walking speed was established, starting at 80% to 90% of the true 6MWD pace. A walk of 15 to 20 minutes was recommended. The walk duration was divided into normal ranges, known as interval training (5-6 or 6-8 minutes), if the patient's disability was significant. The maximum distance that may be walked in 20 minutes, measured in meters ‘20MWD’, equals the actual 6MWD multiplied by 3.33 m.

The recommended walking program involved walking for 20 minutes, twice a day, for 8 weeks. On three weekdays, participants followed the training under the supervision of a physical therapist, while on weekends, they were instructed to walk independently. To promote good posture proper body mechanics, prevent muscle and joint injuries, and enhance respiratory function, stretching exercises were also incorporated. The first and last five minutes of each session were dedicated to stretching and flexibility exercises. Initially, patients were taught how to perform these stretches, and later, they carried out the stretches on their own. Each of the four or five different stretches (such as hamstring stretch, quadriceps stretch, pectoralis major stretch, and overhead reach) was held for 15 to 30 seconds.^{18,19}

Participants engaged in resistance training for both the upper and lower extremities three times a week. The lower body exercises target muscles such as the quadriceps, hamstrings, hip flexors, hip abductors, and hip extensors. These exercises were performed in both sitting and standing positions, using ankle weights for added resistance. For the upper body, exercises using free weights focused on the biceps, triceps, and deltoids, while resistance bands were used for the pectoral muscles. Participants were instructed to complete 15 to 20 repetitions per exercise, with resistance adjusted based on their capacity. Progression was determined by each participant's ability to tolerate the given load. If they could manage the load, the number of sets was increased from 1 set to 2 sets and then to 3 sets as they adapted. Exercise intensity was closely monitored by asking participants to rate their level of dyspnoea on the Borg scale (0-10).^{20,21}

Each session concluded with an educational component focused on improving patient adherence, mood, and disease understanding. The intervention group received a structured

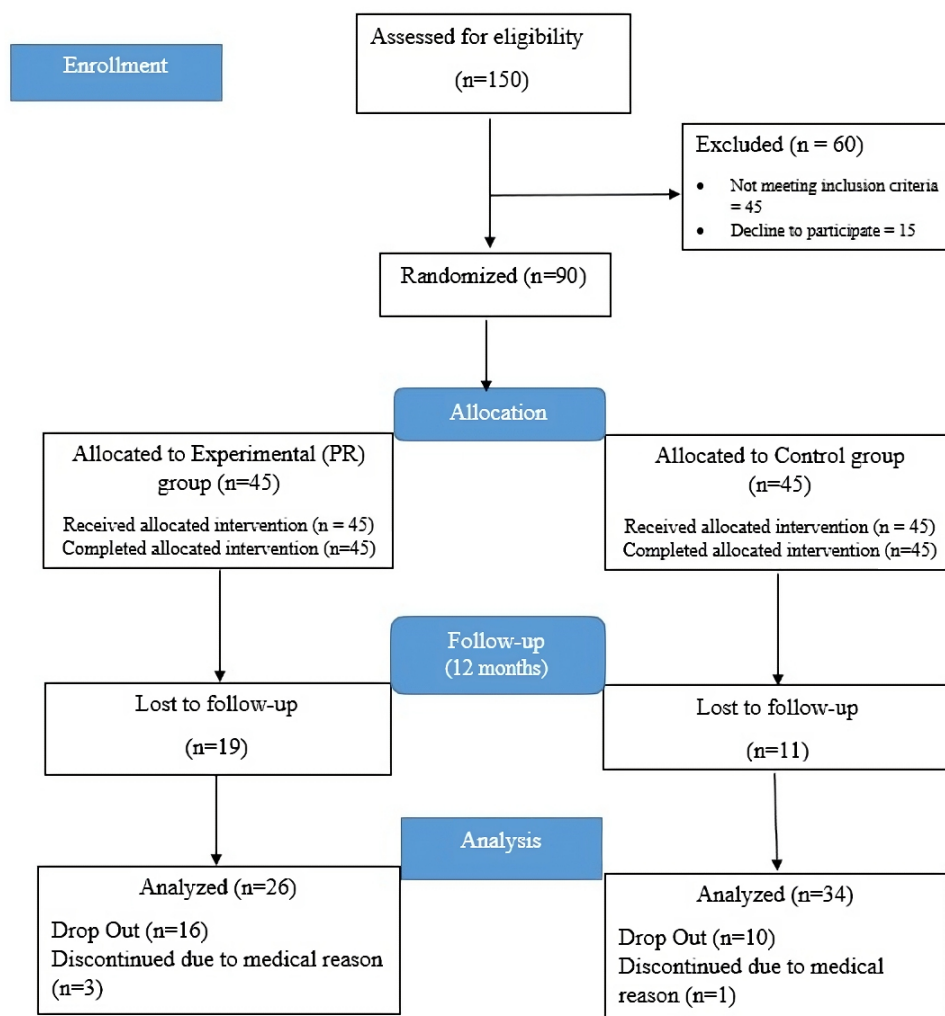


Figure 1. Depicts the study flowchart as per CONSORT guidelines

PR: pulmonary rehabilitation

program on self-management, including information about lung anatomy and physiology, the impact of PTB on the lungs, and chronic lung disease pathophysiology. They were also taught how to manage stress, prevent risk factors, recognize and treat exacerbations, control shortness of breath, conserve energy during daily tasks, and use medical devices effectively.²² Additionally, patients were educated on secretion clearance, the benefits of physical activity, and essential dietary measures.²³

The control group continued their routine daily activities and did not receive any form of structured exercise training or educational intervention during the study period.²⁴ Wherever practicable, standard care and spirometry were utilized to check for airway illnesses: practitioner-administered antibiotic therapy for infectious exacerbations (where appropriate), and verbal encouragement to give up smoking and limit exposure to biomass smoke. If necessary, medical care as prescribed by a qualified practitioner should be administered.

Adherence was measured as the ratio of attended to prescribed sessions or follow-ups. No adverse effects related to the

exercise training were noted during the program. Reasons for lack of adherence included lack of motivation, excessive focus on respiratory symptoms, insufficient family support, non-medical reasons such as holidays or family obligations, financial difficulties, relocation, or a belief that their condition was too mild to benefit from PR.

Statistical Analysis

The data were analyzed using Statistical Package for the Social Sciences (SPSS) (IBM SPSS Statistics for Windows, version 23.0). The baseline characteristic is indicated as mean±standard deviation (SD) for the PR group and is indicated as mean±SD for the control group. The normality of the data was assessed using the Shapiro-Wilk test, skewness, and histograms. The outcome variables between groups were compared at baseline and four weeks later using an independent t-test. A 2x3 repeated measures ANOVA was used to evaluate the main effects of time, group, and their interaction, with Bonferroni pairwise corrections applied for post hoc analysis when significant effects were found. When baseline differences in outcome

measures existed between groups, a 2x3 repeated measures ANCOVA was used, with baseline values as covariates. The significance level was set at $P \leq 0.05$, with a 95% confidence interval.

RESULTS

As shown in Table 1, there were no significant differences in baseline demographic characteristics between the PR and control groups. However, at baseline, the PFT and SGRQ scores differed significantly between the groups, while the 6MWD and Borg scores did not, as shown in Table 1. The t-test analysis reveals significant improvements in 6MWD in the experimental group after 24 sessions of PR and at 12-month follow-up, with large effect sizes, $P = 0.002$. Repeated measures ANOVA confirms significant group, time, and interaction effects, with

post hoc comparisons showing 88.89% improvement in 6MWD after PR, and 58.33% improvement at 12-month follow-up, respectively as shown in Tables 2, 3. The experimental intervention significantly improved Borg scores compared to the control group, with large effect sizes and a low P value ($P = 0.002$) at both post-treatment and follow-up. Repeated measures ANOVA showed significant group, time, and interaction effects, with post hoc comparisons revealing a 4-point reduction in Borg after 24 sessions and a 3-point reduction at 12 months, follow-up as shown in Tables 4, 5.

SGRQ scores significantly differed between groups after 24 sessions of PR ($P = 0.002$) and at 12-month follow-up ($P = 0.002$). Repeated measures ANOVA revealed significant group, time, and interaction effects, with post hoc comparisons showing significant differences between pre-intervention and

Table 1. Baseline clinical and demographic features of the subject (n = 90)

Variables	PR group (n = 45) Mean±SD	Control group (n = 45) Mean±SD	P value
Age	35.20±11.66	35.04±7.74	0.955
Height	163.76±6.591	157.92±7.28	0.005*
Weight	65.07±6.59	63.19±9.69	0.431
BMI	24.29±4.26	25.35±2.60	0.293
6MWD (m)	243.84±59.74	255.28±68.31	0.532
6MWD (%)	38.34±10.28	41.12±12.65	0.398
6MWD, RHR (bpm)	81.95±9.36	76.3±11.4	0.48
PFT FEV ₁ L	1.19±0.44	1.24±0.31	0.670
FEV ₁ (%)	24.80±7.18	35.32±10.89	<0.001*
FVC (L)	1.88±0.496	1.48±0.348	0.002*
FVC (%)	23.76±8.60	34.64±12.93	0.001*
FEV ₁ /FVC	39.64±19.30	32.80±11.59	0.135
Borg	8.64±0.90	8.72±0.678	0.726
SGRQ Impact	78.32±9.62	75.32±9.84	0.281
Activity	72.12±10.80	75.53±6.50	0.183
Symptom	86.48±7.98	81.68±8.73	0.048*
Total	74.72±11.62	82.20±9.20	0.015*

Except as otherwise noted, in terms of values, mean standard deviation is used. Level of importance PFT, PR, and BMI are abbreviations for pulmonary function testing and body mass index, respectively. * $P < 0.05$, statistically significant.

SD: standard deviation, PFT: pulmonary function test, PR: pulmonary rehabilitation, BMI: body mass index, FVC: stands for forced vital capacity, FEV₁: forced expiratory volume in one second, SGRQ: Saint George Respiratory Questionnaire, 6MWD: 6-minute walk distance

Table 2. Comparison of exercise capacity (6MWD) in two groups after 24 sessions of PR and at 12-month follow-up

Outcome measures	Experimental group	Control group	t-value	Effect size	Mean difference	95% of CI of difference	P value
6MWD (m)							
After 24 session	460.60±62.33	209.44±73.46	13.03	3.68	251.16	212.41 to 289.9	<0.001*
12-month follow-up	386.08±64.51	174.72±66.11	11.44	3.23	211.36	174.21 to 248.5	<0.001*
6MWD (%)							
After 24 sessions	71.89±11.92	33.50±12.09	11.3	3.19	38.39	31.56 to 45.22	<0.001*
12-month follow-up	59.80±12.59	27.68±10.70	9.71	2.74	32.12	25.47 to 38.76	<0.001*

* $P < 0.05$, statistically significant.

6MWD (m): 6-minute walk distance in meters, 6MWD (%): 6-minute walk distance in percentage predicted, PR: pulmonary rehabilitation, CI: confidence interval

post-treatment ($P = 0.002$) and pre-intervention and follow-up ($P = 0.002$), but no difference between post-treatment and follow-up ($P = 0.199$), as shown in Tables 6, 7. The experimental group showed a 46-unit decline after 24 sessions and a 42-unit decline after 12 months, compared to pre-intervention.

FEV₁ (L) and FEV₁ (%) showed significant improvements in the experimental group after 24 PR sessions and at 12-month follow-up, with effect sizes indicating moderate to large effects. Repeated measures ANOVA confirmed significant group, time, and interaction effects, with a 41.1% increase in FEV₁ (L) after

Table 3. Comparison of ANOVA results of exercise capacity (6MWD) in both the groups

Outcome measure	Experimental group	Control group	Pairwise comparison					
			Group effect		Time effect		GxT interaction	
			η^2 (P value)	F value	η^2 (P value)	F value	η^2 (P value)	F value
6MWD (m)								
12-month follow-up	386.0±64.5	174.7±66.1	0.000	89.18	0.000	53.2	0.000	142.24
6MWD (%)								
12-month follow-up	59.8±12.5	27.6±10.7	0.000	60.15	0.000	45.8	0.000	128.03
6MWD (m): 6-minute walk distance in meters, 6MWD (%): 6-minute walk distance in percentage predicted, sizes (η^2): partial eta square, F value: f test statistic								

Table 4. Comparison of breathlessness (Borg) in both the groups after 24 sessions of PR and at 12-month follow-up

Outcome measures	Experimental group	Control group	t-value	Effect size	Mean difference	95% of CI of difference	P value
After 24 sessions	4.40±0.957	8.80±0.764	17.96	5.11	-4.4	-4.89 to -3.9	<0.001*
12-month follow-up	4.92±0.997	9.52±0.586	19.89	5.66	-4.6	-5.06 to -4.1	<0.001*

* $P < 0.05$, statistically significant.
PR: pulmonary rehabilitation, CI: confidence interval

Table 5. Comparison of ANOVA results Borg dyspnoea scale scores in both groups

Outcome measure	Experimental group	Control group	Pairwise comparison					
			Group effect		Time effect		GxT interaction	
			η^2 (P value)	F value	η^2 (P value)	F value	η^2 (P value)	F value
12-month follow-up	4.92±0.997	9.52±0.586	0.000	343.7	0.000	107.529	0.000	153.7

Sizes (η^2): partial eta square, F value: f test statistic

Table 6. Comparison of HRQoL (SGRQ) in both the groups after 24 PR sessions and at 12-month follow-up

Outcome measures	Experimental group	Control group	t-value	Effect size	Mean difference	95% of CI of difference	P value
SGRQ Impact							
After 24 sessions of PR	27.24±7.54	76.64±7.07	23.877	6.758	-49.40	-53.56 to -45.24	<0.001*
12-month follow-up	41.92±16.91	95.80±2.29	15.779	4.465	-53.88	-60.74 to -47.01	<0.001*
SGRQ activity							
After 24 sessions of PR	39.77±11.95	76.40±6.09	13.643	3.862	-36.62	-42.02 to -31.22	<0.001*
12-month follow-up	55.37±14.02	78.00±6.87	7.241	2.049	-22.62	-28.90 to 16.34	<0.001*
SGRQ symptom							
After 24 sessions of PR	27.56±6.23	82.08±8.14	26.561	7.521	-54.52	-58.6 to -50.3	<0.001*
12-month follow-up	51.64±6.95	84.92±9.09	14.535	4.113	-33.28	-37.88 to 28.67	<0.001*
SGRQ total							
After 24 sessions of PR	28.36±11.57	84.96±10.10	18.417	5.211	-56.60	-62.7 to -50.4	<0.001*
12-month follow-up	32.40±12.69	86.88±8.33	17.935	5.075	-54.48	-60.58 to 48.37	<0.001*

* $P < 0.05$, statistically significant.

HRQoL: health-related quality of life, SGRQ: Saint George's Respiratory Questionnaire, CI: confidence interval

24 sessions and a 45% increase at follow-up. FVC (L) showed significant differences between the groups after 24 PR sessions ($P = 0.002$) and at 12-month follow-up ($P = 0.002$). However, post hoc comparisons revealed no significant changes in FVC (L) after 12 months, despite a 4.78% increase after 24 sessions. FVC% showed a significant time effect, with no improvement in the experimental group after 24 sessions or 12 months, although significant changes were observed at follow-up compared to pre-intervention, as shown in Tables 8, 9.

DISCUSSION

This is the first study to show the long-term benefits of a 24-session outpatient PR program for patients with post-PTB at a 1-year follow-up. The experimental group demonstrated significant improvements in 6MWD after 24 PR sessions (>217 m, $>33.5\%$ predicted) and at one-year follow-up (>143 m, 21.5% predicted). This result confirms the observations of previous investigations conducted by other researchers. They concluded that after a complete rehabilitation program, the benefits are maintained for approximately 1 year, as evidenced

Table 7. Comparison of ANOVA results of health-related QoL (SGRQ) scores in both groups

Outcome measures	Experimental group	Control group	Pairwise comparison					
			Group effect		Time effect		GxT interaction	
			η^2 (<i>P</i> value)	F value	η^2 (<i>P</i> value)	F value	η^2 (<i>P</i> value)	F value
SGRQ (impact)								
12-month follow-up	41.92±16.91	95.80±2.29	0.000	331.5	0.000	96.27	0.000	149.12
SGRQ (activity)								
12-month follow-up	55.37±14.02	78.00±6.87	0.000	122.16	0.000	39.37	0.000	44.07
SGRQ (symptom)								
12-month follow-up	51.64±6.95	84.92±9.09	0.000	113.3	0.000	12.61	0.000	366.59
SGRQ (total)								
12-month follow-up	32.40±12.69	86.88±8.33	0.000	407.05	0.000	16.32	0.000	183.83
SGRQ: Saint George’s Respiratory Questionnaire, effect sizes (η^2): Partial eta square, F value: f test statistic								

SGRQ: Saint George's Respiratory Questionnaire, effect sizes (η^2): Partial eta square, F value: f test statistic

Table 8. Comparison of forced expiratory volume in one second PFT after 24 sessions of PR and at 12-month follow-up in both the groups

Outcome measures	Experimental group	Control group	t-value	Effect size	Mean difference	95% of CI of difference	P value
FEV₁ (L)							
After 24 sessions	1.68 $\pm$ 0.423	1.07 $\pm$ 0.336	5.590	1.596	0.604	0.38 to 0.82	<0.001*
12-month follow-up	1.45 $\pm$ 0.457	1.00 $\pm$ 0.377	3.776	1.074	0.448	0.20 to 0.68	<0.001*
FEV₁ (%)							
After 24 sessions	27.08 $\pm$ 8.81	34.36 $\pm$ 11.75	2.478	0.701	-7.280	-13.18 to 1.37	0.017*
12-month follow-up	24.48 $\pm$ 7.12	31.00 $\pm$ 6.67	3.340	0.945	-6.520	-10.4 to 2.59	0.002*
FVC (L)							
After 24 sessions	1.97 $\pm$ 0.520	1.25 $\pm$ 0.304	6.030	1.690	0.727	0.48 to 0.96	0.000*
12-month follow-up	1.86 $\pm$ 0.50	1.48 $\pm$ 0.34	3.149	0.888	0.384	0.13 to 0.63	0.003
FVC (%)							
After 24 sessions	22.52 $\pm$ 11.74	32.16 $\pm$ 10.87	3.012	0.853	-9.640	-16.07 to -3.20	0.004*
12-month follow-up	21.32 $\pm$ 8.43	28.56 $\pm$ 9.0	2.936	0.830	-7.240	-12.19 to -2.28	0.005
FEV₁/FVC (%)							
After 24 sessions	40.96 $\pm$ 17.20	31.28 $\pm$ 9.96	2.434	0.688	9.680	1.68 to 17.67	0.019*
12-month follow-up	40.12 $\pm$ 14.19	29.60 $\pm$ 9.02	3.127	0.884	10.520	3.75 to 17.28	0.003*

* $P < 0.05$, statistically significant.

FEV₁ (L): forced expiratory volume in one second in liters, FEV₁ (%): forced expiratory volume in one second in percentage predicted, 95% CI: 95% confidence interval, FVC (L): forced vital capacity in (liters), FVC (%): forced vital capacity in percentage predicted, FEV₁/FVC: ratio of forced expiratory volume in one second to forced vital capacity, CI: confidence interval, PFT: pulmonary function test, PR: pulmonary rehabilitation

Table 9. Comparison of ANOVA results of pulmonary function test scores in both groups

Outcome measures	Experimental group	Control group	Pairwise comparison					
			Group effect		Time effect		GxT interaction	
			η^2 (P value)	F value	η^2 (P value)	F value	η^2 (P value)	F value
FEV₁ (L)								
12-month follow-up	1.45±0.45	1.00±0.37	0.001	13.22	0.009	5.365	0.000	18.93
FEV₁ (%)								
12-month follow-up	24.48±7.12	31.00±6.67	0.002	11.21	0.002	0.007	0.574	0.509
FVC (L)								
12-month follow-up	1.86±0.502	1.48±0.345	0.000	21.71	0.036	6.84	0.000	23.85
FVC (%)								
12-month follow-up	21.32±8.43	28.56±9.0	0.090	26.05	0.000	3.005	0.097	2.68
FEV₁/FVC								
12-month follow-up	40.12±14.19	29.60±9.02	0.020	364.42	0.409	0.855	0.255	1.384

Exp group: experimental group, FVC (L): forced vital capacity in liters, FVC (%): forced vital capacity percentage predicted, effect sizes η^2 : partial eta square, F value: f test statistic, FEV₁ (L): forced expiratory volume in one second in liters, FEV₁ (%): forced expiratory volume in one second in percentage predicted

by many clinical trials; therefore, these patients should always be reinstated in rehabilitation programs.²⁵ Post-PTB patients often experience muscle weakness due to inactivity, systemic inflammation, and poor nutrition, exacerbated by poverty, creating a vicious cycle of weight loss, increased morbidity, and higher mortality. PR helps break this cycle, improving activity capacity and overall health. Another factor contributing to improving functional capacity is a reduction in ventilation demand and blood lactic acid levels, which enhances muscle aerobic metabolism and, consequently, reduces muscle fatigue.²⁶

Consistent with previous research, baseline SGRQ scores in PTB patients were elevated, indicating a decline in QoL. After 8 weeks of PR, significant improvements were observed: symptom score decreased by 27, activity score decreased by 39, impact score decreased by 27, and total score decreased by 28. At the 12-month follow-up, the scores were 51 (symptom), 41 (impact), 55 (activity), and 32 (total). These improvements exceeded the MCID value (13.5 U), indicating a meaningful enhancement in QoL. This suggests that rehabilitation, by increasing maximum oxygen consumption and work capacity, led to improved functional capacity and QoL over the long term.²⁷

Similar to Withers et al.,²⁸ this study found that a multimodal PR program significantly reduced anxiety symptoms. Multi-component programs combining exercise and education effectively decrease anxiety severity. Exercise alone or in combination with stress management and education, helped patients experience less breathlessness, increased motivation, and reduced fear and sadness related to dyspnea. These improvements were reflected in significant gains in SGRQ scores. Cognitive-behavioral theories suggest that exercise may disrupt the link between physical symptoms and anxiety, acting as a form of exposure treatment.

Improvements in HRQoL in patients undergoing PR may be linked to reductions in dyspnoea, improved breathing patterns, and increased capacity for daily activities. Exercise during PR may also alleviate symptoms of depression and anxiety through biological mechanisms such as altered central monoamine function, enhanced hypothalamic-pituitary-adrenal axis regulation, improved endogenous opioid release, and reduced systemic inflammation.²⁹ After 24 sessions of PR, dyspnoea, as measured on the Borg scale, decreased significantly from 8.64 to 4.40 points, after 12 months. This reduction in exertion-induced dyspnoea suggests a substantial improvement in the patient's condition. Enhanced breathing mechanics, reduced ventilatory demand, and better ventilatory muscle performance, along with psychological benefits, likely contribute to this improvement in dyspnoea and overall HRQoL.

The experimental group showed an improvement of 41% improvement in FEV₁ after 24 sessions of PR and an improvement of 45% improvement after 12 months, indicating significant gains in lung function at both the end of the program and during follow-up. After 12 months, while the intervention group's FVC values did not improve, the PR group saw a 4.78% increase in FVC. Notably, the PR group exhibited lower baseline FEV₁ and FVC values compared to controls, suggesting more advanced post-tuberculosis pulmonary impairment—potentially due to greater fibrotic damage or unresolved sequelae. This baseline disparity may have contributed to the magnitude of improvement observed. Alternatively, it could indicate heterogeneity in disease phenotype, underscoring the need for stratified analyses in future studies to better interpret treatment effects.

Additionally, the intervention group experienced a 3.3% increase in FEV₁/FVC after 24 sessions and a 1.2% increase at 12 months. PTB can lead to persistent airflow obstruction and limited ventilation due to fibrotic scarring, which may

worsen with delayed diagnosis, severe disease, or prolonged treatments. These changes in lung mechanics and gas exchange can hinder daily activities, reduce exercise capacity, and lower QoL. Our findings highlight the importance of PR interventions to mitigate the long-term effects of PTB on lung function.

This study has several limitations. Patient motivation and incomplete contact information contributed to challenges in data collection. Key measures, such as arterial blood gases, DLCO, airway resistance, and radiographic surveillance [chest radiography and computed tomography (CT)], were not assessed as they were outside the study's primary objectives. Additionally, radiological assessments such as chest X-rays or CT scans were not incorporated into the study protocol. This limits the ability to correlate functional improvements with structural changes in the lung parenchyma. Future studies should include imaging-based classification to better understand the impact of PR in patients with varying extents of radiological sequelae. Attrition, particularly in the control group due to scheduling conflicts and missed appointments, introduced potential bias. Additionally, incomplete data on smoking habits and comorbidities hindered the evaluation of their impact on lung function, and the single-site design limits the generalizability of the findings. Future studies should address these limitations by offering incentives to reduce dropout rates, conducting multi-site research, and collecting more comprehensive data on smoking and other relevant factors.

Despite these limitations, this study is the first of its kind to evaluate the long-term response to PR among post-treatment PTB sequelae. We believe that our findings make a significant contribution to the field despite the existence of published research on the short-term effects of PR for this particular set of participants. Furthermore, post-PTB complications have not been studied as extensively as COPD; hence there are no PR guidelines for PTB patients. This study's findings could be utilized to develop recommendations, for when these individuals should start receiving physical therapy as part of a tailored treatment plan.

Post-PTB patients often face long-term deficits in lung function, exercise capacity, and QoL, even after completing therapy, underscoring the need for further research into the underlying causes and whether these issues resolve over time. The absence of long-term follow-up data and clear post-PTB PR guidelines highlights the importance of a comprehensive approach to care beyond microbiological cure. Future studies should track patients after rehabilitation to assess sustained benefits and recurrence rates. Comparing different PR programs (e.g., duration, intensity, specific interventions) could identify optimal strategies for improving long-term outcomes. Additionally, integrating other healthcare disciplines, exploring telerehabilitation for remote areas, and evaluating the cost-effectiveness of PR will be key to enhancing care. Collaboration across research, clinical, and public health sectors is essential to translate findings into clinical practice and promote the widespread adoption of evidence-based rehabilitation.

CONCLUSION

The results of this study indicate the significant benefits of PR for patients with PTB, demonstrating improvements in functional capacity, QoL, and dyspnea after 24 sessions. Notably, these gains were sustained at the 12-month follow-up, underscoring the long-term effectiveness of structured rehabilitation programs. The findings provide strong evidence for incorporating PR into the comprehensive management of PTB, offering the potential for enhanced health outcomes and QoL in these patients.

Ethics

Ethics Committee Approval: This randomized controlled trial received ethical approval from the Institutional Ethics Committee, SMA & R and Sharda Hospital, Sharda University approved on 26 July 2021, (approval no: SU/SM&R/76-A/2021/91) and was registered with the Clinical Trials Registry of India (CTRI/2022/08/045006).

Informed Consent: Written informed consent was obtained from each participant in accordance with the ethical standards outlined in the Declaration of Helsinki (1964).

Clinical Trial Registry: CTRI/2022/08/045006.

Footnotes

Authorship Contributions

Concept: A.S., Design: A.M., Data Collection or Processing: M.O., R.K., Analysis or Interpretation: R.K., Literature Search: M.O., M.J., I.A., Writing: M.O., M.J., I.A.

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Original Article



Effect of Ambient Air Pollutants on Acute changes in Pulmonary Variables and Inflammatory Markers in Healthy Adults: A Pilot Study

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Abstract

OBJECTIVE: Air pollution is associated with adverse health effects, particularly on respiratory and cardiovascular systems. Smog, prevalent in Northern India, contains particulate matter (PM₁₀, PM_{2.5}) and gaseous pollutants that can impair pulmonary function. Ambient air pollution can be quantified by the air quality index (AQI). Understanding the acute effects of air quality on respiratory physiology and inflammation is essential.

MATERIAL AND METHODS: A pilot prospective longitudinal observational study evaluated healthy volunteers during high (HAQI, AQI >350) and low pollution (LAQI, AQI <150) phases. Spirometry and impulse oscillometry (IOS) assessed lung function; and biomarkers (interleukin-6, tumor necrosis factor alpha) were measured from exhaled breath condensate (EBC) and serum. Paired t-tests or Wilcoxon signed-rank tests were used for analysis.

RESULTS: A total of 21 participants (mean age 25.4±7.4 years, female 33.3%, body mass index 23.9±3.5 kg/m²) completed measurement at both HAQI (395.7±43.8) and LAQI (85.4±9.7). Spirometry revealed significantly lower slow vital capacity (SVC%, 81.6±11.2 vs. 87.7±7.7%, *P* = 0.008) and forced vital capacity (FVC%, 86.2±9.8 vs. 90.9±9.4%, *P* = 0.0005) under HAQI compared to LAQI. Forced expiratory volume at 1 second (FEV₁) was also reduced (*P* < 0.0001), while FEV₁/FVC remained unchanged. IOS showed higher airway resistance (R_s, R₂₀) during HAQI (*P* < 0.0001). Inflammatory biomarkers in serum and EBC showed no statistical differences between HAQI and LAQI. Despite measurable differences, spirometry and IOS parameters remained within normal limits.

CONCLUSION: Acute air pollution exposure impairs lung function and increases airway resistance in healthy adults. These findings underscore the need for larger longitudinal studies to clarify the mechanisms linking acute air pollution exposure to chronic health outcomes.

KEYWORDS: Air pollution, spirometry, impulse oscillometry, particulate matter, inflammatory markers

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INTRODUCTION

Air pollution has been associated with detrimental health effects and reduced life expectancy.¹ The composition of air pollutants exhibits marked regional and temporal variation with differential health effects. Smog is a particularly detrimental type of air pollution, prevalent in Northern India due to a combination of emissions from vehicles, industries, and crop residue burning, which undergo photochemical reactions in sunlight. During winter, temperature inversion in this part of the country traps these pollutants near the surface, leading to dense, persistent smog.² Smog contains high concentrations of small particulate matter, i.e., PM_{2.5} (≤2.5 μm diameter) and PM₁₀ (≤10 μm diameter). PM_{2.5} and PM₁₀ are known to have significant negative effects on human health.³ These particles, although small, have a relatively large surface area that facilitates the attachment of toxic substances. Due to their small size, they can evade

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nasal filtration, penetrate deep into the respiratory system, and reach the alveoli. Once deposited in the lungs, $PM_{2.5}$ and PM_{10} can induce local inflammation and may even enter the bloodstream, causing systemic adverse effects.⁴ Apart from particulate matter, ozone (O_3), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and lead are the main contaminants of outdoor air.

The Central Pollution Control Board's website (Ministry of Environment, Forestry and Climate Change, India) provides real-time access to the air quality index (AQI).⁵ The AQI ranges from 0–500 and is calculated from the concentration of 7 pollutants: PM_{10} , $PM_{2.5}$, NO_2 , O_3 , CO, SO_2 , ammonia (NH_3). There are 6 categories of AQI: good, satisfactory, moderately polluted, poor, very poor, and severe. AQI is the generally accepted method for monitoring air pollution in India.

Acute exposure to air pollutants might result in respiratory symptoms, cardiovascular problems, hospital admissions, and even death.⁶ Further, lung cancer, atherosclerosis, chronic bronchitis, and increased mortality have all been connected to prolonged exposure to air pollution.⁷ Understanding the acute effects of air pollution on the respiratory system physiology is also important for comprehending the pathophysiological mechanisms of chronic detrimental effects.

In this study, we assessed the acute effects of changes in ambient air quality (measured by AQI) on lung volumes, capacities, airway mechanics and inflammatory biomarkers in North India.

MATERIAL AND METHODS

This was a prospective longitudinal observational study aimed at generating pilot data. Healthy volunteers aged 18–40 years who were never smokers, with no history of chronic lung diseases, thoracic surgery, cardiovascular and systemic diseases, and with no acute upper respiratory diathesis (runny nose, cough, sore throat, etc.) or fever, were recruited through convenience sampling at a tertiary care center in New Delhi, India. Given the exploratory nature of the study, a formal sample size and power calculation was not performed. However, we aimed to maximize enrollment to achieve the highest possible power within real-world resource limitations.

The AQI is the air quality metric determined by the Central Pollution Control Board of India, calculated the highest indexed value among seven ambient pollutants: PM_{10} , $PM_{2.5}$, NO_2 , O_3 , CO, SO_2 , and NH_3 .⁵ Their official AQI calculator and its

recommended interpretation are available in the Supplementary Material 1. Briefly, AQI values of 0–50 are classified as “good” (minimal impact), 51–100 as “satisfactory” (minor breathing discomfort), 101–200 as “moderate” (discomfort for sensitive individuals), 201–300 as “poor” (discomfort with prolonged exposure), 301–400 as “very poor” (potential respiratory illness with prolonged exposure), and values above 400 as “severe” (respiratory effects even in healthy individuals).

For each volunteer, comprehensive evaluations of respiratory parameters were made in two phases: an initial high pollution phase (HAQI) and a later low pollution phase (LAQI). Phase definitions were determined based on typical local AQI trends in New Delhi in 2018, the year preceding the study, to ensure adequate contrast between high and low AQI exposures while maintaining sufficient sampling windows. In 2018, the mean AQI during winter months (November–January) was 341 ± 59 , during the rainy season (July–September) it was 109 ± 42 , and during the remaining months it was 231 ± 70 . Therefore, HAQI was defined as an average daily AQI of >350 for at least 7 consecutive days, and LAQI as an average daily AQI of <150 for at least 7 consecutive days. Written informed consent was obtained from all participants at the time of enrollment.

Spirometry was used to measure lung volumes and capacities, and impulse oscillometry (IOS) was used to estimate respiratory impedance at two time points, i.e., HAQI and LAQI. Exhaled breath condensate (EBC) and blood were collected to measure airway and systemic inflammation by estimating biomarkers, including tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6), at both time points.

The study was approved by the All-India Institute of Medical Sciences, New Delhi's Ethics Committee for human subjects (ref. no.: IEC-622/6.09.2019, RP-15/2019).

Assessment of Lung Volumes and Capacities by Spirometry (Spiro'air Pulmonary Function Test System-Medisoft)

Spirometry was performed as per the guidelines of the American Thoracic Society and the European Respiratory Society (ERS).⁸ Of the three acceptable and repeatable slow vital capacity (SVC) and forced vital capacity (FVC) maneuvers, the highest values were considered. The parameters recorded were SVC, FVC, forced expiratory volume in the first second (FEV_1), FEV_1 /FVC ratio, and peak expiratory flow (PEF).

Assessment of Respiratory Impedance by Impulse Oscillometry (MS-IOS Digital JAEGER System)

IOS, is a simple, non-invasive technique that mainly uses forced oscillations, to evaluate the mechanics of the lungs or airways. The participant's effort is minimal when this method is compared to spirometry, to evaluate lung function. Sound waves of different frequencies ranging between 5Hz and 35Hz are superimposed over normal tidal breathing, and impedance is measured by the ratio of pressure signal to flow signal. Sound waves of smaller frequencies (<15 Hz) can reach the alveoli, but higher frequencies lose their strength in the central airways. The procedure was explained to the participants, and while the participants were in a sitting position, the sound waves were

Main Points

- Acute exposure to air pollution can cause measurable worsening of respiratory function and airway parameters in healthy subjects.
- Higher air quality index (AQI) (worse air pollution) is associated with lower slow vital capacity and forced expiratory volume at 1 second.
- Higher AQI is associated with increased respiratory impedance (R_5 and R_{20}) as measured on the impulse oscillometry.

superimposed onto normal tidal breathing for 90 seconds. A tight seal between lips and mouthpiece was ensured. The cheeks were held firmly by the participant with their hands. The parameters recorded were airway impedance (Z), airway resistance at 5Hz and 20Hz (R_5 , R_{20}), and airway reactance at 5Hz and 20Hz (X_5 , X_{20}). The other oscillometry indices taken into consideration were peripheral airway resistance (R_5 - R_{20}), resonant frequency, and an area under reactance.⁹

Assessment of inflammatory biomarkers using EBC and enzyme-linked immunosorbent assay (ELISA). EBC was performed according to ERS guidelines.¹⁰ EBC was collected using an R-tube (Respiratory Research, Inc., USA). R-tube is a disposable collection system that consists of a large Tee section made of polypropylene, which separates saliva from the exhaled breath, a one-way valve (made of silicone rubber), and a polypropylene collection tube, which is cooled by a cooling aluminium sleeve placed around it. Subjects were instructed to breathe tidally by inhaling through the nose and exhaling through the mouthpiece connected to the R-tube for 10 minutes. Approximately 1.5 mL of the condensate was collected and immediately stored at -20 °C. Separated serum from peripheral blood samples was also stored at -20 °C. Human ELISA kits of Boster Biotech, USA (Cat No: EK0525, EK0410) were used to quantify serum levels of TNF- α and IL-6, respectively. According to the manufacturer's instructions, ELISA was performed, and a microplate reader (BioTek, EpochTM 2 microplate reader) was used to read the colour that developed in the 96-well plates. The detection range was 15.6-1000 pg/mL for TNF- α (sensitivity 1 pg/mL) and 4.69-300 pg/mL for IL-6 (sensitivity 0.3 pg/mL).

Statistical Analysis

GraphPad Prism 9.0.1 for Windows (GraphPad Software, Inc., USA) was used for analysis. Each parameter was tested for distribution of the data based on standard normality tests (the D'Agostino-Pearson normality test, the Anderson-Darling test, the Shapiro-Wilk test). Based on the normality of the data, group comparisons were carried out using the paired t-test or

the Wilcoxon signed-rank test along with the appropriate post-hoc comparison tests. The level of statistical significance was set at $P < 0.05$. Bonferroni corrections were applied within each test domain (spirometry, IOS, and biomarkers) to adjust the significance thresholds for multiple comparisons.

RESULTS

A total of 21 participants (mean age 25.4 ± 7.4 years, female 33.3%, body mass index 23.9 ± 3.5 kg/m²) who completed recordings at both time points was considered for analysis. The mean AQI was 395.7 ± 43.8 during HAQI and 85.4 ± 9.7 during LAQI phases ($P = 0.0001$). Detailed distribution of pollutants during the two phases is available in Table 1.

Spirometry Parameters

SVC_(%pred) was lower in HAQI (81.6 ± 11.2) compared to LAQI (87.7 ± 7.7 , $P = 0.0008$). Similarly, FVC_(%pred) was lower in HAQI (86.2 ± 9.8 vs. 90.9 ± 9.4 , $P = 0.0005$). While FEV_{1(%pred)} was lower during HAQI [83 (75-89) vs. 89 (86-94), $P < 0.0001$], FEV₁/FVC was similar between both groups (95.0 ± 11.2 vs. 96.4 ± 10.0 , $P = 0.6$). Results of spirometry are summarized in Table 2.

IOS Parameters

The airway resistance was higher in HAQI compared to LAQI, as measured by R_5 (%pred) [104.0 (94.2-123.2) vs. 75.0 (68.4-92.8), $P < 0.0001$] and R_{20} (%pred) [108.7 (100.0-122.6) vs. 77.3 (69.5-89.6), $P < 0.0001$]. The reactance [X_5 (%pred) and X_{20} (%pred)] was similar in both groups ($P = 0.3$ and $P = 0.4$), although absolute values of X_5 were more negative in HAQI [-0.11 (-0.16-(-0.09)) vs. -0.07 (-0.09-(-0.05)), $P = 0.001$]. The results of the IOS parameters are summarized in Table 3.

Inflammatory Biomarkers

There was no difference in the serum and EBC levels of TNF- α ($P = 0.1$ and $P = 0.4$) and IL-6 ($P = 0.3$ and $P = 0.5$) between the two groups. These results are summarized in Table 4.

Table 1. Air pollution parameters at two different time-points

Parameters	High Pollution (AQI >350 for 7 consecutive days)	Low pollution (AQI <150 for 7 consecutive days)	P value
AQI	395.7 ± 43.8	85.4 ± 9.7	<0.0001
PM _{2.5}	394.6 ± 43.9	54.0 ± 17.0	<0.0001
PM ₁₀	369.6 ± 55.7	64.7 ± 19.4	<0.0001
NO ₂	51 (49-58)	39 (26-41)	0.02
NH ₃	6.6 ± 1.3	23.1 ± 0.7	<0.0001
SO ₂	14.0 ± 1.2	16.4 ± 2.7	0.07
CO	55.4 ± 10.0	64.6 ± 34.8	0.5
O ₃	19.6 ± 1.7	35.1 ± 9.9	0.01

Values presented are mean $\pm$ standard deviation or median (minimum-maximum), analyzed by Paired t-test (two-tailed) or Wilcoxon signed-rank test (two-tailed), respectively

AQI: air quality index, PM_{2.5}: particulate matter 2.5, PM₁₀: particulate matter 10, NO₂: nitrogen dioxide, NH₃: ammonia, SO₂: sulfur dioxide, CO: carbon monoxide, O₃: ozone

Table 2. Spirometry parameters at two different time-points

Spirometry parameters	High pollution (AQI >350 for 7 consecutive days)	Low pollution (AQI <150 for 7 consecutive days)	P value*
SVC (%predicted)	81.6±11.2	87.7±7.7	0.0008
FVC (%predicted)	86.2±9.8	90.9±9.4	0.0005
FEV ₁ (%predicted)	83 (75-89)	89 (86-94)	<0.0001
FEV ₁ /FVC	95.0±11.2	96.4±10.0	0.6
MMEF (%predicted)	75.5±23.1	88.0±18.5	0.003
PEF (%predicted)	83.2±24.1	95.5±17.8	0.003

*The Bonferroni-corrected significance threshold was set at $P < 0.0083$ (6 comparisons)

Values presented are mean ± standard deviation or median (minimum-maximum), analyzed by Paired t-test (two-tailed) or Wilcoxon signed-rank test (two-tailed) respectively

AQI: air quality index, SVC: slow vital capacity, FVC: forced vital capacity, FEV₁: forced expiratory volume at 1st second, MMEF: maximum mid expiratory flow, PEF: peak expiratory flow

Table 3. Impulse oscillometry parameters at two different time-points

Impulse oscillometry parameters	High pollution (AQI >350 for 7 consecutive days)	Low pollution (AQI <150 for 7 consecutive days)	P value*
R ₅ [kPa/(L/s)]	0.27 [0.25-0.39]	0.22 [0.18-0.29]	<0.0001
R ₅ (%predicted)	104.0 [94.2-123.2]	75.0 [68.4-92.8]	<0.0001
R ₂₀ [kPa/(L/s)]	0.25 [0.23-0.34]	0.18 [0.15-0.23]	<0.0001
R ₂₀ (%predicted)	108.7 [100.0-122.6]	77.3 [69.5-89.6]	<0.0001
R ₅ -R ₂₀ [kPa/(L/s)]	0.04 [0.02-0.05]	0.03 [0.02-0.05]	0.09
X ₅ [kPa/(L/s)]	-0.11 [-0.16-(-0.09)]	-0.07 [-0.09-(-0.05)]	0.001
X ₅ (%predicted)	-333.3 [-491.7- 412.5]	-200.0 [-308.3-395.8]	0.2
X ₂₀ [kPa/(L/s)]	.06 [-0.01- 0.09]	0.04 [0.01-0.07]	0.2
X ₂₀ (%predicted)	66.7 [-11.7-100.0]	57.1 [18.3-88.9]	0.4
Ax [kPa/L]	0.30 [0.21-0.90]	0.28 [0.17-0.56]	0.03
Fres [1/sec]	13.8 [10.7-18.7]	15.1 [11.3-18.4]	0.8

*The Bonferroni-corrected significance threshold was set at $P < 0.0045$ (11 comparisons)

Values presented are mean ± standard deviation or median (minimum-maximum), analyzed by Paired t-test (two-tailed) or Wilcoxon signed-rank test (two-tailed) respectively

AQI: air quality index, R₅: resistance at 5Hz, R₂₀: resistance at 20 Hz, R₅-R₂₀: peripheral airway resistance, X₅: reactance at 5Hz, X₂₀: reactance at 20Hz, Ax: area under reactance, Fres: resonant frequency

Table 4. Inflammatory biomarker parameters at two different time-points

Inflammatory biomarkers	High pollution (AQI >350 for 7 consecutive days)	Low pollution (AQI <150 for 7 consecutive days)	P value*
TNF-α in EBC (pg/mL)	6.4±1.7	7.2±0.6	0.1
TNF-α in serum (pg/mL)	4.6 (0.8-7.5)	4.71 (0.0-6.5)	0.4
IL-6 in EBC (pg/mL)	0.3 (0.1-0.7)	0.3 (0.2-0.5)	0.3
IL-6 in serum (pg/mL)	0.5 (0.2-1.1)	0.4 (0.0-1.6)	0.5

*The Bonferroni-corrected significance threshold was set at $P < 0.0125$ (4 comparisons)

Values presented are mean ± standard deviation or median (minimum-maximum), analyzed by Paired t-test (two-tailed) or Wilcoxon signed-rank test (two-tailed), respectively

AQI: air quality index, TNF-α: tumor necrosis factor-alpha, IL-6: interleukin 6, EBC: exhaled breath condensate

DISCUSSION

To the best of our knowledge, this is the first study to prospectively evaluate comprehensive respiratory parameters using spirometry, IOS, and inflammatory markers in healthy volunteers regarding short-term changes in air pollution. Despite a small sample size for a pilot study, we found statistically significant differences associated with higher air pollution, including lower lung capacities, lower expiratory volume, and higher airway resistance. It is important to note, however, that these values remained within the normal prescribed limits. There was no statistically significant difference in the inflammatory markers noted in our study. Overall, higher ambient air pollution was associated with deleterious effects on clinically measurable pulmonary and airway parameters even over relatively short exposure periods in healthy individuals.

Our spirometry results are supported by conclusions from previous studies. In a 2019 systematic review, Edington et al. reported that short-term exposure to higher $PM_{2.5}$ level was associated with a statistically significant decrease in FEV_1 .¹¹ In a retrospective cohort study in Belgium, Int Panis et al.¹² reported that FVC, FEV_1 , and PEF were negatively correlated with PM_{10} concentrations on the day of examination. In a study on asthmatic patients in Thailand, Chujit et al.¹³ found that PEF was most affected by NO_2 levels 2 days before and PM_{10} levels 6 days before spirometry, proposing that this lag is required for these pollutants to affect the airway.

While SVC and FVC are generally expected to be similar in healthy individuals, a reduction in FVC and FEV_1 with a preserved SVC may serve as a sensitive marker of small airway limitation. Therefore, both parameters were measured and reported. In our study, however, the mean SVC% was lower than the mean FVC%, likely reflecting a measurement artifact. Given the more relaxed nature of the SVC manoeuvre, suboptimal respiratory effort may occur despite extensive participant coaching, particularly when compared to the more forceful and dynamic effort required during the FVC manoeuvre.

Although there is less literature exploring the acute impact of air pollution on IOS parameters, previous studies provide a theoretical framework for understanding the increased resistance observed during HAQI. In a cross-sectional study, De¹⁴, observed that long-term exposure to high levels of ambient air pollution during early life is associated with increased respiratory impedance in children, compared to those with lower pollution levels. This finding shows that ambient air pollution affects small airway resistance and elastic characteristics but not proximal airway resistance. Additionally, children who live in more polluted areas had a greater absolute magnitude of X_5 (more negative), suggesting that exposure to ambient air pollution may alter the respiratory system's elastic properties or increase ventilation heterogeneity.¹⁴ In a retrospective study of chronic obstructive pulmonary disease (COPD) patients, Zhu et al.¹⁵ found that short-term exposure to higher $PM_{2.5}$ was associated with worsening of IOS parameters, including respiratory impedance and reactance.

Friedman et al.¹⁶ measured spirometry and IOS parameters among area workers and residents, who had breathed dust and fumes from the World Trade Centre tragedy in 2001. Among

these participants, cases, i.e., those who developed lower respiratory symptoms, were more likely to have abnormal spirometry and increased respiratory impedance compared to controls, which persisted 7-8 years after exposure. They concluded that these abnormalities were primarily associated with dysfunction in the peripheral airways.

We observed that HAQI and LAQI had comparable levels of serum IL-6 and TNF- α in both EBC and serum. This is likely an artifact arising from our small sample size. Robust longitudinal measurements by Sabeti et al.¹⁷ in Iran show that ambient $PM_{2.5}$ and metal concentrations in places with high pollution levels is positively associated with increased TNF- α but negatively correlated with IL-6. A study on healthy Swiss adults found that serum levels of IL-6 and TNF- α were positively associated with short-term exposure to PM_{10} . These findings provide strong support for the notion that short-term exposure to PM_{10} is probably sufficient to induce systemic inflammation. Nevertheless, it is plausible that the very short duration of exposure to high pollution in our study (7 days), within a setting characterized by year-round elevated pollution levels, may have limited our ability to detect appreciable changes in inflammatory markers. Furthermore, unmeasured factors such as occult infections and other environmental exposures could have influenced baseline inflammatory status, potentially obscuring subtle differences.

Acute exposure to air pollutants can significantly impair respiratory function through several pathophysiological mechanisms. Inhaled pollutants, including particulate matter ($PM_{2.5}$ and PM_{10}), O_3 , NO_2 , and heavy metals, can irritate the respiratory mucosa, triggering oxidative stress and inflammation.¹⁸⁻²⁰ This leads to increased production of inflammatory cytokines, recruitment of immune cells, and disruption of epithelial barriers in the airways and gaseous exchange surfaces.^{21,22} Further, this can cause bronchoconstriction, airway edema, and reduced mucociliary clearance, as evidenced by exacerbations of conditions like asthma and COPD.²³ Our study demonstrates, even in apparently healthy individuals, these processes can cause small yet measurable adverse effects on airway mechanics and pulmonary function. Further research is needed to elucidate the exact mechanisms by which this acute inflammatory reaction to air pollutants translates to long-term respiratory complications and other detrimental health effects.

While our results demonstrate a correlation between higher pollution levels and worse respiratory parameters, it is important to note that we did not adjust for other environmental confounders, including ambient temperature and humidity. Since the HAQI phase was predominantly recorded during winter months, cold temperatures may have influenced the spirometry and IOS measurements. Although cold dry air is generally known to induce bronchoconstriction, the effect of the winter season on spirometry parameters is complex. Recent studies suggest a paradoxical linear increase in FEV_1 and FVC with colder temperatures,²⁴ likely driven by factors such as reduced outdoor allergen exposure during winter months. The impact of seasonal variation in temperature and humidity on IOS parameters remains unclear. Future analyses should adjust for these covariates to better isolate the independent effect of ambient air pollution.

Interestingly, ambient levels of NH_3 , SO_2 , CO , and O_3 during the HAQI phase were similar to or paradoxically lower than those during the LAQI phase compared to the LAQI phase, despite substantially higher $\text{PM}_{2.5}$, PM_{10} , and AQI. This trend may reflect chemical conversion of these gases into particulate matter or other compounds, leading to artificially low readings during the HAQI period.²⁵ Temperature, humidity, and local wind patterns may also contribute. Nevertheless, it is important to note that despite lower gas levels, the elevated particulate matter and smog, during HAQI periods, result in worse overall air quality.

Study Limitations

This study should be interpreted in the context of several limitations. The use of a small convenience sample introduces potential selection bias and increases the risk of type II errors. Airway measurements may have been influenced by environmental confounders, beyond pollution, including ambient temperature, humidity, air conditioning, and circulating seasonal viruses. Participant-level factors such as time since last meal, recent exercise, stress, sleep, and caffeine intake were also not accounted for. Additionally, we did not record information regarding time spent indoors versus outdoors and recent travel history, which could impact cumulative exposure to air pollution. We have also not used any instrument to measure the volunteers' personal exposure to air pollution. Given the relatively young age of our study population, these findings may not be generalizable to older individuals. Finally, we were unable to evaluate a dose-response relationship as only two measurements were made for each participant.

CONCLUSION

Acute increase in air pollution adversely affects spirometry parameters and respiratory impedance in healthy adults. Larger longitudinal studies are needed to elucidate the effect of air pollution on local and systemic inflammation, as well as their link to chronic health outcomes.

Ethics

Ethics Committee Approval: The study was approved by the All-India Institute of Medical Sciences, New Delhi's Ethics Committee for human subjects (ref. no.: IEC-622/6.09.2019, RP-15/2019).

Informed Consent: Written informed consent was obtained from all participants at the time of enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Surgical and Medical Practices: G.B., A.T., Concept: G.B., A.T., Design: G.B., A.G., A.T., Data Collection or Processing: A.G., L.M., S.G., K.S., Analysis or Interpretation: K.S., K.N.J., G.B., A.T., Literature Search: K.S., A.G., K.N.J., L.M., S.G., G.B., A.T., Writing: A.G., K.S., G.B.

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

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Systematic Review



Adverse Events in Non-invasive Ventilation Approaches: Systematic Review

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Abstract

Non-invasive ventilation (NIV) plays a critical role in the management of acute and chronic respiratory failure, offering benefits over invasive mechanical ventilation. However, its use is associated with various adverse events that may impact clinical outcomes. This systematic review aimed to evaluate the types, frequencies, and clinical consequences of complications related to NIV. A systematic search of PubMed, EMBASE, and Cochrane Library databases was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses 'PRISMA' guidelines, covering studies published between 2000 and February 2023. Eligible studies included randomized controlled trials, observational cohorts, and systematic reviews reporting adverse events in adults receiving NIV for respiratory failure. Thirty-two studies involving approximately 6,000 patients were analyzed. NIV-related complications were frequently reported, including, physiological (e.g., hypercapnia 2-10%, hypoxemia 1-5%), mechanical (e.g., skin breakdown 5-15%, air leaks 5-25%), and patient-related events (e.g., discomfort 10-30%, anxiety 5-15%). Face masks were linked to higher rates of air leaks and intolerance, while helmet interfaces showed fewer complications. Helmet interfaces and newer ventilator technologies showed advantages in minimizing certain adverse events. Although NIV offers substantial benefits compared to invasive ventilation, its effectiveness can be compromised by preventable complications. Structured monitoring, early intervention, and a multidisciplinary care approach are essential for maximizing outcomes. Further research is needed to develop strategies that enhance patient comfort, minimize complications, and optimize NIV application across different clinical settings.

KEYWORDS: Non-invasive ventilation, complications, adverse effects, tolerance

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INTRODUCTION

Non-invasive ventilation (NIV) has gained an important place in the management of acute and chronic respiratory failure in recent years and stands out as a less invasive alternative to mechanical ventilation. NIV is preferred especially in conditions such as acute hypercapnic respiratory failure, cardiogenic pulmonary edema, chronic obstructive pulmonary disease (COPD), and congestive heart failure due to its potential to prevent patient intubation, reduce complications related to invasive procedures, and shorten hospital stay.¹⁻⁶ These advantages support the widespread clinical use of NIV, ranging from intensive care units (ICUs) to emergency departments.

However, in addition to the benefits of NIV, adverse events that may occur during the implementation process are important clinical problems that should not be ignored. The frequency and severity of these adverse events may vary depending on patient factors, interface type, ventilation settings, and clinician experience.⁷⁻⁹ In addition to local complications such as mask-related pressure sores, nasal and oral mucosal dryness, aerophagia, gastric distension, respiratory problems such as synchronization disorders between the ventilator and the patient, and hyperventilation or inadequate ventilation may adversely affect the effectiveness of NIV.^{10,11} Since these adverse events may lead to treatment failure, increased need for intubation and increased overall mortality rates, they are considered conditions that require early diagnosis and intervention.

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Despite various studies investigating the incidence, mechanisms, and clinical outcomes of adverse events associated with NIV, comprehensive systematic reviews in this area remain limited. Considering the increasing use of NIV across different clinical settings, a systematic evaluation of related adverse events could be valuable for optimizing patient safety and improving clinical outcomes. Furthermore, supportive studies aimed at helping clinicians anticipate and manage potential complications during NIV application may contribute significantly to enhancing patient safety and treatment efficacy.

This systematic review aims to fill this gap by providing a comprehensive review of adverse events in different NIV approaches, detailing their pathophysiology, clinical implications, and management strategies. By synthesizing existing data and highlighting under-researched mechanisms, this review aims to enhance patient safety, improve clinical outcomes, and contribute to more effective NIV practices in a variety of clinical settings.

MATERIAL AND METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹² A detailed search strategy was developed to capture studies reporting adverse events or complications associated with NIV. Multiple databases, including MEDLINE (PubMed), EMBASE, and the Cochrane Library, were searched from the year 2000 through February 2025. The search combined terms related to NIV (e.g., 'non-invasive ventilation', 'NIPPV', 'BiPAP', 'CPAP') with terms related to adverse events or complications (e.g., 'complications', 'adverse effects', 'side effects', 'failure', 'tolerance'). For practical reasons, only studies published in English were included. Additionally, reference lists of relevant review articles and clinical practice guidelines were manually screened to identify further eligible studies.

Main Points

- Non-invasive ventilation (NIV) significantly reduces the need for invasive mechanical ventilation but is associated with specific physiological, mechanical, and patient-related complications.
- Early recognition and management of adverse events such as hypercapnia, hypoxemia, skin breakdown, and patient-ventilator asynchrony are crucial for successful NIV outcomes.
- Appropriate patient selection, optimized ventilator settings, and interface choice (e.g., helmet vs. face mask) can minimize complication rates and improve tolerance.
- Multidisciplinary care teams and structured protocols are key to maximizing the benefits of NIV while reducing treatment failure and mortality rates.
- Future research should focus on improving NIV interface design, patient comfort strategies, and early detection of complications to further enhance clinical outcomes.

Inclusion criteria: We included randomized controlled trials, observational cohort studies, and large case series reporting adverse events, complications, or safety outcomes in adult patients receiving NIV for acute or chronic respiratory failure. Studies directly comparing NIV with invasive mechanical ventilation in terms of complications were also included for comparative analysis. Both acute care settings (e.g., ICU, emergency departments) and non-ICU settings (e.g., step-down units) where NIV was used were considered (Table 1).

Exclusion criteria: We excluded case reports and small case series (<10 patients) due to limited generalizability. Studies focusing solely on pediatric populations (given differences in physiology and interfaces in children) and those evaluating NIV use in non-acute contexts (e.g., sleep apnea or chronic home use) were also excluded. Furthermore, studies that did not specifically report adverse events and that combined NIV and invasive ventilation outcomes without stratifying by modality were omitted (Table 1).

Two independent reviewers screened titles and abstracts for eligibility, and full texts were retrieved for all studies meeting the inclusion criteria. From each study, detailed data were extracted regarding study design, patient population, NIV indication, and reported complications. Additionally, outcome measures such as NIV failure rates (need for intubation), length of stay, and mortality rates (when reported) were recorded, particularly if they were associated with complications. This review adheres to the structured format recommended by JAMA for systematic reviews, incorporating a clearly defined methodology and structured reporting of outcomes.¹³

RESULTS

The search yielded 1,245 records (PubMed: 512, EMBASE: 589, Cochrane: 144). After removing duplicates ($n = 312$), 933 titles and abstracts were screened. Of 102 full-text articles assessed, 32 studies met inclusion criteria (10 register of controlled trials, 10 observational studies, 8 systematic reviews, 4 meta-analyses), involving approximately 6,000 patients across acute respiratory failure (ARF), COPD, Coronavirus disease-2019 (COVID-19), and mixed conditions. These studies encompassed various clinical contexts, including acute hypercapnic respiratory failure, acute hypoxemic respiratory failure [pneumonia, acute respiratory distress syndrome (ARDS), cardiogenic pulmonary edema], and postoperative or immunocompromised patient populations. The study selection process is summarized in a PRISMA flow diagram (Figure 1).

Adverse events were categorized as physiological, mechanical, and patient-related, with frequencies and associated studies summarized in Tables 2, 3. Studies included ARF ($n = 14$), COPD ($n = 10$), COVID-19 ($n = 5$), and mixed conditions ($n = 3$). Table 3 lists the studies.

Table 1. Inclusion and exclusion criteria for study selection

Criteria type	Details
Inclusion criteria	- Randomized controlled trials, observational cohort studies, and large case series (≥ 10 patients) - Adult patients receiving NIV for acute or chronic respiratory failure - Studies reporting adverse events, complications, or safety outcomes - Studies comparing NIV with invasive mechanical ventilation for complications - Settings: ICU, emergency department, step-down or other acute care units - Published in English - Study period: 2000-February 2025
Exclusion criteria	- Case reports or small case series (< 10 patients) - Studies limited to pediatric populations - Studies evaluating non-acute or home use of NIV (e.g., sleep apnea) - Studies not reporting adverse events or complications - Studies combining NIV and invasive ventilation outcomes without stratification

NIV: non-invasive ventilation, ICU: intensive care unit

Table 2. Summary of adverse events in NIV studies

Category	Adverse event	Frequency (%)	Notes
Physiological	Hypercapnia and respiratory acidosis	2-10% ^{2,6,8,27,32}	Common in COPD with suboptimal settings; mitigated by monitoring. ^{9,25}
	Hypoxemia	1-5% ^{7,10,28,31}	Seen in ARF with inadequate oxygenation; helmet NIV may improve. ^{1,5}
	Hemodynamic effects	1-3% ^{1,7,8,18}	Rare, linked to severe ARF or cardiovascular comorbidities. ²⁷
	Barotrauma	$< 1\%$ ^{4,7,14,20}	Rare, associated with high BiPAP pressures. ⁸
Mechanical	Pressure ulcers/skin breakdown	5-15% ^{1,5,14,21,22,28,33}	Higher in ICU with prolonged use; helmets reduce incidence. ^{5,23}
	Air leaks	5-25% ^{1,8,17,22,23,28,29,34}	More frequent with face masks; impacts ventilation efficacy. ^{6,24}
	Gastric insufflation and aspiration	0.5-10% ^{2,6,11,27}	Insufflation common with BiPAP; aspiration rare in conscious patients. ⁷
	Patient-ventilator asynchrony	2-8% ^{6,17,29}	Affects COPD and ARF; trigger sensitivity adjustments help. ⁸
Patient-related	Discomfort and pain	10-30% ^{3,7,18,24,30,32,34}	Higher with face masks vs. helmets; education improves tolerance. ^{5,23}
	Anxiety, claustrophobia and psychological distress	5-15% ^{4,7,9,10,16,25}	Contributes to intolerance; psychological support beneficial. ⁷
	Delirium	1-5% ^{1,7,22}	Seen in ICU settings; sedation protocols needed. ¹⁸
	Sleep disturbances	5-10% ^{9,25}	Common in home NIV for COPD; humidification helps. ¹⁶

COPD: chronic obstructive pulmonary disease, ARF: acute respiratory failure, NIV: non-invasive ventilation, ICU: intensive care unit

Table 3. Included studies on adverse events in NIV

Author (year)	Study design	Population	NIV type	Key adverse events
Antonelli et al. ¹ (2000)	RCT	ARF (post-transplant)	BiPAP	Skin breakdown (10%), air leaks (15%)
Lightowler et al. ² (2003)	Systematic review	COPD	BiPAP	Hypercapnia (5%), gastric distension (8%)
Keenan et al. ³ (2004)	Systematic review	ARF	CPAP/BiPAP	Mask intolerance (20%), air leaks (20%)
Burns et al. ⁴ (2013)	Meta-analysis	ARF	CPAP/BiPAP	Claustrophobia (10%), air leaks (20%)
Navalesi et al. ⁵ (2007)	RCT	COPD	BiPAP	Skin breakdown (5%), air leaks (12%)
Carrillo et al. ⁶ (2012)	Observational	COPD	BiPAP	Hypercapnia (8%), asynchrony (6%)
Ferreyro et al. ⁷ (2020)	Meta-analysis	ARF	CPAP/BiPAP	Mask intolerance (15%), skin breakdown (10%)
Girault et al. ⁸ (2009)	RCT	ARF	BiPAP	Hypercapnia (7%), air leaks (18%)
Pisani et al. ⁹ (2012)	Observational	COPD	BiPAP	Claustrophobia (12%), sleep disturbances (8%)
Bellani et al. ¹⁰ (2017)	Observational	ARDS	CPAP/BiPAP	Nasal dryness (18%), claustrophobia (12%)
Vital et al. ¹¹ (2013)	Systematic review	ARF (post-surgery)	CPAP	Gastric distension (5%), aspiration (1%)
Cabrini et al. ¹⁴ (2015)	Meta-analysis	ARF	CPAP/BiPAP	Skin breakdown (6%), air leaks (10%)
Frat et al. ¹⁵ (2015)	RCT	ARF	HFNC	Nasal dryness (15%), discomfort (10%)
Rochweg et al. ¹⁶ (2017)	Systematic review	ARF	HFNC	Nasal dryness (20%), discomfort (15%)
Carteaux et al. ¹⁷ (2016)	Observational	ARF	BiPAP	Asynchrony (5%), air leaks (20%)
Hess ¹⁸ (2013)	Systematic review	ARF	CPAP/BiPAP	Mask intolerance (15%), skin breakdown (10%)
Nava et al. ¹⁹ (2011)	RCT	ARF	CPAP	Air leaks (12%), skin breakdown (8%)
Liu et al. ²⁰ (2016)	Meta-analysis	ARF	CPAP/BiPAP	Skin breakdown (5%), mask intolerance (8%)
Franco et al. ²¹ (2020)	Observational	COVID-19	CPAP	Skin breakdown (6%), air leaks (10%)
Aliberti et al. ²² (2020)	Observational	COVID-19	CPAP	Skin breakdown (8%), air leaks (10%)
Grieco et al. ²³ (2021)	RCT	COVID-19	CPAP	Air leaks (12%), skin breakdown (4%)
Perkins et al. ²⁴ (2022)	RCT	COVID-19	CPAP	Mask intolerance (20%), air leaks (15%)
Windisch et al. ²⁵ (2005)	Observational	COPD	BiPAP	Sleep disturbances (10%), mask intolerance (22%)
Rochweg et al. ²⁶ (2020)	Systematic review	ARF	HFNC	Nasal dryness (18%), discomfort (10%)
Hill et al. ²⁷ (2007)	Systematic review	ARF	CPAP/BiPAP	Hypercapnia (6%), gastric distension (7%)
Esquinas et al. ²⁸ (2014)	Systematic review	ARF	CPAP/BiPAP	Skin breakdown (5%), air leaks (12%)
Carron et al. ²⁹ (2013)	Observational	ARF	BiPAP	Asynchrony (5%), air leaks (20%)
Conti et al. ³⁰ (2002)	RCT	COPD	BiPAP	Mask intolerance (15%), skin breakdown (10%)
Hilbert et al. ³¹ (2001)	Systematic review	ARF	CPAP/BiPAP	Claustrophobia (10%), nasal dryness (15%)
Tan et al. ³² (2024)	RCT	COPD	HFNC/BiPAP	Hypercapnia (6%), discomfort (15%)
Squadrone et al. ³³ (2005)	Observational	ARF	CPAP	Skin breakdown (3%), air leaks (12%)
Nava et al. ³⁴ (2006)	RCT	ARF	BiPAP	Discomfort (10%), air leaks (12%)

RCT: register of controlled trial, HFNC: high-flow nasal cannulas, COPD: chronic obstructive pulmonary disease, ARF: acute respiratory failure, NIV: non-invasive ventilation, CPAP: continuous positive airway pressure, BiPAP: bilevel positive airway pressure, ARDS: acute respiratory distress syndrome, COVID-19: Coronavirus disease-2019

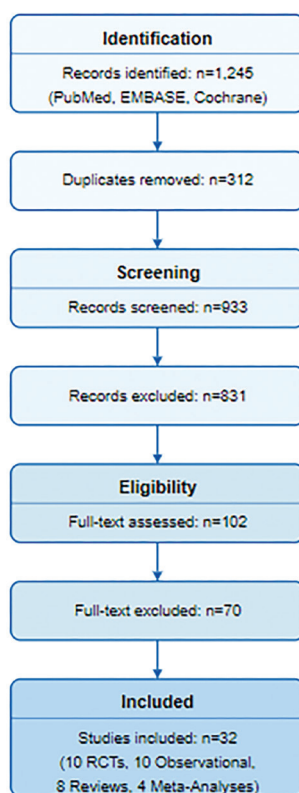


Figure 1. PRISMA flow diagram of study selection

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs: register of controlled trials

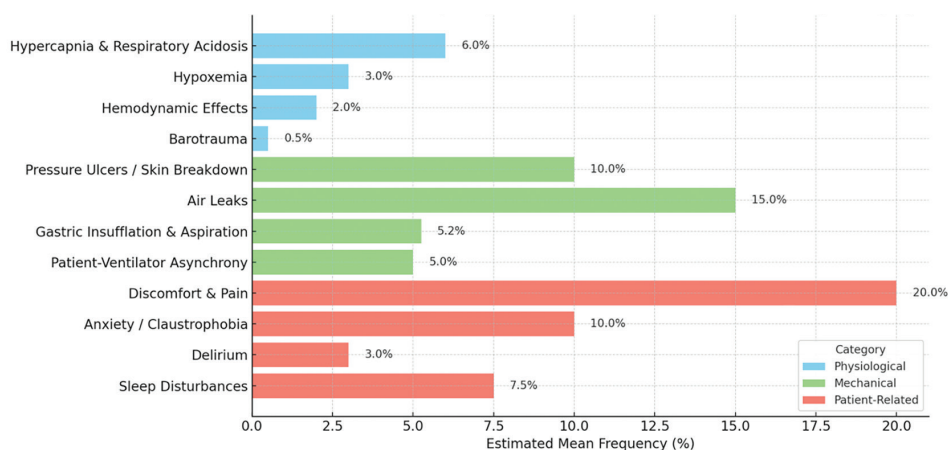


Figure 2. Estimated mean frequency of adverse events in NIV studies (by category)

NIV: non-invasive ventilation, RCTs: randomized controlled trials

DISCUSSION

This review synthesizes NIV adverse events across 32 studies, categorizing them into physiological, mechanical, and patient-related complications (Figure 2). The findings inform clinical practice and highlight areas for improvement.

Physiological Complications of Non-invasive Ventilation

Hypercapnia and Respiratory Acidosis: While NIV is commonly used to manage hypercapnic respiratory failure, inadequate ventilator settings or worsening of the patient's condition can lead to persistent or worsening CO_2 retention.

Insufficient tidal volume or backup rate on a bilevel device may result in elevated PaCO_2 levels and respiratory acidosis.^{2,6,8,27} This often serves as an early indicator of NIV failure and reflects inadequate ventilatory support. In patients with severe ARDS or pneumonia, NIV may fail to provide sufficient ventilation, with reported intubation rates ranging from 30% to 50% across multiple series.^{2,6,8,27} If hypercapnia is unrecognized, it can lead to CO_2 narcosis (altered mental status or coma) and cardiac arrhythmias. Therefore, timely monitoring of arterial blood gases during NIV is essential.³² Worsening or non-improving hypercapnia and acidemia within the first few hours of NIV use are strong predictors of failure and the need for intubation.

Clinical guidelines recommend severe acidosis ($\text{pH} < 7.25$) or rising CO_2 levels as criteria for early intubation instead of prolonged NIV to avoid adverse outcomes.

Hypoxemia: Similarly, refractory hypoxemia (inability to maintain adequate oxygen saturation or PaO_2), is a critical complication. NIV typically improves oxygenation through positive end-expiratory pressure (PEEP) and pressure support; however, in conditions such as ARDS or severe pneumonia, it may not fully correct gas exchange deficits.^{7,10,28,31} Worsening hypoxemia during NIV (e.g., inability to maintain $\text{SpO}_2 > 88\text{-}92\%$ despite high FiO_2) indicates that the patient's respiratory failure may be too severe for non-invasive support. Helmet NIV may improve oxygenation compared to face masks.⁵ Life-threatening hypoxemia is generally considered a relative contraindication to NIV. In studies included in this review, development of severe hypoxemia despite NIV frequently prompted intubation, and delayed intubation was often associated with worse outcomes.^{7,10,31} Hypoxemic complications of NIV also include cardiac arrhythmias and myocardial ischemia triggered by low oxygen levels. Thus, as with hypercapnia, ongoing or worsening hypoxemia requires urgent reassessment and transition to invasive ventilation. Some evidence suggests that early application of NIV in acute hypoxemic respiratory failure may reduce intubation rates (e.g., one study reported a decrease from approximately 52% to 25%),⁷ but this benefit is limited to patients who show an early improvement in oxygenation; patients who do not improve are at risk if NIV is prolonged.

Hemodynamic Effects: Application of positive intrathoracic pressure during NIV can have significant impacts on a patient's hemodynamics. Increased intrathoracic pressure can reduce venous return, leading to decreased cardiac output and hypotension, particularly in patients with hypovolemia or underlying cardiac dysfunction.^{1,7,8,18} Most patients tolerate the hemodynamic effects of NIV well if appropriately resuscitated; however, hemodynamic instability (e.g., shock or severe hypotension) is generally considered a contraindication or a criterion for NIV failure. In this review, episodes of hypotension were reported during NIV, especially when higher PEEP levels were applied or when patients had concurrent myocardial infarction or sepsis.^{1,7,8,18} Myocardial ischemia may also be triggered by elevated intrathoracic pressures (reducing coronary perfusion) or by hypoxemia and hypercapnia when NIV fails to meet ventilatory demands. Additionally, arrhythmias such as tachycardia or bradycardia can occur in the setting of respiratory acidosis or hypoxemia. Although NIV is not typically a direct cause of arrhythmias, the physiological stress associated with respiratory failure and the application of positive pressure may reveal underlying arrhythmic predispositions.

Barotrauma: Barotrauma is a rare but serious complication associated with NIV, with pneumothorax being the most concerning manifestation. Positive pressure ventilation can cause alveolar rupture, particularly in fragile lungs (e.g., in patients with bullous COPD or ARDS), leading to air leakage into the pleural space. Although the incidence is lower than invasive mechanical ventilation, case series, have reported that pneumothorax complicating NIV.^{4,7,14,20} New-onset chest pain, hypotension, or unilateral absence of breath sounds in a patient

undergoing NIV should raise suspicion for pneumothorax. Under these circumstances, immediate initiation of invasive management, including chest tube placement, is necessary

Mechanical Complications

Pressure Ulcers and Skin Injury: Prolonged application of a mask, especially when tightly secured, can cause skin injuries and ischemia. The nasal bridge, cheeks, and forehead are particularly vulnerable areas. Patients often develop erythema or skin rashes at mask contact points, which, if left unaddressed, can progress to open pressure ulcers. A systematic review and meta-analysis reported that the incidence of facial pressure injuries in adults receiving NIV is approximately 25%, indicating that about one in four patients may experience some degree of skin breakdown.^{1,5,14,21,22,28,33} Reports from ICUs show that the incidence of pressure ulcers among NIV patients varies between 10% and 30%, depending on the preventive measures implemented.⁷ These injuries are not only painful but also carry a risk of secondary infection. Risk factors for mask-associated pressure injuries include prolonged use of non-invasive ventilation, use of a non-rotating single mask, excessive mask tightness to prevent air leaks, and patient-related factors such as fragile skin or edema. It should also be noted that newer NIV interfaces, such as helmets or full-face masks, may distribute pressure more evenly and potentially reduce the incidence of facial ulcers.

Air Leaks: A certain amount of air leak is expected during NIV, as most circuits (especially single-limb systems) use an intentional leak port to remove exhaled CO_2 . However, excessive or uncontrolled leaks around the mask seal are clinically challenging. Large leaks can impair effective ventilation by reducing tidal volumes and contributing to hypercapnia, and trigger ventilator alarms, disrupting therapy. Air leaks directed toward the eyes can cause dryness, irritation or, in severe cases, corneal ulceration. Other consequences of significant leaks include patient discomfort (sensation of air blowing on the face or eyes), sleep disturbances, and patient-ventilator asynchrony.^{1,8,17,22,23,28,29,34} Clinically, persistent large leaks may prevent the ventilator from properly sensing breaths or delivering target pressures, leading to inadequate gas exchange.¹⁴ Although modern NIV devices incorporate leak compensation algorithms, these mechanisms have limitations. Tightening mask straps may reduce leaks but can exacerbate pressure injuries. Therefore, clinicians are advised to aim for minimal, controlled leaks rather than striving for complete leak elimination.

Gastric Insufflation and Aspiration: Another mechanical consequence of positive pressure is gastric insufflation, particularly if elevated mask pressures overcome lower esophageal sphincter tone or if the patient develops aerophagia. This can lead to abdominal distension, discomfort, and nausea. More concerning, in the event of vomiting, the unprotected airway during NIV increases the risk of aspiration, which can result in chemical pneumonitis or aspiration pneumonia.^{2,6,11,27} Although the exact incidence is unclear, aspiration events during NIV have been reported, especially in agitated, sedated, or delirious patients. The literature identifies active vomiting and impaired airway protection as absolute contraindications

to NIV.⁷ To mitigate aspiration risk, clinicians often minimize or avoid sedation, elevate the head of the bed, and consider gastric decompression with a nasogastric tube in patients undergoing prolonged NIV—although the tube itself may slightly increase nasal air leaks.

Patient-ventilator Asynchrony: Asynchrony refers to the mismatch between the patient's spontaneous respiratory effort and the ventilator's support in timing or delivery. During NIV, asynchrony can manifest as missed triggers, auto-triggering, double triggering, or early/late cycling. Significant asynchrony (typically defined as an asynchrony index >10%) is associated with reduced comfort, sleep fragmentation, and poor treatment tolerance in NIV patients.^{6,17,29} While asynchrony during invasive mechanical ventilation has been associated with adverse outcomes, such as prolonged ventilation and increased mortality, in NIV it is primarily linked to patient discomfort and reduced tolerance. Causes of asynchrony in NIV include excessive air leaks, inappropriate trigger sensitivity settings, and irregular breathing patterns.⁸ Asynchrony is particularly problematic during sleep, where it can lead to frequent arousals.

Patient-related (Tolerance and Psychological) Complications

Discomfort and Pain: Patients often report pain at pressure points (such as the nasal bridge and around the ears due to straps) and general discomfort from the sensation of forced airflow. Dryness of the oral and nasal passages, especially if humidification is inadequate, can lead to throat irritation and coughing. Some patients develop sinus or ear pain due to continuous positive pressure. This physical discomfort can make patients reluctant to wear the mask. In our review, many studies noted that a portion of patients (typically 10-15%) refused or removed NIV despite appropriate indications due to intolerable discomfort.^{3,7,18,24,30,32,34} Adjustments such as using softer masks, adding humidification, or allowing short mask-off breaks can help, although severe pain may necessitate alternative strategies or analgesics.⁸ An advantage of NIV compared to invasive ventilation is that patients can communicate their discomfort, allowing for timely interventions; however, unlike intubated patients, they may actively resist therapy.

Anxiety, Claustrophobia, and Psychological Distress: NIV can be frightening for some patients. The sensation of having a tight mask on their face may trigger claustrophobia or panic. Patients already experiencing respiratory distress are often anxious, and the added challenge of synchronizing with a machine can exacerbate this anxiety.^{9,16,25} Anxiety is common during NIV; patients may feel they have lost control of their breathing, which is distressing. Many clinicians have observed that some patients may not tolerate NIV at all due to claustrophobia, necessitating intubation or an alternative approach like high-flow nasal cannula when appropriate.^{4,7,9,10} Untreated anxiety can lead to tachypnea, ventilator struggles, worsened synchronization, and compromised efficacy. Therefore, addressing the patient's psychological comfort is a priority. Simple measures, such as explaining the procedure, having a family member or staff member stay with the patient, or choosing interfaces that cover less of the face (e.g., nasal masks instead of full-face masks), can help reduce panic.^{20,23}

Delirium and Sleep Disturbances: In a large prospective study of ICU patients on NIV, the incidence of delirium was approximately 18%.^{1,7,22} Outcomes were significantly worse in patients who developed delirium: NIV failure (requiring intubation) was much more common among delirious patients (37.8% vs. 21.0% in non-delirious patients), and ICU mortality was higher (33% vs. 14%).^{1,7,22}

Delirium may present as agitation (attempting to remove the mask, non-cooperation) or as quiet confusion (more difficult to detect and may rapidly deteriorate). Both hyperactive and hypoactive forms have been observed; some data suggest that patients with mixed or hypoactive delirium may remain on NIV longer, possibly because they tolerate the mask but they require prolonged ICU stays. Patients on NIV should be regularly assessed for delirium. Being on NIV while awake can cause significant difficulties in initiating or maintaining sleep due to noise, mask discomfort, and patient-ventilator asynchrony. When the ventilator fails to synchronize with the patient's effort, the resulting discomfort may wake the patient or prevent deep sleep. Sleep deprivation can worsen delirium, reduce NIV tolerance, and impair immunity over time, indirectly affecting recovery.^{9,25} Strategies include minimizing nighttime disturbances, adjusting ventilator settings for comfort (e.g., lower backup rate or modes like AVAPS or NAVA for more natural breathing), and cautious use of sleep aids (since sedatives can cause hypoventilation).¹⁶ In summary, insomnia and poor sleep quality are major patient-related complications of NIV, intricately linked with delirium and anxiety, potentially undermining NIV success.

CONCLUSION

In conclusion, NIV offers invaluable ventilatory support in modern critical care without the risks associated with intubation. This systematic review highlights that while NIV provides significant benefits, it can also lead to a series of adverse events that clinicians must recognize and manage. Complications associated with NIV can generally be categorized as physiological disturbances (including hypercapnia, hypoxemia, and hemodynamic effects), mechanical/interface issues (including pressure ulcers, air leaks, and ventilator asynchrony), and patient-centered problems (including anxiety, delirium, and sleep disturbances). Evidence suggests that although many of these complications are common, they are largely predictable and can often be prevented with proactive measures. Strategies such as careful patient selection, meticulous monitoring, protective interface measures, and selective sedation can significantly mitigate these risks. Patients successfully managed with NIV tend to have shorter ICU stays and, in many cases, better survival rates than those requiring intubation. However, NIV is not suitable for every patient, and its inappropriate use may lead to preventable morbidity. Successful NIV implementation relies on appropriate patient selection, exclusion of high-risk cases, and predefined intubation criteria. When guided by an experienced multidisciplinary team, this structured approach minimizes complications and optimizes clinical outcomes. In recent years, smart ventilator modes that can self-adjust in response to patient effort and artificial intelligence-based algorithms that

provide real-time asynchrony detection have shown promising results in improving patient-ventilator interaction and reducing complications. Such advanced technologies have significant potential, especially for the development of personalized NIV applications. Large randomized trials investigating structured NIV weaning and rest breaks or comparing different interface strategies (nasal, full-face, or helmet) would be valuable in guiding best practices. Moreover, considering current findings related to delirium, research focusing on early mobilization and delirium prevention specifically in NIV patients may improve outcomes.

Clinical Implications of NIV

- Patient selection: Carefully select patients based on established criteria to maximize NIV success and exclude those at high risk of failure.
- Monitoring: Implement meticulous monitoring to detect and manage physiological disturbances (e.g., hypercapnia, hypoxemia) early.
- Interface management: Use protective measures to prevent mechanical issues such as pressure ulcers and air leaks.
- Patient comfort: Address patient-centered issues like anxiety and delirium through selective sedation and early mobilization strategies.
- Infection control: Leverage NIV's lower risk of severe infections, particularly ventilator-associated pneumonia, compared to invasive ventilation.
- Structured framework: Apply a structured approach with clear intubation endpoints to minimize complications and optimize outcomes.
- Multidisciplinary team: Engage an experienced team of physicians, nurses, and respiratory therapists to ensure successful NIV implementation.

Ethics

Footnotes

Authorship Contributions

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

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Systematic Review



Acute and Chronic Effect of Resistance Training on Cardiac Autonomic Function in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review

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Abstract

This systematic review aimed to evaluate the acute and chronic effects of resistance training (RT) on cardiac autonomic function in patients with chronic obstructive pulmonary disease (COPD). Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, this review was registered in International Prospective Register of Systematic Reviews (CRD4202127541). A systematic search was conducted across PubMed, Web of Science, and Scopus using predefined search criteria. Studies were included if RT was the primary intervention and autonomic markers were assessed in COPD patients. Research involving other exercise types or significant comorbidities was excluded. From 5,159 records, five studies comprising 129 participants met the criteria. Interventions varied from single acute RT sessions to training programs lasting up to eight weeks. All studies measured heart rate variability (HRV), with most reporting significant improvements in time-domain measures and mixed results for frequency-domain parameters. Risk of bias was assessed with the Risk of Bias in Non-randomized Studies of Interventions tool, and evidence quality was appraised using Grading of Recommendations Assessment, Development, and Evaluation approach. Acute RT produced immediate but short-lived changes in autonomic function, while chronic RT consistently improved HRV time-domain indices. RT appears to beneficially influence cardiac autonomic regulation in COPD patients, as reflected by enhanced HRV parameters. These results support RT's role in addressing both muscular and cardiovascular health in this population. However, the limited number of studies, methodological differences, and serious risk of bias highlight the need for larger, well-designed randomized controlled trials to strengthen the evidence base.

KEYWORDS: Cardiac autonomic function, chronic obstructive pulmonary disease, heart rate variability, resistance training

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) affected 10.6% of the population in 2020 and is still a growing global health concern.¹ The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 report, defines COPD as, “a heterogeneous lung disease that causes persistent, frequently worsening airflow obstruction due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) leading to chronic respiratory symptoms (dyspnea, cough, expectoration, exacerbations).”² COPD not only affects the lungs but also causes systemic manifestations, such as musculoskeletal dysfunction, which diminish exercise capacity and quality of life, and autonomic dysregulation, which increases cardiovascular risks. These effects are largely driven by systemic inflammation, oxidative stress, and chronic hypoxia, which impair baroreflex sensitivity (BRS) and promote sympathetic overactivity. Autonomic dysfunction, marked by impaired heart rate variability (HRV), heart rate recovery (HRR), and BRS is a significant predictor of mortality.^{3,4}

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Autonomic regulation of the heart is mediated by the sympathetic and parasympathetic branches of the autonomic nervous system, which function involuntarily. Cardiac autonomic control is a key indicator of cardiovascular health.⁵ Impaired autonomic control is associated with increased cardiovascular and all-cause mortality, as demonstrated in prospective cohort studies.⁶ This can be clinically evaluated by measuring HRV, BRS, and post-exercise HRR using linear and non-linear methods.^{7,8} HRV, in particular, provides a non-invasive measure of autonomic function by analyzing the variability between successive R-R intervals on an electrocardiogram.⁹ A previous systematic review by Mohammed et al.¹⁰ reported a strong level of evidence for decreased HRV, reduced BRS, and increased muscle sympathetic nerve system (SNS) activity, suggesting potential sympathetic dominance in COPD.

COPD is managed effectively by assessment, reduction of risk factors, achieving stable conditions, and treatment of exacerbations. Among non-pharmacological interventions, pulmonary rehabilitation stands out as one of the most effective treatment options for COPD.^{3,11} For those patients with peripheral muscle weakness, the combination of resistance training (RT) and endurance training is recommended.¹² A meta-analysis by Bhati et al.¹³ comprising 21 studies across various clinical populations found that RT significantly improves cardiac autonomic control. However, this evidence is not COPD-specific, highlighting the need for a systematic review to evaluate RT's autonomic effects, specifically in COPD patients.¹³ Regarding COPD, a systematic review showed aerobic exercise training positively impacted most parameters of autonomic function, but a limited extent on the frequency domain parameters of autonomic function in COPD.¹⁴ RT effects on cardiac autonomic function can be categorized into acute and chronic outcomes. Immediate changes in autonomic regulation following a single session of RT are referred to as an acute effect, while chronic effects are the changes that evolve as a sustained training over weeks or months. Understanding these distinct effects is essential for optimizing exercise prescriptions in COPD rehabilitation programs, as improving autonomic function could decrease cardiovascular risk and improve overall health outcomes.

The available data in the literature suggest that RT may lead to improvement in autonomic functions in COPD patients. However, a deeper understanding awaits a synthesis of the literature. The focus of our review is to assess the effects of one component of pulmonary rehabilitation and physiotherapy, specifically RT, on the autonomic function indices in COPD patients. However, its specific impact on cardiac autonomic function is less well understood. Studies investigating the impact of RT on the autonomic markers and outcomes have not been consistent. This systematic review aims to evaluate the acute and chronic impacts of RT on cardiac autonomic function in COPD patients. By summarizing the findings from existing studies, this review seeks to clarify the role of RT in autonomic modulation and identify gaps in the literature that warrant further investigation.

MATERIAL AND METHODS

This review is conducted to evaluate the acute and chronic impacts of RT on cardiac autonomic function in individuals with COPD in accordance with the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁵ The protocol for this systematic review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number: CRD42021275418.

1. Inclusion and Exclusion Criteria

Inclusion criteria of the review: Only studies randomized controlled trials (RCTs), non-RCTs, or pre-post experimental studies that examine the impact of RT on autonomic function in COPD patients were considered. Study participants must have COPD as outlined by GOLD criteria (forced expiratory volume in 1 second <0.70). The review focused on studies that include RT as the primary intervention and that assess parameters related to autonomic nervous system function, such as HRV, including linear, non-linear, geometric, and fractal indices, HRR, and BRS. Additionally, studies must be published in English and report on findings that are directly relevant to RT in COPD.

Studies were excluded if they involved exercise interventions other than RT (e.g., yoga, Tai Chi, inspiratory muscle training, aerobic exercise, or multicomponent pulmonary rehabilitation) or if they reported COPD exacerbations during or after the intervention. Studies that were not original research, such as reviews, case reports, theses, conference papers, and pilot studies, and epidemiological study designs like cross-sectional, cohort, and case-control studies were excluded. Additionally, studies including participants with significant comorbid conditions that could confound the assessment of autonomic function, such as uncontrolled hypertension, heart failure, or diabetes, should be excluded unless these conditions were adequately controlled or accounted for in the analysis.

2. Search Strategy and Information Sources

To find clinical trials that assessed the RT impact on cardiac autonomic function in patients with COPD, a methodical literature search was carried out across several electronic databases, including PubMed, Web of Science, and Scopus. We did not include grey literature (such as conference abstracts and theses) or unpublished studies in our search. The search terms were carefully selected to encompass key concepts related to the intervention, outcomes, and population of interest. For the intervention, terms such as "resistance exercise," "resistance training," and "strength training" were used. Outcome variables were described using terms such as "cardiac autonomic control," "heart rate variability (HRV)," "baroreflex sensitivity (BRS)," "arterial baroreflex function," "heart rate recovery (HRR)," and "autonomic function." The population of interest was described using the terms "COPD" and "chronic obstructive pulmonary disease." Boolean operators "AND" and "OR" were employed to connect these terms, ensuring that the search yielded relevant and focused results. In addition to the database search, the reference lists of every primary article were manually examined, to find more relevant research.

This step was included to ensure the review captured all potentially important studies, including those not indexed in the primary databases. The exact search strategy used in PubMed was as follows: ("resistance exercise" OR "resistance training" OR "strength training") AND ("cardiac autonomic function" OR "heart rate variability" OR "heart rate recovery"

OR “baroreflex sensitivity” OR “arterial baroreflex function”) AND (“COPD” OR “chronic obstructive pulmonary disease”). Although this strategy was tailored for each database, it ensured that all relevant studies were captured across PubMed, Web of Science, and Scopus. In order to assess if an article met the inclusion criteria, it was initially screened by evaluating its titles and abstracts. Abstract screening is conducted as an initial step to evaluate compliance with inclusion criteria. Subsequently, articles which did not meet all of the criteria were excluded from the review.

3. Selection of Studies

The search strategy was applicable to each database, and the studies obtained were processed using the Mendeley Desktop reference manager, where results were combined and duplicates were removed. Author A.N. assessed the remaining papers’ titles and abstracts using the predetermined inclusion and exclusion criteria. At this point, studies that failed to meet the inclusion requirements were eliminated.

For articles that passed the title and abstract screening, the full texts were obtained for further evaluation. Full-text screening was conducted by author A.N. to ensure that the studies met all inclusion criteria. Any disagreements that arose during the screening were resolved through discussions with a second author (S.Z.). If consensus could not be reached, a third author (A.M.) was consulted to resolve the disagreement. Additionally, all full-text article references that were included in the review were further reviewed to ensure no relevant studies were missed (Figure 1).

4. Data Extraction

Comprehensive information was gathered for each included study using a standardized data extraction form. Extracted

data included study characteristics such as author, year of publication, study location, and study design, participants’ characteristics (e.g., sample size, age, body mass index, and spirometry measures), and detailed descriptions of the intervention (e.g., type of RT, intensity, frequency, volume, progression, number of sessions, and supervision). For studies that included a control group, the control treatment was also described. The key measures related to autonomic function were extracted, including various HRV indices such as linear, non-linear, geometric, and fractal measures. Finally, the main findings of each study regarding the effects of RT on autonomic function were documented (Table 1).

Disagreements arising from the data extraction methods in between reviewers were resolved either through consensus discussions or through the inclusion of a third author (A.M.) at certain stages. This process ensured that data extraction was thorough and accurate, providing a solid foundation for the subsequent analysis and synthesis of the included studies. To achieve a reliable synthesis of evidence, this review focused on all relevant research on the impact of RT on cardiac autonomic function in COPD patients, using a thorough search strategy.

5. Quality Assessment

The quality of the included studies was evaluated based on two established frameworks: the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for non-randomized studies and the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach for evaluating the overall quality of evidence. These tools provided a comprehensive evaluation of both study-level bias and the strength of evidence for the outcomes of interest.

5.1. Risk of Bias in Included Studies

The quality assessment of the non-randomized studies of interventions was performed using the ROBINS-I tool.¹⁶ This tool, which was developed specifically to assess the risk of bias in non-randomized research, examines studies in seven key areas: confounding bias, participant selection bias, intervention classification bias, deviations from intended interventions, missing data bias, outcome measurement bias, and reported result selection bias. Each domain has signalling questions intended to direct the evaluation of bias for every criterion that assist in forming a conclusion on the risk of bias for the study. Since the majority of studies included in this review were non-randomized or pre–post intervention trials, the use of ROBINS-I was considered appropriate as it provides a structured, domain-based evaluation that aligns with Cochrane standards for non-randomized evidence.

Two authors, A.N. and S.Z., assessed bias risk for each study individually across the seven domains, reconciling disagreements through discussion. A third author, A.M., was consulted to make the final decision in instances where consensus could not be reached. Each domain was given a judgment as low, moderate, serious, critical risk, or no information. Responses to signaling questions within the domains determine the level of risk categorization.¹⁶

Main Points

- Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, five studies (n = 129) were analyzed after screening 5,159 records. Heart rate variability (HRV) parameters (time and frequency domains) were assessed using Risk of Bias in Non-randomized Studies of Interventions and Grading of Recommendations, Assessment, Development, and Evaluations for bias and evidence quality.
- Resistance training (RT) improved time-domain HRV (e.g., standard deviation of normal to normal intervals, root mean square of successive differences) consistently, while the frequency-domain outcomes (low frequency/high frequency ratio) were mixed. Acute RT induced short-term autonomic changes, whereas chronic RT (up to 8 weeks) showed sustained benefits. Non-linear HRV measures improved (RR triangular index, triangular interpolation of the NN interval histogram, SD1/SD2).
- RT appears beneficial for cardiac autonomic regulation in chronic obstructive pulmonary disease, but larger randomized controlled trials are needed to confirm findings and optimize training protocols.
- Small sample sizes, methodological heterogeneity, and serious bias risk limit conclusions.

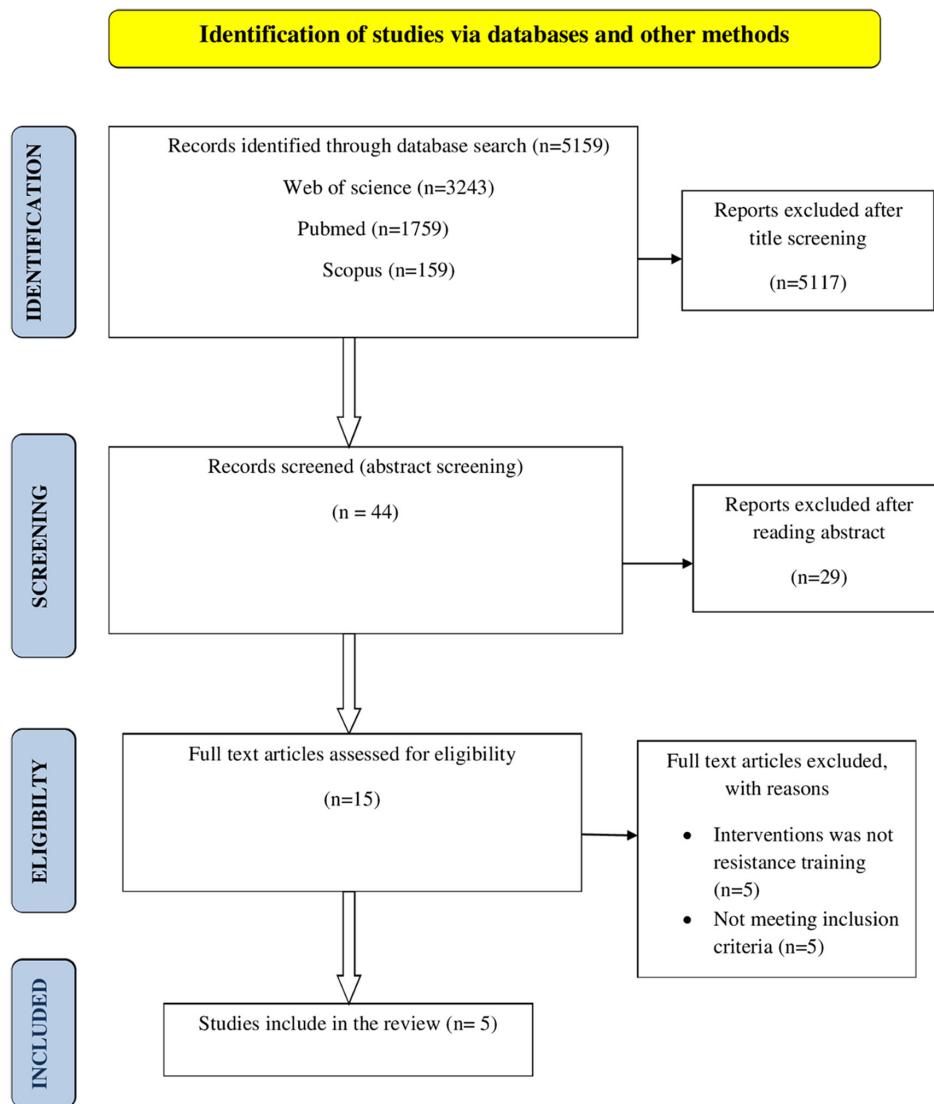


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart

The final risk of bias assessment for each study was based on the cumulative risk judgments across the seven domains. Every domain has to be rated at low risk for the study to be labeled a low risk of bias. Any single domain with a moderate level of concern limits the assessment to moderate concerns. More than one domain with serious concerns, or a single domain with high risk, is labeled as high risk of bias. By summarizing the risk of bias assessment results for each domain across the included research, a clear indication of the methodological limitations and potential biases in the review was then provided. For every domain, a summary of the included studies' risk of bias is provided (Figures 2, 3).

5.2. Quality of Evidence

The overall quality of the evidence supporting each outcome was evaluated using the GRADE approach.¹⁷ GRADE was applied to evaluate the strength of evidence related to the outcome, i.e., HRV. The GRADE framework assesses the quality of evidence in five primary areas: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

The risk of bias in the included studies was initially evaluated using the ROBINS-I tool. Studies with low risk across all domains positively influenced the overall GRADE rating. However, the presence of serious or critical bias in key studies resulted in a downgrade of the evidence quality. Inconsistency was assessed by examining heterogeneity in study outcomes, and any unexplained variations among results also led to a reduction in the quality of evidence. The domain of indirectness was assessed based on how closely the study populations, interventions, and outcomes aligned with the review's objectives. Imprecision was related to sample size and confidence intervals, with smaller studies or wide intervals reducing certainty about the effect estimates, which resulted in lower GRADE ratings. Publication bias was considered in terms of the likelihood that only studies with positive results were published, thus skewing the overall body of evidence.

The GRADE evaluation categorized the overall quality of evidence as high, moderate, low, or very poor. High-quality evidence suggests strong confidence in the findings, while lower levels indicate greater uncertainty and the need for further research. The combined use of ROBINS-I and GRADE ensured

Table 1. Characteristics and results of included studies on resistance exercises

Author/year/ study location	Study design	Sample size	Intervention Methods control and exercise supervised or unsupervised	Outcomes	Findings	
Ricci-Vitor et al., ¹⁸ 2013 Brazil	Single arm-pre post experimental trial	n = 20	24 morning sessions	Time domain,		
		Age=68	Frequency – 3/week	RMSSD	↑	
		BMI=27.18	Intensity – 60% of 1RM and progressed to 80%	SDNN	↑	
		FEV1=46.93	Volume – 3 sets of 10 repetitions	Frequency domain,		
		FVC=70.12	Type – global stretching, lower limb strength training (knee flexion and extension on leg extension); upper limb strength training (shoulder flexion and extension and elbow flexion on simple pulley)	LF	↑	
		FEV1/FVC=56	Time – 60 min	HF	↑	
Santos et al., ²¹ 2017 Brazil	Single arm-pre post experimental trial	n = 21	24 morning session	RRtri	↑	
		Age = 68.50	Frequency – 3/week	TINN (ms)	↑	
		BMI= 26.70	Intensity – 60% of 1RM and progressed to 80%	SD1 (ms)	↑	
		FEV1=47.54%	Volume – 3 sets of 10 repetitions	SD2 (ms)	↑	
		FVC=70.15%	Type – global stretching, lower limb strength training (knee flexion and extension on leg extension); upper limb strength training (shoulder flexion and extension and elbow flexion on simple pulley)	SD1/SD2	→	
		FEV1/FVC=55.30%	Time – 60 min			
Ricci-Vitor et al., ²⁰ 2018 Brazil	Non randomised control trial	n = 55	Frequency – 3 times a week	RMSSD (ms)	↑	
			Elastic tubing (n = 27)	Warm-up before, and cool-down at the end of the session.	SDNN (ms)	↑
			BMI=26.47	Resistance elastic tubing training for upper and lower limbs.	LF (ms ²)	↑
			FEV1=52.34	Two sets and volume of exercise was increased by one set every two sessions upto seven sets.	HF (ms ²)	↑
			FVC=70.17	2 minutes rest interval between each set.	LF/HF	↑
			FEV1/FVC=54.60		VLF (ms)	↑
					TINN	↑
					RRtri	↑
					SD1 (ms)	↑
		Conventional training (n = 28)			SD2 (ms)	↑
					SD1/SD2	↑
					RMSSD (ms)	↑
					SDNN (ms)	↑
					LF (ms ²)	↑
					HF (ms ²)	↑
					LF/HF	↓
					VLF (ms)	↑
					TINN	↑
	Conventional training: using weight lifting with pulley equipment. Three sets of 10 repetitions at 60-80% 1 RM were performed.			RRtri	↑	
				SD1 (ms)	↓	
				SD2 (ms)	↑	
				SD1/SD2	↑	

Table 1. Continued

Author/year/ study location	Study design	Sample size	Intervention Methods control and exercise supervised or unsupervised	Outcomes	Findings
Ricci-Vitor et al., ¹⁹ 2014 Brazil	Single arm- Longitudinal clinical trial	n = 21	24 morning sessions	RMSSD (ms)	↑
		Age=68.50	Frequency – 3/week	SDNN (ms)	↑
		BMI (kg/m ²)=26.70	Intensity – 60% of 1 RM and progressed to 80%	LF (ms ²)	↑
		FEV1 (%)=47.54	Volume – 3 sets of 10 repetitions	HF (ms ²)	↑
		FVC (%)=70.14	Time – 60 min	LF (nu)	→
		FEV1/FVC (%)=55.3	Type - global stretching (trunk, arm and leg muscles) at the beginning and end of the session, strength training for lower limbs (knee flexion and extension), strength training for the upper limbs (shoulder flexion, shoulder abduction and elbow flexion).	HF (nu)	→
Nicolino et al., ²² 2015 Brazil	Cross-over design	n = 12	Intensity – 60% and 90% RM	Time domain,	I 5 10 15
		Age=66	Time – 50 min	RMSSD	↑ ↑ ↑ ↑
		BMI=23	Type – weight training equipment by pulley	SDNN	↑ ↑ ↑ ↑
		FEV1=42	Volume – 3 series of 10 reps with 1 min rest intervals	Frequency domain,	
		FEV1/FVC=42		LF (ms)	↑ ↑ ↑ ↑
				LF (nu)	↓ ↑ ↓ ↑
				HF (ms)	↑ ↑ ↑ ↓
				HF (nu)	↑ ↓ ↑ ↑
				LF/HF	↑ ↑ ↓ ↓

N: sample size, BMI: body mass index, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, RM: repetitions maximum, RMSSD: root mean square of successive differences, SDNN: standard deviation of normal to normal intervals, LF: low frequency, HF: high frequency, VLF: very low frequency, TINN: triangular interpolation of the NN interval histogram, RRtri: RR triangular index, SD1: standard deviation of width of Poincaré plot, SD2: standard deviation of length of Poincaré plot, nu: normalized units, ms: milliseconds

(↑ = increase; ↓ = decrease; → = no change)

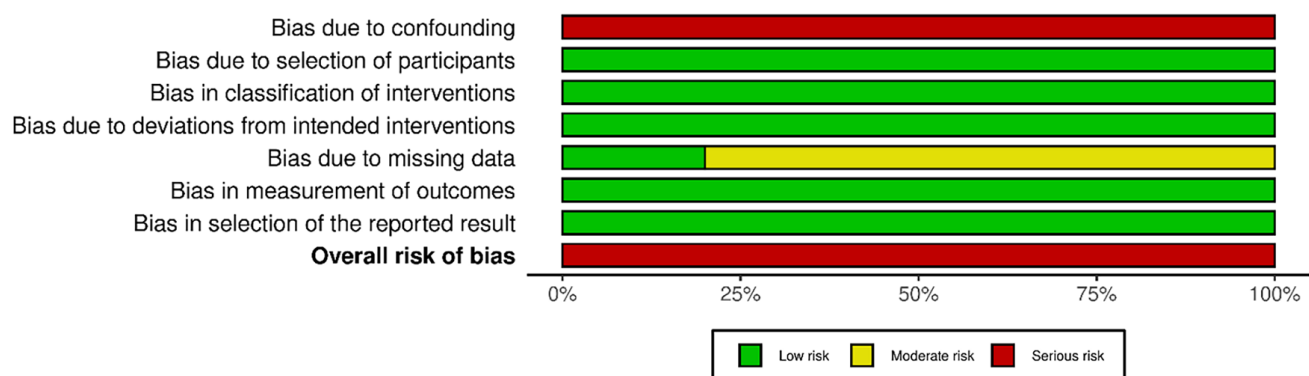


Figure 2. Summary of the included studies by Risk of Bias in Non-randomized Studies of Interventions

a thorough and transparent evaluation of both individual studies and the overall strength of the evidence in this review.

RESULTS

Figure 1 shows that a total of 5,159 studies were initially identified across various databases: 3,243 from Web of Science, 1,759 from PubMed, and 159 from Scopus. After

title screening, 5,117 articles were excluded, resulting in 44 studies being selected for abstract screening. Of these, full texts were obtained for 15 articles, which were then assessed based on predefined inclusion and exclusion criteria. During this process, five articles did not meet the inclusion criteria, and an additional five involved interventions that were not related to RT.

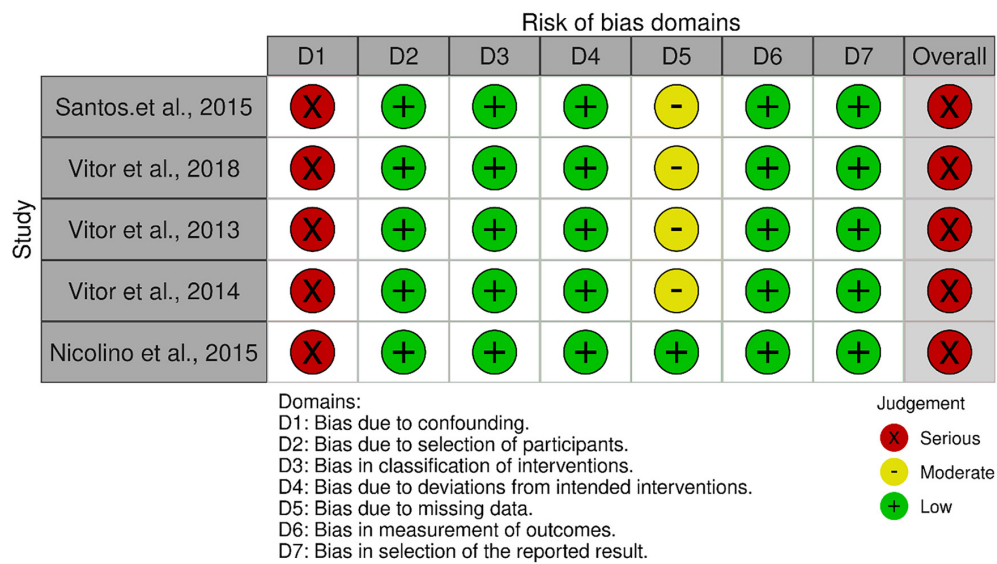


Figure 3. Summary of the included studies by Risk of Bias in Non-randomized Studies of Interventions

1. Participants

Five studies¹⁸⁻²² consisted of 129 COPD patients with each study's sample size varying between 12 and 55. Variation in sample sizes (12-55 participants) among included studies likely contributed to heterogeneity in the findings. The mean age of the group was 68.50 years, with interventions ranging from one session (acute) to eight weeks of RT (chronic). Among the five included studies, four 18-21 evaluated chronic RT effects, while one²² assessed acute effects following a single RT session. All studies solely assess cardiac autonomic function by using HRV. HRV was assessed using linear analysis (time and frequency domains) in three studies,^{18,19,22} while one study,²¹ used only non-linear analysis. Another study²⁰ employed both linear and non-linear methods for HRV analysis.

2. Exercise Training Interventions

Each study utilized dynamic RT as an intervention. The majority of the studies used a pulley system, while one study used elastic tubing²⁰ for RT. Exercise intensity was set at moderate to high intensity and was based on repetition maximum (RM) in the majority of the trials,^{18,19,21,22} except in one study that was based on maximum voluntary contraction.²⁰ The duration of the interventions varied, with some studies implementing sessions three times per week lasting 50-60 minutes, ranging from a single bout of RT (acute), to an extended program lasting 8 weeks (chronic).

3. Outcome Measures

All studies included in the analysis evaluated and reported HRV as an indicator of cardiac autonomic regulation. The majority of studies reported linear HRV indices,^{18-20,22} while one study also incorporated non-linear measures.²⁰ Another study specifically focused on non-linear HRV assessment using geometric indices, without including linear measures.²¹ Additionally, one study analyzed the fractal characteristics of heartbeats intervals through detrended fluctuation analysis (DFA), reporting Alpha1, Alpha2, Alpha1/Alpha2 ratios, and overall DFA indices.²⁰ All studies employed short-term HRV recordings for their

assessments.¹⁸⁻²² HRV was measured under resting conditions in all studies,¹⁸⁻²² with one study also evaluating post-exercise HRV at 5, 10, and 15 minutes after exercise.²²

4. Heart Rate Variability

Following RT, all studies showed improved adaptation in cardiac autonomic regulation. Linear measures of HRV - standard deviation of N-N intervals (SDNN), low frequency (LF) ms², and high frequency (HF) ms² were significantly increased after RT in the majority of the study.¹⁸⁻²⁰ One study reported geometric indices of HRV observed significant increased in triangular index of R-R interval histogram (RRtri), triangular interpolation of N-N interval histogram (TINN), standard deviation 1 (SD1) which measures short-term HRV derived from Poincaré plot & SD2 which measures long-term HRV also from Poincaré plot and SD1/SD2 ratio after training.²¹ Following an acute session of RT, SDNN showed a significant increase at all recovery time points, whereas root mean square of successive differences between N-N intervals (RMSSD) remained unchanged from baseline at both 60% and 90% of 1RM. In the frequency domain, there was a significant rise in LF (ms²) and HF (ms²), while LF (nu), HF (nu), and the LF/HF ratio showed no significant changes during any recovery time point for both intensity levels.

4.1. Time Domain Parameter

SDNN: The data from two studies revealed significant improvement in SDNN after the exercise program.^{18,19} However, one study showed no statistically significant difference between the effect of elastic tubing and conventional training.²⁰ The acute effect of RT did not show significant differences between the protocols at all time points analyzed ($P > 0.05$). Regardless, SDNN was significantly higher at all timepoints after RT relative to baseline at both 60% and 90% of 1 RM.²²

RMSSD: One study reported a significant increase in RMSSD following the exercise program when comparing pre- and post-intervention values,¹⁹ while another study observed an increase in RMSSD that did not reach statistical significance.¹⁸

Additionally, a separate study found no significant differences between elastic tubing and conventional training protocols. However, intra-group analysis revealed a statistically significant increase in RMSSD.²⁰ Regarding the acute effects of RT, RMSSD showed no significant changes across any of the time points analyzed.

4.2. Frequency Domain Parameters

LF ms²: Only one study shows LF significantly increased after the exercise program.¹⁸ The acute effect of RT shows that the LF (ms²) index is greater during all recovery times compared to rest, for both 60% and 90% of 1RM protocols.²² Other studies show no significant differences after the exercise program.^{19,20}

HF ms²: One study shows HF significantly increases after the exercise program.¹⁸ The acute effect of RT shows that the HF ms² index is higher during all recovery periods compared to rest in both the 60% and 90% of 1RM protocols.²² However, one study shows no significant differences before and after the exercise program.¹⁹ One study shows no statistically significant differences between the effect of elastic tubing and conventional training; however, intra-group differences showed a significant increase in HF.²⁰

LF/HF: The data from two studies revealed no statistically differences when compared before and after exercise and training.^{20,22} The acute effect of RT showed LF/HF decrease immediately, 10 and 15 minutes after the exercise session, but improves after 5 minutes.²² One study revealed LF/HF increases after elastic tubing training and decreases after conventional training.²

DISCUSSION

The objective of this systematic review is to explore the most recent evidence on the influence of RT on cardiac autonomic function in patients with COPD as measured by HRV. Although RT shows promise as a non-pharmacological intervention for autonomic regulation in COPD, the current evidence is based on a small number of studies with methodological variability. The inconsistencies in findings, particularly for frequency-domain HRV parameters, suggest the need for cautious interpretation.

An efficient non-invasive way to assess autonomic function is to use HRV. The overall activity of autonomic nerve function is represented by the time domain parameter SDNN. The frequency domain parameter LF, is mainly mediated by sympathetic activity. Parasympathetic activity is represented by the RMSSD and pNN50.²³ Impaired cardiac autonomic control has been shown in prospective longitudinal cohort studies to be a strong predictor of all-cause and cardiovascular disease mortality, and it can be diagnosed clinically by HRV.^{13,24} Previous research showed that RT significantly improved cardiac autonomic regulation in clinical populations.¹³ Our research revealed that the frequency domain parameter exhibits inconsistent results, while the time domain parameters SDNN and RMSSD are significantly improved. These findings suggest that RT can enhance parasympathetic activity and sympatho-vagal balance in patients with COPD. The findings align with prior systematic review by Bhati et al.¹³ which demonstrated a

significant improvement in cardiac autonomic control across diverse populations with various health conditions following RT. The meta-analysis concluded that RT enhances vagal tone, reflected in improved HRV indices. Our findings align with a previous review that reported enhanced cardiac autonomic control following RT in various populations, and demonstrate similar improvements in parasympathetic activity among COPD patients.¹³ Notably, one study using non-linear HRV analysis (geometric and fractal measures) also observed significant improvements, reinforcing the beneficial effects of RT on autonomic function.²¹ Contrary to Camillo et al.²⁵ suggested that aerobic exercise is superior for autonomic modulation, our results indicate that RT also plays a significant role, especially when considering non-linear HRV indices, which may capture autonomic dysfunction more sensitively in COPD.²⁵

Acute Effects of RT: Acute bouts of RT were associated with transient improvements in HRV indices, indicating a short-term parasympathetic rebound post-exercise. For instance, studies reported significant increases in time-domain parameters such as SDNN and RMSSD immediately following RT sessions.²² These findings suggest that even a single session of RT can elicit favorable autonomic responses, potentially reducing cardiovascular stress in the short term.

Chronic Effects of RT: Chronic RT programs, typically lasting 8 weeks, demonstrated more pronounced and sustained improvements in autonomic regulation. Most studies reported significant improvement in time-domain HRV indices (e.g., SDNN, RMSSD) and some frequency-domain parameters (e.g., LF, HF).¹⁸⁻²⁰ These long-term adaptations suggest that regular RT can enhance parasympathetic activity and improve sympatho-vagal balance, which is crucial for reducing cardiovascular risk in COPD patients.

The improvement in HRV following RT may be attributed to several physiological mechanisms. RT improves BRS, which is often impaired in COPD due to chronic inflammation and oxidative stress.²¹ Increased muscle strength and endurance reduce exertional sympathetic overactivity, allowing for better parasympathetic reactivation.²⁰ COPD patients often exhibit elevated SNS activity due to chronic hypoxia and systemic inflammation.²⁶ RT may attenuate SNS hyperactivity by improving cardiovascular efficiency and reducing resting heart rate.¹⁸ RT enhances stroke volume and cardiac output, reducing the heart's workload at rest, which may contribute to better HRV.²² Increased nitric oxide bioavailability from endothelial adaptations post-RT may also improve autonomic balance.²¹ Chronic inflammation in COPD contributes to autonomic dysfunction.²⁶ RT has been shown to reduce pro-inflammatory cytokines, which may indirectly improve HRV.²⁰

Despite the overall positive findings, significant heterogeneity was noted in the assessment methods and exercise protocols across studies. For example, while most studies used linear HRV indices, non-linear measures were less frequently reported but provided additional insights into autonomic modulation complexity. Variability in exercise intensity, volume, and type (e.g., pulley systems vs. elastic tubing) might have influenced outcomes, particularly in frequency-domain parameters like LF/HF ratio. This variability underscores the need for

standardized protocols in future research to ensure consistent and comparable results.²¹

However, variability in methods and outcomes among studies necessitates caution in generalization. For instance, one study²⁰ showed significant within-group improvements, while others reported mixed results for specific HRV indices, particularly in frequency-domain parameters like LF/HF ratio. Furthermore, differences in RT intensity, volume, and type might have influenced outcomes. For instance, frequency-domain parameters such as LF/HF ratios showed mixed results across studies, as seen in Ricci-Vitor et al.²⁰ and Nicolino et al.²² This variability might stem from differences in exercise intensity, methodology, or patient heterogeneity. Consistent with earlier reviews Mohammed et al.¹⁴ also noted such inconsistencies in aerobic training studies, suggesting that autonomic responses can vary significantly based on the type and context of exercise.

The majority of the included studies were small-scale, non-randomised or single-arm trials with limited sample sizes (ranging from 12 to 55 participants), which weakens the strength of the evidence. The exclusion of unpublished studies may have introduced potential bias. Across multiple domains, the risk of bias was generally moderate to high, mainly due to confounding variables and inconsistencies in intervention protocols. Although HRV was frequently measured, other indicators of autonomic function such as HRR and BRS were not evaluated. Incorporating these additional markers in future studies could lead to a more comprehensive understanding of RT effects on cardiac autonomic regulation in COPD. The GRADE assessment also reflected moderate to low confidence in the overall evidence quality. While the ROBINS-I tool was used for risk of bias assessment, its applicability is limited for single-arm pre-post studies, which comprised a significant portion of the included research; in such cases, alternative tools like the NIH Quality Assessment Tool may provide more appropriate evaluation. To address these limitations, upcoming research should focus on larger, well-designed RCTs with standardized methods. Furthermore, assessing the impact of RT on a broader range of autonomic outcomes and across more diverse COPD populations would help strengthen its potential clinical relevance.

CONCLUSION

RT appears to positively modulate cardiac autonomic function in COPD patients, with both acute and chronic benefits evident in improved HRV indices. While this review supports the potential of RT to improve cardiac autonomic function in COPD, particularly in time-domain HRV measures, limitations such as small sample sizes, heterogeneity of protocols, and a high risk of bias underscore the need for more rigorous trials. These trials are necessary before widespread clinical adoption. Future investigations should aim to address current gaps, standardize protocols, and validate findings in diverse and larger cohorts to integrate RT as a core component of COPD rehabilitation programs.

Ethics

Footnotes

Authorship Contributions

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

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

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Review



Assessment of Worldwide Bronchoscopy Practices and Training Methods: A WABIP Survey

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Abstract

The practice of bronchoscopy is not standardized. Regional and global variations in bronchoscopy practice are exacerbated by the paucity of recommendations regarding technical aspects in major bronchoscopy guidelines. The aim of this survey was to examine the prevalent practices, adherence to guidelines, and training requirements of bronchoscopy in different countries. The Membership Committee and the Education Committee of the World Association for Bronchology and Interventional Pulmonology designed an online survey that was sent to 1,300 consultant physicians in adult respiratory medicine from 64 countries across five continents. The questionnaire included questions regarding bronchoscopy practice. We obtained 879 responses (67.0%). In 81.2% of cases, the practice occurred in cities with over 200,000 inhabitants. The median number of years in practice was 14 (range 1-50). Only 11% of respondents perform routine bronchoscopy without anesthesia. Spirometry was always performed before bronchoscopy by only 106 physicians (12.4%), blood coagulation tests were always required by 533 (60.6%) and an electrocardiography was always required by 339 (38.5%). The main indications for performing a bronchoscopy were suspicion of cancer (78.6%), suspicion of non tuberculosis (TB) infection (10.6%), and suspicion of TB (6.7%). 39.3% of responders received formal training for at least 6 months with a formal certificate. Despite the wide availability of bronchoscopy guidelines, the way to do them in terms of preparation, anesthesia, technical aspects, etc., varies greatly in each country and physician.

KEYWORDS: Bronchoscopy, interventional pulmonology, global survey

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INTRODUCTION

The practice of bronchoscopy is not standardized. Regional and global variations in bronchoscopy practice are exacerbated by the paucity of recommendations regarding technical aspects of bronchoscopy in major guidelines. Therefore, the practice of bronchoscopy varies based on the physician's preferences and the availability of resources. The practice relies heavily on the transmission of skills from preceptor to trainee because structured teaching or learning methodologies are not routinely implemented. The diagnostic and therapeutic utility of bronchoscopy for pulmonologists has been substantially improved by the incorporation of cutting-edge techniques. To date, a handful of investigations on the use of new technologies have revealed the heterogeneity of individual operator procedures,^{1,2} and the frequent disregard for guidelines.^{3,4}

The World Association for Bronchology and Interventional Pulmonology (WABIP) is a non-profit organization consisting of over 10,500 medical professionals representing over 60 regional and national societies. Not all countries have their own society; therefore, in some cases, multiple countries share a single society. As the primary objective of WABIP is to meet the educational demands of its member societies, the aim of this survey was to examine the prevalent practices, adherence to guidelines, and training requirements of flexible and interventional bronchoscopy in different countries.

This was a worldwide retrospective survey of bronchoscopic procedures. The Membership Committee and the Education Committee of the WABIP conceptualized and designed the online survey. The survey included queries

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that were written in English. No names or other personal information, including email addresses, was requested from respondents. The questionnaire included general information, patient preparation and monitoring, sedation, and topical anesthesia, procedural/technical aspects, and bronchoscope disinfection/staff protection. The questions required either descriptive or multiple-choice responses. Some questions asked about the availability of different bronchoscopic technologies. The authors conducted a trial run in which they responded to the survey themselves and identified areas for improvement. A final section inquiring into received training and evaluation of training requirements was included. Neither second questionnaires nor reminders were sent. Comparisons were made using Student's *t*-test or Fisher's exact test, where appropriate.

WABIP is a federation of societies, each of which is represented by a Regent as its local society's official representative (potentially more than one for the same country). Each of the sixty-five active Regents was instructed to disseminate the survey to a minimum of five or ten and a maximum of ten or thirty members of their society, based on the number of active members in that society, in order to ensure broad participation from various countries. There were 1,300 surveys available for distribution.

The type of income of each country is classified according to the strata defined by the World Bank Group: low, lower-middle,

upper-middle, and high income. For this purpose, they use gross national income per capita data in U.S. dollars, converted from local currency using the World Bank Atlas method, which is applied to smooth exchange rate fluctuations.

A few months after the survey distribution began, the outbreak of Coronavirus disease-2019 (COVID-19) significantly changed the practice of bronchoscopy. Participants were instructed to respond regarding their resources and working conditions before the modifications imposed by the pandemic. The survey was run from November 2019 to March 2021. A total of 1,300 surveys were distributed by Regents after excluding early respondents from China whose working conditions were affected by the COVID-19 outbreak.

We obtained 879 responses (67.0%). Respondents (73.6% male, age 56.2, ranging 34-70 years old) represented 64 countries across 5 continents (Table 1). 89.4% of respondents identified as pulmonologists, 4.9% as thoracic surgeons, and 1% as interventional pulmonologists. The majority of them perform bronchoscopy exclusively (55.3%) or partially (24.7%) in the public sector, referring to government-funded healthcare facilities, as opposed to privately funded institutions. In 81.2% of cases, their practice occurred in cities with over 200,000 inhabitants. The median number of years in practice was 14 (range 1-50), with 328 (37.3%) having 20 or more years and 364 (41.4%) having 10 or fewer years. Four hundred and forty-three physicians (50.3%) had performed 200 or more bronchoscopies in the previous year, compared to 278 physicians (31.6%) who reported that they did not manage to perform as many procedures.

The most prevalent method ($n = 729$, 82.9%) for nasal lignocaine administration was lignocaine jelly. Five hundred and nine physicians (57.9%) utilized nebulized lidocaine for topical anesthesia either routinely or intermittently. The concentration of lignocaine used most frequently (534, or 60.9%) for nebulization was 2%. A substantial number ($n = 744$, 84.7%) used 10% lignocaine spray for pharyngeal anaesthesia either routinely or occasionally.

Only 11% of respondents perform routine bronchoscopy without anaesthesia. For sedation, only 2.7% of physicians used opiates alone, 14.3% used benzodiazepines alone, and 44.3% used a combination of benzodiazepines and opiates. 51% of respondents routinely administered propofol, and 7% administered fentanyl. 13.3% of physicians preferred general anaesthesia, while 12.5% completed more than 50% of procedures without sedation. Only 1% of bronchoscopists deferred to the anesthesiologist for sedation protocol decisions. The majority of respondents added that they chose the mode

Main Points

- The practice of bronchoscopy is not standardized worldwide, with significant regional variations influenced by physician preferences, resource availability, and the lack of specific technical recommendations in major guidelines.
- Most bronchoscopists prefer to perform procedures with intravenous sedation, often using a combination of benzodiazepines and opiates. Despite limited supporting evidence, routine pre-bronchoscopy tests such as coagulation studies and electrocardiography are frequently requested.
- Advanced bronchoscopic technologies, such as EBUS and cryobiopsy, are available in many centers regardless of a country's income level, yet access remains uneven. Formal bronchoscopy training is inconsistent, with a significant proportion of practitioners learning through mentorship or self-training rather than structured certification programs.
- While most bronchoscopists follow protective measures, adherence varies. For example, fewer than half of the staff work in bronchoscopy suites with high-efficiency particulate air filters for tuberculosis cases, and close-fitting eyewear is used less consistently than gowns.
- The presence of specialized support staff, the role of anesthesiologists in sedation, and the availability of equipment vary significantly across institutions and economic settings. High-income countries are more likely to have structured training programs and anesthesia-administered sedation, whereas lower-income settings often rely on bronchoscopist-led sedation and informal training methods.

Table 1. Regional distribution of participants

North America	120	14%
South America	149	17%
Europe	269	31%
Asia	279	32%
Oceania	39	4%
Africa	23	3%

of sedation based on the type of procedure. Anesthesiologists administered sedation in 37.1% of cases, bronchoscopists in 34.5%, and nurses in 19% of cases. In countries with high income, anesthesiologists were in charge of sedation significantly less frequently (24.3%, $P < 0.001$) compared to countries with middle income (41.5%) or upper middle income (53.8%).

Spirometry was always performed before bronchoscopy only by 106 physicians (12.4%), blood coagulation tests were always required by 533 (60.6%) and an electrocardiography (ECG) was always required by 339 (38.5%) and frequently by 167 (19%).

The support measures implemented during the procedure are outlined in Table 2. The vast majority of bronchoscopists routinely give oxygen supplementation during bronchoscopy; 86% maintain intravenous (IV) access throughout the procedure. All respondents reported having resuscitation equipment immediately available in the event of complications. Details of protective equipment worn by physicians are shown in Table 3. Nearly half of the responders ($n = 413$, 46.9%) have access to high-efficiency particulate air (HEPA) filters in the bronchoscopy suite during procedures with a suspected or known diagnosis of tuberculosis, but 254 (28.9%) never have access to that protection. Even when 73.8% of responders always wore gowns, only 30% routinely wore close-fitting eyeglasses. Seven hundred ninety-seven physicians, (90.7%) had received vaccination against hepatitis.

The main indications for performing a bronchoscopy were suspicion of cancer, ($n = 691$, 78.6%), non-tuberculous infection ($n = 94$, 10.6%), tuberculosis ($n = 59$, 6.7%).

All participants said that their bronchoscopy department offered bronchial biopsies, with 819 (93.1%) offering conventional transbronchial biopsies and 447 (50.8%) offering transbronchial

needle aspiration. A total of 388 respondents, accounting for 44.1% of the sample, reported working in a unit where EBUS was utilised. Laser utilization was reported by 200 respondents, representing 22.7% of the sample, while electrocautery was used by 319 respondents, accounting for 36.2%. Three hundred thirty-nine responders (38.5%) informed that airway stents were placed at their unit, and 268 (30.4%) included cryotherapy in the practice of their center. Three hundred and twenty-six endoscopists (37.1%) had access to cryobiopsy, and 188 (21.3%) also placed valves or coils as part of their clinical practice.

Table 4 shows that physicians in countries with a high or upper middle income were overrepresented in this sample. In countries with a lower middle income, cryobiopsy was significantly less available ($P < 0.05$). Intriguingly, the proportion of respondents working in centres with access to other more costly technologies was independent of the average national income (Table 5).

Only 37 respondents (4.2%) reported not having access to a videobronchoscope, independent of the general income of their country. Less than half of the respondents used fluoroscopy when performing a transbronchial biopsy, in all cases ($n = 231$, 26.2%) or frequently ($n = 127$, 14.4%). Only 3 respondents reported performing the procedures without any help from ancillary personnel; the remaining had the support of 1-4 nurses or technicians. The average number of ancillary personnel was 2.09 ± 0.7 with no significant difference between public and private facilities. Even when 347 responders (39.3%) received a formal training for at least 6 months with a formal certificate of training (post residency courses, masters, diplomas, fellowships, etc.), 337 bronchoscopists (37.2%) did not received any sort of training and learned by working with a mentor, practicing during pulmonary residence, or simply self-training. Among the 347 physicians who had received formal training of at

Table 2. Frequency of use of monitoring and support during bronchoscopy

	Always	Frequently	Occasionally	Never
Pulse oximetry	867 (98.5%)	10 (1.1%)	3 (0.3%)	0 (0%)
Use of supplemental oxygen	765 (86.9%)	70 (8%)	45 (5.1%)	0 (0%)
ECG monitoring	610 (69.3)	117 (13.3%)	130 (14.8%)	23 (2.6%)
Venous cannula	758 (86.1%)	60 (6.8%)	37 (4.2%)	25 (2.8%)
Blood pressure monitoring	730 (83%)	78 (8.9%)	64 (7.3%)	8 (0.9%)
Wearing gloves	872 (99.1%)	5 (0.6%)	3 (0.3%)	0 (0%)
Wearing face masks	737 (83.2%)	60 (6.8%)	65 (7.4%)	18 (2%)
Wearing close fitting eye glasses	269 (30%)	174 (19.8%)	341 (38.8%)	96 (10.9%)

ECG: electrocardiography

Table 3. Frequency of adherence to safety practices measures before or after the procedure

	Always	Frequently	Occasionally	Never
Minimum 20 min of disinfection	801 (91%)	49 (5.6%)	8 (0.9%)	22 (2.5%)
Minimum of 60 min of disinfection when suspicion of tuberculosis	628 (71.4%)	118 (13.4%)	81 (9.2%)	53 (6%)
Rinsing with sterile or filtered water	689 (77.2%)	80 (9.1%)	59 (6.7%)	53 (6%)

least 6 months with certification, 173 (49.8%) practiced in a high-income country, 127 (36.5%) in an upper-middle-income country, and 45 (13%) in a lower-middle-income country. Only 45 physicians (28%) practicing in lower-middle-income countries had a formal certification of training vs 174 (40.6%) in high-income countries ($P \leq 0.05$) (Table 6).

DISCUSSION

This survey is a comprehensive representation of bronchoscopy practices around the world. Despite the diverse origins of the participants (65 countries from 6 regions on 5 continents), there are remarkable similarities in certain aspects of the practice.

Table 4. Type of training received by the participants

	n	%
Formal training for at least 6 months with a formal certificate of training (post residency courses, masters, diplomas, fellowships, etc.)	347	39.3
Formal training for at least 6 months without a formal certificate of training (post residency courses, masters, diplomas, fellowships, etc.)	140	15.9
Formal training shorter than 6 months	54	6.1
Informal training (practice with an experienced bronchoscopist)	157	17.8
Practice during residence	160	18.2
Self-training	20	2.3

Table 5. Frequency of availability of different procedures according to the general income of the country of the responders

Practice	High income (n = 428)	Upper middle income (n = 290)	Lower middle income (n = 159)
Conventional TBB	412 (96%)	290 (100%)	129 (81%)
TBNA	183 (43%)	165 (57%)	98 (62%)
EBUS	140 (33%)	157 (54%)	90 (57%)
Laser	37 (9%)	63 (22%)	50 (31%)
Electrocautery	109 (25%)	125 (43%)	84 (53%)
Stents placement	128 (30%)	129 (40%)	81 (51%)
Cryotherapy	102 (24%)	103 (36%)	63 (40%)
Valves or coils placement	53 (12%)	90 (31%)	35 (22%)
Cryobiopsy	211 (49%)	89 (31%)	26 (16%)

TBB: transbronchial needle aspiration, EBUS: endobronchial ultrasound

Table 6. Distribution of national income of the country of the responders (World Bank)

Income	n	%
High	428	48.6%
Upper middle	290	32.9%
Lower middle	159	19.1%
Lower	1	0.1%

Greater adherence to safety practices recommendations than previously reported, the frequent requirement of pre-bronchoscopy tests without solid evidence of their utility, the widespread use of sedation, and the greater availability of complex technology compared to the formal training required to manage it appeared to be fairly consistent across countries.

Despite the lack of substantial evidence, certain practices continue to be performed routinely. In patients without coagulopathy, the risk of haemorrhage is <1%, whereas it can reach 7.5% in those with an abnormal coagulation profile.⁵ Several retrospective studies in patients undergoing transbronchial lung biopsy (TBLB) showed that routine coagulation testing could not predict the risk of post-TBLB bleeding.⁶

The majority of guidelines⁷⁻⁹ do not recommend routinely conducting coagulation studies, platelet counts, and haemoglobin levels prior to bronchoscopy. Instead, these tests are reserved for patients with clinical risk factors for bleeding, such as ongoing anticoagulation, bleeding diathesis, and chronic liver and kidney disease. Nonetheless, 60.6% of respondents always request routine blood tests that include coagulation.

There is no consensus on a specific minimum age for patients without specific cardiovascular risk factors, and the majority of recommendations suggest that ECG may be indicated only for patients with known cardiovascular risk factors.^{10,11} Despite this, an ECG is always requested 40% of bronchoscopies. The widespread practice of ordering ECGs might be a result of the comorbidities of many patients who are candidates for it, driven by institutional protocols, defensive medicine, or routine habits, rather than individual anesthesiologists' decisions. The indication for routine spirometry was only 12%, which is significantly lower than the prevalence among Australian-New Zealand bronchoscopists,¹² but more comparable to the practice in Italy.¹³ Even when it has been cited as a limitation due to the high prevalence of chronic obstructive pulmonary disease in bronchoscopy candidates, there is no evidence that sedation increases the rate of complications.^{14,15}

According to the guidelines by the American Institute of Health Architects and the Centers for Disease Control and Prevention in 2003, it is recommended that procedures that induce coughing, such as bronchoscopy, be conducted in rooms equipped with HEPA filters. Additionally, these guidelines suggest that the air should be directly exhausted to the external environment, in accordance with the guidelines and documents.¹⁶⁻¹⁸ Several sources suggest that in cases where the recirculation of air cannot be avoided, the expulsion of exhaust air outdoors should be directed away from patient care areas. Additionally, the utilization of HEPA filters is deemed necessary. Nevertheless, fewer than half of the respondents reported working in a room equipped with a HEPA filter, even when conducting bronchoscopy procedures on patients suspected, or confirmed to have tuberculosis.

The majority of physicians adhere to the guidelines for protective measures. However, it is noteworthy that the use of gowns was more consistently observed compared to the use of close-fitting eyeglasses, which were only regularly worn

by 30% of the participants. The survey specifically requested responses regarding practices before the onset of the COVID-19 pandemic, and it is evident that these practices have inevitably undergone changes both during and in the aftermath of the pandemic.

A considerable proportion of respondents reported being employed in facilities that possess extensive access to state-of-the-art technology, regardless of the welfare status of the nation. The composition of physicians in a global association is likely to exhibit bias, since it attracts individuals who are inclined towards engaging in the practice of contemporary and costlier advanced¹⁹ while a survey in Cairo showed that several bronchoscopists performed electrocautery, cryotherapy, argon plasma coagulation, endobronchial ultrasound, laser therapy, auto-fluorescence bronchoscopy, and balloon dilatation.²⁰ It is noteworthy that numerous facilities, despite possessing costly equipment like lasers, valves, or coils, lack access to a more affordable and highly cost-effective technology like cryobiopsy. Interestingly, the accessibility of cryobiopsy is contingent upon the income level of the country.

In our research, a majority of bronchoscopists indicated a preference for conducting the procedure with the aid of IV sedation, whereas 12% expressed a preference for utilising solely local anaesthesia. The findings of the Australia and New Zealand survey, indicate a lack of major divergence from the results mentioned, since 94% of respondents reported providing IV sedation, assuming there were no contraindications. Similarly, the UK survey revealed that only 10% did not offer any form of sedative regimen. A survey conducted in India found that the prevailing practice (59.4%) for bronchoscopy involved solely the use of topical anaesthesia, without any accompanying conscious sedation. Despite several concerns regarding the safety of sedation and the potential for severe consequences, multiple studies have demonstrated the following: a notable enhancement in patient tolerance through the utilization of IV sedation;^{20,21} a reduced necessity for pausing or cancelling the procedure; and the absence of any further difficulties, except for a more profound though reversible decline in oxygen saturation.¹⁵ Additionally, the Putinati et al.²¹ study exhibited a noteworthy decrease in the frequency of abandoned procedures resulting from patient resistance when sedation was administered. A study that conducted a meta-analysis of nine studies to assess the safety and effectiveness of moderate sedation in the context of bronchoscopy revealed that participants who received sedation were more inclined to undergo the procedure again, and the duration of the procedure was shorter compared to those who did not receive sedation. Additionally, the occurrence of hypoxic episodes was found to be similar in both groups.²²

The requirement for sedation is expected to exhibit variability across patients, possibly influenced by the level of explanation and reassurance provided by healthcare professionals.

The study participants predominantly employ a dual-drug sedation protocol, irrespective of the delivering personnel (i.e., bronchoscopist, anaesthetist, or nurse). There was no statistically significant disparity observed in the sedation usage rate between the private and public healthcare

settings. However, it is noteworthy that in less than 40% of cases, the administration of sedation was performed by an anesthesiologist. A Latin American survey showed that sedation performed by a bronchoscopist was deemed “safe” or “quite safe” by approximately two-thirds of respondents, and, one-third believed that the bronchoscopist should “always” or “almost always” be in charge of the sedation.^{22,23}

Despite the absence of agreement among other regional surveys, our study revealed that bronchoscopists, across various countries and working in both the public and private sectors, strongly endorse the regular utilisation of sedation. This endorsement is likely a result of advancements in sedation techniques, drugs, and monitoring, as well as the evidence presented by numerous studies.

The majority of societal recommendations, specifically those from India, BTS, and Argentina, propose that the provision of IV sedation be considered as a means to enhance patient tolerance during bronchoscopy. The American College of Chest Physicians strongly recommends the use of topical anaesthesia, analgesia, and sedation in all patients having bronchoscopy, unless there are specific reasons not to do so. This approach is advocated due to its potential to improve patient tolerance and satisfaction throughout the procedure.²⁴

The utilization of propofol in the endoscopy suite by non-anesthesiologists is contentious and depends on regional rules. Our design did not facilitate the determination of the frequency with which an anesthesiologist was present during the administration of propofol. Patients who are administered propofol should undergo monitoring and get appropriate care in accordance with the standards for deep sedation. In cases where propofol is provided by non-anesthesia workers, it is essential that these individuals possess the necessary qualifications to effectively manage patients whose level of sedation exceeds the initially anticipated depth. The majority of guidelines^{7,9,24} emphasise that the administration of IV sedation using midazolam or fentanyl by the proceduralist is safe. However, it is advised that propofol administration be carried out by an anesthetist or medical staff who have received specialized training. Differences in local protocols, resource availability, and task delegation contribute to the lower involvement of anesthesiologists in sedation practices in high-income countries, where sedation is often managed by pulmonologists or trained nursing staff.

Any additional analysis must acknowledge the significant limitations of the study. The fact that the respondents were all members of the WABIP suggests that they have a special interest in bronchoscopy that may not be shared by the numerous general pulmonologists who perform bronchoscopy in various countries. Second, the proportion of respondents disproportionately represents physicians practicing in upper-middle-and high-income countries, whereas only a negligible proportion of members practice in low-income countries. Even though WABIP membership dues are kept intentionally low (5 U.S. dollars per year) in order to remove membership costs as a barrier to participation, countries with greater unmet health care needs may have distinct priorities, resources, training opportunities, and practice conditions. The third limitation is

that China is absent from this survey. China is home to a sizable proportion of WABIP members who operate in a variety of bronchoscopy facilities. Lastly, as with any survey, those who respond to a questionnaire about bronchoscopy represent a biased population with a particular interest in bronchoscopy practice and/or working in more specialised centres.

CONCLUSION

One noteworthy observation is that nearly 40% of physicians, despite being deeply committed to bronchoscopy and operating in technologically advanced centres, did not undergo any form of formal training. Another limitation of the study is that only 1% of the respondents are interventional pulmonologists. Instead, many acquired their skills through mentorship, practical experience during pulmonary residency, or self-directed learning. There is a significant disparity in the proportion of physicians who received formal training, with a higher frequency observed among those practicing in high-income countries compared to the 28% practicing in lower-middle-income countries. The previously mentioned statement highlights the limited availability of formal training options in certain nations as well as the lack of mandatory certification for individuals in bronchology facilities equipped with costly and intricate technology. The training programmes for respiratory endoscopy exhibit significant heterogeneity across many countries, irrespective of their comparable levels of economic development. Numerous countries and scientific organisations continue to depend on the completion of a specific set of procedures. The prevailing criterion is evidently inadequate; the sufficient quantity of bronchoscopies performed does not guarantee the attainment of adequate competence. The global implementation of comprehensive and standardised training curricula is important. The responsibility for conceptualising and implementing these programmes primarily lies with scientific societies. However, bronchoscopy technology companies should demonstrate responsible behaviour by incorporating, in addition to a successful marketing strategy, training opportunities that enable countries, regardless of their economic resources, to acquire the necessary competence for utilising these technologies effectively. Simultaneously, it is imperative for health care authorities to collaborate with scientific societies to enhance training opportunities, establish regulations for certification in performing intricate procedures, and ensure advantageous incentives for individuals who invest in their bronchoscopy education so they can practice with the utmost proficiency.

Ethics

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Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Q., A.B., S.G., Concept: S.Q., S.G., Design: S.Q., S.G., Data Collection or Processing: S.Q., A.B., Analysis or Interpretation: S.Q., A.B., Literature Search: S.Q., Writing: S.Q., A.B.

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Review



Artificial Intelligence in Medicine

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Abstract

Artificial intelligence (AI) holds the potential to influence and change the world through many different fields such as science, economics, technology, and art. The modern foundations of AI, with theoretical roots dating back to ancient Egyptian and Greek civilisations, were laid by Alan Turing and John McCarthy in the twentieth century. Early practices in the medical field focused on the archiving and interpretation of radiologic images and possible preliminary diagnoses. As the processing capacity of computers has advanced, so has their skill competence, and it has become possible to implement them in different specialty branches of medicine. On the other hand, ethical, and social problems, dilemmas, and conflicts have begun to arise with practices in the healthcare field. In this sense, AI should be addressed with its potential benefits and problems, knowing that it is tool, free from social prejudices, demographic changes, socio-economic inequalities, and cultural differences and without indulging in dichotomies such as technophilia and technophobia.

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INTRODUCTION

Health can be defined as a dynamic process of adaptation between individuals and their continuously changing physical, social, and psychological environments. As these environments evolve, temporary periods of maladaptation are an inherent part of this process, underscoring the fluid and context-dependent nature of health.

Although ideal health may never be achieved, striving for a healthy life improves human civilization. However, it is a reductionist approach to explain this development through the biomedical model. History has shown humankind that the incidence of most infectious diseases fell before the discovery of vaccines and antibiotics. In tuberculosis, for example, mortality due to the disease began to fall long before the discovery of any biomedical intervention. Indeed, reforms inspired by the sanitation movement and a rising standard of living due to socioeconomic progress led to a more significant decline in mortality caused by diseases in society than the introduction of germ theory.

Epidemics, particularly the plague, and the research of competent scientists, notably Louis Pasteur and Robert Koch, popularized the “germ theory” and led to the refinement of antimicrobial therapies. However, besides these gains, the germ theory also led to a world where lacking a “One Health” approach, the correlation between health and the environment was overlooked and the medical paradigm was constructed on the pillars of *specific aetiology*, *the internal environment*, and *the machine body*.

Today, similar to the past, “genetic theory” is once again seeking to shape the new medical paradigm based on the concepts of specific aetiology, internal environment, and machine body, all founded on genes and interactions. Particularly, the positive potential of the combination of omics technology and artificial intelligence (AI) indicate that the existing health problems will be solved to a significant extent and the advancing technology will upgrade human civilisation. This article aims to examine AI alongside its possibilities and challenges for medical doctors.

Artificial Intelligence

Although the term AI today is associated with futuristic concepts, the origins of the term date back to ancient Egypt and ancient Greece. Indeed, the hermetic scriptures of the era describe mechanical sculptures as *wise* and *full of emotion*.¹

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These scriptures refer to the desire of the artisans, who crafted these sculptures, to replicate that creativity by analysing God's nature and magic.¹

Although the idea of AI appeared in many literary works throughout history, it was tangibly introduced in computer science in 1950 with the words by Alan Turing, "machines can think too," and was named by John McCarthy in 1955.²

To understand the notion of AI, it is first necessary to properly define "intelligence". Intelligence refers to the ability to learn and utilise knowledge and skills. In this regard, it must be clearly distinguished from "consciousness"; the ability of an entity to recognise, perceive, comprehend, and realise its environment and what goes on around it. Since the advent of life, intelligence began to survive and excel at it contributes to the ability to sustain life as a part of the evolutionary process.

AI is the ability to function mentally through its own hardware. Its genesis and progression have been gradual, just like those of organic beings. Neurological research in the late 1930s showed that the human brain is a network of neurons that emit electrical pulses, paving the way for the idea that an electronic brain could be developed by computer scientists. Through the fields of logic and mathematics, the "Theory of Computation" was developed and steps began to be taken to endow computers with the ability to perform mental operations.³ The research was inspired by nature and progressed until the formation of an artificial neural network through codes and algorithms using inorganic silicon instead of organic neurones, and the possibility of machines that can learn.⁴ However, much like certain neuronal pathways in the human brain remain incompletely understood, the internal workings of advanced AI models have become increasingly opaque—even to experts. This complexity gives rise to what is known as the "black-box" problem, where the reasoning behind an AI system's outputs cannot be easily explained or interpreted.

Language Models

The first examples of speech robots, that can recognise and respond to spoken language, today referred to as AI in society, date back sixty years.⁵ In this context, Dendral® software was developed to analyse organic substances spectrophotometrically and was made available for academic and industrial use in 1965.⁶ However, since this software was inadequate for finalising the analyses on its own, specialists in the field of biochemistry had to use it.

Over the years, AI has evolved along with the advancement of computer technologies. During the period 1950-2000, the processing capacity of computers increased one billion times.⁷ Along with such acceleration, the processing volume of AI has also expanded, reaching the capacity to achieve much more than a human can in specific fields per unit of time. However, the "electronic brain" dreamed of for AI was actually turned into a tangible form called "neural networks," and the ability to learn could be taught to AI through analyzing large amounts of data.⁸

On the other hand, the "big bang" regarding the capability repertoire of AI occurred with the advent of the language model

called ChatGPT®. ChatGPT® has reached a level far beyond the performance of its predecessors in language analysis, translation, summarisation, and solving several mathematical problems. However, despite this advancement, ChatGPT® has a narrow spectrum of intelligence. Even if it can analyse, summarise, and write data within this framework, it lacks the capacity to "understand" what has been written. None of the AI models developed so far have been able to exhibit anything similar to the general intelligence of a human being.

Artificial Intelligence and Medicine

The first and simplest use of AI is for medical archiving. As internet-based medical literature search engines were developed, it became easier to access medical resources. Over time, as computer technologies have advanced and their processing capacities have expanded, data processing by AI has also accelerated; its applicability in evidence-based medicine is being discussed. Basically, logic sentences derived from "if so, do as follows" have laid the groundwork for AI-based diagnostic programmes.⁹ "computer aided detection" (CAD) developed for primary care physicians has been one of the earliest practices.¹⁰ Similarly, the software called MYCIN®, developed by Stanford University in 1972, was a computer program that analysed the symptoms and examination data of the patient, especially for patients with blood infections, and suggested the probable diagnosis, additional examinations that may be required, and antibiotherapy options.¹⁰

As medical imaging techniques became digitalised in the 1990s, the potential of AI to analyse and make reports on these examinations was brought to the forefront. Scientific research has shown that analysing mammography examinations used in breast cancer screening using AI provides support to radiologists when specialised breast radiologists are not available, improving the diagnostic accuracy of the physician.¹¹ In 2017, the United States of America (USA) Food and Drug Administration (FDA) also approved Arterys®—an AI algorithm model, using neural networks. This model, approved by the FDA, interpreted cardiac magnetic resonance images in seconds and delivered reliable data on ejection fraction.⁹

The digitisation of endoscopic examinations led to the use of computer-aided diagnostic practices in this field. Gastroenterology has accomplished pioneering practices in this field. AI has assisted physicians with high accuracy, especially for the diagnosis of chronic pancreatitis and pancreatic cancer, both of which are very difficult to differentiate with endoscopic ultrasonography.⁹ Analysis of the localisation and morphology of polyps detected in colonoscopic procedures facilitated the differentiation of malignant from benign.

Complicated relationships within the organism have also begun to be identified through "deep learning"—one of the basic learning methods of AI. Tracking chronic diseases and monitoring the response to oncotherapies were made possible through deep learning. Besides the diagnosis of chronic diseases such as diabetes and hypertension, critical data such as the prognosis of the disease, the risk of complications, and the key points to focus on in order to avoid them have also been predicted through AI.¹²

Artificial Intelligence and Chest Diseases

Lung cancer: Due to the mortality burden imposed by lung cancer and the contributions of AI to the field of imaging, the AI-based radiologic approach to thoracic malignancies was the pioneering AI practice in the field of chest diseases in the 1960s. It rapidly became popular with the advancement of AI. AI-integrated radiologic practices aim to screen chest roentgenograms for nodules to give a preliminary idea to the physician involved in the case.¹³ Due to the limited nature of the human eye and the variability in diagnostic interpretation among physicians, small nodules are often skipped in screening.¹⁴ Research with AI-integrated CAD systems have shown that these systems can provide accurate diagnoses with equal power or at a higher rate compared to radiologists, but also have a higher rate of false positive errors compared to physicians.^{15,16} Furthermore, it has become possible to reduce artefacts and achieve clearer images by processing low-dose lung computed tomography images with AIs trained in a deep learning system after imaging.¹⁷ On the other hand, it has been found that AIs, which were trained using validated pathological materials, achieve great success in the detection of adenocarcinoma and squamous cell carcinoma subtypes.¹⁸ Some additional algorithms that were developed allowed AI to obtain preliminary information about genetic mutations, normally detected by genetic sequencing under normal conditions with a detection time of up to two weeks, by analysing the image of the malignant tissue.¹⁹

Interstitial lung diseases: AI holds great promise in this field. A study conducted at Sapporo Medical School Hospital reported that the probability score of AI that was trained using chest radiography and thoracic computed tomography achieved high diagnostic sensitivity for chronic fibrosing interstitial disease.²⁰ A meta-analysis comparing radiologists and AI in analyzing the tomographic findings of interstitial lung diseases showed that the diagnostic accuracy of AI ranged between 78% and 91%.²¹

Asthma-chronic obstructive pulmonary disease: A study showed that the success rate for recognising spirometry patterns was 74.4% for clinicians and 100% for AI.²² The rate of correct diagnosis of asthma-chronic obstructive pulmonary disease (COPD) patients by AI was 82%.²² Furthermore, an AI program that records and interprets lung sounds together with medical records has been shown to differentiate asthma, COPD, and asthma-COPD overlap syndrome (ACOS).²³ Furthermore, the AI programme was able to obtain preliminary information on managing episodes in asthma patients, taking into account the frequency of episodes and previous treatments.^{24,25} Similarly, environmental factors such as dust, particulate matter, temperature, and humidity to which children diagnosed with asthma are exposed, and physiological data such as pulse rate and blood pressure were monitored with several sensors. These parameters were interpreted with AI to identify the risk of an episode with a success rate of 80% and to communicate the episode via mobile notification.²⁶

Respiratory failure and acute respiratory distress syndrome: In addition to its applications in chronic pulmonary conditions, AI has also demonstrated value in the early detection of acute respiratory syndromes. Among these, acute respiratory distress syndrome (ARDS) poses particular diagnostic difficulties due

to its complex presentation. Recent systematic reviews suggest that AI-based models can support clinicians by identifying ARDS more accurately and efficiently than traditional methods, contributing to earlier recognition and improved management strategies.²⁷ As these technologies continue to evolve, their integration into critical care settings holds potential for enhancing diagnostic confidence and clinical outcomes.

Coronavirus disease-2019: During the pandemic, many programmes related to diagnosis, treatment, filiation, and transmission predictions based on AI have been introduced. An information network was built by using AI to take into account the polymerase chain reaction results of the nasal swabs of the patients, the location where the cases resided, and the people with whom they were in contact.²⁸

Tuberculosis: There are AI programmes developed for the interpretation of chest radiographs, used as a screening method for tuberculosis in peripheral health institutions where specialist physicians are not available. The only commercially available computer-aided diagnostic program for tuberculosis is CAD4TB®, developed in the Netherlands. This software was developed based on deep learning algorithms and can screen a chest radiograph for abnormalities in less than 15 seconds.²⁹

Smoking cessation: Another pandemic by itself, yet the support of healthcare providers is far behind the number needed to assist patients smoking cessation. Beyond just diagnostics and disease management, AI has also shown considerable promise in behavioral health, particularly in supporting smoking cessation. AI-driven interventions—especially conversational agents or chatbots—offer personalized, on-demand guidance that can adapt to the user's needs over time. Recent systematic reviews have demonstrated that such tools can significantly enhance quit rates when compared to standard care, emphasizing their value as scalable, low-cost solutions in public health.^{30,31} By carefully integrating AI into smoking cessation strategies, it would become possible to extend support to wider populations, including those with limited access to traditional healthcare services, while also reducing the burden of tobacco-related diseases.

Bronchoscopy: Invasive procedures are one of the areas where technology has been used extensively. One of the most novel diagnostic opportunities in chest diseases is robotic bronchoscopy. Unlike traditional video bronchoscopy, this type of procedure involves no manual manipulation of the bronchoscope by the bronchoscopist, but rather, a robotic mechanism that manoeuvres the bronchoscope behind a console. Using specialised and thin bronchoscopes, this system allows easier access and sampling of lesions than video bronchoscopy, because of a three-dimensional bronchial tree map, created by thoracic computed tomography before the procedure. On the other hand, the digital processing of the images in traditional video bronchoscopy by computers and the real-time tracking of these images by AI, have made it possible to identify a pathway by analysing morphology and tissues in scenarios where it is difficult to differentiate endobronchial anatomy.³²

Neoliberalism and Medicine - Artificial Intelligence

Neoliberalism is a political and economic paradigm that emerged prominently in the late 20th century, characterized by

an emphasis on free markets, privatization, deregulation, and reduced state intervention in social services. It promotes the idea that sustained economic growth is the driver of progress, and that economic growth is best achieved through freedom of trade and capital, with minimal government interference. Originating in economic theory, neoliberalism has gradually permeated numerous sectors—including healthcare and scientific research—by redefining public goods as commodities and public services as market-driven enterprises. Within this ideology, success is often measured through productivity, profitability, and consumer satisfaction rather than collective well-being or equity. As a result, healthcare and scientific institutions have gradually shifted away from values like solidarity and universal access, adopting priorities that reflect corporate and market-driven interests.

In the field of medicine, this ideological influence has and is still leading to a significant transformation in how healthcare is organized, delivered, and evaluated. Medical systems influenced by neoliberal logic prioritize cost-effectiveness, competition among providers, and the use of performance-based metrics. Clinical decision-making is increasingly shaped by standardized protocols, output targets, and financial incentives. At the same time, public funding for health infrastructure and preventive care has declined in many regions, while privatized services and direct payment models have expanded.³³ Scientific research has, perhaps unfortunately, not been immune to this influence, with priorities having begun to align with commercial viability and industry sponsorship, creating an environment where innovation is driven by profitability rather than public health need. AI technologies developed and implemented within this context reflect and often amplify these systemic priorities. Predictive algorithms used to allocate healthcare resources may be optimized for efficiency or revenue generation rather than equitable access.³⁴ Health surveillance tools, biometric sensors, and wearable devices are frequently marketed as consumer products, with data flows directed toward private platforms that profit from behavioral analytics.³⁵ These tools risk exacerbating disparities should they encode structural biases or be selectively deployed in high-income markets while neglecting underserved populations. Furthermore, the framing of health data as a commercial asset—rather than a collective resource—raises ethical concerns regarding consent, ownership, and accountability.

Neoliberal discourse also tends to individualize responsibility for health, framing outcomes as a function of personal choice rather than acknowledging the structural determinants—such as poverty, housing, education, and environmental exposure—that shape health trajectories. Within this framework, AI-based interventions risk reinforcing narratives that blame individuals for poor outcomes while obscuring the broader socioeconomic forces at play.³⁶ As AI systems become increasingly embedded in clinical workflows, it is vital to ensure that they are designed and governed in ways that prioritize equity, transparency, and patient autonomy.

To guide ethical AI integration in medicine, policymakers, developers, and healthcare leaders must move beyond purely technological or market-based solutions and instead

address the underlying power dynamics that shape how these tools are funded, deployed, and evaluated. This requires a multidisciplinary effort that includes ethicists, clinicians, public health experts, and communities affected by health inequities. Only through such inclusive governance can AI technologies avoid reproducing the limitations of the systems they are intended to improve.

The Other Side of the Coin

Given the digitalisation and virtualisation of the stethoscope identified with medicine, the prevalence of robotic surgeries, and the rapid inclusion of big data in the field of health within the framework of the personalised medicine approach in the near future, it is essential to acknowledge that it is not possible to avoid digitalisation and AI within this framework—and even if it were possible, such an attitude would not be appropriate. In fact, AI itself imagines an all-digital world as the future healthcare delivery setting that will encircle the physician (Figure 1). Therefore, the pulmonologists of the future need to be physicians who have adapted to digital technology and utilize it rationally for the benefit of patients and the public.

Smartphone applications that have expanded in recent years, wearable smart devices, and access to internet-based medical resources can empower individuals to protect and improve their own health and allow them to make accurate and conscious decisions about their health based on information.

However, this transformation, alongside the problems of personal privacy, stigma, and exclusion in a surveillance civilisation, where everything and every value turns into quantifiable data, may turn the concept of health into an obsession with disease. People may believe they are not healthy enough due to information and warnings that constantly reach them through big data and AI, causing them to make their lives unhealthy and maximize the consumption of healthcare services to achieve a better quality of health.

Health and science literacy can mitigate some of these problems. However, studies indicate that the telehealth approach has the potential to exacerbate social health inequalities, contrary to expectations, and income and ethnicity are determinants in such inequality.³⁷ As a reflection of the inequality in the world, the ever-growing 'digital inequality' poses both a barrier and a problem that aggravates inequality in the digitalisation of health. Since most of the software and hardware produced in the field of health requires continuous internet access and mobile data usage, it is possible for people with medium-high socioeconomic status and/or those who live in urban centres with adequate infrastructure for base stations to access AI-assisted applications. In contrast, people with low socioeconomic status and/or those who live in rural areas with limited internet access, who lack adequate infrastructure for base stations despite having access to smart devices, are unable to use the same devices and channels effectively.³⁸ This places people who lack easy access to healthcare services and therefore have the potential to benefit more from telehealth applications at a disadvantage and leads to the persistence of the reverse service problem. The problems created by the inequality that exists around the world with regard to AI applications and the ethical issues that may arise due to such inequality are realities

that have been acknowledged and stated by organizations or experts in AI as of today (Figure 2).

Another problem with smart devices and telehealth applications is the inattention to cultural diversity and the under-representation of different social groups within the scope of these applications. It has been found that telemedicine and telehealth applications, which have grown with the Coronavirus disease-2019 (COVID-19) pandemic, are used more by women than men in high-income countries.³⁹ However, it appears that the languages and images used in health and sports applications, in particular, are often designed with sexist biases, and as a consequence of the patriarchal approach, emphasizing muscle gain and strength for men while highlighting a slim physique and fitness for women are brought to the forefront.⁴⁰ Similarly, the role of women is almost always emphasised in the practices used for following the pregnancy process, and applications aimed at men or promoting men's support before and during pregnancy remain in the minority.⁴¹ Babylon®—an AI-based diagnostic application implemented by the National Health Service of the United Kingdom reports the probable diagnosis of individuals based on their history and the need for elective or urgent consultation with a physician. It diagnoses depression and panic attacks in a 59-year-old female smoker when she complains of chest pain, shortness of breath, and restlessness, while the AI reports suspicion of myocardial infarction in a male patient with the same background.⁴² Similar problems are also experienced in ethnicity.

Such examples reflect the broader issue of opacity in AI systems, many of which function as “black boxes” with internal processes that cannot be readily explained or interpreted. This

lack of transparency poses serious concerns in clinical settings, where the inability to understand how an AI model arrives at a conclusion can wound the trust between patients and physicians, and complicate medico-legal accountability. These risks highlight the urgent need for clear regulatory frameworks to guide the ethical integration of AI into healthcare. International efforts such as the World Health Organization's guidelines on AI ethics and the European Union's AI Act emphasize principles like transparency, accountability, human oversight, and fairness to help ensure that technological advancement does not come at the cost of justice or patient safety.^{43,44}

Beyond the concerns on lack of structure, the integration of AI in medical decision making also raises bioethical dilemmas. The principle of informed consent would be brought into question: Could an AI-driven decision, one that the mechanisms behind couldn't be fully understood by a patient, or maybe even a physician, fit the definition of informed consent? Questions arise over how clinical responsibility and decision-making should be shared between patient and machine, especially as AI systems are becoming increasingly prevalent in areas where they assist and even supplant human judgment. The need for a sufficiently clear AI infrastructure becomes even more apparent when ethical concerns are addressed.

AI-assisted wearable health devices are another technological innovation that will be more important for chest diseases in the future. Smartwatches, which are one type of these devices, have started to be used for clinical follow-up. The integration of glucose sensors and insulin pumps with smartwatches within the scope of wearable health devices aims to be used successfully in many different areas, such as recognising the



Figure 1. AI when prompted to predict the practice setting of 50 years in the future (Dall-E 3)

AI: artificial intelligence

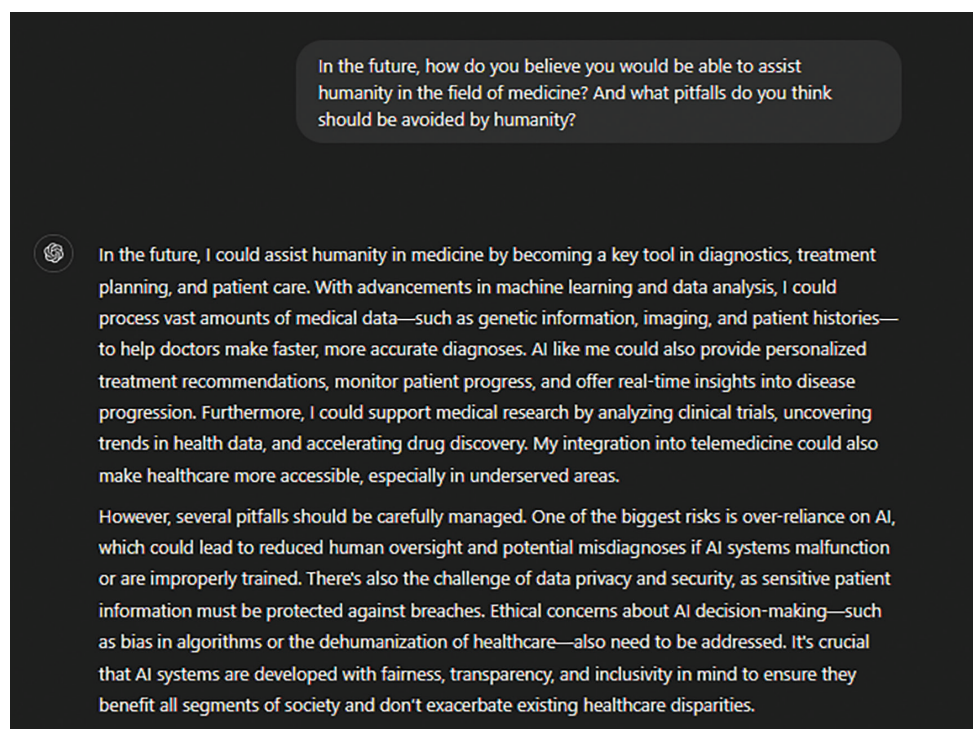


Figure 2. AI's answer when prompted to write on future with AI (ChatGPT)

AI: artificial intelligence

moment of seizure in patients with epilepsy and calling for emergency services, tracking sleep data, detecting cardiac arrhythmias, or dose monitoring of inhaler drugs. The collection of such data can also be added to a person's electronic records, allowing multiple healthcare professionals to access immediate and reliable data on a patient's history. However, today,, the limited use of resources only for people with a certain status, as a reflection of economic and social inequality, exacerbates the existing inequality in the field of health.

The advancement of technology not only significantly improves the possibilities of medical diagnosis and treatment but also provides a better understanding of the physiopathological basis of diseases. In this sense, medical genetic technologies are noteworthy. On the other hand, such a technological advancement will also enable the shaping of a prevention-treatment approach that prioritises the patient over the disease and is patient-specific. Certainly, such new knowledge can both better elucidate the developmental mechanisms of diseases and create new treatment options that target these developmental pathways. However, it should be noted that omics approaches are not the Holy Grail possessing miraculous powers. More importantly, this kind of research should not lead to ignoring the social determinants of health or describe health as an individual issue.

Finally, the next century holds the potential to usher in a new era of transhumanism, described as *positive eugenics*. Accordingly, the concept of transhumanism was introduced by Chinese scientist He Jiankui to the agenda of physicians by intervening in the genetics of infants named Lulu and Nana, and ensuring their birth despite ethical sanctions. Transhumanism means allowing people to transcend their biologically limited

capacities with up-to-date technology and upgrading their bodies. Undoubtedly, such an intervention would eliminate some hereditary diseases such as sickle cell anaemia. However, it also involves the danger of transforming the existing socioeconomic inequality into an anatomobiological structure on an individual and corporeal basis and bringing about new hierarchical inequalities in a world where national and global inequalities have been increasing.⁴⁵ On the other hand, this transformation, which is called the 'digital health revolution,' may also entail a process of commercialisation leading to digital health colonialism, accompanied by the rhetoric of *modernity*, *rationality*, and *progress*.⁴⁶ Digital health data may become a new area for transnational companies in the global north, where they can maximise their profits.⁴⁶ Therefore, physicians should not be satisfied with merely technically adapting to the knowledge and developments in their own professional fields; they should take into account the meaning and background of the varying demographic structure, disease burden, and novel technologies of the forthcoming age and their impact on inequalities, primarily in their own professional practices, and take a stand for a more equitable humanitarian health setting.

Neoliberal Life and AI

In 1840, the longest life expectancy in the world was 48 years in Sweden. In 2019, it was 88 years in Japan.⁴⁷ However, this positive change has not been equally applicable to people all over the world. On the other hand, the future of the world seems bleak. Besides the destruction caused or will be caused by the climate crisis and the migrations that this destruction will trigger, 3 billion people are predicted to have difficulty in accessing water—one of the most basic factors of health, in

2025. In 2050, one-third of the world's population will be over 60 years old.

The major problem is that life expectancy in the USA as a developed country has shortened for the first time in this century. The life expectancy was shortened in non-hispanic middle-aged white Americans between 1999 and 2013.⁴⁸ In 2014-2015, life expectancy was observed to shorten in all groups in the USA.⁴⁹ However, these shortened life expectancies have in no way meant that social classes were 'equalised at the bottom'. Moreover, the inequality that existed in the first two years of the COVID-19 pandemic further deepened, and the gap between the lowest and highest life expectancy reached 20.4 years in 2021.⁵⁰ More interestingly, contrary to what was expected before the COVID-19 pandemic, life expectancy in groups that earned the most, such as "White Americans" who held a high school degree, did not rank first but fourth or fifth.⁵⁰

Epidemiological studies indicate that health outcomes in the USA have been declining since the 1990s, particularly among middle-class populations adversely affected by industrial and economic restructuring. The rise in substance use disorders, including alcohol and opioid dependency, alongside increasing suicide rates, has been described in public health literature as "deaths of despair".⁴⁷ These patterns are closely tied to structural changes driven by neoliberal economic policies, which have contributed to worsening social determinants of health and heightened political polarization.

In a global context marked by growing inequality in access to income, housing, nutrition, and social security, the integration of AI into healthcare systems raises significant ethical concerns. Without appropriate safeguards, AI technologies may disproportionately benefit private stakeholders while reinforcing existing power asymmetries—particularly in politically repressive environments. The proliferation of biometric sensors and wearable devices, although intended for health monitoring, also poses risks of large-scale surveillance and data exploitation if deployed without strong regulatory oversight.

CONCLUSION

AI holds immense potential to advance medical practice by enhancing diagnostic accuracy, streamlining workflows, enabling real-time data analysis, and expanding access to care—particularly in underserved regions. AI tools can assist clinicians in making more informed decisions, improve resource allocation, and facilitate predictive modeling for early disease detection and public health planning. As data infrastructures and computational power continue to grow, AI will likely become an integral part of medical ecosystems worldwide. Its expansion offers an unprecedented opportunity to improve health outcomes, personalize treatments, and optimize healthcare delivery—provided it is implemented with clear goals, robust oversight, and alignment with clinical needs.

However, the integration of AI into medicine does not occur in a vacuum. It is shaped by the economic, social, political, and ideological systems in which it is embedded. When AI technologies are developed and deployed within these systems,

they risk reinforcing inequities, privatizing health data, and shifting healthcare toward profit-driven rather than patient-centered models. Ethical AI integration requires users to be aware of the landscape in which they operate and not to solely rely on technical safeguards already implemented. Addressing these concerns is essential to ensure that AI contributes not only to innovation, but also to justice, inclusivity, and the collective well-being of societies.

Ethics

Footnotes

Authorship Contributions

Concept: U.K., O.E., Design: U.K., O.E., Analysis or Interpretation: U.K., O.E., Literature Search: U.K., O.E., Writing: U.K., O.E.

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Review



A Novel Approach to High-flow Nasal Oxygen Delivery: Physiological and Clinical Perspectives on Asymmetrical Cannulas

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Abstract

High-flow nasal cannula (HFNC) therapy has become an essential therapeutic modality across a broad spectrum of indications, and it is currently regarded as the optimal initial therapeutic option for patients presenting with acute hypoxemic respiratory failure. A novel HFNC interface with an asymmetrical cannula has recently been introduced to optimize the physiological benefits of HFNC. It features prongs, one with a smaller diameter and another with a larger diameter, to enhance positive end-expiratory pressure and carbon dioxide washout. This is achieved by modulating the prong-to-nare area ratio to maintain a balance between airway pressure and dead space clearance. Recent studies have indicated that the use of an asymmetrical design may result in enhanced upper airway pressure and dead space washout. Asymmetrical cannulas may enhance patient comfort, reduce work of breathing, and lower minute ventilation. However, they do not significantly differ from standard cannulas in terms of gas exchange, oxygenation, diaphragm activity, lung compliance, dorsal fraction of ventilation, or lung impedance. Further research is needed to determine whether asymmetrical cannulas offer clinical advantages in specific patient populations, to identify optimal sizing parameters, and to assess their long-term safety and efficacy in diverse clinical settings.

KEYWORDS: Acute respiratory failure, asymmetrical cannula, dead space washout, high-flow nasal cannula, positive end-expiratory pressure

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INTRODUCTION

The high-flow nasal cannula (HFNC) delivers a mixture of warmed, humidified air and oxygen at a specified concentration and temperature through a nasal interface at high-flow rates.¹ An air-oxygen mixer allows for precise adjustment of the fraction of inspired oxygen (FiO₂) from 21 to 100%, regardless of the flow rate.¹ HFNC is considered to be the optimal first-line option for patients with acute hypoxemic respiratory failure.² Moreover, there is a wide range of potential indications for HFNC, and they vary depending on the clinical situation. Such indications include, postoperative patients, non-surgical patients with a low-risk of extubation failure, patients with acute pulmonary edema, and patients with chronic obstructive pulmonary disease (COPD).²⁻⁵

The physiological effects of HFNC treatment have been demonstrated in numerous studies. HFNC improves mucus hydration and mucociliary function through effective inspired gas humidification, aiding expectoration, mucus clearance, and preventing airway dryness and injury.⁶ The main factors influencing alveolar oxygen delivery include the FiO₂, the flow rate of supplemental oxygen, and inspiratory demand.⁷ In cases of respiratory distress or acute hypoxemic respiratory failure, patients may require high-flow rates that exceed those of conventional oxygen delivery systems.⁸ This can result in the inhalation of more ambient air, which contains 21% oxygen, further reducing the overall oxygen concentration of the inspired air.^{1,8} The HFNC system delivers oxygen through the nasal prongs at a rate that generally exceeds the patient's flow rate. This ensures that very little room air is entrained, resulting in a more

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reliable delivered oxygen concentration.⁹ Increasing the flow rate improves the respiratory pattern by increasing the tidal volume and decreasing the respiratory rate, thereby reducing the inspiratory effort.¹⁰⁻¹² The nasopharyngeal airway pressure increases in correlation with the flow rates produced by HFNC, reaching a peak at the end of expiration.^{13,14} This positive end-expiratory pressure (PEEP) effect may increase end-expiratory lung volumes compared to low-flow devices.¹¹ The PEEP effect of HFNC is reduced during open mouth breathing.¹⁵ Other factors affecting PEEP include body type, resistance to flow, patient position, and lung disease distribution.^{1,16} HFNC therapy can reduce dead space rebreathing by facilitating the rapid clearance of carbon dioxide from the nasal cavity.¹⁷ The nasopharyngeal dead space functions as a reservoir for fresh gas under HFNC treatment, thereby ensuring that during the initial phase of inspiration, the inhaled oxygen volume is maximized while carbon dioxide is efficiently washed out. This results in more efficient ventilation and gas exchange.¹⁸ Moreover, decreasing dead space ventilation could lead to a reduction in the work of breathing.¹²

The impact and intensity of these physiological effects may vary depending on the set flow rate and the patient's specific characteristics.¹² In combination, the physiological effects result in a reduction in excessive respiratory drive, minute ventilation, and inspiratory effort.¹² As a result, the most obvious effects are increased patient comfort and oxygenation.¹⁰⁻¹² Additionally, HFNC may lower the risk of self-inflicted lung injury by decreasing the driving transpulmonary pressure.¹²

It is expected that these physiological effects and clinical benefits will enhance clinically meaningful outcomes, such as length of hospital stay, intubation rates, and, most importantly, mortality. Nevertheless, studies have not demonstrated a decline in either the rate of intubation or mortality.¹⁹ In addition, the failure rate of HFNC support remains considerable.²⁰ Failure of the HFNC may result in admission to the intensive care unit (ICU).²¹ The major concern is that the use of HFNC may delay necessary intubation and worsen outcomes in patients with acute respiratory failure.²² Delayed intubation in patients who have failed HFNC is associated with an increased risk of adverse outcomes and mortality.^{22,23}

Several strategies have been proposed to enhance the effectiveness of HFNC therapy in preventing failure and ICU admission.²⁴⁻²⁷ To achieve this goal, studies have focused on a number of variables, including the HFNC interface, flow selection, prone positioning, and respiratory rate.²⁴⁻²⁷ Nevertheless, the implementation of these strategies did not yield the anticipated substantial outcomes.^{25,26}

A novel HFNC interface with an asymmetrical cannula design [Optiflow® Duet system (Fisher & Paykel, Healthcare, Auckland, New Zealand)] has been approved for clinical use to improve the efficacy of HFNC therapy. The objective of this narrative review is to provide an updated synthesis of the physiological mechanisms and clinical effects of HFNC therapy, with a specific emphasis on prong geometry and the potential advantages of the recently introduced asymmetrical cannula design.

The Role of Prong Size and Cannula Type on PEEP Effect and Wash-out Effect

The primary mechanisms of HFNC are believed to be the PEEP effects and washout effects.²⁸ Studies investigating cannula prongs have primarily focused their effects on these two main effects.²⁷⁻³⁰

The Relationship Between Prong Size and Airway Pressure

The nasal cannulas are constructed with a relaxed fit to enable the removal of expired gases from the anatomical dead space through the annular space between a person's nostrils and the outer prong walls of the cannula.^{17,27,30} Airway pressure results from flow and resistance.^{17,27} Variations in cannula prong sizes can lead to different levels of resistance at varying flow rates, resulting in varying airway pressures.^{17,27} It is hypothesized that by constricting the oxygen flow to a smaller area, the velocity increases, thereby enabling the flow to enter with greater kinetic energy, which can subsequently be transformed into pressure further downstream.^{30,31} On the other hand, other studies suggested that an increase in the airway pressure can be identified with the use of large cannulas, which help to reduce leakage around the prongs.^{31,32} In assessing the impact of cannula size on the efficacy of HFNC, it is essential to consider not only prong size, but also the prong-to-nare area ratio or the relationship between prong and nare.^{27,29,30} Zhao et al.³¹ investigated the factors influencing nasal airway pressure during HFNC in a cohort of 35 healthy adults, comprising 16 males and 19 females. Upon reaching a flow rate of 30 L/min, the end-expiratory pressure generated by the larger cannulas began to exceed that of the smaller cannulas, with the discrepancy becoming increasingly pronounced as the flow rate increased.³¹ The effect of the nasal cannula on end-inspiratory pressure was not as significant as on end-expiratory pressure.³¹ They suggested that increasing the cannula size may reduce the HFNC jet flow and result in increased end-expiratory pressure due to a greater decrease in gas leakage, although they did not measure the occlusion ratio. They also found that women had higher end-expiratory pressure than men, possibly due to their smaller body size, resulting in lower nasal volume and a reduced air leakage at the same flow rate and cannula size.³¹

The Relationship Between Prong Size and Wash-out Effect

The influence of nasal prong size on dead-space clearance remains a topic of incomplete understanding. The results of animal experimental studies have indicated, that the clearance of extra thoracic dead space is dependent upon the presence of a less occlusive prong.^{30,33} In a randomized controlled trial involving stable hypercapnic COPD patients, researchers investigated the impact of different levels of air leakage on PCO₂. They investigated the impact of different flow rates and levels of leakage. The leakage level was achieved by inserting a cannula through one or both nasal orifices. The results showed a significant correlation between increased leakage and decreased capillary PCO₂ levels.³⁴ In their investigation of the three-dimensional geometry of the human airway, Miller et al.³⁵ reached similar findings as previous studies. However, they found that the gas clearance of the extra thoracic dead space is more closely linked to the kinetic force of the airflow, generated

by the higher velocity from the narrower prong nozzle, rather than to the reduced blockage of the nostrils.

Mechanism of Action of the Asymmetric Cannula and an Overview of Relevant Studies

Mechanism of Action of the Asymmetric Cannula Design

An optimal nasal cannula is expected to impact both airway pressure and dead space clearance. In order to achieve the maximum possible increase in upper airway pressure, the velocity of the flow can be increased both in the cannula and in the nostrils by the use of narrow-inner-diameter, thick-walled cannula prongs.³⁰ Although the use of this cannula model may result in an elevation of tracheal pressure, it could lead to prolonged clearance times due to augmented nasal occlusion.³⁰ Additionally, in patients with a high prong/nare area ratio, closing the mouth may increase airway pressure depending on the flow rate, which may limit the ability to breathe through the nose.²⁸ Caution is warranted when selecting the cannula size for certain vulnerable patients receiving HFNC, as pulmonary barotrauma — caused by increased transalveolar pressure and subsequent alveolar rupture — may lead to serious complications such as pneumothorax and subcutaneous emphysema.^{36,37} A 14-year-old girl who underwent allogeneic hematopoietic cell transplantation for high-risk acute myeloid leukemia developed severe chronic graft-versus-host disease and was treated for presumed bronchiolitis obliterans syndrome. Despite cautiously administered nasal high-flow therapy (14–20 L/min) for refractory dyspnea, she experienced progressive respiratory failure; autopsy revealed pulmonary barotrauma with alveolar overdistension and septal destruction, without histopathological evidence of bronchiolitis obliterans.³⁶ Another case report described a 2-month-old infant who developed massive right lung overinflation with mediastinal shift and left lung atelectasis while receiving HFNC therapy (2 L/kg/min, FiO₂ 0.6), which occurred despite appropriate device settings, highlighting a potential association between HFNC and barotrauma in infants.³⁷

Design of the Asymmetrical Nasal Cannula

A novel asymmetrical nasal cannula interface has recently been approved for clinical use (Figure 1).²⁸ The asymmetrical cannula is designed with one prong featuring a smaller and the other a larger one.²⁸ This results in an increase in the total cross-sectional area of both prongs by approximately 30% to 40%.²⁸ The higher prong-to-nare area ratio resulting from the larger cannula may enhance the pressure experienced by higher occlusion. In comparison, the ratio of prongs to nares is reduced in the nasal cavity compared to the other side. Consequently, leakage around the cannula is maintained, and dead-space washout is enhanced (Table 1).²⁸

Bench Studies

A bench study compared an asymmetrical large-size nasal cannula with a standard medium-size cannula. The asymmetrical large-sized nasal cannula demonstrated a higher end-expiratory nasopharyngeal pressure than the standard medium-sized cannula. Furthermore, the asymmetrical large-

size nasal cannula exhibited more efficient CO₂ clearance in the upper airways than the standard medium-size cannula by reducing the volume of CO₂ rebreathing from the upper airways.³⁸

In another bench study, Tatkov et al.²⁸ compared the standard nasal cannula with an asymmetrical nasal cannula on an upper-airway model. The study utilized three cannula interfaces: a large standard for the augmentation of nasal occlusion, a control standard, and an asymmetrical cannula. The occlusion areas of the large standard and asymmetrical cannulas were similar. The larger symmetrical cannula did not enhance dead space clearance. At higher respiratory rates, the device reduced clearance, compared to the symmetrical control cannula. At a respiratory rate of 15/min and a flow of 60 L/min, dead space clearance was similar between large standard nasal cannula and asymmetrical nasal cannula. However, at a respiratory rate of 35/min, the large standard nasal cannula clearance decreased, while the asymmetrical nasal cannula clearance increased significantly. The study highlighted that the asymmetrical interface led to notable improvements in performance when the breathing pattern exhibited reduced clearance time, due to increased frequency or expiratory flow limitation.

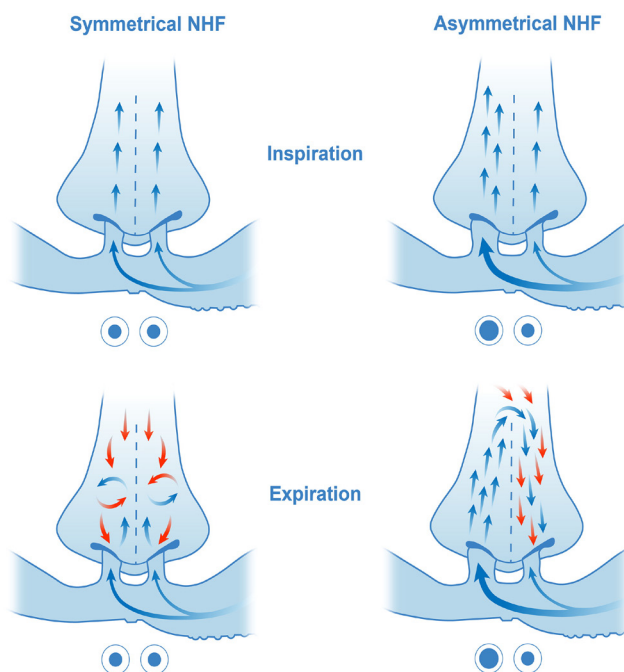
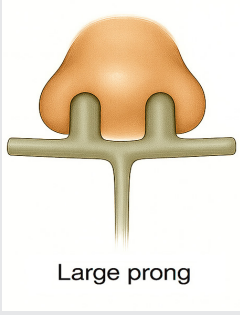
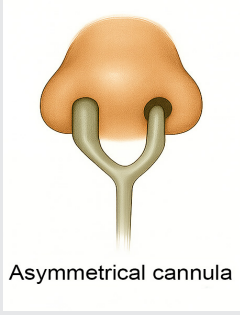


Figure 1. Flow dynamics in symmetrical and asymmetrical nasal cannula interfaces. Adapted from Tatkov et al.²⁸ (2023)

Schematic representation of the flow direction in cannulae and the upper airways during inspiration (top) and expiration (bottom) in a symmetrical interface (SI) (left) and an asymmetrical interface (AI) (right). Blue arrows indicate nasal high-flow (NHF), which is equally split between the prongs in the SI. In the AI, NHF is biased toward the larger prong due to its lower resistance and the streamline of gas velocity within the cannula. Expired gas flow is indicated by red arrows. During expiration, the SI leads to equal mixing and purging via both nares. In the AI, the nare occluded by the smaller prong creates a lower resistance path for the expired gas to be cleared from the nasal cavity. The biased flow from the larger prong is also directed to the contralateral nasal cavity via the choanae, forming the reverse flow that peaks at the end of expiration.

Table 1. Effects of cannula type and nostril fit on PEEP and dead space washout

			
Small prong			
Large prong			
Asymmetrical cannula			
PEEP effect	Since the oxygen flows through a narrower prong, its velocity and kinetic energy increase, which may then be converted into pressure downstream.^{30,31}	Increasing the cannula size may reduce the HFNC jet flow but result in increased end-expiratory pressure due to a greater decrease in gas leakage.³¹ Closing the mouth may increase airway pressure, depending on the flow rate, and limit the ability to breathe through the nose.²⁸	A higher prong-to-nare area ratio from a larger cannula may enhance pressure generation due to increased occlusion.²⁸
Wash-out effect	The clearance of extrathoracic dead space may depend on the use of less occlusive prongs, which facilitate washout through increased leakage.³⁴ Gas clearance of the extrathoracic dead space may be more closely linked to the kinetic force of the airflow — generated by the higher velocity from the narrower prong nozzle — rather than to the reduced blockage of the nostrils.³⁵	When occlusive prongs are used, gas washout may be less effective due to minimal leakage.³⁴	By contrast, a lower prong-to-nare ratio in the opposite nasal cavity preserves leakage and facilitates dead space clearance.²⁸
PEEP: positive end-expiratory pressure, HFNC: high-flow nasal cannula			

Clinical Studies

In a study conducted by Slobod et al.,³⁹ ten spontaneously breathing patients with acute respiratory failure, presenting within the prior seven days and exhibiting a PaO₂/FiO₂ ratio of less than 300 mmHg, were assessed using a conventional HFNC interface and an asymmetrical cannula interface. The objective was to examine the influence of the asymmetrical cannula on minute ventilation, work of breathing, and the underlying physiological mechanisms using esophageal manometry and electrical impedance tomography. The implementation of an asymmetrical interface resulted in a reduction in minute ventilation and work of breathing at both flow rates, 40 and 60 L/min. However, using the asymmetrical cannula did not affect oxygenation levels, regional or global dynamic lung compliance, the dorsal fraction of ventilation, or end-expiratory lung impedance.

Boscolo et al.⁴⁰ conducted a pilot physiological crossover randomized controlled study involving 20 adult patients who had received invasive mechanical ventilation for at least 24 hours and experienced acute hypoxemic respiratory failure after extubation. Patients were randomly assigned to receive asymmetrical or standard nasal cannulas. An asymmetrical cannula improved patient comfort compared to a standard cannula. However, there were no significant differences between the two nasal cannula interfaces regarding lung

aeration, diaphragm activity, ventilatory efficiency, dyspnea, and gas exchange.

CONCLUSION

The asymmetrical HFNC interface may represent a promising advancement in the delivery of high-flow nasal oxygen therapy. It offers a more individualized approach to achieving effective airway pressure and dead space clearance. Its unique design allows for the optimization of PEEP and carbon dioxide clearance by varying the prong-to-nare area ratio. While improvements have been observed in certain areas, the evidence is primarily based on studies with limited sample sizes. Further research is needed to determine whether asymmetrical cannulas offer clinical advantages in specific patient populations, optimal sizing parameters, and their long-term safety and efficacy in diverse clinical settings.

Ethics

Footnotes

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: All authors contributed equally to all contribution sections.

Conflict of Interest: One author of this article, Begüm Ergan, is member of the Editorial Board of the Thoracic Research and Practice. However, she was not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. Begüm Ergan reports educational grants from Fisher and Paykel outside the submitted work.

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