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ABOUT

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Original Article

Retrospective Evaluation of Safety of Using a Semi-automatic Robotic System for Transthoracic Biopsy of Lung Mass Under Positron Emission Tomography-computed Tomography Guidance

Mudalsha Ravina[1], Ranganath Ganga[2], Rutuja Kote[2], Prateek Prasanth[1], Ajoy K. Behera[2], Praveen Kumar Dubey[2], Ramkishore Velmurugan[2]

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ABSTRACT

OBJECTIVE: Lung cancer poses unique challenges due to heterogeneity in tumor and metastatic cellular composition. The use of ^{18}F-fluorodeoxy glucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) integrates functional and anatomical imaging. This study assessed the safety and diagnostic yield of PET-CT–guided transthoracic needle biopsy for intrathoracic mass lesions using a semi-automatic robotic system.

MATERIAL AND METHODS: Forty consecutive patients underwent whole-body PET-CT imaging following which they underwent transthoracic biopsy, using a semi-automatic robotic biopsy system (Maxio™ III; Perfint Healthcare Pvt Ltd., Chennai, Tamil Nadu, India), consisting of docking system, digital screen and a stereotactic arm. Clinicodemographic profile, PET-CT and biopsy findings, histopathology reports, and complications were retrieved from patient records.

RESULTS: The mean age of the patients was 57.08±12.39 years, and the mean maximum standardized uptake value was 16.71±8.61. PET-CT revealed a unilateral lung mass in 92.5% (n = 37) and bilateral lesions in 7.5% (n = 3) of patients. Heterogeneous ^{18}F-FDG uptake was noted in 97.5% (n = 39). The average target lesion distance was 40±12.7 mm. At least four biopsy cores were obtained in all patients except one. Core length was 2 cm in 90% of cases. The most common complication was local pain, followed by pneumothorax in 12.5% (n = 5). Tissue was adequate for analysis in all cases. None of the patients had to undergo repeat PET-CT or biopsy. The diagnostic yield was 100%, with malignancy in 82.5% (n = 33), acute inflammation in 10% (n = 4), and tuberculosis in 7.5% (n = 3). 50% (n = 20) underwent next-generation sequencing for targeted mutation testing.

CONCLUSION: Semiautomatic robotic assistance can be a safe option for diagnosing intrathoracic mass lesions, with an acceptable diagnostic yield.

KEYWORDS: Lung cancer, lung biopsy, positron emission tomography, robotic biopsy, thoracic imaging

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INTRODUCTION

Lung cancer is the second most common cancer, accounting for 11.4% of all cancers and 18% of the 1.7 million cancer-related deaths. The five-year survival still varies between 10-20% due to delayed presentation.[1] A suspicious nodule once detected radiologically, obtaining an adequate tissue sample is vital for immunohistochemical analysis and for detecting gene mutation of cancer.[2] Computed tomography (CT)-guided transthoracic needle biopsy (TTNB) is reliable, with diagnostic accuracy varying between 70-93%.[3] However, TTNB may yield non-diagnostic results when lung masses are associated with fibrosis, atelectasis, necrosis, or obstructive pneumonia, which is not uncommon.[4] ^{18}F-fluorodeoxy glucose positron emission tomography (^{18}F-FDG PET)-CT serves as an important imaging modality for diagnosis and treatment planning in patients with lung cancer. It is essential for staging and response evaluation at follow-up.[5,6] ^{18}F-FDG PET-CT can detect viable tumor cells within a mass that contain nonmalignant areas like necrosis, fibrosis and collapsed lung due to differential uptake of ^{18}F-FDG thereby improving diagnostic yield.[7] Additionally, PET-CT–guided TTNB aids in acquiring better quality samples for further immunohistochemistry and genomic studies.[8,9]

The successful experience of use of semi-automatic robotic system is mainly from liver biopsies and experience of using it in lung is limited to a few studies[10,11] and case reports.[12] There is a dearth of data on the real-life safety and diagnostic yield of such a procedure for lung masses. This is a retrospective evaluation of our initial experience using semi-automatic robot-guided biopsy of lung masses.

MATERIAL AND METHODS

This retrospective study was conducted in the departments of Pulmonary, Critical Care and Sleep Medicine and Nuclear Medicine, All India Institute of Medical Sciences (AIIMS), Raipur, India from October 2022 to May 2024. The study was approved by the Institute Ethics Committee of AIIMS Raipur vide letter no: OW/RC/AIIMS-RPR/2022/1028 dated 4th February 2022 and conducted as per recommendations of amended declaration of Helsinki. Informed written consent was obtained from all patients undergoing biopsy. Inclusion criteria: patients aged more than eighteen years and willing to undergo a biopsy procedure were included in the study. Exclusion criteria were: patients aged less than eighteen years, hemodynamic instability, inability to lie down, coagulopathy, and active hemoptysis.

Main Points

- Diagnosis of intrathoracic mass lesions can be challenging, particularly for lesions located deep inside the thorax or with internal necrosis.
- Positron emission tomography-computed tomography can improve tumor sampling by targeting ^{18}F-fluorodeoxy glucose-avid areas of the tumor, thereby improving diagnostic yield and potentially reducing complications.
- Semi-automatic robotic systems can improve tumor sampling by guiding to the preferred area within the tumor and safety by avoiding surrounding by vascular structures and has the potential to improve diagnostic yield.

^{18}F-FDG PET-CT Imaging Technique

All PET-CT scans were conducted using a GE DISCOVERY MIDR PET-CT scanner (GE Healthcare, Milwaukee, Wisconsin, USA). The scans were performed after six hours of fasting. Prior to the scan, fasting blood glucose was checked; if the levels were below 150 mg/dL, ^{18}F-FDG was injected. The scans were performed 45–60 min after injection. Images were acquired from the vertex to the thigh in 7 to 8 bed positions, with an acquisition time of 1 to 2 minutes per bed position. PET images were reconstructed using iterative methods. Patients were taken for biopsy when slots became available on the same day. The resulting images were then transferred to the semiautomatic robotic biopsy system.

Biopsy Procedure

We followed the CIRSE Guidelines on Percutaneous Needle Biopsy, incorporating PET-CT guidance for optimal targeting.[13] Biopsy was performed by a team of nuclear physician and pulmonologist using a semi-automatic robotic biopsy system under ^{18}F-FDG PET-CT guidance.[14]

Semiautomatic Robotic Biopsy System (Maxio™ III; Perfint Healthcare Pvt Ltd, Chennai, Tamil Nadu, India)

The system features a docking system that can be adjusted on either side of the patient bed, a digital screen for 2D and 3D visualization of the lesion and planning the biopsy. It also includes a stereotactic arm with the ability to move in 5 degrees of freedom along axes X, Y, Z, A, and B, providing sub-millimeter and sub-degree accuracy. The arm is equipped with a needle holder, a stabilizer, and a gripper with specifically sized bushes to hold a coaxial needle. Figure 1 describes the biopsy system used.

Positioning and Planning Before the Procedure

After establishing the biopsy plan, the patient was immobilized in a vacuum-assisted immobilizer on the PET-CT table. A thoracic ^{18}F-FDG PET-CT (120 kVp, 40 mA, 1.25 mm section thickness, 1 mm section interval) was reconstructed for biopsy planning. This imaging decisively identified the target point within the lung mass with the highest ^{18}F-FDG avidity and the skin entry point. Other key aspects such as needle trajectory, lesion depth, and angulations were determined using the automated robotic-arm system. The interventionist assessed the planned trajectory in relation to nearby organs. Once the robotic system was actuated, the stereotactic arm automatically positioned itself according to the planned coordinates on the console.

Coaxial Needle Placement

The site of entry was cleaned and draped. 7–10 mL of lidocaine 1% was infiltrated into the skin and the target area. A suitable bush and bush-adaptor assembly was then mounted in the end effector of the robotic arm. This was done to firmly hold and guide the needle along the planned trajectory. An 18-gauge ×20-cm coaxial core biopsy system (Bard Mission; BD) was



Figure 1. ^{18}F-FDG PET-CT–guided coaxial core needle biopsy using a robotic stereotactic navigation platform. A) Robotic arm–based guidance system (Perfint MAXIO) integrated with the PET-CT gantry, docked on the right side of the gantry with the patient positioned supine. B) Laser cross-hair projection onto the marked skin entry site over the chest wall, localising the planned puncture point. C) Navigation workstation display with a three-dimensional skeletal reconstruction, fused axial PET-CT images of the hypermetabolic left lung mass target, and trajectory parameters (needle length, orbital and craniocaudal angles, target depth, table height) for reproducible metabolically guided sampling

^{18}F-FDG: ^{18}F-fluorodeoxy glucose, PET-CT: positron emission tomography-computed tomography

manually introduced through the bush and advanced through the skin (entry site) to reach the target site. After the bush and adaptor were detached from the robotic arm, the coaxial needle placement was confirmed by a regional computed tomogram (120 kVp; 40 mA; section thickness, 1.25 mm; interval, 1 mm), and multiple specimen cores were obtained using the biopsy system. We tried to obtain a maximum of four tissue cores from all patients through a single puncture site. The samples were collected in both formalin and 0.9% normal saline. Haemostasis was achieved by slowly pulling out the needle during expiration, followed by manual compression. After the procedure, a chest CT scan was performed to assess for any post-procedural complications, such as bleeding or pneumothorax. Figure 2 shows the procedural images of the biopsy. After the procedure, participants were observed for a day in the day-care ward. Pain was assessed using the visual analogue scale (VAS).

Statistical Analysis

As there are no robust data on the diagnostic yield of using a semi-automatic robotic system for lung mass biopsies with PET-CT guidance, this pilot study included 40 consecutive patients at the time of this analysis. Demographic characteristics, clinical history, PET-CT findings, details of the procedure, histopathological findings, and complications were retrieved from these patients' records. The data were entered into Microsoft Excel 2023 and analyzed using the IBM SPSS version 20.0 (IBM Corp, Armonk, USA). The quantitative variables were expressed as means and standard deviations (SD). Categorical data were expressed as percentages.

RESULTS

All 40 patients were included in the analysis. The mean ± SD age was 57.08±12.39 years. Thirty-one patients (77.5%) were male. Thirty patients (75%) were symptomatic for more than two months. The most common symptom reported was cough (87.5%, n = 35), followed by dyspnea (47.5%, n = 19). The mean ± SD maximum standardized uptake value was 16.71±8.61. Table 1 shows the dimensions of lung lesions on PET-CT. Three (7.5%) patients had mass lesions abutting the diaphragm; 2 (5%) patients each had mass lesions abutting the pericardium and the aorta; and 1 (2.5%) had a mass lesion near the pulmonary trunk. The mean ± SD target distance from the lesion was 40±12.7 millimeters (mm). Four biopsy cores were obtained in all patients except one, in whom three cores were obtained due to excessive bleeding. The core length was 2 centimeters (cm) in 36 (90%) patients. Complications observed in the study were minor local site pain (100%), median [interquartile range (IQR)] VAS score was 1 (1–2), excessive cough (15%), pneumothorax in 5 patients (12.5%). One patient had excessive local biopsy site bleeding, which was managed with local pressure bandage application. All complications were successfully managed conservatively. The diagnostic yield of the procedure was 100%. The most common diagnosis was malignancy 82.5% (n = 33), followed by acute inflammatory lesions in 4 patients (10%). Three (7.5%) patients were diagnosed with tuberculosis. Patients with acute inflammatory lesions and those with tuberculosis were followed up after treatment and were found to have radiological resolution. Table 2 shows the diagnostic outcomes of the biopsies performed in the study.

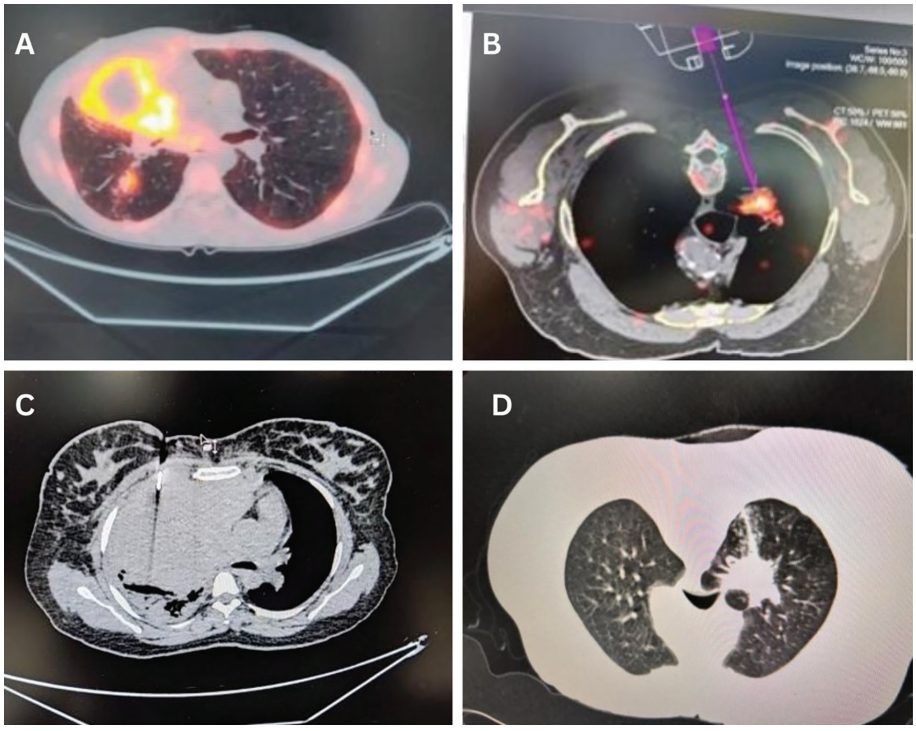


Figure 2. PET-CT–guided coaxial core needle biopsy of lung lesion. A) Axial fused PET-CT image shows a heterogeneously hypermetabolic right lung mass with a photopenic, necrotic core and intense peripheral ^{18}F-FDG uptake, which represents the metabolically viable component selected for sampling. B) Fused axial PET-CT with the planned magenta trajectory directed toward a focal ^{18}F-FDG-avid left lung nodule; the target lesion is indicated, illustrating metabolically guided targeting. C) Axial CT soft-tissue window confirming coaxial core needle placement within the lung mass, with the needle tip indicated prior to tissue acquisition. D) Axial CT lung window depicting the post-procedural bleeding along biopsy tract within the lung parenchyma

PET-CT: positron emission tomography-computed tomography, ^{18}F-FDG: ^{18}F-fluorodeoxy glucose

Table 1. Features of lung masses in PET-CT scan (n = 40)

Variable	
SUV_{max} (mean ± SD)	16.71±8.61
AP diameter in cm (mean ± SD)	5.20±2.53
Transverse diameter in cm (mean ± SD)	4.80±2.46
Cranio-caudal diameter in cm (mean ± SD)	6.79±4.11
	n (%)
Unilateral lung mass	37 (92.5%)
Bilateral lung mass/nodules	3 (7.5%)
Heterogeneous ^{18}F-FDG enhancement	39 (97.5%)

PET-CT: positron emission tomography-computed tomography, SUV_{max}: maximum standardized uptake value, SD: standard deviation, AP: anteroposterior, cm: centimeters, ^{18}F-FDG: ^{18}F-fluorodeoxy glucose

Table 2. Diagnosis established via PET-CT–guided lung mass biopsy (n = 40)

Diagnosis	**n (%)**
Lung adenocarcinoma	20 (50%)
Inflammatory lesion	4 (10%)
Lung squamous cell carcinoma	3 (7.5%)
Metastatic adenocarcinoma from GI system	3 (7.5%)
Tuberculosis	3 (7.5%)
Lung adenosquamous carcinoma	2 (5%)
Small cell cancer lung	2 (5%)
Metastasis from breast cancer	1 (2.5%)
Metastasis from FCT	1 (2.5%)
Neuroendocrine tumor	1 (2.5%)

PET-CT: positron emission tomography-computed tomography, GI: gastrointestinal, FCT: follicular carcinoma of the thyroid

DISCUSSION

Early detection of primary tumors greatly improves the chances of successful intervention and better outcomes. Tumor sampling is the cornerstone for diagnosing lung cancer and for guiding treatment through molecular and genetic testing. Various biopsy techniques, such as fiberoptic bronchoscopy, endobronchial ultrasound-guided biopsy, navigation bronchoscopy, and percutaneous biopsy, are currently in use.[15] Percutaneous lung biopsy, a minimally invasive procedure, is performed under ultrasonography, CT, and PET guidance to ensure accurate lesion targeting. But ultrasound and CT is unable to differential viable tumor from necrosis to a large extent, while CT-guided biopsy carries the drawback of increased radiation exposure and a false-negative rate of up to 10-24%.[16,17] Technological advancements such as laser targeting, augmented reality, and interventional robotic systems have been introduced to improve yield.[18,19] PET-CT-guided biopsies are particularly useful, as increased ^{18}F-FDG uptake is seen in metabolically active tumor cells within a mass lesion, enabling precise targeting and successful biopsy procedures, thus overcoming the limitations

of CT-guided biopsies.[7,16,17] In India, limited studies have been conducted on the use of robotic biopsy systems for lung lesions. Results of our study demonstrated a diagnostic yield of 100%, and the most common diagnosis was lung adenocarcinoma (50% of patients). As per our institutional protocol, all samples of adenocarcinoma were tested for targeted mutations by next-generation sequencing, and the samples were adequate for mutation testing. The results of our study are in line with previous studies and highlight the advantages of PET-CT guidance in obtaining biopsies from peripheral thoracic lesions.

A study conducted by Cerci et al.[7] and Guralnik et al.[8] found that PET-CT–guided TTNB was superior than other conventional methods, including CT–guided TTNB, since fewer repeat procedures were required using PET-CT– guided biopsy, with improved diagnostic yield. Radhakrishnan et al.[20] performed robotic-assisted PET-CT–guided biopsy for thoracic lesions on 25 patients with a diagnostic yield of 100%, similar to our study suggesting that PET-CT–guided TTNB effectively improves success rate of obtaining biopsy from peripheral thoracic lesions.

In the present study, pneumothorax occurred in 12.5% of cases; this incidence is comparable to previous studies of CT–guided TTNB, which reported an incidence of 5-25%.[21] Nath et al.[22] in their study reported pneumothorax and hemothorax each in 4% (n = 1) patients. The VAS score for pain was 1 (IQR: 1–2) following biopsy. All these findings highlight the results of previous studies indicating that PET-CT–guided TTNB is a safe technique for obtaining biopsy from peripheral thoracic lesions and do not carry any additional risk when compared to CT–guided TTNB.[9]

The diagnostic yield of PET-CT-guided TTNB in the current study surpassed that of previously reported traditional CT-guided TTNB, reinforcing the importance of PET-CT in identifying appropriate target lesions for obtaining biopsies from peripheral thoracic lesions. However, this finding should be interpreted with caution due to the pilot nature of the study and its small sample size. Piacentino et al.[9] in their study found that TTNB obtained under PET-CT guidance improved the sample adequacy for performing molecular studies for targeted therapies similar to our study. While the current study demonstrates the safety of PET-CT–guided TTNB, there are certain limitations that should be acknowledged. The sample size (n = 40) is relatively small, and the generalizability of the results to a larger population needs to be further explored. Additionally, a head-to-head comparison with CT-guided biopsy in the same patient cohort would have provided stronger evidence supporting the superiority of PET-CT-guided biopsy. Further research is needed to weigh the benefit of early and better diagnostic yield with high cost involved in PET-CT–guided TTNB on lung cancer management.

CONCLUSION

This study demonstrates that PET-CT-guided TTNB is a safe technique for sampling intrathoracic mass lesions, with good diagnostic yield and a similar safety profile even in tumors with internal necrosis. Future large-scale studies can further validate these results and explore additional clinical applications of PET-CT in interventional pulmonology.

Ethics

Ethics Committee Approval: The study was approved by the Institute Ethics Committee of AIIMS Raipur vide letter no: OW/RC/AIIMS-RPR/2022/1028 dated 4th February 2022 and conducted as per recommendations of amended declaration of Helsinki.

Informed Consent: Informed written consent was obtained from all patients undergoing biopsy.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.R., R.G., R.K., P.P., Concept: M.R., R.G., A.K.B., P.K.D., R.V., Design: M.R., R.G., R.K., P.P., P.K.D., R.V., Data Collection or Processing: M.R., R.G., R.K., P.P., P.K.D., R.V., Analysis or Interpretation: M.R., R.G., P.P., A.K.B., P.K.D., R.V., Literature Search: M.R., R.G., R.K., P.P., A.K.B., P.K.D., R.V., Writing: M.R., R.G., R.K., P.P., A.K.B., P.K.D., R.V.

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Original Article

Comparison of AI-based Chatbot Performance in Analyzing Clinical Scenarios versus Medical Residents: A Novel Approach in Chest Diseases Education

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ABSTRACT

OBJECTIVE: Rapid advancements in artificial intelligence (AI) technologies offer new opportunities in medical education. The aim of this study is to compare the performance of large language models, specifically ChatGPT-4 and Gemini, in analyzing clinical scenarios with that of chest diseases research assistants (residents), and to evaluate their potential roles in medical education.

MATERIAL AND METHODS: This cross-sectional, comparative study included 28 resident physicians working in the department of chest diseases at a tertiary-care university hospital. Four clinical scenarios involving diagnoses of massive pulmonary embolism, chronic obstructive pulmonary disease, asthma, and severe pneumonia/sepsis were presented to both participants and AI models (ChatGPT-4 and Gemini). Responses were scored by blinded experts based on current guidelines (Global Initiative for Chronic Obstructive Lung Disease, Global Initiative for Asthma, American Thoracic Society).

RESULTS: AI models achieved significantly higher scores than residents, particularly on structured questions requiring theoretical knowledge, classification skills, and the listing of contraindications ($P < 0.05$). However, it was observed that residents achieved success levels similar to those of AI models in situations requiring emergency intervention (e.g., shock management) through practical, results-oriented approaches. While AI models provided a broader spectrum in differential diagnosis, residents preferred "telegraphic" and practice-oriented responses.

CONCLUSION: ChatGPT and Gemini have significant potential as clinical decision-support systems and educational assistants. However, rather than replacing human factors in clinical reasoning and emergency management, they should be positioned as complementary tools that accelerate physicians' access to theoretical knowledge.

KEYWORDS: Education, medical, artificial intelligence, diagnosis, differential, clinical reasoning, decision support systems, clinical, humans

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INTRODUCTION

Artificial intelligence (AI), particularly chatbots with natural language processing capabilities, promises transformative changes in healthcare services and medical education. As stated by Davenport and Kalakota[1], the potential of AI to provide data analysis and diagnostic support in healthcare spans a wide range, from reducing administrative workloads to complex clinical decisions. With the introduction of Generative Pre-trained Transformer models like ChatGPT, a paradigm shift is occurring in how patients access information and in physicians' decision-making processes.[2]

Medical education is evolving from the traditional master–apprentice relationship to digitally supported learning models. In a widely cited study by Kung et al.[3], it was demonstrated that ChatGPT could pass the United States Medical Licensing Examination (USMLE) without any specific training. This suggests that AI is capable not only of storing information but also of demonstrating clinical reasoning abilities. Similarly, Singhal et al.[4] reported that Med-PaLM and Gemini models

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developed by Google performed at near-expert levels in medical questions.

However, the reliability of these models in clinical practice remains a subject of debate. Huang et al.[5], in their study comparing family medicine residents with AI models, noted that while AI showed high success in structured examinations, human reasoning remains critical in complex cases involving "diagnostic uncertainty." Studies in specific branches such as ophthalmology and cardiology also indicate that while AI's capacity to provide information is promising, the risk of "hallucination" (generating false information) must not be ignored.[6,7]

The practice of pulmonology (chest diseases) is a complex field in which emergency decision-making (e.g., pulmonary embolism, sepsis) and chronic disease management [chronic obstructive pulmonary disease (COPD), asthma] are intertwined. This study aims to reveal the place of these tools in residency training by using concrete data to compare the performance of AI models (ChatGPT and Gemini) in clinical scenarios with that of residents actively working in the field.

MATERIAL AND METHODS

Study Design and Ethical Approval

This study is a cross-sectional simulation conducted at the department of chest diseases of a tertiary care university hospital. Approval for the study was obtained from the Van Yüzüncü Yıl University Ethics Committee (decision dated: 31.10.2025 and numbered: 34319). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Participants

The study sample consisted of 28 resident physicians who were receiving specialization training in the relevant clinic and who volunteered to participate. ChatGPT-4 developed by OpenAI and Gemini Advanced (utilizing the Ultra 1.0 model; Google, Mountain View, CA).

Main Points

- Artificial intelligence (AI) models (ChatGPT-4 and Gemini) demonstrated superior performance compared with residents in assessments of theoretical knowledge and guideline-based classification tasks.
- Residents achieved success rates similar to those of AI models in emergency scenarios and exhibited more practical, action-oriented approaches.
- AI models show high potential as educational support tools in residency training, but they require human oversight for clinical reasoning and ethical decision-making.

Data Collection Tools (Scenarios)

Four standard clinical scenarios, prepared by expert faculty members, were used to assess participants' knowledge and clinical approach.

- Scenario 1 (Vascular Emergency): A case of massive pulmonary embolism (MPE) in the post-op period presenting with shock.
- Scenario 2 (Obstructive Lung Disease): A case of COPD presenting with exacerbation.
- Scenario 3 (Chronic Airway): An asthma case presenting in an outpatient setting.
- Scenario 4 (Infection): A young patient with severe pneumonia and sepsis.

For each scenario, 5–6 open-ended questions were asked regarding diagnosis, differential diagnosis, test requests, treatment plans, and discharge criteria. To ensure standardization, a specific prompt was used to query the AI models. The prompt was structured as follows: "Act as a senior chest diseases specialist. Evaluate the following clinical case according to current guidelines [Global Initiative for Chronic Obstructive Lung Disease (GOLD), Global Initiative for Asthma (GINA), American Thoracic Society] and answer the questions step by step." The clinical scenarios were presented to both AI models and residents in the same order. To prevent bias during the evaluation, the outputs from the AI models and the handwritten responses from the residents were transcribed into a uniform digital format (Times New Roman, 12 pt) to ensure effective blinding. The evaluators were unaware of whether a response belonged to an AI or a resident.

The residents completed the evaluation in a supervised classroom environment as a "closed-book" exam, without access to external resources, internet, or mobile devices. In contrast, AI models utilized their internal databases. This difference in access to information is acknowledged as a limitation of the study.

Implementation and Evaluation

Residents answered the questions under supervision without using external resources. The same questions were presented to the AI models without employing prompt-engineering techniques. Instead, a single neutral instruction was used to initiate the session: "Act as an expert chest diseases specialist and answer the following clinical scenario questions based on current medical guidelines." Subsequently, the scenario texts were entered directly. The responses were evaluated by two independent blinded experts using a standardized scoring system based on current guidelines. Each scenario was evaluated based on five key components: (1) Correct Diagnosis, (2) Appropriate Diagnostic Tests, (3) Treatment Strategy, (4) Dosage and Duration Accuracy, and (5) Follow-up Plan. Each component was scored on a scale of 0 to 2 (0: Incorrect/Missing, 1: Partially Correct, 2: Fully Correct/Guideline-Compliant), resulting in a maximum total score of 10 points per scenario. The average score given by the two experts was recorded as the final score.

Statistical Analysis

Categorical data were summarized as numbers and percentages, and continuous variables that were not normally distributed were presented as medians and interquartile ranges. Categorical data were compared between groups using Pearson's χ^2 test and Fisher's exact test. Because the numerical variables were not normally distributed, the Mann-Whitney U test, a non-parametric test, was used to compare continuous variables.

RESULTS

The responses of 28 resident physicians were compared with those of the ChatGPT-4 and Gemini models.

Score Comparison

Overall, AI models achieved significantly higher scores than the resident group ($P < 0.05$). However, when analyzed by scenario, the gap between resident success scores and AI scores narrowed in scenarios requiring emergency management, such as MPE. The detailed score distribution is presented in Table 1.

Diagnostic Accuracy and Theoretical Knowledge

In all scenarios, both the resident group and the AI models demonstrated nearly 100% success in making the "correct diagnosis." However, significant differences were detected in the level of detail of treatment protocols and in the classification questions (Table 2).

• COPD Scenario: While 75% of the residents performed GOLD staging (groups A, B, E) correctly, AI models responded with 100% accuracy and provided references to current guidelines.

• MPE: In the section questioning thrombolytic treatment contraindications, residents were able to list an average of 1.8±0.6 items (usually "active bleeding" and "surgery"), whereas AI models listed an average of 8 items (all absolute and relative contraindications).

Clinical Approach Differences (Qualitative Analysis)

It was observed that resident responses were shorter, more concise, and "action-oriented." For example, in the pneumonia scenario, while residents directly wrote the antibiotic from the hospital protocol (e.g., "Start Pip-Tazo"), AI models listed all alternatives in the guidelines (Quinolones, Macrolide combinations, etc.). Residents demonstrated high proficiency in the practical application of the qSOFA and CURB-65 scoring systems. The qualitative differences between human and AI responses are summarized in Table 3.

DISCUSSION

This study found that large language models (LLMs) such as ChatGPT-4 and Gemini performed better than residents receiving specialization training in solving clinical scenarios in the field of chest diseases, particularly in terms of theoretical knowledge and mastery of structured guidelines. Our findings reveal that LLMs can be powerful assistants in medical education and decision-support processes, but they cannot yet fully replace the "human factor" in practical decision-making.

Regarding theoretical knowledge and guideline mastery, AI models provided more comprehensive responses than residents, especially in questions requiring "recall," such as listing COPD staging and thrombolytic treatment contraindications. This finding supports Kung et al.'s[3] work on ChatGPT's success in the USMLE exam and Gilson et al.'s[8] studies on knowledge assessment in medical education. AI models drew an "ideal resident" profile by presenting current classifications in GOLD and GINA guidelines without error. Nori et al.[9], in their study on the medical proficiency of GPT-4, suggested that the model does not merely memorize but can also synthesize complex

Table 1. Comparison of scenario-based success scores between resident physicians and AI models

Scenario	Resident physicians (n = 28) (mean score ± SD)	ChatGPT-4 (score)	Gemini (score)	*P* value*
Scenario 1: massive PE	82.5±12.4	95.0	98.0	**0.042**
Scenario 2: COPD exacerbation	78.0±14.1	92.0	94.0	**0.038**
Scenario 3: asthma	88.0±9.5	96.0	96.0	0.112
Scenario 4: severe pneumonia/sepsis	85.5±11.2	95.0	97.0	0.085
General average	83.5±11.8	94.5	96.25	**<0.05**

*Mann-Whitney U test (significance of difference between resident mean and AI models)
AI: artificial intelligence, PE: pulmonary embolism, COPD: chronic obstructive pulmonary disease, SD: standard deviation

Table 2. Correct response rates according to evaluation criteria

Evaluation criteria	Resident physicians (correct response %)	AI models (correct response %)	Statistical significance *(P)*
Diagnostic accuracy	96.4%	100%	>0.05
Scope of differential diagnosis	65.0%	100%	**<0.001**
Compliance with guidelines (GOLD/GINA)	71.4%	100%	**<0.05**
Listing treatment contraindications	60.7%	100%	**<0.001**
Emergency management/practical approach	92.8%	90.0%	>0.05

GOLD: Global Initiative for Chronic Obstructive Lung Disease, GINA: Global Initiative for Asthma

clinical data; the high success rate in asthma/COPD differential diagnosis in our study confirms this synthesis ability.

However, a distinct difference emerged between clinical reasoning and the "human touch". When the responses of our residents were examined, they exhibited an "action-oriented" approach rather than focusing on theoretical details. For example, in emergency scenarios such as MPE, residents focused on stabilizing vital functions, whereas AI provided a more didactic breakdown. This fundamental difference in approach — human pragmatism versus AI exhaustiveness — is visually summarized in Figure 1, which contrasts the action-oriented nature of residents with the information-centric nature of AI.

As stated by Sabaner et al.[6], although medical chatbots are successful in providing information, they remain insufficient in areas requiring empathy, intuition, and ethical responsibility, which are the cornerstones of patient management. As emphasized by Lee et al.[10] in the New England Journal of Medicine, while GPT-4 shows remarkable capabilities, it requires human oversight to mitigate risks such as hallucinations; therefore, AI can currently serve only as a "co-pilot" rather than a replacement for physicians. Furthermore, as noted by Rao et al.[11], since AI models cannot know local hospital conditions and resource constraints, residents' treatment arrangements based on available facilities (e.g., antibiotic stock on hand) represent a more realistic approach.

Another critical aspect to consider is the risk of "hallucination" and the issue of reliability. One of the biggest handicaps of AI models is the condition defined in the literature as hallucination.[12] No significant hallucinations were detected in the AI models used in our study, because the scenarios were based on standard medical guidelines. This suggests, as indicated by Johnson et al.[13], that AI reliability is high in well-defined diseases. However, considering the warning by Shaw et al.[14], it is critically important for students not to develop "automation bias" (over-reliance) when using these tools in education.

These findings have significant educational implications. Our findings indicate that AI can serve as an "information provider" in chest disease education. Just as Jang and Kim[15] emphasized the success of video-based learning models, LLM-based interactive scenarios can reinforce learning in residency

Table 3. Qualitative comparison of human (resident) and AI responses

Feature	Resident physicians (human)	AI models (ChatGPT/Gemini)
Response style	Result-oriented, concise, "telegraphic"	Structured, detailed, didactic
Information source	Clinical experience + theoretical knowledge	Extensive database + guidelines
Differential diagnosis	Focuses on the most likely 2–3 diagnoses	Lists all possible diagnoses (including rare ones)
Treatment approach	Based on hospital facilities/protocols	Presents all options in academic guidelines
Most common error	Omission in listing questions (forgetting items)	Rarely presenting contextually detached suggestions

AI: artificial intelligence

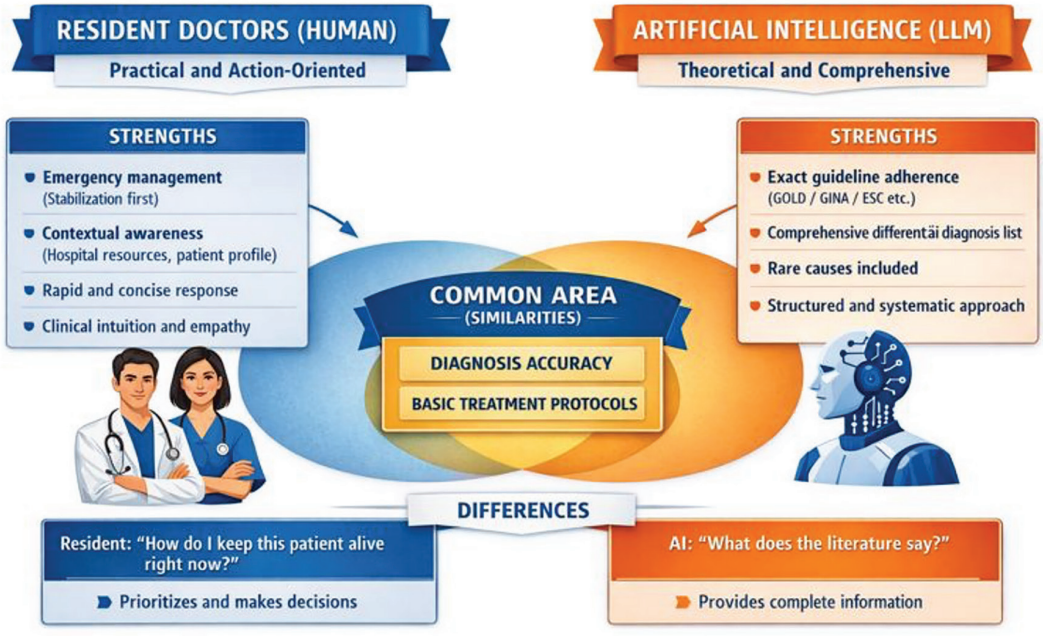


Figure 1. Conceptual comparison of clinical approaches: while resident physicians focus on "practical action" and "contextual awareness," AI models excel in "theoretical knowledge" and "structured listing." Both groups intersect at "diagnostic accuracy"

AI: artificial intelligence, LLM: large language model, GOLD: Global Initiative for Chronic Obstructive Lung Disease, GINA: Global Initiative for Asthma, ATS: American Thoracic Society, ESC: European Society of Cardiology

training. As highlighted in the systematic review by Tozsin et al.[16], AI applications have the potential to significantly contribute to medical education by providing personalized feedback and increasing student engagement. Therefore, integrating AI tools into the curriculum as a supplementary resource, rather than a replacement, appears to be the most beneficial approach. These results suggest that residency training should evolve to focus less on rote memorization and more on practical bedside skills and crisis management, because AI can effectively support theoretical queries.

Study Limitations

This study has several limitations. First, the study was conducted at a single center and included a relatively small sample of resident physicians (n = 28). This constraint may restrict the generalizability of our findings to other institutions or healthcare systems with different residency training curricula. Second, the scenarios were text-based, and visual data (such as chest X-rays or computed tomography scans) were not directly analyzed by the AI models; direct analysis of such visual data is an integral part of daily pulmonology practice. Finally, resident physicians responded under potential examination-related stress and time constraints, whereas AI models were exempt from such psychological pressures and fatigue, a factor that might have influenced the performance gap. Another limitation is the inherent disparity in testing conditions: residents answered without access to external resources, whereas AI models had instant access to vast datasets. This "unfair comparison" highlights the difference between human cognitive recall and AI data retrieval.

CONCLUSION

ChatGPT and Gemini demonstrate high accuracy in diagnosis and treatment planning for clinical scenarios involving chest diseases. AI is more effective than human memory at recalling theoretical knowledge and guideline details. However, resident physicians demonstrate their clinical competence through practical and goal-oriented approaches in emergency situations. AI models should be used as powerful educational support tools capable of rapidly addressing residents' knowledge gaps, but decision-making must always remain under the control of the physician.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Van Yüzüncü Yıl University Ethics Committee (decision dated: 31.10.2025 and numbered: 34319). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

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

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Original Article

Validation and Reliability Assessment of the Test of Adherence to Inhalers (TAI) in Turkish Patients with Chronic Obstructive Pulmonary Disease (COPD)

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ABSTRACT

OBJECTIVE: Accurate assessment of inhaler adherence is essential for optimizing treatment outcomes in patients with chronic obstructive pulmonary disease (COPD). This study aimed to evaluate the validity and reliability of the Turkish version of the Test of Adherence to Inhalers (TAI) in a multicentre COPD cohort.

MATERIAL AND METHODS: A total of 277 patients were included. Sociodemographic characteristics and adherence status [assessed by the Turkish version of the Medication Adherence Report Scale-5 (MARS-5); *İlaç Uyumunu Bildirim Ölçeği* (İUBÖ)] were recorded. Construct validity was evaluated using confirmatory factor analysis (CFA), criterion validity was evaluated by agreement with İUBÖ using kappa statistics, and known-groups validity was evaluated by comparing the number of inhaler devices used. Reliability was assessed using Cronbach's alpha coefficients and item-total correlations.

RESULTS: The mean age was 66.3±8.3 years, 81.9% of participants were male. Most patients (73.6%) used at least two inhaler devices, and 28.9% were classified as non-adherent according to İUBÖ. Based on TAI scores, 43.3% of patients had good adherence, 23.8% had intermediate adherence, and 32.9% had poor adherence. CFA supported the two-factor structure of the TAI (Tucker-Lewis Index: 0.965; Comparative Fit Index: 0.972; Root Mean Square Error of Approximation: 0.114). Criterion validity was demonstrated by good agreement between TAI and İUBÖ (kappa: 0.637, $P < 0.001$). Patients using more than one inhaler device were more likely to be non-adherent according to the TAI-10 ($P = 0.02$). Internal consistency was high for both the 10- and 12-item versions (Cronbach's alpha >0.90), with item-total correlations indicating adequate reliability.

CONCLUSION: The Turkish version of the TAI is a valid and reliable tool for assessing inhaler adherence in patients with COPD and is suitable for both clinical practice and research settings in Türkiye.

KEYWORDS: TAI, medication adherence, COPD, inhaler therapy

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable non-communicable disease that contributes substantially to global morbidity and mortality. The primary goals in the management of COPD are to reduce symptoms, exacerbations, and hospitalizations, and ultimately to lower the risk of death.[1] Long-term patient adherence to treatment plans plays a crucial role in achieving these outcomes.

However, treatment adherence in chronic diseases is generally low, averaging around 50%,[2] and has been reported to range between 35% and 70% for COPD across different settings.[3-7] A recent observational cross-sectional study of adult COPD patients in Türkiye and Saudi Arabia assessed treatment adherence using the 8-item Morisky Medication Adherence Scale (MMAS-8). The study reported an overall low adherence rate of 49.2%.[8]

Inhalers are the cornerstone of COPD treatment, and both adherence and appropriate inhalation technique play a pivotal role in successful disease management. Currently, there are multiple inhaler devices available, each requiring specific critical steps to ensure adequate drug delivery, which may be confusing for patients.[9]

Several self-report scales, such as the MMAS,[10] the Medication Adherence Report Scale (MARS),[11] and the Test of Adherence to Inhalers (TAI),[12] have been developed to assess medication adherence, and all have been validated for use in COPD. Among these instruments, the MARS can be applied to both oral and inhaled therapies, whereas the TAI was specifically developed for, and validated in, patients using inhaled therapies. Considering the critical importance of medication adherence, we aimed in this study to evaluate the validity and reliability of the Turkish version of the TAI, which is designed to assess inhaler adherence in patients with COPD.

MATERIAL AND METHODS

Study Design and Population

This multicentre cross-sectional study was conducted across various clinical settings in Türkiye. Between June 2021 and June 2022, the electronic medical records of participating centers were screened to identify patients with a diagnosis of COPD, based on the International Classification of Diseases, 10th revision codes J44, J44.0, J44.1, J44.8, and J44.9.

Eligible patients were 40–80 years of age, had been diagnosed with COPD for at least one year, and were receiving at least one COPD maintenance medication [long-acting β_2-agonist (LABA), long-acting muscarinic antagonist (LAMA), inhaled corticosteroid (ICS), LABA/ICS, LAMA/LABA, LAMA + ICS, or triple therapy (LABA/ICS/LAMA)]. Of the 291 eligible patients identified during the screening period, 277 consecutive, clinically stable patients presenting for routine COPD follow-up/diagnostic evaluation, comorbidity management, or other non-exacerbation-related reasons between June and September 2022 were included in the study.

COPD diagnosis was confirmed by spirometry, defined by a post-bronchodilator forced expiratory volume in one second to forced vital capacity ratio <0.7. Exclusion criteria included experiencing an exacerbation within the previous month (because our aim was to assess the psychometric properties of the TAI under stable clinical conditions), inability to understand or speak Turkish sufficiently to comprehend the questionnaires, and cognitive impairment.

The study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (approval number: İ11-722-20, date: 05/01/2021)

Data Collection

For all included patients, sociodemographic data (age, sex, educational status, smoking history, and comorbidities) were collected. Disease-related characteristics were systematically assessed, including the severity of dyspnea using the modified Medical Research Council (mMRC) dyspnea scale. Additional information on factors potentially influencing adherence, such as treatment regimens and history of exacerbations, was also recorded.

Adherence Assessment

Medication adherence was evaluated using two validated self-report instruments:

1. The Turkish version of the original MARS-5,[13,14] was validated in Turkish by Temeloğlu-Şen et al.,[15], and titled "*İlaç Uyumunu Bildirim Ölçeği* (İUBÖ)".

2. The Turkish version of the TAI.[12]

Both questionnaires were administered by trained investigators during face-to-face interviews at the participating centers. Before administration, the aim and structure of each questionnaire were carefully explained to participants. Interviews were conducted in a quiet clinical setting to minimize distractions, with each session lasting approximately 15–20 minutes.

Main Points

- The Turkish version of the Test of Adherence to Inhalers (TAI) demonstrated strong psychometric validity, as evidenced by confirmatory factor analysis and good agreement with an established adherence measure (İUBÖ).
- TAI effectively discriminated between patient groups with different adherence profiles, including those using multiple inhaler devices.
- Internal consistency was high for both the 10-item and 12-item TAI, indicating reliable assessment across both domains.
- The TAI is a practical and reliable tool for evaluating inhaler adherence in Turkish COPD patients, supporting its implementation in clinical practice and future research.

Scoring of the Questionnaires

İUBÖ

The İUBÖ comprises five items rated on a 5-point Likert scale (1= always, 5= never), with total scores ranging from 5 to 25. Higher scores indicate better adherence. The five items assess: (1) forgetting to take medication, (2) altering the dose, (3) stopping treatment temporarily, (4) skipping a dose, and (5) taking less than prescribed. Consistent with previous studies, a score of <23 points was considered indicative of non-adherence. The Turkish version of MARS-5 "İUBÖ" has been previously validated and used with permission.

TAI

The TAI is a validated instrument developed to assess the extent to which patients adhere to their prescribed inhaler regimens, particularly in the management of chronic airway diseases such as asthma or COPD. The TAI comprises two complementary components.

The first component, the 10-item TAI, is completed by the patient and designed to determine the overall level of treatment adherence. Each item is rated on a five-point Likert scale ranging from 1 (indicating the lowest level of adherence) to 5 (indicating the highest level of adherence), yielding a total score between 10 and 50. Based on the total score, adherence is classified as good (50 points), intermediate (46–49 points), or poor (≤45 points).

The second component in the 12-item TAI incorporates two additional questions completed by healthcare professionals. These items are scored on a two-point scale: a score of 1 reflects poor knowledge of the treatment regimen and/or the correct inhalation technique, and a score of 2 reflects good knowledge.

When the assessment objective is limited to determining the level of adherence**,** the 10-item version of the TAI is recommended. In contrast, when the aim is to evaluate both the degree of adherence and the underlying patterns of non-compliance**,** the 12-item version should be used. Furthermore, the TAI enables classification of non-compliance behaviors through predefined item groupings**:** items 1–5 assess sporadic non-compliance**,** items 6–10 assess deliberate non-compliance, and items 11–12 assess unconscious non-compliance.

The original version of the TAI, developed by Plaza et al.,[12] was translated and culturally adapted into Turkish in accordance with internationally accepted guidelines for cross-cultural adaptation of patient-reported outcome measures. The process was coordinated by the TAI Scientific Committee in collaboration with Chiesi and the MAPI Research Institute.[16] The adaptation procedure included forward translation by independent bilingual translators, backward translation into the source language, expert panel review, reconciliation of discrepancies, and cognitive debriefing interviews to ensure conceptual equivalence, linguistic accuracy, and cultural appropriateness. Permission to use the Turkish version was obtained from the original developers, and this validated version was used in the present study for validity and reliability analyses.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean ± standard deviation for normally distributed continuous variables, median (minimum–maximum) for non-normally distributed variables, and frequency (percentage) for categorical variables.

The normality of the data distribution was assessed using the Shapiro–Wilk test and visual methods (histograms and Q–Q plots). For comparisons between groups, the independent samples t-test was used for normally distributed continuous variables, whereas the Mann–Whitney U test was used for non-normally distributed continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. A sample-size justification, based on recommendations for CFA (a minimum of 10 participants per item), was applied. With 12 items, the required sample was ≥120; our sample of 277 exceeded this threshold, ensuring adequate power for factor analysis.

The validity was evaluated using construct, criterion, and known-groups validity tests.

Internal Construct Validity: Two-factor confirmatory factor analysis (CFA) for categorical data was performed in MPlus (17) to evaluate the dimensionality of TAI. Factor loadings that were positive or greater than 0.35 were retained in the scale. Tucker-Lewis Index (TLI; >0.90 acceptable, >0.95 excellent), Comparative Fit Index (CFI; >0.90 acceptable, >0.95 excellent), and Root Mean Square Error of Approximation (RMSEA; <0.08 acceptable, <0.05 excellent) were used as goodness-of-fit statistics.[18]

External Construct Validity: Within this scope, the agreement between categorical classifications obtained from the TAI and İUBÖ scales was assessed using Cohen's kappa coefficient (κ). The strength of agreement was interpreted according to Landis and Koch's criteria, where κ values <0.20 indicate slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and >0.80 almost perfect agreement.

Known Groups Validity: The known-groups method evaluates the instrument's ability to distinguish between groups known to differ on a clinically relevant attribute. In the present study, known-groups validity was examined using the chi-square test, based on predefined categories of the number of inhaler devices used. The number of inhalers representing treatment complexity was considered within the known-groups validity framework to assess the discriminatory capacity of the instrument, rather than implying a direct relationship with disease severity.

Reliability: After the internal and external construct validity was confirmed, the reliability was tested for internal consistency using Cronbach's alpha coefficient,[19] with values ≥0.70

considered acceptable and ≥0.80 indicating good reliability. Item-total correlations were calculated to further evaluate internal consistency using Spearman's correlation coefficients. A moderate to strong positive correlation was expected to support criterion validity. All tests were two-tailed, and a *P* value <0.05 was considered statistically significant.

RESULTS

A total of 277 patients from nine different centers (mean age 66.3±8.3 years) were included in the study, of whom 81.9% were male. The overall educational level was low; 61.5% of the patients had only primary or secondary school education. Active smoking was reported by 37.5% of the participants. The median COPD assessment test score was 14 (min: 1, max: 40), and the median mMRC dyspnea scale score was 2 (min: 0, max: 4).

According to the GOLD classification at diagnosis, 44.0% of patients were in stage D and 14.8% were in stage C. According to the 2023 GOLD classification, 58.5% of the patients were categorized as group E, representing the most severe clinical group. The majority of patients (73.6%, n = 204) were prescribed at least two inhaler devices, and 76.5% (n = 212) received at least one additional medication for comorbid conditions other than COPD. Long-term oxygen therapy was used by 30.7% of patients, while 19.5% were on home non-invasive ventilation. Comorbidities were present in 74.0% of the study population. No significant difference was observed in TAI scores across GOLD severity stages.

According to the İUBÖ, 80 patients (28.9%) were classified as non-adherent. Based on the TAI, 120 patients (43.3%) demonstrated good adherence, 66 (23.8%) demonstrated intermediate adherence, and 91 (32.9%) demonstrated poor adherence. Regarding non-compliance patterns, 145 (52.3%) patients exhibited sporadic non-compliance, 105 (37.9%) exhibited deliberate non-compliance, and 100 (36.1%) exhibited unconscious non-compliance.

Validity was assessed using construct, criterion, and known-groups validity tests.

Internal Construct Validity: Following the CFA performed on 12 questions with a 2-factor structure (where patient-completed items and healthcare professional-completed items were analysed separately), the goodness-of-fit statistics were: TLI: 0.965, CFI: 0.972, and RMSEA: 0.114. The factor loadings of the questions on the factors were presented in Table 1.

External Construct Validity: Within the scope of external construct validity, the agreement between the scores obtained from the TAI and those obtained from the İUBÖ scale was evaluated using the κ. The overall agreement was 0.637 ($P < 0.001$) for 10 items, indicating a good level of agreement. The patients classified as non-adherent according to the İUBÖ had lower TAI scores compared with the İUBÖ-adherent group in both domains ($P < 0.001$) (Table 2).

Known-Groups Validity: The majority of patients identified as non-adherent based on the TAI-10 were using more than one inhaler device (n = 59, 64.9%) ($P = 0.02$).

Reliability: It has been tested for internal consistency. The Cronbach's alpha coefficient ranged from 0.913 to 0.925 for the patient domain (Q1-10) and from 0.901 to 0.911 (Q1-12) for the patient/healthcare professional domains (Table 3). Item-total correlations were found ranging from 0.442–0.657 ($P < 0.001$) for patient domain, 0.439–0.644 ($P < 0.001$) for the patient/healthcare professional domains demonstrating a moderate positive correlation that supported criterion validity (Table 4).

DISCUSSION

Medication adherence remains a cornerstone of chronic disease management; however, it continues to be suboptimal, with global estimates indicating that only about half of patients adhere to prescribed treatment regimens.[2] In COPD, adherence to inhaled therapy is particularly critical, as it directly influences symptom control, exacerbation rates, and overall disease progression.[20] Poor adherence is associated with increased healthcare utilization, exacerbations, poorer quality of life, and higher mortality.[3-7,20] Therefore, accurate assessment of inhaler adherence is essential to identify barriers and guide targeted

Table 1. Two-factor confirmatory factor analysis of 12-item Test of Adherence to Inhalers with categorical data

	Factor 1 Patient domain	Factor 2 Healthcare professional domain
Q1	0.868	-
Q2	0.854	-
Q3	0.857	-
Q4	0.901	-
Q5	0.864	-
Q6	0.866	-
Q7	0.910	-
Q8	0.871	-
Q9	0.895	-
Q10	0.801	-
Q11	-	1.205
Q12	-	0.691

Q: Question

Table 2. The relation between Test of Adherence to Inhalers items according to Medication Adherence Report Scale-5

	İUBÖ adherent (n = 197)	İUBÖ non-adherent (n = 80)	*P* value
TAI (Q1–5)	25 (11–25)	19 (9–25)	<0.001
TAI (Q6–10)	25 (15–25)	21.5 (11–25)	<0.001
TAI (Q1–10)	50 (23–50)	38.5 (24–50)	<0.001
TAI (Q1–12)	53 (27–54)	42.5 (26–54)	<0.001

TAI: Test of adherence to inhalers, İUBÖ: *İlaç Uyumunu Bildirim Ölçeği* [Medication Adherence Report Scale-5 (MARS-5)], Q: Question

Table 3. Internal consistency (Cronbach's alpha values) of the Test of Adherence to Inhalers

Patient domain	When item removed	Cronbach alpha for Q (1–5)[a] Q (6–10)[b] Q (11–12)[c]	Cronbach alpha for Q (1–10)	Cronbach alpha for Q (1–12)
Q1–Q5	1	0.865[a]	0.917	0.904
	2	0.863[a]	0.919	0.907
	3	0.856[a]	0.918	0.906
	4	0.847[a]	0.913	0.901
	5	0.872[a]	0.915	0.903
Q6–Q10	6	0.860[b]	0.916	0.903
	7	0.833[b]	0.915	0.902
	8	0.867[b]	0.916	0.902
	9	0.846[b]	0.917	0.904
	10	0.886[b]	0.925	0.911
Healthcare professional domain				
Q11–Q12	11	0.912[c]	-	0.916
	12	0.769[c]	-	0.921

Q: Question

Table 4. Item total score correlation for the Test of Adherence to Inhalers

		Q (1–5)[a]/Q (6–10)[b]		Q (1–10)		Q (1–12)	
Patient domain	Q	r	*P*	r	*P*	r	*P*
Q1–Q5	1	0.701[a]	<0.001	0.450	<0.001	0.480	<0.001
	2	0.832[a]	<0.001	0.564	<0.001	0.556	<0.001
	3	0.824[a]	<0.001	0.657	<0.001	0.644	<0.001
	4	0.775[a]	<0.001	0.620	<0.001	0.606	<0.001
	5	0.702[a]	<0.001	0.626	<0.001	0.615	<0.001
Q6–Q10	6	0.795[b]	<0.001	0.617	<0.001	0.609	<0.001
	7	0.827[b]	<0.001	0.608	<0.001	0.607	<0.001
	8	0.858[b]	<0.001	0.607	<0.001	0.616	<0.001
	9	0.796[b]	<0.001	0.592	<0.001	0.587	<0.001
	10	0.606[b]	<0.001	0.442	<0.001	0.439	<0.001
Healthcare professional domain							
Q11–12	11			0.262	<0.001	0.369	<0.001
	12			0.085	0.156	0.304	<0.001

Q: Question

interventions. In this context, the present study evaluated the validity and reliability of the Turkish version of the TAI and demonstrated that it has robust psychometric properties in patients with COPD. CFA supported the original two-factor structure; criterion validity showed substantial agreement with the validated İUBÖ (κ: 0.637); and internal consistency was excellent (Cronbach's alpha >0.90). Additionally, the instrument demonstrated adequate discriminatory capacity in known-groups analysis.

The validity was evaluated by construct, criterion, and known-groups validity tests. The construct validity of the Turkish version of the TAI was confirmed by CFA, which demonstrated an acceptable model fit with two underlying domains: the patient-completed items (questions 1–10) and the healthcare professional-completed items (questions 11–12). This structure aligns with the original version developed by Plaza et al.[12] and has been replicated in several cross-cultural validations, including studies from Spain, China, Iran, Malaysia, and most recently, Taiwan.[21-25] The goodness-of-fit indices in our analysis (TLI: 0.965, CFI: 0.972, RMSEA: 0.114) were consistent with or superior to those reported in previous validations (RMSEA range 0.07–0.12), supporting the construct validity of the instrument.

Criterion validity was evaluated by comparing TAI and İUBÖ scores, which demonstrated a good level of agreement (κ: 0.637, $P < 0.001$). These findings are consistent with earlier reports showing modest correlations between self-reported adherence scales and electronic monitoring or pharmacy refill data.[12,21] Such moderate associations are expected since self-report tools capture the behavioural dimensions of adherence,

whereas electronic or pharmacologic metrics assess dose-based adherence. A 2024 systematic review and meta-analysis by Vauterin et al.[20] reinforced that patient-reported measures remain valuable in clinical practice, especially when used alongside objective adherence monitoring to understand non-adherence subtypes.

Known-groups validity analysis in this study demonstrated that the majority of patients identified as non-adherent based on the TAI-10 were using more than one inhaler device, suggesting that increasing treatment complexity may adversely affect adherence. This finding is consistent with the comprehensive review by Usmani et al.,[26] which included 114 articles and reported that simplifying inhaler regimens—particularly by using the same type of device for concomitant inhaled medications—minimizes device-related errors, improves adherence, and enhances clinical outcomes. Similarly, in another study, multivariable analysis showed that the use of multiple inhaler devices (adjusted odds ratio: 11.68; 95% confidence interval: 3.29–41.51) were independently associated with an increased likelihood of making critical inhaler technique errors.[27] Different inhaler types (e.g., dry powder inhaler, metered-dose inhaler, soft-mist inhalers) may also independently affect usability and adherence. However, stratified or multivariable analyses by inhaler device type were not prespecified within the study's psychometric validation framework. This limitation has now been explicitly acknowledged.

Regarding reliability, the internal consistency of the Turkish TAI was excellent: Cronbach's alpha coefficients exceeded 0.9 for both the 10-item and 12-item TAI, surpassing the acceptable reliability threshold. Item-total correlations were at least moderately positive, confirming homogeneity among items. These findings are in line with previous psychometric evaluations, which reported Cronbach's alpha values of 0.843 in China,[22] 0.873 in Spain,[21] 0.986 in Iran,[23] 0.823 in Malaysia,[24] and 0.82 in Taiwan.[25] This consistency across different cultures shows that the TAI is a reliable and standardized tool for measuring inhaler adherence.

Study Limitations

Despite these findings, this study has some limitations. First, its cross-sectional design does not allow conclusions about causality. Second, adherence was measured using self-report questionnaires, which may lead to reporting bias. Third, most participating centers were tertiary referral hospitals, which may have resulted in a higher proportion of severe COPD cases and may have limited the generalizability of the results. Finally, although exploratory analyses were conducted, the effects of treatment complexity and inhaler device type cannot be completely ruled out.

CONCLUSION

This multicenter study demonstrates that the Turkish version of the TAI is a valid and reliable instrument for assessing inhaler adherence in patients with COPD. The tool showed strong internal consistency, a supported factor structure, and substantial agreement with an established adherence scale. Its implementation may facilitate standardized assessment of inhaler adherence in both clinical practice and research settings in Türkiye.

Ethics

Ethics Committee Approval: The study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (approval number: İ11-722-20, date: 05/01/2021)

Informed Consent: Consent forms are obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Y., E.S.Ö., D.P.Y., A.M.Ş., E.S., N.K., A.M., Y.V., A.B., F.E., İ.Ç.C., Concept: A.Ö.A., E.Ş., S.A.N., D.P.Y., N.K., A.B., A.G., İ.Ç.C., M.P., İ.Ş., G.U., O.Y.T., A.K., Design: A.Ö.A., E.Ş., A.B., Data Collection or Processing: A.Ö.A., E.Ş., S.Y., D.G., S.A.N., E.S.Ö., D.P.Y., A.M.Ş., E.S., N.K., A.M., Y.V., F.E., A.G., İ.Ç.C., Analysis or Interpretation: A.Ö.A., D.G., Literature Search: A.Ö.A., İ.Ç.C., M.P., İ.Ş., G.U., O.Y.T., A.K., Writing: A.Ö.A.

Conflict of Interest: Aylin Özgen Alpaydın, MD, and İpek Çaylı Candemir, MD, are Editors of Thoracic Research and Practice. They were not involved in the peer-review process of this article and had no access to any information regarding its peer review. Nurdan Köktürk, MD, is a member Editorial Board of Thoracic Research and Practice. She was not involved in the peer-review process of this article and had no access to any information regarding its peer review. The other authors declare no conflicts of interest.

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Declaration of AI Use: During the preparation of this work, the author(s) utilized OpenAI's ChatGPT to review the language of the manuscript. After carefully reviewing and editing the content as necessary, full responsibility for the publication's content is taken by the author(s). This incorporation of AI tool usage primarily impacted the editing of the manuscript.

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Original Article

Subcutaneous Adipose Tissue Attenuation Change on Chest CT Is Associated with Overall Survival After Allogeneic Hematopoietic Stem Cell Transplantation

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ABSTRACT

OBJECTIVE: Early chest computed tomography (CT) examinations are frequently performed after allogeneic hematopoietic stem cell transplantation (allo-HSCT) due to respiratory symptoms or clinical deterioration. Subcutaneous adipose tissue attenuation (SATA) has recently been proposed as a quantitative imaging marker of systemic tissue alterations related to fluid redistribution and inflammatory processes. This study aimed to evaluate interval changes in SATA after allo-HSCT and to investigate their association with overall survival.

MATERIAL AND METHODS: In this retrospective single-center study, adult allo-HSCT recipients who underwent non-contrast chest CT both before transplantation and within 30 days after transplantation were included. SATA was measured in Hounsfield units (HU) using standardized circular regions of interest placed in the anterior chest wall. The interval change in attenuation Hounsfield units (ΔHU) was calculated as post-transplant minus pre-transplant values. Cox proportional hazards regression was used to assess the association between ΔHU and survival. Kaplan–Meier analysis was performed after dichotomization according to the median ΔHU value.

RESULTS: A total of 104 patients were included. SATA increased on early post-transplant CT compared with baseline ($P < 0.001$). Higher ΔHU values were associated with worse overall survival (hazard ratio per 5-HU increase: 1.18; 95% confidence interval: 1.03–1.35; $P = 0.016$). Patients with ΔHU above the median (16-HU) demonstrated significantly poorer survival compared with those below the median (log-rank $P = 0.0003$).

CONCLUSION: SATA increases after allo-HSCT, and greater interval increases are associated with worse survival outcomes. Quantitative assessment of SATA may provide a simple, non-invasive imaging biomarker for early risk stratification in allo-HSCT recipients.

KEYWORDS: Allogeneic hematopoietic stem cell transplantation, chest CT, subcutaneous adipose tissue attenuation, imaging biomarker, overall survival

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a potentially curative treatment for a wide range of hematologic malignancies and bone marrow failure syndromes. Despite advances in conditioning regimens, donor selection, and supportive care, allo-HSCT continues to be associated with substantial early morbidity and mortality related to treatment toxicity, immune activation, endothelial injury, and systemic inflammatory responses.[1-3] Early identification of patients at increased risk of adverse outcomes remains an important clinical challenge in the post-transplant period.

Chest computed tomography (CT) is frequently performed in allo-HSCT recipients during the early post-transplant phase because of respiratory symptoms, fever, or non-specific clinical deterioration.[4-6] In addition to detecting pulmonary complications such as infection, drug-related lung injury, or graft-related inflammatory processes, CT examinations also provide quantitative information regarding extrapulmonary tissues. Increasingly, CT-derived body composition and tissue attenuation parameters have been recognized as potential imaging biomarkers reflecting systemic physiological or pathological states.[7]

Adipose tissue is no longer considered a passive energy storage compartment but rather a metabolically active tissue with important structural and endocrine functions.[8,9] In recent years, CT-based measurements of adipose tissue quality—commonly assessed through attenuation values in Hounsfield units (HU)—have been associated with cardiometabolic risk and other adverse clinical outcomes.[10-12]

In particular, increased attenuation of subcutaneous adipose tissue on CT may reflect changes in tissue composition and fluid content. In a recent chest CT study, subcutaneous fat tissue density was markedly higher in patients with pulmonary edema than in patients with viral or Pneumocystis jirovecii pneumonia and healthy controls.[11] Histologic data from other clinical settings also suggest that higher subcutaneous adipose tissue radiodensity can be accompanied by smaller adipocytes and expansion of the interstitial compartment.[12] Because CT examinations are commonly performed in transplant recipients, quantitative assessment of subcutaneous adipose tissue attenuation (SATA) may provide additional information beyond conventional radiologic findings.

However, the potential clinical relevance of SATA in allo-HSCT recipients has not been systematically investigated. In particular, it remains unclear whether interval changes in SATA following transplantation may be associated with clinical outcomes such as overall survival.

Therefore, the aim of the present study was to evaluate changes in SATA on chest CT before and after allo-HSCT and to investigate whether the interval change in attenuation Hounsfield units (ΔHU) is associated with overall survival. We hypothesized that early changes in SATA may reflect systemic tissue alterations detectable on CT and may be associated with prognosis in allo-HSCT recipients.

MATERIAL AND METHODS

Study Design and Population

This retrospective single-center study was approved by the Koç University Biomedical and Retrospective Research Ethics Committee (approval number: 2026.077.IRB2.039; February 11, 2026). The requirement for informed consent was waived by the Ethics Committee because of the retrospective design of the study. Patient anonymity was preserved, and all data were handled in accordance with institutional and international ethical standards.

Chest CT examinations of patients who underwent allo-HSCT between December 4, 2017, and June 13, 2025, were retrospectively reviewed. As shown in Figure 1, patients with radiological or clinical evidence of infection, those diagnosed with pulmonary edema, those with non-120 kVp CT acquisition, and patients with insufficient CT image quality were excluded from the analysis. Among the remaining patients, adult recipients (≥18 years) who had both pre-transplant and early post-transplant non-contrast chest CT examinations were included.

Early post-transplant CT examinations were defined as CT scans obtained within the first 30 days after transplantation. After applying the inclusion and exclusion criteria, the final study population consisted of patients with available paired pre- and post-transplant CT examinations suitable for quantitative analysis. The interval between the baseline CT examination and allogeneic HSCT was recorded and summarized as the median and interquartile range (IQR).

Clinical information including age, sex, underlying hematologic diagnosis, transplantation date, mortality status, and follow-up duration was obtained from institutional electronic medical records. In addition, the hematopoietic cell transplantation-comorbidity index (HCT-CI) and the occurrence of clinically significant graft-versus-host disease (GVHD) were recorded. GVHD was analyzed as a binary variable and defined as the presence of grade III–IV acute GVHD (yes/no).

Computed Tomography Acquisition Protocol

All chest CT examinations were performed using 64–detector row CT systems (Somatom® Definition AS and Somatom® Definition Flash; Siemens Healthineers, Forchheim, Germany). Scans were obtained without intravenous contrast administration with patients in the supine position during end-inspiratory breath-hold and with the arms positioned above the head.

The scan range extended from the lung apices to the costophrenic angles. Tube voltage was standardized at 120 kVp, and tube current was adjusted using automatic exposure modulation. Images were acquired with a 512 × 512 matrix and a patient-adapted reconstruction field of view. Images were reconstructed using a medium soft-tissue convolution kernel with slice thicknesses ranging from 1 to 3 mm. For each patient, pre- and post-transplant CT examinations were evaluated using image series reconstructed with the same slice thickness.

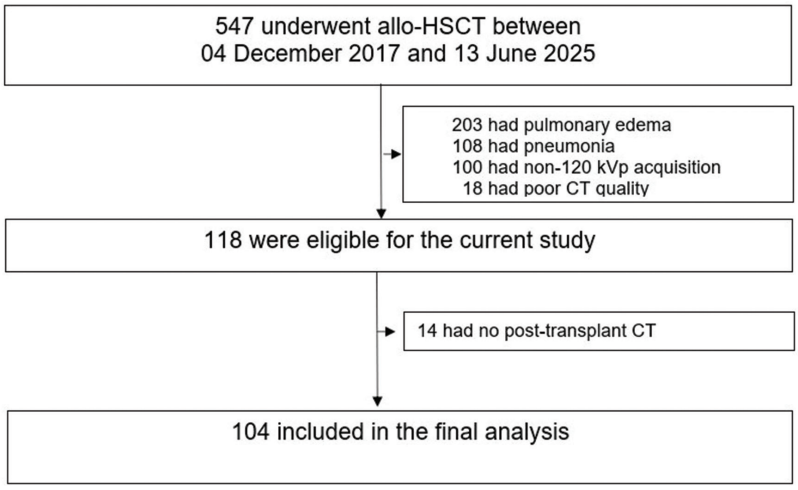


Figure 1. Flowchart of the study population

HSCT: hematopoietic stem cell transplantation, CT: computed tomography

Measurement of Subcutaneous Adipose Tissue Attenuation

SATA was measured on axial CT images. Mediastinal window settings (window width: 350 HU; window level: 50 HU) were used only to facilitate consistent anatomical localization and region of interest (ROI) placement.

A circular ROI with a diameter of approximately 1 cm was placed within the subcutaneous adipose tissue of the anterior chest wall at a standardized anatomical location defined by the intersection of the midclavicular line and the level of the xiphoid tip. At the predefined anatomical level, three separate circular ROI measurements were obtained from the subcutaneous adipose tissue while avoiding skin, breast tissue, muscle, vessels, fibrous septa, and imaging artifacts. The mean of these three measurements was used as the final SATA value for each CT examination. Care was taken to avoid inclusion of skin, breast tissue, muscle, vessels, fibrous septa, or imaging artifacts.

Mean attenuation values were recorded in HU. Measurements were performed on both pre-transplant and post-transplant CT scans. The ΔHU was calculated as: ΔHU = Post-transplant SATA − Pre-transplant SATA. To assess measurement reproducibility, all CT examinations were re-measured by the same thoracic radiologist after a 4-week interval while blinded to the initial measurements. For the primary analyses, the initial measurements were used. Repeat measurements were performed solely for intraobserver reproducibility assessment and were not averaged with the initial measurements. Intraobserver agreement was assessed using the intraclass correlation coefficient (ICC).

Representative pre- and early post-transplant CT images demonstrating ROI placement are shown in Figure 2.

Assessment of Pleural and Pericardial Effusions

Pleural and pericardial effusions were evaluated on early post-transplant CT examinations. Effusion thickness was measured on axial images at the point of maximal fluid accumulation perpendicular to the adjacent pleural or pericardial surface. Measurements were recorded in millimeters.

These findings were evaluated as contextual imaging parameters reflecting possible fluid redistribution in the early post-transplant period.

Outcome Definition

The primary outcome of the study was overall survival. Survival time was calculated from the date of allo-HSCT to the date of death or last clinical follow-up. Patients who were alive at the last follow-up were censored at that date.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (IQR), as appropriate. Categorical variables were presented as counts and percentages.

Pre- and post-transplant SATA measurements were compared using the paired-samples t-test.

Overall survival was calculated from the date of allo-HSCT to death from any cause or last clinical follow-up. The association between the ΔHU and overall survival was first evaluated using univariable Cox proportional hazards regression with ΔHU analyzed as a continuous variable (per 5 HU increase). Multivariable Cox regression analysis was then performed to adjust for clinically relevant covariates including age, sex, underlying hematologic diagnosis, the HCT-CI, and GVHD. Because pleural and pericardial effusions may represent downstream manifestations of the same biological pathway reflected by ΔHU, these variables were evaluated in separate sensitivity analyses rather than included in the primary multivariable model. Owing to missing values for HCT-CI and GVHD, analyses including these variables were performed using complete-case data. As an additional sensitivity analysis, the interval between the baseline CT examination and transplantation was included in the multivariable model to assess whether variability in baseline CT timing influenced the observed association between ΔHU and survival.

To facilitate visualization of survival patterns, patients were additionally dichotomized according to the cohort median

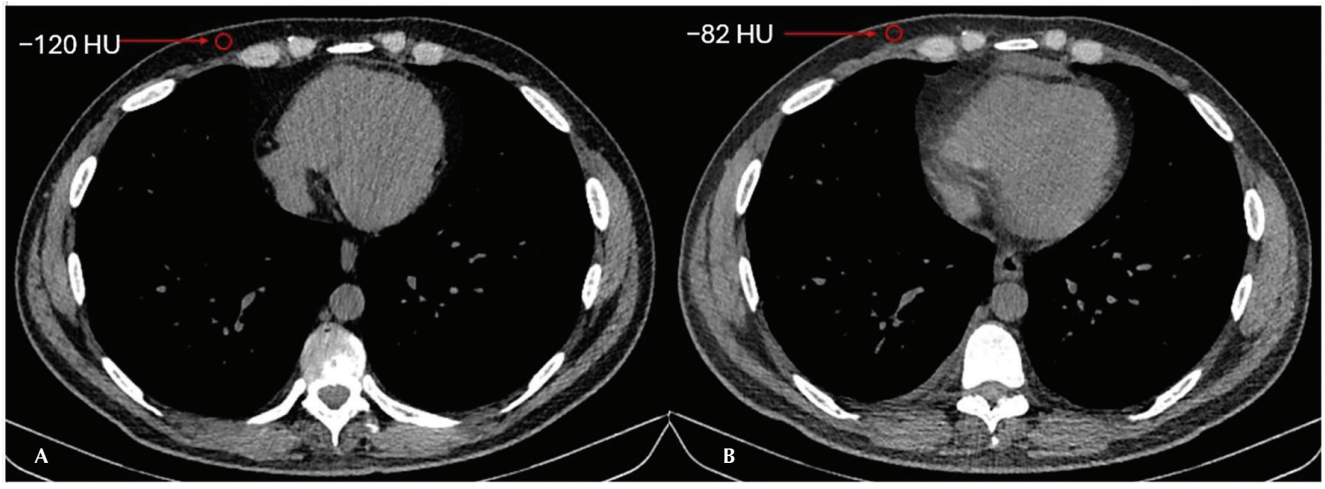


Figure 2. Representative axial non-contrast chest CT images demonstrating subcutaneous adipose tissue attenuation measurements before (A) and after (B) allogeneic hematopoietic stem cell transplantation. A circular region of interest (ROI) was placed within the anterior chest wall subcutaneous adipose tissue at the level of the xiphoid tip while avoiding skin, muscle, vessels, fibrous septa, and imaging artifacts. The displayed attenuation values represent the mean ROI attenuation (HU)

CT: computed tomography, HU: Hounsfield units

ΔHU value, and Kaplan–Meier survival curves were compared using the log-rank test. Because the median represented a data-derived cutpoint, this analysis was considered descriptive and intended for visualization rather than confirmatory inference. Univariable Cox regression was also performed using the dichotomized ΔHU variable.

The proportional hazards assumption was evaluated for the Cox regression models, and the linearity of the continuous ΔHU term was assessed before final model interpretation. All statistical tests were two-sided, and a *P* value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient Characteristics

As illustrated in Figure 1, a total of 104 patients were included in the final analysis. As summarized in Table 1, the baseline CT examination was performed a median of 10 days before transplantation (IQR: 9–16 days). The mean age of the study population was 51.5±14.5 years, and 63 patients (60.6%) were male. The most common indications for allo-HSCT were acute myeloid leukemia, acute lymphoblastic leukemia, and non-Hodgkin lymphoma. During the follow-up period, 54 deaths (51.9%) were observed. The median follow-up duration was 15.2 months (IQR: 3.9–40.1 months).

Changes in Subcutaneous Adipose Tissue Attenuation

SATA increased significantly on early post-transplant CT compared with pre-transplant baseline measurements. The mean pre-transplant SATA value was −113.0±8.4 HU, whereas the mean post-transplant SATA value was −96.5±9.6 HU. The mean ΔHU was 16.5±10.8 HU, indicating a substantial increase in adipose tissue attenuation after transplantation (Table 2). Intraobserver reproducibility was good for both pre-transplant and early post-transplant SATA measurements, with ICC values of 0.789 [95% confidence interval (CI), 0.705–0.845] and 0.879 (95% CI, 0.825–0.911), respectively.

Association Between ΔHU and Survival

Overall survival was calculated from the date of transplantation. In univariable Cox regression, increasing ΔHU values were

Table 1. Baseline characteristics of the study population

Variable	Value
Number of patients	**104**
Age (mean ± SD), years	51.5±14.5
Male sex	63 (60.6%)
Female sex	41 (39.4%)
Underlying hematologic diagnosis	
• Acute myeloid leukemia	37 (35.6%)
• Acute lymphoblastic leukemia	16 (15.4%)
• Non-Hodgkin lymphoma*	20 (19.2%)
• Myelodysplastic syndrome	8 (7.7%)
• Myelofibrosis	5 (4.8%)
• Hodgkin lymphoma	4 (3.8%)
• Other diagnoses	14 (13.5%)
GVHD > grade II†	11/54 (20.4%)
HCT-CI‡	Median 2 (IQR 0–3)
Deaths	54 (51.9%)
Median follow-up (IQR), months	15.2 (3.9–40.1)

Data are presented as mean ± standard deviation (SD), number (percentage), or median [interquartile range (IQR)] as appropriate. Follow-up time was calculated from the date of allogeneic hematopoietic stem cell transplantation to the date of death or last clinical follow-up

*Includes diffuse large B-cell lymphoma, follicular lymphoma, peripheral T-cell lymphoma, and other non-Hodgkin lymphoma subtypes.

†Available in 54 patients

‡Available in 82 patients

GVHD: graft-versus-host disease, HCT-CI: hematopoietic cell transplantation–comorbidity index

associated with higher mortality risk (HR per 5–HU increase, 1.18; 95% CI: 1.03–1.34; $P = 0.017$). After adjustment for age, sex, and underlying hematologic diagnosis, this association remained significant (HR per 5–HU increase, 1.18; 95% CI: 1.03–1.35; $P = 0.016$) (Table 3). Additional adjustment for HCT-CI and GVHD in complete-case analyses yielded similar results. Sensitivity analyses further showed that additional adjustment for pleural and pericardial effusions, as well as for the interval between the baseline CT examination and transplantation, did not materially alter the observed association between ΔHU and overall survival.

For visualization of survival differences, patients were dichotomized according to the cohort median ΔHU value (16 HU). Patients with ΔHU above the median had a significantly higher mortality risk than those below the median in univariable analysis (HR: 2.61; 95% CI: 1.51–4.51; $P = 0.0006$). As shown in Figure 3, Kaplan–Meier analysis demonstrated significantly poorer survival in patients with ΔHU above the median (log-rank $P = 0.0003$). Because the median represented a data-derived cutpoint, this analysis was performed for visualization of survival patterns rather than confirmatory inference. No evidence of non-linearity was observed for the continuous ΔHU term.

DISCUSSION

In this study, we evaluated interval changes in SATA on chest CT in patients undergoing allo-HSCT and investigated their association with overall survival. Our results demonstrate three principal findings. First, SATA increased significantly on early post-transplant CT compared with pre-transplant baseline values. Second, greater ΔHU were consistently associated with worse overall survival across univariable and multivariable Cox regression models, including sensitivity analyses incorporating clinically relevant transplant-related factors. Third, Kaplan–Meier analysis showed significantly poorer survival in patients with ΔHU values above the cohort median. The stronger separation observed in the median-based Kaplan–Meier analysis compared with the continuous per-5–HU model may partly reflect the limited sample size and the use of a data-derived cutpoint, which can accentuate apparent between-group differences; therefore, the dichotomized analysis should be interpreted as descriptive rather than confirmatory.

Allo-HSCT is associated with profound systemic physiological changes related to conditioning regimens, immune activation, endothelial injury, and inflammatory responses.[1-3] These processes may lead to alterations in vascular permeability, tissue fluid balance, and inflammatory signaling pathways. While CT imaging in this population is primarily performed to evaluate pulmonary complications, the technique also provides quantitative information regarding extrapulmonary tissues.[4-7] Pleural effusion, ascites, and pericardial effusion have also been reported after allo-HSCT and may represent manifestations of systemic fluid imbalance and endothelial dysfunction.[13-15]

To our knowledge, this is the first study to investigate interval changes in SATA on CT in patients undergoing allo-HSCT and to evaluate their association with overall survival. In recent

Table 2. Subcutaneous adipose tissue attenuation measurements

Measurement	Mean (HU)	SD
Pre-transplant SATA	−113.0	8.4
Post-transplant SATA	−96.5	9.6
ΔHU	16.5	10.8

SATA: subcutaneous adipose tissue attenuation, HU: Hounsfield unit, ΔHU: interval change in attenuation Hounsfield units

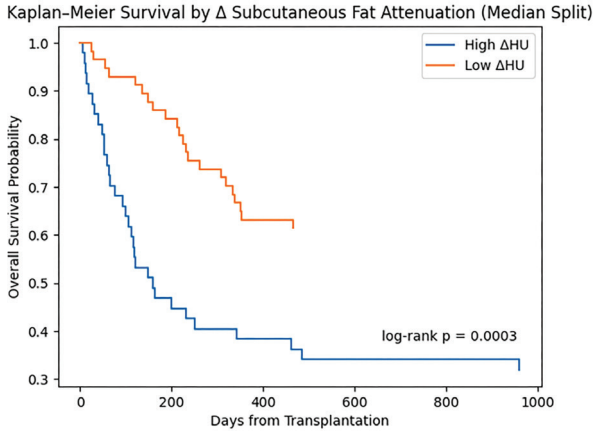


Figure 3. Kaplan–Meier survival curves stratified by the median interval change in attenuation Hounsfield units (ΔHU). Patients with ΔHU above the cohort median (16 HU) showed significantly worse overall survival compared with those below the median (log-rank $P = 0.0003$)

Table 3. Cox regression models for overall survival

Model	Variables included	n/deaths	ΔHU HR per 5 HU	95% CI	*P* value
Univariable	ΔHU	104/54	1.18	1.03–1.34	0.017
Model 1	ΔHU, age, sex, diagnosis	104/54	1.18	1.03–1.35	0.016
Model 2	Model 1 + HCT-CI	82/39	1.24	1.04–1.48	0.016
Model 3	Model 1 + GVHD >2	54/22	1.45	1.13–1.85	0.003
Model 4	Model 1 + HCT-CI + GVHD >2	49/21	1.44	1.09–1.89	0.009
Sensitivity model	Model 4 + any effusion	49/21	1.48	1.12–1.97	0.006

Hazard ratios were estimated using Cox proportional hazards regression. ΔHU represents the interval change in subcutaneous adipose tissue attenuation and is expressed per 5–HU increase. Models including HCT-CI and GVHD were performed as complete-case analyses because of missing data. The sensitivity model additionally included the presence of pleural and/or pericardial effusion

ΔHU: interval change in attenuation Hounsfield units, CI: confidence interval, GVHD: graft-versus-host disease, HCT-CI: hematopoietic cell transplantation–comorbidity index, HR: hazard ratio

years, increasing attention has been directed toward CT-derived tissue attenuation measurements as potential biomarkers of systemic disease states.[7,10-12] Unlike traditional measures of fat quantity, attenuation-based metrics may capture structural or compositional differences within adipose tissue.[10-12]

Subcutaneous adipose tissue is a biologically active tissue whose CT attenuation reflects its composition rather than fat volume alone.[8-10] Higher attenuation values may be associated with lower lipid content and with alterations in the interstitial or cellular components of adipose tissue.[10-12] In the study by Ebadi et al.[12], higher subcutaneous adipose tissue radiodensity was associated with smaller adipocytes, expansion of the interstitial compartment, and increased mortality in patients with cirrhosis.

Previous CT-based studies have shown that adipose tissue attenuation can carry clinically relevant information beyond adipose tissue quantity. Rosenquist et al. demonstrated associations between visceral and subcutaneous fat attenuation and cardiometabolic risk, while Pickhardt et al. showed that automated CT-derived body composition biomarkers can contribute to prediction of future cardiovascular events and mortality.[7,10] In addition, Ebadi et al.[12], reported an association between higher subcutaneous adipose tissue radiodensity and mortality. Together, these findings support the concept that CT-derived adipose tissue attenuation may reflect clinically relevant tissue characteristics.

Our findings extend this concept to the allo-HSCT population. The observed increase in SATA following transplantation suggests that adipose tissue attenuation may be sensitive to early post-transplant systemic changes. Although the precise biological mechanisms underlying these attenuation changes cannot be determined from imaging data alone, several potential explanations may be considered. Conditioning-related endothelial injury, inflammatory activation, and altered vascular permeability are well-described features of the early post-transplant period. These processes may promote interstitial fluid shifts or inflammatory alterations within adipose tissue, potentially leading to measurable changes in CT attenuation.

Importantly, our results demonstrate that the magnitude of attenuation change, rather than the absolute attenuation value at a single time point, was associated with survival. This observation suggests that dynamic changes in adipose tissue attenuation may capture clinically relevant physiological alterations occurring during the early post-transplant phase. In this context, ΔHU may function as a surrogate imaging marker of systemic stress or tissue injury.

From a clinical perspective, quantitative evaluation of SATA may provide complementary information beyond conventional CT findings. Chest CT examinations are frequently performed in allo-HSCT recipients for various clinical indications, and SATA measurements can be obtained without additional imaging or radiation exposure. Therefore, assessment of adipose tissue attenuation could potentially be incorporated into routine radiologic evaluation as an additional quantitative parameter.

An important methodological consideration is that pleural and pericardial effusions may represent downstream manifestations of the same pathophysiological processes reflected by increasing ΔHU, including endothelial dysfunction, capillary leak, and interstitial fluid redistribution. Therefore, these imaging findings may function as mediators rather than true confounders. For this reason, adjustment for pleural and pericardial effusions was considered a sensitivity analysis rather than the primary multivariable model.

Importantly, patients with clinically or radiologically overt pulmonary edema and pneumonia were excluded from the present study to minimize potential confounding by established pulmonary pathology. Nevertheless, exclusion of overt pulmonary edema does not exclude more subtle systemic endothelial injury, increased vascular permeability, or interstitial fluid redistribution, all of which are recognized features of the early post-transplant period. Accordingly, the observed increase in ΔHU may reflect these subclinical systemic alterations rather than clinically apparent pulmonary edema.

Nevertheless, these findings should be interpreted cautiously. Although increased ΔHU values were associated with worse survival, this observational study cannot establish a causal relationship between adipose tissue attenuation changes and mortality. Rather, ΔHU should be considered a potential imaging biomarker reflecting underlying systemic processes that may influence prognosis. Although these mechanisms are biologically plausible, the present imaging study cannot determine which pathway predominates, and the observed association should not be interpreted as evidence of causality. Future studies integrating imaging biomarkers with circulating markers of endothelial dysfunction and inflammation are warranted to clarify the underlying mechanisms.

Study Limitations

Several limitations should be acknowledged. First, the retrospective design may introduce selection bias related to the clinical indications for CT imaging. Second, measurements were obtained from a single standardized ROI on a single axial CT slice. Although this approach demonstrated good intraobserver reproducibility, future studies should evaluate whether multi-slice or bilateral averaging further improves measurement robustness. Third, biochemical inflammatory markers were not systematically analyzed, limiting the ability to directly correlate imaging findings with laboratory measures of systemic inflammation. Although adjustment for HCT-CI and GVHD yielded similar findings, these analyses were performed on complete-case data because these variables were unavailable for a subset of patients. In addition, several established transplant-related prognostic factors, including conditioning intensity, donor characteristics, HLA matching, remission status at transplantation, and other disease-specific variables, were not available and therefore could not be incorporated into the multivariable analyses. Residual confounding cannot be excluded. Additionally, only overall survival was analyzed. Although the proposed biological mechanisms may be more directly related to non-relapse mortality, reliable cause-of-death classification distinguishing relapse-related from non-relapse mortality was not consistently available. Future studies with adjudicated relapse-related and non-relapse mortality outcomes are needed to clarify whether ΔHU is preferentially

associated with specific causes of death. Finally, external validation in independent cohorts will be necessary to confirm the prognostic value of ΔHU in allo-HSCT recipients.

CONCLUSION

SATA on CT increases following allo-HSCT, and greater interval increases are associated with worse overall survival. These findings suggest that quantitative assessment of adipose tissue attenuation on routine chest CT may serve as a potential imaging biomarker for systemic physiological alterations and risk stratification in allo-HSCT recipients. Prospective studies are warranted to validate these observations and to further investigate the biological mechanisms underlying adipose tissue attenuation changes in this population.

Ethics

Ethics Committee Approval: This retrospective single-center study was approved by the Koç University Biomedical and Retrospective Research Ethics Committee (approval number: 2026.077.IRB2.039; February 11, 2026).

Informed Consent: The requirement for informed consent was waived by the Ethics Committee because of the retrospective design of the study. Patient anonymity was preserved, and all data were handled in accordance with institutional and international ethical standards.

Footnotes

Authorship Contributions

Concept: Z.A., Y.P., Design: Z.A., Y.P., Data Collection or Processing: Z.A., T.T., Analysis or Interpretation: Z.A., T.T., Y.P., Literature Search: Z.A., Writing: Z.A., Y.P.

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

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Original Article

Evaluation of the Prognostic Nutritional Index in Conjunction with Lung Cancer Stage and PET-CT SUVmax

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ABSTRACT

OBJECTIVE: Lung cancer is among the malignancies with the highest mortality rates globally, where nutritional and immune status significantly influence disease progression and prognosis. The study aimed to investigate the relationship of the prognostic nutritional index (PNI) with both the maximum standardized uptake value (SUVmax), measured by positron emission tomography-computed tomography, and the clinical stage of lung cancer.

MATERIAL AND METHODS: Patients who underwent fiberoptic bronchoscopy and were diagnosed with lung cancer at the Department of Pulmonology, Kütahya Health Sciences University, between January 1, 2022 and May 31, 2025, were retrospectively evaluated. A total of 241 patients diagnosed with lung cancer via bronchoscopy were evaluated; of these, 205 patients diagnosed with non-small-cell lung cancer (n = 205) were assessed according to stage.

RESULTS: A total of 241 lung cancer patients were included; the mean age was 68.35±8.52 years and 95.0% were male. The mean PNI was 41.41±9.50 and the mean primary tumor SUVmax was 10.53±5.22. PNI and primary tumor SUVmax showed a very weak negative association that did not reach statistical significance (Spearman ρ = -0.127; $P = 0.055$). Clinical stage was positively associated with SUVmax (ρ = 0.253; $P < 0.001$) and negatively associated with PNI (ρ = -0.186; $P = 0.007$).

CONCLUSION: Higher clinical stage was associated with higher primary tumor SUVmax and lower PNI. The association between PNI and SUVmax was weak and not statistically significant; therefore, it should not be considered clinically discriminative on its own. PNI may serve as an adjunctive indicator of nutritional and immune status, but prospective studies with survival outcomes and multivariable adjustment are required before it can be used as a prognostic or staging tool.

KEYWORDS: Lung cancer, prognostic nutritional index, nutrition, PET-CT, SUVmax, staging

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INTRODUCTION

Lung cancer represents a major public health concern, ranking as the most frequently diagnosed malignancy and the leading cause of cancer-related mortality worldwide. According to World Health Organization data, approximately 2.2 million new cases of lung cancer are diagnosed annually, and the disease accounts for more than 1.8 million deaths per year.[1]

In Türkiye, lung cancer remains the most common cancer among men and the leading cause of cancer-related deaths.[2] Advanced stage at diagnosis is among the most critical factors adversely affecting prognosis; a substantial proportion of cases present with metastatic disease.

The determinant role of nutritional and immunological status in the clinical course of cancer is increasingly recognized. Malnutrition and immunosuppression accelerate tumor progression, impair treatment response, and shorten overall survival.[3,4] In this context, there is growing interest in indices that use simple laboratory parameters to assess nutritional

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and immune status. The prognostic nutritional index (PNI) was originally developed by Onodera et al.[5] in 1984 to predict postoperative complications in gastrointestinal surgery patients. It is calculated using the following formula: PNI = 10 × serum albumin (g/dL) + 0.005 × peripheral lymphocyte count (cells/mm^3). The index reflects nutritional status through albumin levels and immune competence through lymphocyte count.

Positron emission tomography-computed tomography (PET-CT) is the standard imaging modality used for staging, assessment of treatment response, and detection of recurrence in lung cancer. The maximum standardized uptake value (SUVmax), measured by ^{18}F-fluorodeoxyglucose (FDG) PET-CT, reflects the metabolic activity of the tumor and has been shown to correlate with distant metastasis and prognosis.[6,7] High SUVmax values are known to be associated with advanced stage, rapid tumor progression, and poor prognosis.[8]

Research investigating the effects of PNI on clinical stage, tumor metabolic activity, and survival in lung cancer patients has markedly increased in recent years. Nevertheless, the number of studies examining the relationship between PNI and SUVmax, as measured by PET-CT, remains relatively limited. This study aimed to evaluate PNI alongside primary tumor SUVmax measured on PET-CT and clinical stage in patients diagnosed with lung cancer by fiberoptic bronchoscopy.

MATERIAL AND METHODS

Study Design and Patient Selection

This retrospective observational study was conducted in the Department of Pulmonology at Kütahya Health Sciences University Evliya Çelebi Training and Research between January 1, 2022, and May 31, 2025. The study was approved by the Kütahya Health Sciences University Rectorate Non-Interventional Clinical Research Ethics Committee (decision no: 2025/07-08, date: 29.05.2025) and was performed in accordance with the Declaration of Helsinki. Adults who underwent fiberoptic bronchoscopy for diagnostic purposes and had lung cancer confirmed by bronchoscopic biopsy were eligible. During review, the cohort was independently re-audited at the individual-patient level by cross-matching bronchoscopy records, final pathology records, laboratory records, and PET-CT records. A total of 241 unique eligible patients constituted the final analytic cohort.

Patients with benign biopsy results, insufficient pre-bronchoscopy laboratory data, active infection or inflammatory disease, or no PET-CT imaging were excluded.

Main Points

- In 241 bronchoscopically confirmed lung cancer patients, higher clinical stage was significantly associated with higher primary tumor maximum standardized uptake value (SUVmax) ($\rho = 0.253$, $P < 0.001$) and lower prognostic nutritional index (PNI) ($\rho = -0.186$, $P = 0.007$).
- The direct correlation between PNI and SUVmax was weak and not statistically significant ($\rho = -0.127$, $P = 0.055$), indicating these parameters are not interchangeable measures of tumor burden.
- PNI may serve as a complementary marker of nutritional and immune status, but prospective studies with survival outcomes and multivariable adjustment are required before it can be used as a prognostic or staging tool.

Data Collection

Patient age, sex, smoking history (active smoker, former smoker, never smoker), pack-year exposure, comorbid conditions, histological subtype, and clinical stage were recorded. Clinical staging was performed according to the International Association for the Study of Lung Cancer eighth edition tumor, node, metastasis (TNM) classification.[9] For analytic comparability, TNM stage groups I–IV were used for all tumors; the limited-stage/extensive-stage category for small cell lung cancer was retained only as a clinical descriptor and was not used in the stage-correlation analyses.

Serum albumin levels (g/dL) and peripheral lymphocyte counts (cells/mm^3) were obtained from routine blood tests performed before bronchoscopy. Laboratory albumin values, originally exported in g/L, were divided by 10 before PNI calculation and reporting in g/dL. PNI was calculated as follows: PNI = 10 × albumin (g/dL) + 0.005 × lymphocyte count (cells/mm^3).[5] Primary tumor SUVmax values were obtained from nuclear medicine PET-CT reports.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation and median; categorical variables were presented as number and percentage. Kolmogorov-Smirnov tests showed significant departures from normality for both PNI and SUVmax ($P < 0.05$ for both). Because clinical stage was ordinal and the continuous variables were non-normally distributed, the Spearman rank correlation was used. Stage-group comparisons were performed using the Kruskal-Wallis test. Statistical significance was set at $P < 0.05$.

RESULTS

Demographic and Clinical Characteristics

Of the 308 patients who underwent bronchoscopy during the study period, 241 received a diagnosis of lung cancer and were included in the analysis. The patient selection diagram was shown in Figure 1. Of these, 229 (95.0%) were male and 12 (5.0%) were female. The mean age was 68.35±8.52 years (range: 43–92 years). Smoking status was available for 195 patients: 71 (36.4%) were active smokers, 115 (59.0%) were former smokers, and 9 (4.6%) had never smoked; smoking data were unavailable for 46 patients. Mean tobacco exposure among patients with available smoking data was 50.23±22.44 pack-years (Table 1).

Histological evaluation identified squamous cell carcinoma in 52.9%, adenocarcinoma in 24.3%, and small-cell lung cancer in 14.93% of patients. The remaining 7.87% consisted of other

or not otherwise specified lung cancer histologies. Except for descriptive data, the analysis included cases of non-small cell lung cancer (NSCLC). Among the 205 staged patients, 17 (8.3%) had stage I disease, 27 (13.2%) had stage II disease, 69 (33.7%) had stage III disease, and 92 (44.9%) had stage IV disease.

Prognostic Nutritional Index, Albumin, and Lymphocyte Values

The mean serum albumin concentration was 3.40±0.73 g/dL (range: 1.4–5.3 g/dL), the mean peripheral lymphocyte count was 1491.09±788.27 cells/mm^3. The mean PNI was 41.41±9.50 (range: 17.30–61.30).

Mean PNI values by clinical stage were 45.94±6.52 for stage I, 43.45±9.28 for stage II, 41.01±9.10 for stage III, and 39.34±9.70 for stage IV. PNI differed significantly across stage groups (Kruskal-Wallis $P = 0.027$) (Table 2).

SUVmax Values and Correlation with NSCLC Stage

The mean primary tumor SUVmax was 10.53±5.22 (range: 1.7–42.4). Mean SUVmax values by clinical stage were 7.53±3.31 for stage I, 9.66±4.18 for stage II, 10.56±4.53 for stage III, and 11.94±5.96 for stage IV. SUVmax differed significantly across stage groups (Kruskal-Wallis $P < 0.001$) (Table 2).

Correlation Analyses

Kolmogorov-Smirnov test with Lilliefors correction indicated that PNI (D = 0.072, $P = 0.008$) and SUVmax (D = 0.121, $P < 0.001$) were non-normally distributed; clinical stage was treated as an ordinal variable. Therefore, all reported associations were evaluated using Spearman's rank correlation, with pairwise available-case sample sizes. PNI and primary tumor SUVmax showed a very weak negative association that did not reach conventional statistical significance (Spearman ρ = –0.127; $P = 0.055$; n = 205) (Figure 2, Table 3). The small effect size indicates substantial overlap across PNI values and limits clinical interpretability.

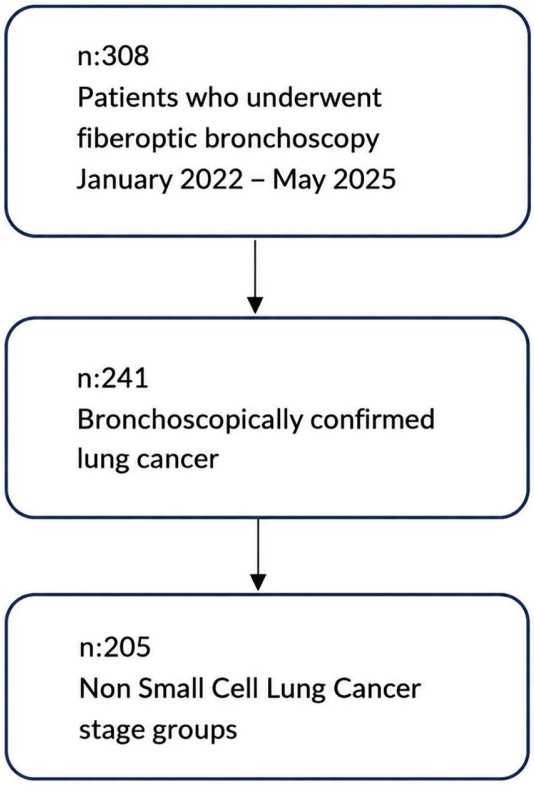


Figure 1. Patient-selection flow diagram. The full bronchoscopy pool, the bronchoscopically confirmed lung cancer cohort, and the non-small-cell lung cancer stage groups are shown separately

Clinical stage was positively associated with primary tumor SUVmax (Spearman ρ = 0.253; $P < 0.001$; n = 205), indicating a weak-to-moderate monotonic trend toward higher metabolic activity with advancing stage.

Clinical stage was negatively associated with PNI (Spearman ρ = –0.186; $P = 0.007$; n = 205), indicating a weak monotonic tendency toward lower nutritional and immune status at more advanced stages.

DISCUSSION

This retrospective study included 241 patients with bronchoscopically confirmed lung cancer; 205 NSCLC patients had complete staging data. Clinical stage was positively associated with primary tumor SUVmax and negatively associated with PNI.

Studies investigating the prognostic value of PNI in lung cancer patients have markedly increased in recent years. A meta-analysis demonstrated that lower PNI scores were associated with worse survival outcomes.[10]

Shoji et al.[11] reported that lower preoperative PNI predicted postoperative recurrence in surgically resected pathological stage I NSCLC. That population is not directly comparable with the present bronchoscopy-based cohort, which was heterogeneous, predominantly advanced-stage, frequently inoperable, and included 14.93% small-cell lung cancer cases. Accordingly, the Shoji et al.[11] study supports the general biological relevance of PNI, but should not be used for direct effect-size or prognostic comparisons with our cohort. In the present study, PNI declined across clinical stage groups and showed a weak negative association with stage (ρ = –0.186; $P = 0.007$).

Albumin is the primary component of the PNI calculation. Hypoalbuminemia serves as an indicator of protein-calorie malnutrition, inflammation, and hepatic dysfunction and is frequently encountered in cancer patients. Low serum albumin levels are associated with poor performance status and reduced treatment tolerance.[3] Lymphocytes, on the other hand, are the principal effectors of cellular immunity and play a critical role in sustaining antitumor immune responses within the tumor microenvironment.[12] Lymphopenia in cancer patients can be interpreted as evidence of immune suppression by the tumor and an indication of disease progression. The PNI, which integrates both parameters, provides more comprehensive prognostic information than albumin or lymphocyte measurements alone.

SUVmax is a semiquantitative measure of tumor glucose uptake on FDG-PET. Increased glycolysis, commonly described as the Warburg[13] effect, is a hallmark of malignant metabolism. The positive association between primary tumor SUVmax and

Table 1. Demographic and clinical characteristics of patients who bronchoscopically confirmed lung cancer (n = 241)

Variable	n (%) or mean ± SD	Min–max
General characteristics		
Total number of patients	241	-
Age (years)		
Mean ± SD	68.35±8.52	43–92
Median	69	
Sex		
Male	229 (95.0%)	-
Female	12 (5.0%)	-
Smoking history		
Active smoker	71 (36.4%)	-
Former smoker (ex-smoker)	115 (59.0%)	-
Never smoker	9 (4.6%)	-
Smoking pack-years (mean ± SD)	50.23±22.44	0–130
Laboratory values		
Serum albumin (g/dL), mean ± SD	3.40±0.73	1.4–5.3
Peripheral lymphocyte count (cells/mm^3), mean ± SD	1491.09±788.27	60–5000
PNI, mean ± SD*	41.41±9.50	17.30–61.30
PET-CT primary tumor SUVmax, mean ± SD	10.53±5.22	1.7–42.4

*PNI = 10 × albumin (g/dL) + 0.005 × lymphocyte count (cells/mm^3)
SD: standard deviation, PNI: prognostic nutritional index, PET-CT: positron emission tomography-computed tomography, SUVmax: maximum standardized uptake value, Min: minimum, max: maximum

Table 2. Comparison of PNI, SUVmax, albumin, and lymphocyte values according to NSCLC stage groups (n = 205)

Parameter	Stage I (n = 17)	Stage II (n = 27)	Stage III (n = 69)	Stage IV (n = 92)	*P* value
PNI					
Mean ± SD	45.94±6.52	43.45±9.28	41.01±9.10	39.34±9.70	0.027†
Median	45.05 (42.05–51.55)	44.25 (39.40–51.27)	41.20 (35.62–47.74)	41.32 (30.73–45.90)	
PET-CT primary tumor SUVmax					
Mean ± SD	7.53±3.31	9.66±4.18	10.56±4.53	11.94±5.96	<0.001†
Median	7.50 (5.80–8.80)	9.90 (7.05–10.95)	9.70 (7.22–12.53)	10.80 (8.03–14.10)	
Serum albumin (g/dL)					
Mean ± SD	3.82±0.58	3.55±0.64	3.32±0.68	3.25±0.76	0.002†
Median	3.90 (3.60–4.20)	3.60 (3.40–3.95)	3.30 (2.90–3.98)	3.40 (2.70–3.85)	
Peripheral lymphocyte count (cells/mm^3)					
Mean ± SD	1548.18±535.81	1588.14±847.90	1569.56±762.93	1373.26±823.31	0.283†
Median	1510 (1010–1810)	1310 (1115–2160)	1500 (952–2072)	1360 (690–1945)	

†Kruskal-Wallis test
PNI: prognostic nutritional index, SUVmax: maximum standardized uptake value, SD: standard deviation, NSCLC: non-small cell lung cancer, PET-CT: positron emission tomography-computed tomography

clinical stage in our cohort (ρ = 0.253; $P < 0.001$) is consistent with studies linking higher primary tumor FDG uptake to greater extent or metastatic potential in NSCLC.[6,8,14] Nevertheless, the observed coefficient indicates only a weak-to-moderate monotonic association and does not imply that SUVmax can substitute for formal anatomic staging.

In 186 patients with advanced NSCLC treated with PD-1 blockade, Ito et al. found associations between FDG-derived metabolic tumor burden and several inflammatory or nutritional indices, including PNI.[15] Dolan et al.[16] evaluated 119 patients with lung cancer undergoing radiotherapy and reported that higher PET-CT-derived tumor metabolic activity was associated with more advanced stage, greater nutritional risk, systemic inflammation, and poorer survival. These studies support a relationship between tumor metabolism and host inflammatory-nutritional status, although their populations, PET metrics, treatments, and outcomes differ from those in the present study.

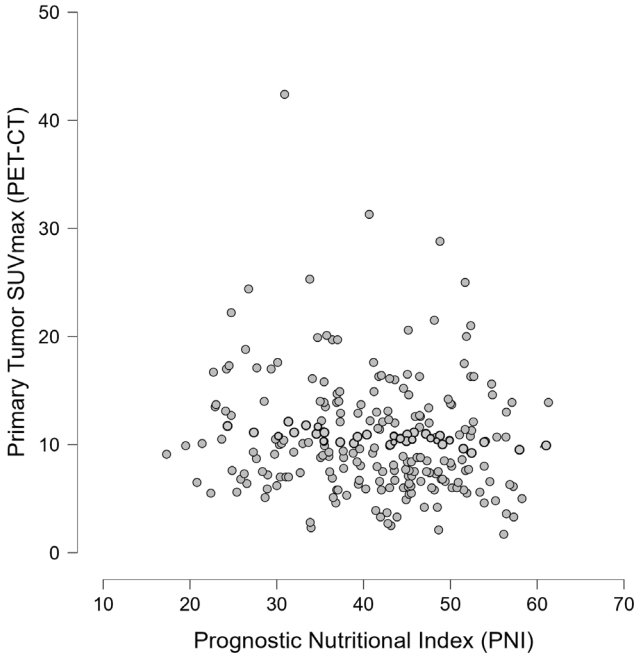


Figure 2. Scatter plot of prognostic nutritional index and primary tumor SUVmax on PET-CT (Spearman ρ = −0.127; *P* = 0.055). Each circle represents one patient. No parametric regression line is displayed because the reported analysis is rank-based

SUVmax: maximum standardized uptake value, PET-CT: positron emission tomography-computed tomography

Table 3. Pairwise Spearman rank correlations among clinical stage, PNI, and primary tumor SUVmax (n = 205)

Comparison	Spearman ρ	*P* value
PNI vs. primary tumor SUVmax	−0.127	0.055
Clinical stage vs. primary tumor SUVmax	0.253	<0.001*
Clinical stage vs. PNI	−0.186	0.007*

*Statistically significant ($P < 0.05$). Pairwise available-case sample sizes are shown

ρ: Spearman rank correlation coefficient, PNI: prognostic nutritional index, SUVmax: maximum standardized uptake value

In our corrected analysis, the association between PNI and SUVmax was very weak and did not reach conventional levels of statistical significance (ρ = -0.127; *P* = 0.055). Therefore, this finding should not be interpreted as evidence that SUVmax meaningfully predicts PNI, or vice versa, at the individual-patient level. The unadjusted association may be influenced by shared determinants such as stage, histology, inflammation, comorbidity, and tumor burden. A biologically plausible link between metabolically active tumors and lower albumin or lymphocyte levels remains possible, but causality cannot be inferred from this cross-sectional retrospective analysis.

Study Limitations

This study has several limitations. First, the retrospective, single-center design may introduce selection bias and limit generalizability. Histological heterogeneity, including NSCLC and small-cell lung cancer, also complicates direct comparisons with homogeneous surgical cohorts. Second, the patient cohort is limited to a single center, which may restrict the generalizability of the findings. Furthermore, standardization of the timing of albumin and lymphocyte measurements used in PNI calculation presents a challenge, as active infection, corticosteroid use, and other inflammatory conditions may influence lymphocyte counts. Survival analysis was not incorporated into the present study; therefore, the long-term impact of PNI on mortality could not be assessed. Despite these limitations, the study makes a contribution through its real-world cohort and observed relationship between PNI and SUVmax.

CONCLUSION

A higher clinical stage was associated with a higher primary tumor SUVmax and a lower PNI in patients with bronchoscopically diagnosed lung cancer. After patient-level correction of PNI components, the PNI-SUVmax association was very weak and not statistically significant, and it should not be interpreted as clinically discriminative on its own. PNI may be considered an adjunctive marker of nutritional and immune status, but it cannot replace formal staging or validated prognostic assessment. Prospective studies with standardized laboratory timing, survival outcomes, and multivariable adjustment are required before PNI can be used as a prognostic or staging tool.

Ethics

Ethics Committee Approval: The study was approved by the Kütahya Health Sciences University Rectorate Non-Interventional Clinical Research Ethics Committee (decision no: 2025/07-08, date: 29.05.2025) and was performed in accordance with the Declaration of Helsinki.

Informed Consent: The requirement for informed consent was waived by the local ethics committee because of the retrospective design of the study and the use of anonymized data.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.K., Ü.E., Ş.E.P., F.M., M.D., Ş.K., J.K., Concept: İ.K., Ü.E., M.D., Design: İ.K., Ş.E.P., Ş.K., J.K., Data Collection or Processing: İ.K., Ü.E., Ş.E.P., F.M., Ş.K., J.K., Analysis or Interpretation: İ.K., F.M., M.D., Literature Search: İ.K., Writing: İ.K., J.K.

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Original Article

A Qualitative Study on the Difficulties Faced by Healthcare Professionals Working in Smoking Cessation Clinics

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ABSTRACT

OBJECTIVE: Smoking cessation clinics are an essential component of tobacco control policies, providing integrated pharmacological and behavioral interventions to support individuals in overcoming tobacco dependence. The quality and effectiveness of these services are closely associated with healthcare professionals' experiences and the organizational context in which care is delivered. This study aimed to explore healthcare professionals' experiences, perceived barriers, coping strategies, and recommendations regarding smoking cessation services in Türkiye.

MATERIAL AND METHODS: A qualitative phenomenological design was employed. Purposive sampling was used to recruit 13 healthcare professionals working in smoking cessation clinics, addiction units, and Healthy Life Centers. The study was conducted between November 2025 and April 2026. Data were collected through face-to-face semi-structured interviews and analyzed using thematic analysis.

RESULTS: Participants perceived smoking cessation clinics as valuable and effective services but identified several barriers that limited service delivery. Major challenges included low patient motivation, inadequate adherence to follow-up visits, normalization of smoking in social life, heavy workload, limited consultation time, insufficient multidisciplinary support, and medication access problems. Healthcare professionals reported using individualized counseling, motivational interviewing, evidence-based treatment algorithms, and digital follow-up systems to improve treatment adherence and cessation success. Professional motivation was primarily sustained by observing successful patient outcomes and contributing to improved quality of life, despite existing structural constraints.

CONCLUSION: Smoking cessation services are influenced by the interaction of individual, organizational, and systemic factors. Strengthening multidisciplinary teamwork, improving institutional resources, expanding behavioral support, enhancing digital follow-up systems, and increasing public awareness may improve the effectiveness and sustainability of tobacco dependence treatment. Incorporating healthcare professionals' experiences into tobacco control policies may contribute to higher-quality services and better long-term cessation outcomes.

KEYWORDS: Smoking cessation, tobacco dependence, healthcare professionals, qualitative research, phenomenology, tobacco control

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INTRODUCTION

Smoking remains a leading cause of preventable disease and mortality, posing a significant public health challenge at both global and national levels.[1] International policies directed toward tobacco control have established a systematic framework through the MPOWER strategy package developed by the World Health Organization.[2] This package encompasses six core components: monitoring tobacco use (Monitor), protecting individuals from tobacco smoke (Protect), offering cessation services (Offer), warning about the dangers of tobacco (Warn), enforcing bans on advertising and sponsorship (Enforce), and raising taxes on tobacco products (Raise).[2,3]

Türkiye is among the countries that have adopted and implemented MPOWER strategies, and is particularly notable for its smoke-free zones, warning policies on tobacco products, and advertising bans. Furthermore, within the "provision of

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cessation services" component of MPOWER, the expansion and increased accessibility of smoking cessation clinics constitute a significant part of national tobacco control policies. These clinics adopt a holistic approach, offering both pharmacological treatment and behavioral counseling to individuals in their process of overcoming tobacco addiction.[4,5] Recognizing tobacco addiction as a chronic disease characterized by relapses necessitates that clinical interventions be planned not merely as immediate advice but as chronic disease management.

The quality of services offered in smoking cessation clinics is closely related not only to current health policies but also to the experiences, approaches, and structural conditions faced by the healthcare workers providing these services. Therefore, evaluating service delivery processes from a healthcare worker's perspective is critical for identifying strengths and areas for improvement in practice. Qualitative research methods allow for a better understanding of this complex process by deeply examining the experiences and perceptions of healthcare professionals.[6]

This study aims to examine, from a qualitative perspective, the experiences and approaches of healthcare workers in smoking cessation clinics regarding the services they provide. Accordingly, the goal is to gain a more comprehensive understanding of the relationship between tobacco control policies and clinical practices in Türkiye by analyzing healthcare workers' views on service delivery processes, the difficulties they encounter, and the strategies they develop.

Main Points

- Multifaceted Barriers in Smoking Cessation: Healthcare professionals experience systemic challenges in service delivery, primarily attributable to heavy workloads, brief consultation times (5–10 minutes), and recurring disruptions in medication and nicotine replacement therapy supply chains.
- The Need for Multidisciplinary Teams: Delivering effective tobacco dependence treatment is constrained by insufficient human resources; integrating dedicated psychologists and nurses into clinics is vital to alleviating administrative burdens on physicians and enhancing behavioral counseling.
- Sociocultural Normalization of Smoking: Tobacco addiction is heavily normalized and highly visible in social environments, creating significant social pressure that undermines patients' motivation and lowers long-term treatment adherence.
- Cognitive and Behavioral Resistance is a Key Clinical Obstacle: The public perceives smoking as a mere "habit" rather than a chronic disease, which frequently results in low patient motivation, poor follow-up attendance, and premature discontinuation of treatment.
- The findings of the current study suggest that structuring smoking cessation clinics under the umbrella of a more comprehensive, holistic "Addiction Treatment Center" could address the logistical and administrative challenges encountered in the field.

MATERIAL AND METHODS

This research involved healthcare professionals working in units providing smoking cessation services in Türkiye. Participants were selected through purposive sampling. Ethical approval for the research was obtained from the Scientific Research and Publication Ethics Committee of Erzurum Technical University Rectorate with decision number: 2025-ETÜ-0052, date: 13.11.2025. Inclusion criteria for employees were as follows: having worked for at least 6 months in a smoking cessation clinic in Türkiye, being a healthcare professional, and being a volunteer. A Personal Information Form and a Semi-Structured Interview Form, each consisting of 7 questions, were used in this study. The Personal Information Form, collected by the researchers, consisted of demographic information such as age, gender, and seniority. The Semi-Structured Interview Form consisted of open-ended questions designed to assess problems encountered in smoking cessation clinics in Türkiye. The study was conducted between November 2025 and April 2026. This research was conducted using face-to-face interviews, in accordance with the phenomenological approach, a qualitative research method. The "bracketing" method was applied during the interviews and the analysis process to prevent researchers' own assumptions and clinical experiences from influencing the findings. Throughout the analysis, data were coded independently of personal interpretations, adhering solely to the participants' statements. Before data collection, participants were informed about the purpose of the study, and their consent was obtained. The demographic information form was completed first, followed by the Semi-Structured Interview Form. Interviews lasted an average of 50 minutes. The discussions were terminated when data saturation was reached (after the 13th participant) and no new themes or codes emerged. The researcher recorded the interviews. Data analysis was conducted on the day of the interviews. Demographic data were analyzed using descriptive statistics expressed as numbers and percentages. Qualitative data were analyzed using thematic analysis. The data were coded by two independent researchers, and themes were clarified through consensus. Since our analysis used thematic analysis, no mathematical coefficient (such as Cohen's Kappa) was calculated; instead, a "consensus process" was employed to ensure reliability in qualitative research. After independently coding the data, the two researchers met, compared the code lists, and debated codes on which they disagreed, returning to the raw data (participant citations) until 100% consensus was reached.

Although the study group has a multidisciplinary structure, physicians' experiences are emphasized at certain points in the Introduction and Discussion sections because of their primary responsibilities for diagnosis, initiation of pharmacotherapy, and clinical management. However, to reflect the common experience of all participants, the term "healthcare workers" is used throughout the text.

RESULTS

As part of the study, in-depth interviews were conducted with 13 healthcare personnel working in smoking cessation clinics. Regarding the participants' sociodemographic characteristics, 9 were women, 9 were married, and 7 were physicians. According to the distribution of the institutions where they work, 7 of the

participants work in tertiary hospitals, 1 works within the Green Crescent (Yeşilay), and the others work in smoking cessation clinics under the umbrella of Healthy Life Centers (Table 1).

As a result of the thematic analysis of the data obtained from the interviews, the functioning of smoking cessation services, operational obstacles encountered, patient-centered barriers, sociocultural factors, and solution-oriented strategies were organized into 5 main themes and 13 sub-themes (Table 2).

Theme 1: Polyclinic Operation within an Institutional and Systemic Framework

Participants stated that smoking cessation polyclinics generally operate systematically and successfully within the framework of the legislation, regulations, and algorithms determined by the Ministry of Health. One participant, stating that the system is well-established, expressed the situation as follows:

"Activities are progressing smoothly within the framework established by the Ministry of Health; the system is well-established" (P5).

However, the functionality of polyclinics varies according to institutional history. While it was emphasized that the system is better established in existing institutions, it was stated that there is a lack of standardization and uniformity in application in some newly opened polyclinics (P3, P6). One participant summarized this situation with the words, "In some places, the standard of application is not fully established" (P3). Although appointment and registration systems are actively used as part of the digital infrastructure, momentary freezes and internet interruptions experienced in the TUBATIS and e-Nabız automation systems are systemic factors that slow down the service (P1, P5, P9, P10). Despite these technical difficulties, patients' success in smoking cessation and their positive feedback constitute the primary source of professional satisfaction, moral fulfillment, and intrinsic motivation among employees (P2, P4, P10, P13). One participant described this situation as follows: "Seeing a patient quit smoking makes me forget all my tiredness" (P2).

Theme 2: Structural and Operational Limitations in Service Delivery

Under this theme, operational, logistical, and administrative obstacles faced by healthcare professionals in providing services were addressed. The problem most widely agreed upon by participants was the lack of a multidisciplinary team structure and of human resources. Due to insufficient staffing of psychologists and nurses, bureaucratic procedures, preliminary interviews, and form-filling processes, which could be carried out by non-physician personnel fall on physicians, increasing their workload and making it difficult to focus on clinical care (P1, P6, P7, P9, P12, P13). Participants described this deficiency as follows:

"This work cannot be carried out by a single physician; team support is essential. Without support from psychologists and nurses, the entire burden falls on the physician" (P6, P10).

Another important structural limitation concerns time management. Participants stated that a quality motivational interview for tobacco addiction should last at least 20–30 minutes, but the current system's 5–10-minute examination times are insufficient (P9, P10, P11, P12, P13). Furthermore, it was noted that the current performance (incentive) system does not adequately reward the time devoted to providing high-quality care (P13). One participant explained the time constraint as follows:

"Actually, we need to dedicate more time to the patient, but it's very difficult to do this within a 5–10 minute timeframe" (P9).

At the logistical and spatial level, it was stated that the inability to perform blood tests and pulmonary function tests in primary care facilities leads to patients being referred to different institutions and prolongs the treatment process (P5, P11). In addition, periodic logistical disruptions in the provision of free medications (nicotine patches and gum) (P1, P10, P13), outpatient clinics located in remote corners of hospitals (P13), and the lack of isolated, private waiting areas where patients do not negatively affect one another (P6, P10, P12) constitute operational obstacles.

Table 1. Sociodemographic characteristics of the participants

No	Age	Marital status	Education degree	Job	Workplace	Total working time (year)
1	25–29	Married	PhD and above	Doctor	Smoking cessation clinic	6–10
2	40–44	Single	Master's degree	Doctor	Smoking cessation clinic	16–20
3	30–34	Single	Master's degree	Doctor	Smoking cessation clinic	6–10
4	55–59	Married	Master's degree	Doctor	Smoking cessation clinic	>26
5	35–39	Married	Bachelor's degree	Nurse	Smoking cessation clinic	16–20
6	50–54	Married	PhD and above	Doctor	Tertiary hospital	>26
7	50–54	Married	Bachelor's degree	Psychologist	Tertiary hospital	11–15
8	25–29	Single	Master's degree	Doctor	Tertiary hospital	0–5
9	45–49	Married	Bachelor's degree	Nurse	Tertiary hospital	16–20
10	35–39	Married	Bachelor's degree	Psychologist	Tertiary hospital	16–20
11	25–29	Single	Bachelor's degree	Nurse	Tertiary hospital	11–15
12	35–39	Married	Bachelor's degree	Psychologist	Yeşilay*	11–15
13	50–54	Married	PhD and above	Doctor	Tertiary hospital	>26

*Yeşilay is a non-governmental organization

Table 2. According to data analysis, main themes, sub-themes, codes, and citations

Main themes	Sub-themes	Codes and contributor citations
Theme 1: Polyclinic operations within an institutional and systemic framework	1.1. Standard procedures and digital infrastructure	• Compliance with Ministry of Health legislation/regulations (P3, P5, P8) • Scheduled patient admission via appointment system (P1, P9, P13) • Preliminary interview, form completion and registration processes (P1, P9, P13) • Slowdown/freezing issues in TUBATIS and e-Nabız automation systems (P1, P5, P9, P10)
	1.2. Degree of institutionalization and standardization	• Polyclinics becoming more systematic over time (P2) • The system being well-established in long-standing institutions (P5, P6, P8, P11) • Lack of uniformity in practice in newly opened units (P3, P6)
	1.3. Service satisfaction and job satisfaction	• Positive feedback from patients who are satisfied with the process (P2, P4) • Emotional satisfaction from patients quitting smoking (P2, P10, P13) • Responsibility to impact human life and health (P2)
Theme 2: Structural and operational limitations in service delivery	2.1. Lack of human resources and multidisciplinary team	• Concentration of workload on a single physician (P1, P6, P7, P9, P12, P13) • Need for psychologists, nurses, and support staff (P3, P6, P8, P9, P10, P11) • Need for psychiatric or other consultations for advanced addictions (P1, P9, P10)
	2.2. Time and logistics constraints	• Insufficient examination times (5–10 min) for motivational talks (20–30 min) (P9, P10, P11, P12, P13) • The performance/incentive system does not reward the dedication of quality time (P13) • Periodic interruptions in the provision of free medication and NRT (nicotine patches/gum) (P1, P10, P13)
	2.3. Spatial and infrastructural limitations	• Referrals due to lack of blood tests and spirometry in primary care (P5, P11) • Location of outpatient clinics in remote corners of hospitals (P13) • Insufficient isolated waiting areas where patients will not be negatively affected (P6, P10, P12)
Theme 3: Patient-centered barriers and adherence problems	3.1. Resistance to behavioral change and non-compliance	• Patients' lack of mental readiness/indecisiveness to quit (P1, P2, P4, P11) • Individuals' irregular attendance at follow-up appointments (P5) • Lack of belief in recovery and early drug discontinuation (P1, P9, P12)
	3.2. Cognitive barriers and communication difficulties	• Difficulty understanding due to advanced age or illiteracy (P1) • Burden of repetitive information regarding form completion and medication regimens (P1) • Unwarranted fears of medication side effects (P1) • Difficulty communicating with younger groups due to the decreasing age of addiction (P4) • Negative perception or tendency towards verbal abuse towards healthcare professionals (P2, P3, P6, P7)
	3.3. Patient's perception and expectations regarding service	• Viewing the polyclinic solely as a means of obtaining "free medication" (P5, P10) • Expecting excessively high levels of tests and analyses from the service unit (P2, P3, P13)
Theme 4: Sociocultural context and perception of addiction	4.1. Social normalization and visibility of tobacco addiction	• Integration of smoking with social life (cafes, social gatherings, etc.) (P1, P13) • High visibility of smoking in public spaces (P4) • Lack of social/family support; negative peer pressure (P1, P3, P6, P7, P9)
	4.2. Misconceptions about health and lack of clinical perception	• Society views tobacco as a simple "habit" rather than an "addiction" (P1, P6, P11, P12, P13) • Smoking is perceived as a means of coping with stress or preventing loneliness (P11, P12, P13)
Theme 5: Clinical strategies and policy recommendations	5.1. Evidence-based methods and individualized approaches	• 5A methods for those ready to quit, 5R methods for those not ready (P9, P10) • Individualized treatment based on the patient's addiction history and demographics (P1) • Offering alternative objects (gum, distraction) for behavioral dimensions (P1)
	5.2. Macro policies and the comprehensive struggle	• Making addiction education a mandatory subject in schools (P6) • Mass campaigns to revive the spirit of "Smoke-Free Zones" (P3, P4, P5, P6, P7, P8, P9, P10, P12) • Increasing clinic recognition through social media and advertising (P3, P5, P9, P10)
	5.3. Empowering healthcare professionals	• Mandatory certification and continuing education before starting work (P5, P11) • Transformation of polyclinics into "Addiction Treatment Centers" (P6) • Automated reminder systems to facilitate follow-up processes (P1, P3, P10, P13)

NRT: nicotine replacement therapy

Theme 3: Patient-centered Barriers and Adherence Problems

Patient-related factors constitute one of the most important dimensions limiting the effectiveness of service delivery. Healthcare professionals reported experiencing difficulties in clinical practice, especially when working with patients who are unmotivated, hesitant, or mentally unprepared to quit smoking (P1, P2, P4, P11).

"We may encounter problems with difficult patients from a health perspective. We encounter problems persuading difficult patients, explaining to them that their situation is serious, and encouraging them to take medication. The primary problem for patients is their indecision and unwillingness to quit" (P4).

Patients' failure to attend follow-up appointments regularly negatively affects the continuity and effectiveness of the treatment process (P5). In addition, individuals' lack of confidence in their ability to overcome addiction and their tendency to discontinue medication prematurely reduce treatment adherence (P1, P9, P12).

At the cognitive level, difficulties in understanding due to advanced age or illiteracy place a constant informational burden on healthcare personnel during form completion and the explanation of medication regimens (P1). Unwarranted fears of medication side effects (P1) and difficulty establishing healthy communication with the younger patients, attributable to the decreasing age of addiction (P4), are additional barriers. Some patients' perceptions of the outpatient clinic as merely a "free medication point" rather than a professional counseling and treatment center (P5, P10) and their lack of adherence to treatment undermine the quality of the process. Finally, negative perceptions or tendencies toward verbal violence against healthcare workers have also been reported occasionally (P2, P3, P6, P7).

Theme 4: Sociocultural Context and Perception of Addiction

One of the most striking findings of the study is the normalization and high visibility of tobacco addiction in social life. Participants emphasized that smoking, unlike other types of addiction, is highly visible and culturally accepted in the public sphere, which directly complicates clinical success.

"As a physician, I welcome the provision of such a polyclinic service for smoking cessation, which is the most common and visible of addictions, and I have personally witnessed its positive results and received favorable feedback from patients" (P4).

The perception of tobacco use in society as a simple "habit" rather than a "disease/addiction," and the framing of smoking as a means of coping with stress or preventing loneliness were identified as incorrect health beliefs (P1, P6, P11, P12, P13). One participant expressed this perception in the words: "Many patients don't see it as a disease, they just consider it a habit" (P11). This normalization leads patients not to receive the support they need from their social environment and even to experience negative social pressure from their friends, because smoking has become so commonplace in daily life (P1, P3, P6, P7, P9, P11).

Theme 5: Clinical Strategies and Policy Recommendations

Healthcare professionals actively use both evidence-based clinical protocols and individualized approaches to cope with these multifaceted challenges and increase treatment adherence (P1). In clinical practice, the "5A" (ask, advise, assess, assist, arrange) algorithm is followed for patients ready to quit, and the motivational "5R" (relevance, risks, rewards, roadblocks, repetition) algorithm is followed for those who are not ready (P9, P10). Treatment processes are individualized according to the patients' demographic information, smoking history, and level of addiction; for behavioral dimensions such as mouth and hand habits, practical suggestions are offered: chewing gum, engaging in alternative activities, or increasing daily activity. Macro-level policy recommendations argue that the fight against tobacco should be transformed into a comprehensive social campaign and education strategy:

"The individual, social, and societal harms of smoking should be taught in compulsory basic education, and a comprehensive campaign encompassing all segments of society should be organized as part of health-promotion efforts to provide accurate information and raise awareness. Türkiye had previously achieved significant successes with the Smoke-Free Air Campaign. We need to recapture this atmosphere. Only in this way can those who want to quit smoking receive support from those around them" (P6).

Stating that leaving a smoke-free, healthy airspace for future generations is the shared responsibility of all stakeholders, the participants suggested the following concrete steps to increase the effectiveness of polyclinics:

- Ensuring that personnel undergo a mandatory and rigorous certification process before starting their duties and providing continuous professional training (P5, P11).

- Ensuring the continuity of free medication, patches, and nicotine replacement therapy (NRT) supply at the institutional level (P13).

- Transforming and integrating polyclinics into broader "Addiction Treatment Centers" (P6).

- Establishing advanced digital monitoring systems integrated with TUBATIS that will automatically manage long-term follow-up appointments, phone calls, and message reminders for patients at 3 months, 6 months, and 1 year (P1, P3, P10, P13).

DISCUSSION

The findings of this study reveal that the services offered in smoking cessation clinics are conducted within a structured framework in accordance with Ministry of Health regulations, but the framework is constrained by operational, patient-centered, and sociocultural limitations. The participants' positive evaluations of the necessity and functioning of the services show that tobacco control policies have elicited an institutional response. However, the lack of standardization and uniformity in application, especially in newly established units, indicates that time and monitoring mechanisms are needed to achieve a homogeneous level of service quality

across the country. The findings show that the difficulties encountered in tobacco addiction treatment largely stem from the interaction of individual and structural factors. Low motivation, indecisiveness, and a tendency among patients to view the process as a simple "habit" rather than a "disease," as emphasized by participants, directly undermine clinical success. It is well established in the literature that the failure to perceive tobacco addiction as a chronic, relapsing brain disease is one of the most fundamental cognitive barriers that reduce treatment adherence.[7-9]

One of the most striking aspects of the study is the high visibility of smoking in public spaces and the sociocultural normalization of smoking. This situation, which participants described as "the most visual of addictions," transforms quitting smoking from a matter of individual willpower into a social phenomenon. Environmental triggers and negative peer pressure cause the individual to lose the motivation gained in the clinical setting when in the social sphere. This finding is consistent with studies arguing that clinical interventions targeting individuals alone are insufficient for tobacco control, and that macro-level environmental and legal regulations that reduce the social appeal and acceptance of tobacco are vital.[1,10]

Institutional limitations regarding service delivery are concentrated particularly with respect to time constraints and insufficient human resources. This outpatient service, which requires intensive communication, in-depth motivational interviewing, and a behavior-change-focused approach, is squeezed into routine 5–10-minute examination slots. This constraint makes it difficult for physicians to thoroughly apply evidence-based "5A" and "5R" algorithms, and the fact that the incentive/performance system does not reward this valuable time exacerbates the problem. Furthermore, a limited multidisciplinary team structure (insufficient staffing of psychologists and nurses) causes administrative tasks, such as secretarial duties and preliminary interviews, to fall on physicians. The challenges encountered in smoking cessation services are reported not only at the national level but also in the international literature. A study of 15 European countries found that staff in smoking cessation clinics experienced significant role conflict and time pressure while providing routine healthcare services and treating tobacco addiction. This situation parallels the administrative challenges and the need for structural transformation of clinics, as expressed by the participants in the study, such as the suggestion to establish Addiction Centers. Therefore, fighting tobacco addiction in a more integrated, multidisciplinary manner within independent units with logistical support is a global necessity.[11,12] The literature shows that combining behavioral therapy with pharmacotherapy significantly increases the success rate of tobacco addiction treatment.[13-15] In this context, the lack of a psychosocial support component (psychologist) in outpatient clinics, or the reduction of the process to merely a "free medication" mode, constitutes the most fragile operational link in the system.

The development of individualized clinical approaches and alternative behavioral interventions (occupational activities, chewing gum, etc.) by healthcare professionals to cope with these challenges is an indicator of their professional competence. However, the success of these strategies is limited by technical and logistical factors, such as periodic interruptions in drug/NRT supply and slowdowns in automation (TUBATIS/e-Nabız). This situation reveals that the knowledge and skills of healthcare workers alone are not sufficient; logistical continuity and suitable working conditions are at least as crucial as clinical knowledge.[16,17]

From the perspective of professional motivation, the greatest sources of satisfaction for healthcare workers are patients' quitting smoking and spiritual fulfillment. Qualitative research indicates that one of the strongest protective factors against burnout among healthcare personnel with heavy workloads is the feeling of "touching human lives and seeing tangible success". However, structural limitations and non-compliant patients who do not attend follow-up appointments can undermine this motivation. Therefore, institutional recognition and support mechanisms are needed to sustain employee motivation.[18,19]

Study Limitations

Although this study provides important data by revealing, in depth, the service delivery and challenges encountered in smoking cessation clinics from the perspective of healthcare professionals, it has some limitations.

Sample and Generalizability Limitation: The most fundamental limitation of the study is that due to its qualitative research design, it is limited to 13 healthcare professionals selected by purposive sampling. This situation restricts the generalizability of the findings to all smoking cessation clinics nationwide and to healthcare personnel with different socioeconomic or regional dynamics.

One-Sided Perspective (Stakeholder Limitation): The research addressed the service process solely from the perspective of service providers (healthcare professionals). The experiences and perceptions of service recipients (patients), administrative managers, and policymakers regarding the process were excluded from the scope of this study. The inability to conduct a multi-stakeholder evaluation may limit a holistic analysis of structural problems.

Limitations in Institutional Diversity: Participants were predominantly employed in tertiary hospitals and Healthy Life Centers, which may have limited representation of diverse institutional operational models and logistical challenges in primary care or in private foundations/non-governmental organizations; only a single participant represented the latter (Yeşilay). Despite these limitations, the research provides a strong micro-level understanding of operational bottlenecks in the field. Future studies should prioritize mixed-methods designs combining quantitative and qualitative methods and include simultaneous patient- and employee-focused monitoring to expand the literature.

CONCLUSION

This study has revealed that smoking cessation clinics, as currently structured, play a critical role in the fight against tobacco, but that multidimensional improvements at the

individual, institutional, and societal levels are needed to maximize service effectiveness. Clinical success is directly related not only to the medication prescribed by the physicians but also to the institutional infrastructure and sociocultural perceptions surrounding the patient. The concrete proposals developed in this direction are listed below:

1. Institutional and Operational Recommendations

Making a Multidisciplinary Team Structure Mandatory: The employment of psychologists and nurses, in addition to physicians, in polyclinics should be standardized. Having bureaucratic processes and preliminary assessments carried out by auxiliary personnel will allow the physician to focus on the main clinical and motivational services.

Revision of Examination Times and Performance System: The time allocated per patient in smoking cessation polyclinics should be 20–30 minutes to allow for behavioral change counseling. The performance (incentive) system should be structured based on qualitative interview time and clinical success rates rather than quantitative patient numbers.

Strengthening Logistics and Digital Infrastructure: Periodic interruptions in the supply chain of treatment materials, such as free medication, nicotine patches, and gum, should be prevented. The integration of TUBATIS and e-Nabız systems should be optimized, and automated digital systems providing SMS or call reminders should be implemented for long-term patient follow-up at 3 months, 6 months, and 1 year.

Standardization and Training: To ensure uniform application, particularly in newly opened units, mandatory certification and continuous professional development training for personnel commencing their duties should be systematized.

2. Social- and Policy-level Recommendations

Transforming Social Perception: To counter the widespread normalization of tobacco use in the social sphere, mass awareness campaigns and public service announcements (reviving the spirit of "Smoke-Free Air Zones") should be implemented, emphasizing that tobacco is not a "habit" but a chronic "health problem/addiction".

Education-Based Interventions: The fundamentals of addiction prevention should be integrated into the formal school curriculum as mandatory courses or modules to raise awareness among future generations early in life.

Accessibility and Promotion: Polyclinics should be relocated from remote corners of hospitals to more visible, accessible locations, and the free and professional nature of these services should be more effectively promoted to the public via social media and mass communication channels.

Ethics

Ethics Committee Approval: Ethical approval for the research was obtained from the Scientific Research and Publication Ethics Committee of Erzurum Technical University Rectorate with decision number: 2025-ETÜ-0052, date: 13.11.2025.

Informed Consent: Before data collection, participants were informed about the purpose of the study, and their consent was obtained.

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Footnotes

Authorship Contributions

Concept: E.D., C.D., Design: E.D., Data Collection or Processing: E.D., C.D., Analysis or Interpretation: E.D., Literature Search: E.D., C.D., Writing: E.D., C.D.

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

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Original Article

Ultrasound- versus CT-guided Biopsy of Pleural-contact Pulmonary Lesions: A Comparative Analysis of Diagnostic Performance and Procedural Complications

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ABSTRACT

OBJECTIVE: To compare the diagnostic performance and complication profiles of ultrasound (US)-guided and computed tomography (CT)-guided biopsy in pleural-contact pulmonary lesions and to evaluate technical factors associated with pneumothorax development after CT-guided biopsy.

MATERIAL AND METHODS: This retrospective single-center study included 197 patients with pleural-contact pulmonary lesions who underwent image-guided transthoracic core needle biopsy between January 2023 and March 2026. Of these, 123 underwent CT-guided biopsies and 74 underwent US-guided biopsies. Diagnostic adequacy, diagnostic accuracy, and procedure-related complications were compared between the groups. Factors associated with pneumothorax after CT-guided biopsy were evaluated using univariate and multivariable logistic regression analyses.

RESULTS: Diagnostic adequacy was comparable between CT-guided and US-guided biopsies (93.5% vs. 89.2%, $P = 0.281$). Similarly, diagnostic accuracy did not differ significantly between the groups (93.0% vs. 97.0%, $P = 0.331$). Pneumothorax occurred in 34 patients (27.6%) following CT-guided biopsy, whereas none occurred after US-guided biopsy ($P < 0.001$). Chest tube placement was required in 7 patients (5.7%) in the CT-guided group and in none in the US-guided group ($P = 0.047$). In univariate analysis, the traversed aerated lung distance was associated with pneumothorax development (odds ratio, 1.056; 95% confidence interval, 1.005–1.110; $P = 0.031$); however, no independent predictor was identified in multivariable analysis.

CONCLUSION: US-guided biopsy of pleural-contact pulmonary lesions demonstrated diagnostic adequacy and diagnostic accuracy comparable to CT-guided biopsy and was associated with lower pneumothorax and chest tube placement rates in this retrospective cohort. When an adequate acoustic window and pleural contact are present, US guidance may be a safe and effective alternative biopsy approach for appropriately selected pleural-contact pulmonary lesions.

KEYWORDS: Biopsy, needle, diagnostic accuracy, lung neoplasms, pneumothorax, tomography, X-ray computed, ultrasonography

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INTRODUCTION

Transthoracic image-guided biopsy is a well-established and widely used procedure for the histopathological diagnosis of pulmonary lesions.[1] Computed tomography (CT)-guided biopsy has traditionally been considered the standard guidance modality because of its high spatial resolution and ability to visualize lesions regardless of location.[1,2] However, CT-guided procedures are associated with ionizing radiation exposure, prolonged procedure times, and procedure-related complications, particularly pneumothorax and pulmonary hemorrhage.[2,3] Pneumothorax remains the most common complication following transthoracic lung biopsy, and several lesion- and technique-related factors, including emphysema, lesion size, traversed aerated lung distance, and the number of pleural punctures, have been shown to influence its occurrence.[2,3]

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Ultrasound (US)-guided biopsy has emerged as a valuable alternative for selected peripheral pulmonary lesions, particularly those in contact with the pleura.[4,5] Compared with CT guidance, US guidance offers several practical advantages, including real-time needle visualization, the absence of radiation exposure, applicability at the bedside, lower cost, and shorter procedural duration.[4] Because US-guided biopsy may minimize or avoid traversal of aerated lung parenchyma, it has the potential to reduce the risk of pneumothorax.[3,4] Nevertheless, thoracic ultrasonography has important limitations, as lesion visualization and safe needle access may be restricted by scapular or rib interference, respiratory motion, or the absence of an adequate acoustic window.[6]

Several recent studies have demonstrated comparable diagnostic performance between US- and CT-guided biopsy techniques in selected peripheral or subpleural pulmonary lesions.[7,8] In a retrospective comparative study, Mychajlowycz et al.[8] reported similar diagnostic adequacy and complication rates between US- and CT-guided biopsy of subpleural lung and pleural lesions, while US-guided procedures were associated with shorter waiting and procedure times. However, previous studies have mainly focused on overall diagnostic success and complication rates, whereas technical parameters potentially contributing to complication development—such as pleural contact length, traversed distance through lung parenchyma, and number of pleural punctures—have not been sufficiently investigated. To our knowledge, few comparative studies have specifically evaluated the effects of pleural contact length and traversed aerated lung distance on pneumothorax development in pleural-contact pulmonary lesions.

Therefore, this study aimed to compare the diagnostic performance and complication profiles of US-guided versus CT-guided biopsies for pleural-contact pulmonary lesions. Factors associated with the development of pneumothorax were evaluated in patients undergoing CT-guided biopsy, with pneumothorax events enabling risk-factor analysis.

MATERIAL AND METHODS

Study Design and Patient Selection

This retrospective, single-center study included consecutive patients who underwent image-guided transthoracic biopsy for pulmonary lesions in contact with the pleura between January 2023 and March 2026. The study was approved by the Atatürk University Non-Interventional Clinical Research Ethics Committee prior to study initiation (decision no: 11; approval date: 02.06.2026), and the requirement for informed consent was waived because of the study's retrospective design.

Main Points

- Ultrasound (US)-guided biopsy of pleural-contact pulmonary lesions demonstrated diagnostic adequacy and accuracy comparable to computed tomography (CT)-guided biopsy.
- No pneumothorax occurred following US-guided biopsy, whereas 27.6% of CT-guided procedures resulted in pneumothorax.
- Chest tube placement was required only following CT-guided biopsy, underscoring the favorable safety profile of US guidance in appropriately selected lesions.
- When an adequate acoustic window and pleural contact are present, US guidance may be a safe and effective alternative approach to biopsy for appropriately selected lesions.

Patients who underwent US-guided or CT-guided transthoracic core needle biopsy for pulmonary lesions demonstrating pleural contact on preprocedural thoracic CT were included in the study. The patient selection process is summarized in Figure 1. A total of 289 patients underwent image-guided transthoracic lung biopsy during the study period. After exclusion of patients with non–pleural-contact pulmonary lesions (n = 74), incomplete clinical or imaging data (n = 8), unavailable pathology results (n = 4), and repeat biopsies of the same lesion (n = 6), 197 patients with pleural-contact pulmonary lesions were included in the final analysis. Of these, 123 underwent CT-guided biopsy and 74 underwent US-guided biopsy.

Pleural-contact lesions were defined as pulmonary lesions demonstrating a visible interface with the visceral pleura on preprocedural CT, without intervening aerated lung tissue between the lesion and pleural surface. Patients with incomplete clinical or imaging data, missing pathology results, or repeated biopsies of the same lesion were excluded.

Demographic characteristics, lesion features, procedural details, diagnostic adequacy, and procedure-related complications were retrospectively reviewed in the institutional electronic medical records and the picture archiving and communication system.

Imaging Evaluation

Preprocedural thoracic CT images were reviewed by an independent thoracic radiologist with 5 years' experience in thoracic imaging to assess lesion characteristics, including size, pleural contact length, location, cavitation, and presence of emphysema. Lesion size was defined as the maximum axial diameter on CT images. Pleural contact length was measured using electronic calipers and defined as the longest interface between the lesion and the pleural surface on axial CT images.

For CT-guided biopsies, the traversed distance through aerated lung parenchyma was additionally measured as the length of aerated lung tissue crossed by the biopsy needle from the pleural entry point to the lesion margin. In all US-guided procedures, the biopsy trajectory was planned through the pleural-contact portion of the lesion without traversing aerated lung parenchyma.

Biopsy Procedures

The choice of imaging guidance modality was determined according to lesion visibility, accessibility, safe needle trajectory, and the presence of an adequate acoustic window.

To minimize operator-related variability, all US-guided and CT-guided biopsy procedures were performed by the same interventional thoracic radiologist with 8 years of experience in thoracic imaging and image-guided transthoracic interventions. The number of pleural punctures and core tissue samples obtained during each procedure was recorded.

Ultrasound-guided Biopsy

US-guided biopsies were performed in real time using a US system (Aplio 500; Toshiba Medical Systems Corporation, Otawara, Japan) equipped with a 3–6 MHz convex transducer. Following sterile preparation and local anesthesia, transthoracic core needle biopsy was performed using a 16-gauge biopsy needle under continuous real-time ultrasonographic guidance (Figure 2). Depending on lesion characteristics and specimen adequacy, one or two core tissue samples were obtained from each lesion.

Immediately after the procedure, a posteroanterior chest radiograph was obtained to assess procedure-related complications. Follow-up posteroanterior chest radiographs were routinely obtained four hours after the procedure.

Computed Tomography-guided Biopsy

CT-guided biopsies were performed using a conventional 320-row detector CT scanner (Aquilion ONE Vision; Toshiba Medical Systems Corporation, Otawara, Japan). Initial planning CT images were obtained to determine the safest needle trajectory while minimizing traversal of aerated lung parenchyma whenever possible. Following sterile preparation and local anesthesia, biopsies were performed using the coaxial technique with an 18-gauge core biopsy needle advanced to the target lesion through a coaxial introducer needle (Figure 3). Because a coaxial technique was routinely used, a single pleural puncture was performed in all patients regardless of the number of tissue cores obtained. Three core tissue samples were routinely obtained from each lesion.



Figure 1. Flowchart of patient selection

CT: computed tomography, US: ultrasound

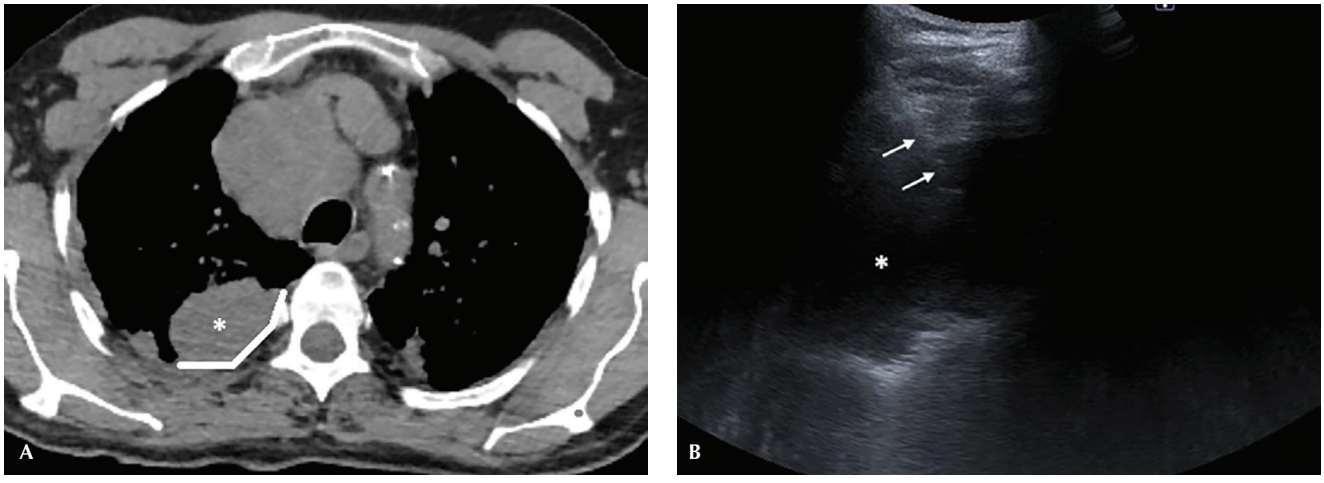


Figure 2. Pleural-contact pulmonary adenocarcinoma in a 65-year-old man. (A) Axial CT image demonstrates a right lower lobe pleural-contact lesion (asterisk); the white line indicates the pleural contact length. (B) Corresponding ultrasound image demonstrates the lesion (asterisk). Arrows indicate the biopsy needle trajectory during ultrasound-guided biopsy

CT: computed tomography

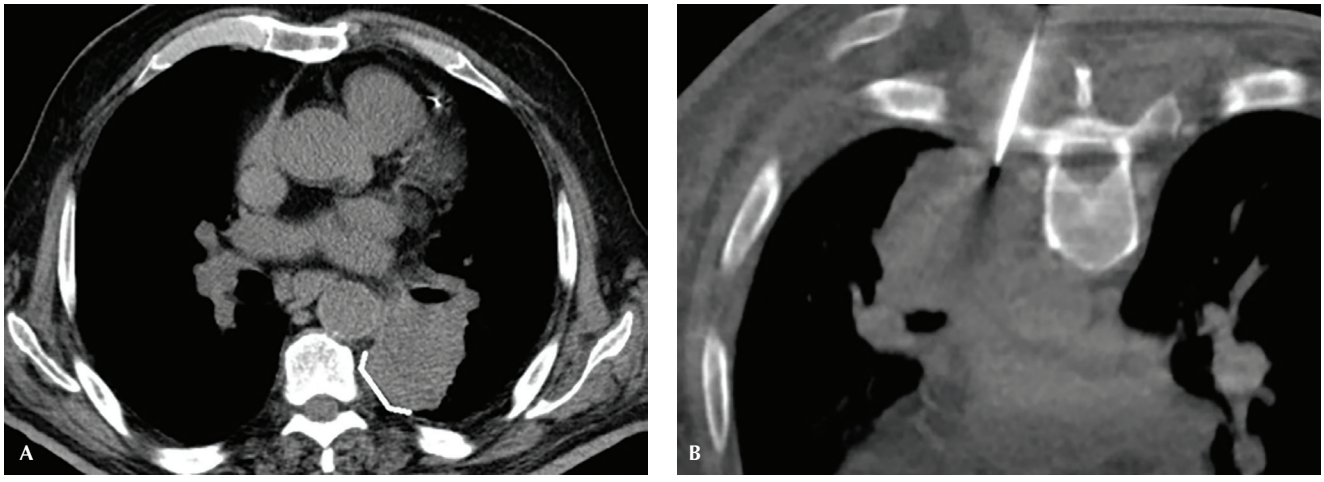


Figure 3. Pleural-contact squamous cell carcinoma in a 68-year-old man. (A) Axial CT image demonstrates the lesion; the white line indicates the pleural contact length. (B) CT-guided core needle biopsy of the lesion

CT: computed tomography

Immediately after the procedure, control CT images were acquired to assess procedure-related complications. In addition, follow-up posteroanterior chest radiography was routinely performed four hours after the procedure.

Outcome Measures

The primary outcomes of the study were diagnostic adequacy and procedure-related complications.

As part of routine clinical practice, histopathological evaluation was performed by experienced pathologists blinded to the imaging guidance modality used for biopsy. Final pathology reports were retrospectively reviewed for this study. Diagnostic adequacy was defined as the acquisition of sufficient tissue for histopathological evaluation. Specimens yielding a malignant diagnosis, benign inflammatory or infectious lesions, granulomatous inflammation, fibrotic/reactive lung tissue, mesenchymal proliferations, or benign lung parenchyma were considered diagnostically adequate. Specimens containing only necrotic material, nonrepresentative tissue (e.g., skeletal muscle, adipose tissue, or fibroadipose tissue), or insufficient material for pathological interpretation were considered non-diagnostic.

Diagnostic accuracy was assessed in diagnostically adequate biopsy specimens. A biopsy result was considered accurate when the histopathological diagnosis was concordant with the final diagnosis established by surgical pathology, repeat biopsy, or clinical-radiological follow-up. Overall diagnostic accuracy was calculated by including all biopsy procedures, with non-diagnostic biopsy results considered clinical failures, thereby reflecting diagnostic performance in the entire study population.

Procedure-related complications, including pneumothorax, the requirement for chest tube placement, and hemoptysis, were recorded. Pneumothorax was defined as the presence of pleural air detected on immediate postprocedural CT or follow-up chest radiography. Complications were classified according to the Society of Interventional Radiology classification system.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test, Q–Q plots, skewness, and kurtosis. Normally distributed variables are presented as mean ± standard deviation, whereas non-normally distributed variables are presented as median and interquartile range. Comparisons between two independent groups were performed using the independent-samples t test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Factors associated with pneumothorax were evaluated only among patients who underwent CT-guided biopsy, because no pneumothorax events occurred in the US-guided biopsy group. Univariate logistic regression analysis was initially performed to assess potential risk factors. Variables with a P value <0.10 in the univariate analysis were subsequently included in the multivariable logistic regression model. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. Odds ratios (ORs) for lesion diameter, pleural contact length, and traversed lung distance were calculated per 1-mm increase in each variable. Statistical significance was defined as a two-sided P value <0.05.

RESULTS

A total of 197 patients with pleural-contact pulmonary lesions were included in the study. Of these, 123 underwent CT-guided biopsy and 74 underwent US-guided biopsy. Baseline patient and lesion characteristics are summarized in Table 1. There were no significant differences between the groups regarding age, sex distribution, emphysema prevalence, or lesion location (all $P > 0.05$). However, lesions in the US-guided group were significantly larger than those in the CT-guided group (median diameter: 77 mm vs. 53 mm; $P < 0.001$) and had a greater pleural contact length (median: 51 mm vs. 32 mm; $P < 0.001$). Cavitary lesions were more frequently encountered in the CT-guided group than in the US-guided group (22.8% vs. 5.4%, $P = 0.001$) (Table 1).

Table 1. Baseline patient and lesion characteristics

Variable	CT-guided (n = 123)	US-guided (n = 74)	*P* value
Age (years)	64.2±11.7	63.6±16.8	0.598
Male sex, n (%)	95 (77.2)	60 (81.1)	0.592
Emphysema, n (%)	60 (48.8)	32 (43.2)	0.451
Lesion diameter (mm)	53 (40–72)	77 (46–99)	<0.001
Pleural contact length (mm)	32 (17–54)	51 (33–95)	<0.001
Cavitation, n (%)	28 (22.8)	4 (5.4)	0.001
Lesion location, n (%)			0.09
• Upper lobe	78 (63.4)	39 (52.7)	
• Middle lobe	2 (1.6)	1 (1.4)	
• Lower lobe	43 (35.0)	34 (45.9)	

Data are presented as mean ± standard deviation, median (interquartile range), or number (%), as appropriate
CT: computed tomography, US: ultrasound

Procedural characteristics, diagnostic performance, and complication rates are presented in Table 2. The median number of pleural punctures was significantly lower in the CT-guided group because a coaxial technique with a single pleural puncture was routinely used, whereas repeated punctures were occasionally required during US-guided procedures ($P < 0.001$). Traversed aerated lung distance was significantly greater in the CT-guided group (3.5 ± 7.8 mm vs. 0 mm, $P < 0.001$).

Diagnostic adequacy was comparable between CT-guided and US-guided biopsy procedures (93.5% vs. 89.2%, $P = 0.281$). Similarly, diagnostic accuracy did not differ significantly between the two groups (93.0% vs. 97.0%, $P = 0.331$). When non-diagnostic biopsy results were considered clinical failures, overall diagnostic accuracy remained comparable between the CT-guided and US-guided groups (87.0% vs. 86.5%, respectively; $P = 0.925$). Regarding procedure-related complications, pneumothorax developed in 34 patients (27.6%) following CT-guided biopsy, whereas no pneumothorax developed following US-guided biopsy ($P < 0.001$). Chest tube placement was required in seven patients (5.7%) in the CT-guided group and in no patients in the US-guided group ($P = 0.047$). The incidence of hemoptysis was low in both groups and did not differ significantly between CT-guided and US-guided biopsies (1.6% vs. 2.7%, $P = 0.629$) (Table 2).

Because no pneumothorax events occurred in the US-guided group, analysis of pneumothorax-related risk factors was performed only among patients who underwent CT-guided biopsy. In univariate logistic regression analysis, traversed aerated lung distance was significantly associated with pneumothorax development [OR, 1.056; 95% confidence interval (CI), 1.005–1.110; $P = 0.031$]. Pleural contact length demonstrated a borderline association with pneumothorax occurrence (OR, 0.986; 95% CI, 0.971–1.002; $P = 0.092$). Age, sex, emphysema, lesion diameter, and cavitation were not significantly associated with pneumothorax development (Table 3). In a subgroup analysis of CT-guided biopsies, pneumothorax rates did not differ significantly between cavitary and non-cavitary lesions [17.9% (5/28) vs. 30.5% (29/95), respectively; $P = 0.234$].

Table 2. Procedural characteristics, diagnostic performance, and complications

Variable	CT-guided (n = 123)	US-guided (n = 74)	*P* value
Procedural characteristics			
Pleural puncture number	1 (1–1)	1 (1–3)	<0.001
Traversed lung distance (mm)	3.5±7.8	0	<0.001
Diagnostic performance			
Diagnostic adequacy, n (%)	115 (93.5)	66 (89.2)	0.281
Diagnostic accuracy among adequate biopsies, n (%)	107/115 (93.0)	64/66 (97.0)	0.331
Overall diagnostic accuracy, n (%)	107/123 (87.0)	64/74 (86.5)	0.925
Complications			
Pneumothorax, n (%)	34 (27.6)	0	<0.001
Chest tube placement, n (%)	7 (5.7)	0	0.047
Hemoptysis, n (%)	2 (1.6)	2 (2.7)	0.629

Diagnostic accuracy among adequate biopsies was calculated after exclusion of non-diagnostic specimens. Overall diagnostic accuracy was calculated by considering non-diagnostic biopsy results as clinical failures
CT: computed tomography, US: ultrasound

Variables with a *P* value <0.10 in univariate analysis were subsequently entered into the multivariable logistic regression model. In multivariable analysis, neither pleural contact length (adjusted OR, 0.989; 95% CI, 0.973–1.005; *P* = 0.175) nor traversed aerated lung distance (adjusted OR, 1.048; 95% CI, 0.998–1.101; *P* = 0.061) remained independently associated with pneumothorax development (Table 4). The Hosmer–Lemeshow goodness-of-fit test indicated adequate fit of the multivariable logistic regression model (*P* = 0.745).

DISCUSSION

In the present study, we compared the diagnostic performance and complication profiles of US-guided and CT-guided biopsies in patients with pleural-contact pulmonary lesions. The principal findings were threefold. First, US-guided biopsy demonstrated diagnostic adequacy and accuracy comparable to those of CT-guided biopsy. Second, procedure-related complications—particularly pneumothorax and the need for chest tube placement— were significantly lower in the US-guided group. Third, although traversed aerated lung distance was associated with the development of pneumothorax in univariate analysis, multivariable analysis did not identify any independent predictors of pneumothorax.

CT-guided transthoracic biopsy remains the reference standard for tissue sampling of pulmonary lesions because of its high diagnostic performance and broad applicability, regardless of lesion location.[2] However, pneumothorax and pulmonary hemorrhage continue to represent the most frequent procedure-related complications, with reported pneumothorax rates ranging from approximately 15% to 35% in contemporary series.[2,9] Consequently, alternative image-guidance techniques that can maintain diagnostic performance while reducing complications remain of considerable clinical interest.

Our findings demonstrated no significant difference in diagnostic adequacy between CT-guided and US-guided biopsies (93.5% vs. 89.2%). Similarly, diagnostic accuracy among adequate specimens was comparable between CT-guided and US-guided biopsy procedures (93.0% vs. 97.0%). These findings are consistent with previous studies that report equivalent diagnostic performance of US-guided biopsy for carefully selected peripheral pulmonary lesions.[7-9] In a comparative study, Yamamoto et al.[7] reported similar diagnostic yields and safety profiles between US-guided and CT-guided biopsy for peripheral lung and pleural lesions. Likewise, Mychajlowycz et al.[8] demonstrated comparable diagnostic adequacy between the two techniques while reporting shorter procedure times and waiting times for US-guided procedures. More recently, Zhou et al.[10] reported comparable diagnostic outcomes between US-guided and CT-guided biopsy in subpleural pulmonary lesions, further supporting the feasibility of US guidance in appropriately selected patients. In addition, a recent meta-analysis by Li et al.[11] confirmed the high diagnostic performance of US-guided core needle biopsy for peripheral pulmonary lesions. Collectively, these findings support the concept that US guidance can provide diagnostic performance equivalent to CT guidance when an adequate acoustic window and pleural contact are present. However, differences in biopsy technique between the two groups should also be considered when interpreting diagnostic outcomes. CT-guided procedures used an 18-gauge coaxial technique with three routinely obtained core samples, whereas US-guided procedures used a 16-gauge needle with one or two core samples. Therefore, differences in needle size, coaxial technique, and the number of tissue samples may have influenced diagnostic performance and should be considered when comparing the two guidance methods. Furthermore, the numerically higher diagnostic accuracy observed in the US-guided group, despite fewer core samples obtained, should not be interpreted as indicating superiority of US guidance alone. This finding may reflect multiple factors, including the selection of technically favorable lesions with larger sizes and broader pleural contact, as well as procedural advantages of US guidance, such as real-time needle visualization and the ability to target viable solid components while avoiding necrotic areas. In addition, the use of a larger 16-gauge biopsy needle in the

Table 3. Univariate logistic regression analysis of factors associated with pneumothorax after CT-guided biopsy

Variable	Odds ratio	95% CI	*P* value
Age	1.015	0.980–1.052	0.408
Male sex	2.026	0.830–4.942	0.121
Emphysema	1.070	0.485–2.358	0.867
Lesion diameter	0.993	0.977–1.009	0.366
Pleural contact length	0.986	0.971–1.002	**0.092**
Traversed lung distance	1.056	1.005–1.110	**0.031**
Cavitation	2.021	0.699–5.841	0.194

ORs for continuous variables are reported per 1-mm increase
OR: odds ratio, CI: confidence interval, CT: computed tomography

Table 4. Multivariable logistic regression analysis of pneumothorax following CT-guided biopsy

Variable	Adjusted odds ratio	95% CI	*P* value
Pleural contact length	0.989	0.973–1.005	0.175
Traversed lung distance	1.048	0.998–1.101	0.061

Variables with *P* < 0.10 in univariate analysis were included in the multivariable model. ORs for continuous variables are reported per 1-mm increase
OR: odds ratio, CI: confidence interval, CT: computed tomography

US-guided group may have contributed to obtaining adequate tissue samples despite yielding fewer core specimens.

An important observation of the present study was the markedly different complication profiles between the two groups. No pneumothorax occurred following US-guided biopsy, whereas pneumothorax developed in 27.6% of CT-guided procedures; chest tube placement was required in 5.7% of patients. Although the absolute complication rates reported in the literature vary depending on patient selection and procedural technique, our findings are consistent with previous reports demonstrating substantially lower pneumothorax rates with US-guided biopsy of pleural-based lesions.[8,12] The most likely explanation is that aerated lung was not traversed during US-guided procedures.[9] Despite a higher median number of pleural punctures in the US-guided group, no pneumothorax occurred after US-guided biopsy. This finding suggests that avoidance of traversing aerated lung tissue may be a more important determinant of pneumothorax risk than the number of pleural punctures. In our study, all US-guided biopsies were performed through the pleural-contact portion of the lesion, resulting in a traversed aerated lung distance of zero. In contrast, even minimal passage through aerated lung tissue during CT-guided biopsy may create a pleural-alveolar communication and increase the risk of pneumothorax.[9]

The study specifically focused on pleural-contact pulmonary lesions, a subgroup that has received limited attention in the literature.[12] Most previous comparative studies have evaluated heterogeneous cohorts containing both pleural-contact and non–pleural-contact lesions.[8,12] By restricting the analysis to lesions with direct pleural contact, we attempted to minimize selection heterogeneity and to better evaluate the clinical utility of US guidance for lesions theoretically amenable to both techniques. Our results suggest that when a lesion is visible sonographically and demonstrates adequate pleural contact, US guidance may be considered an effective first-line approach because it achieves similar diagnostic performance while avoiding radiation exposure and reducing procedure-related complications.

Another notable aspect of this study was the evaluation of technical factors potentially associated with pneumothorax development. Previous studies and consensus guidelines have identified lesion size, emphysema, traversed lung distance, and the number of pleural punctures as important determinants of pneumothorax risk.[9,13,14] In our cohort, the traversed aerated lung distance was significantly associated with pneumothorax on univariate analysis. However, this association did not remain statistically significant in the multivariable model. Although the traversed aerated lung distance remained close to the threshold for statistical significance (P = 0.061), the small number of pneumothorax events may have reduced the statistical power to identify independent predictors. Therefore, the absence of a statistically significant association should be interpreted with caution. Nevertheless, the findings suggest that the development of pneumothorax is likely to be multifactorial and cannot be attributed to a single technical parameter. Similarly, pleural contact length demonstrated a borderline association in univariate analysis but did not retain independent significance after adjustment. This finding differs somewhat from the results reported by Imamine et al.[14], who identified pleural contact length as a significant determinant of the occurrence of pneumothorax during US-guided lung biopsy.

Lesions in the US-guided group were significantly larger and had greater pleural contact lengths than those in the CT-guided group. This finding reflects routine clinical practice, in which the selection of the imaging guidance modality was influenced by lesion characteristics and procedural feasibility. Larger lesions with broader pleural interfaces provide better sonographic visualization and a safer acoustic window; therefore, these lesions were more likely to be selected by the proceduralist for US-guided biopsy. Consequently, some degree of selection bias and confounding by indication is unavoidable in retrospective comparisons between the two techniques. In addition, cavitary lesions were significantly more frequent in the CT-guided group than in the US-guided group. This imbalance likely reflects real-world biopsy selection patterns, since cavitary lesions may provide a less favorable sonographic window and therefore be preferentially referred for CT-guided biopsy. However, an additional subgroup analysis of CT-guided procedures demonstrated that pneumothorax rates did not differ significantly between cavitary and non-cavitary lesions (17.9% vs. 30.5%, respectively). Although the unequal distribution of cavitary lesions represents a potential selection factor, cavitation itself did not appear to be a major determinant of pneumothorax development in our cohort. Despite these baseline differences, diagnostic adequacy and accuracy remained comparable between the two groups. However, these baseline differences should be carefully considered when interpreting the observed differences in complication rates. Larger lesions with broader pleural interfaces provide improved sonographic visibility, facilitate safer needle trajectory planning, and may inherently reduce the risk of pneumothorax. Therefore, the lower pneumothorax rate observed in the US-guided group cannot be attributed solely to the imaging guidance modality, but likely reflects the combined effects of US guidance and favorable lesion characteristics. Accordingly, these findings should be interpreted within the context of appropriately selected pulmonary lesions in contact with the pleura, rather than as evidence that US guidance is universally superior to CT guidance.

The present study has several strengths. All procedures were performed at a single tertiary center using standardized biopsy protocols and were reviewed according to predefined imaging and pathological criteria. Furthermore, we evaluated diagnostic adequacy and diagnostic accuracy separately, and analyzed technical variables such as pleural contact length and traversed aerated lung distance. These factors allowed a more detailed assessment of both diagnostic performance and procedural safety.

Study Limitations

This study has several limitations. First, differences in post-procedural imaging assessments between the two biopsy techniques may have introduced detection bias. CT-guided procedures were evaluated with immediate postprocedural CT imaging, whereas US-guided procedures were assessed using postprocedural chest radiography. Therefore, small

or clinically insignificant pneumothoraces may have been detected more frequently after CT-guided biopsy, and the observed difference in pneumothorax rates may partly reflect differences in detection sensitivity rather than a true difference in complication rates. However, clinically relevant outcomes, such as the need for chest tube placement, are less likely to be influenced by differences in imaging sensitivity. Second, the retrospective single-center design and non-randomized selection of the imaging guidance modality introduce potential selection bias. The choice of imaging guidance modality was influenced by lesion visibility and accessibility. Consequently, the US-guided group included significantly larger lesions with longer pleural contact lengths, which may have facilitated lesion visualization and reduced procedural risk. Although the distribution of lesion locations did not differ statistically between groups, the slightly higher proportion of lower-lobe lesions in the US-guided group may represent a residual confounding factor due to greater respiratory motion. Therefore, the observed differences in complication rates may partly reflect baseline lesion characteristics rather than the imaging guidance modality. Although propensity-score matching could have further reduced the effects of baseline differences between groups, it was not performed because of the relatively limited sample size, particularly in the US-guided cohort, and the potential risk that matching would substantially reduce the analyzable study population. Therefore, the results should be interpreted as reflecting outcomes observed in appropriately selected pleural-contact lesions rather than as a direct comparison between two completely equivalent patient groups. Biopsy techniques were not identical between the two groups, including differences in needle size, in the use of a coaxial system, and in the number of core samples obtained, which may represent a potential source of procedural bias. Third, the relatively limited number of pneumothorax events may have reduced the statistical power of the multivariable analysis. Furthermore, all biopsy procedures were performed by a single experienced thoracic radiologist. Although this approach reduced operator-related variability and provided procedural consistency, it may limit the generalizability of the findings. Therefore, similar diagnostic and safety outcomes may not be directly reproducible in centers with different levels of operator experience or procedural expertise. Finally, procedure duration, radiation exposure parameters, and patient-related procedural outcomes such as pain, comfort, and satisfaction were not systematically recorded due to the retrospective design of the study and, therefore, could not be compared between the two techniques. Although the absence of radiation exposure represents an inherent advantage of US guidance, further prospective studies incorporating procedural time, radiation dose, and patient-centered outcomes are needed to provide a more comprehensive comparison of these guidance modalities.

CONCLUSION

In this retrospective comparison of pleural-contact pulmonary lesions, US-guided biopsy demonstrated diagnostic adequacy and accuracy comparable to those of CT-guided biopsy, and was associated with lower rates of pneumothorax and chest tube placement. Given the non-randomized design and differences in baseline lesion characteristics, these findings suggest that US guidance may represent an effective and safe alternative biopsy approach for appropriately selected pleural-contact pulmonary lesions with an adequate acoustic window.

Ethics

Ethics Committee Approval: The study was approved by the Atatürk University Non-Interventional Clinical Research Ethics Committee prior to study initiation (decision no: 11; approval date: 02.06.2026).

Informed Consent: The requirement for informed consent was waived because of the study's retrospective design.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Y., E.P., A.K., Concept: M.Y., A.K., Design: M.Y., A.T.A., Data Collection or Processing: M.Y., E.P., Analysis or Interpretation: A.T.A., A.K., Literature Search: M.Y., E.P., A.K., Writing: M.Y., A.T.A.

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

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Original Article

Rapid Drug Desensitization to Platinum-based Chemotherapy Agents: A Single-center Experience

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ABSTRACT

OBJECTIVE: To characterize the clinical features of patients with platinum-based hypersensitivity reactions (HSRs) and to evaluate rapid drug desensitization (RDD) outcomes across different platinum agents.

MATERIAL AND METHODS: This retrospective study included patients who underwent RDD for platinum agents between 2019 and 2023 at a tertiary adult allergy clinic. Index reaction characteristics, RDD procedures, and breakthrough reactions (BTRs) were systematically recorded and analyzed.

RESULTS: Of 2,131 patients receiving chemotherapy, 105 (5.0%) developed platinum-induced HSRs and were included in the analysis. The cohort comprised 75 (71.4%) females, with a mean age of 61.3±10.3 years. Carboplatin was the most frequently implicated agent (n = 56, 53.3%), followed by oxaliplatin (n = 35, 33.3%) and cisplatin (n = 14, 13.3%). Index reactions occurred at a median of 5 cycles (range: 1–20) and, according to Brown's classification, were mild in 26 patients (24.8%), moderate in 73 patients (69.5%), and severe in 6 patients (5.7%). A total of 430 RDD procedures were performed, with 62 (14.4%) BTRs occurring in 40 patients (38.1%). The proportion of RDD procedures completed without BTRs did not differ significantly among carboplatin (226/266, 85.0%), oxaliplatin (110/126, 87.3%), and cisplatin (32/38, 84.2%) (P = 0.800). Overall, 414 (94.1%) desensitization procedures were successfully completed. Sex distribution differed significantly by culprit platinum agent, with a male predominance observed among patients reacting to oxaliplatin compared with those reacting to cisplatin and carboplatin (P < 0.001).

CONCLUSION: This study demonstrates that desensitization to platinum-based chemotherapy achieved high success rates and produced comparable outcomes across different platinum agents. Notably, HSRs to oxaliplatin were observed significantly more frequently among male patients than HSRs to other platinum agents.

KEYWORDS: Chemotherapy desensitization, breakthrough reactions, platinum agents

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INTRODUCTION

Hypersensitivity reactions (HSRs) occur in approximately 5% of patients receiving chemotherapeutic agents, representing a significant challenge in oncology practice.[1] Among platinum-based compounds, carboplatin is most frequently implicated in HSRs; its incidence increases cumulatively with repeated exposure and may reach up to 46% after seven or more treatment cycles.[1] Oxaliplatin is associated with HSRs in approximately 15% of patients (range: 1–25%), although severe reactions occur in fewer than 1%. Cisplatin has been reported as the culprit agent in approximately 5% of cases.[1,2]

The pathophysiological mechanism underlying immediate HSRs to platinum agents is thought to be predominantly immunoglobulin E (IgE)–mediated. This mechanism is supported by characteristic clinical features such as the

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requirement for repeated exposures to induce sensitization, the demonstration of positive skin test responses, and the detection of platinum-specific IgE antibodies in some patients.[3] Rapid drug desensitization (RDD) has emerged as an essential therapeutic strategy for patients who have experienced HSRs to first-line chemotherapeutic agents and for whom no equally effective alternative treatments exist.[4] RDD enables the safe and timely reintroduction of culprit agents by inducing a temporary state of tolerance. Previous platinum desensitization studies have reported that most RDD procedures were completed without breakthrough reactions (BTRs), with rates ranging from 71.0% to 75.8%.[5-7] Nevertheless, published studies indicate that severe BTRs may occur in approximately 5.8–11% of desensitization procedures, typically during the first or second RDD cycle.[5,8,9]

Although several studies have evaluated the incidence and characteristics of HSRs associated with individual platinum agents, real-life data describing desensitization outcomes and reaction patterns during RDD remain limited, with heterogeneous outcomes reported across studies.[5-7,9] Therefore, the present study aimed to characterize the clinical features of patients referred to our center for suspected platinum-based chemotherapy HSRs and, among those requiring continued treatment with the culprit agent, to evaluate the success of RDD and the frequency, severity, and nature of BTRs occurring during desensitization.

MATERIAL AND METHODS

This retrospective study included adult patients (≥18 years) who were evaluated for immediate HSRs to platinum-based chemotherapeutic agents and subsequently underwent RDD between 2019 and 2023 in the adult allergy and clinical immunology department of a tertiary referral center. Patients receiving non-platinum chemotherapies, patients desensitized at other institutions, patients with incomplete medical documentation, and patients with delayed-type HSRs were excluded. The primary aim of the study was to characterize the clinical features of patients with platinum-based HSRs. The secondary aim was to assess RDD outcomes among different platinum agents.

Immediate HSRs were defined as reactions occurring during the infusion or within 6 hours after drug administration, including reactions developing after completion of the infusion, in accordance with current guidelines.[1,10,11] Initial reactions were graded according to Brown's[10] classification: grade 1 reactions were limited to skin or subcutaneous tissue; grade 2 reactions included respiratory, gastrointestinal, or cardiovascular symptoms without hypotension; and grade 3 reactions involved hypoxia, hypotension, or neurologic compromise.

Skin testing was performed at least two weeks after the index reaction in accordance with established recommendations.[12] Both skin prick testing (SPT) and intradermal testing (IDT) were conducted. For SPT, undiluted commercial preparations were used: carboplatin 10 mg/mL, cisplatin 1 mg/mL, and oxaliplatin 5 mg/mL.[8,11] When SPT was negative, IDT was performed using increasing concentrations (1:100, 1:10, and 1:1). A positive IDT was defined as a wheal enlargement of ≥3 mm with erythema at 20 minutes. Concentrations used for IDT were: carboplatin 0.1, 1, and 5 mg/mL; cisplatin 0.01, 0.1, and 1 mg/mL; and oxaliplatin 0.005, 0.5, and 5 mg/mL.[1,11] In clinical practice, IDT with carboplatin at the full concentration (10 mg/mL) is generally avoided due to irritant effects and reported risk of local skin necrosis and scarring.[12]

RDD was carried out using modified protocols based on the Castells desensitization regimen.[8] Depending on reaction severity, comorbidities, and skin test results, patients received a 12-step (three-bag), 16-step (four-bag), or 20-step (five-bag) protocol. The 12-step protocol included three dilutions of the final dose (X/100, X/10, X). For patients with previous grade 3 reactions or high-risk features, an additional dilution (X/1000) was added to create a 16-step protocol. A 20-step protocol was used in selected high-risk patients and involved serial dilution of chemotherapy solutions to achieve 1/10, 1/100, and 1/1000 concentrations.[13,14] All desensitization procedures were administered in an inpatient monitored unit. Premedication consisted of intravenous methylprednisolone (40 mg), an H1 antihistamine (pheniramine 45.5 mg), and an H2 antagonist (famotidine 20 mg or ranitidine 50 mg), administered 30 minutes prior to RDD, according to institutional practice.[5]

Ethical approval was obtained from the Hacettepe University Ethics Committee (approval number: SBA 25/917, date: 09.12.2025). Owing to the retrospective study design, informed consent was waived.

Main Points

- Rapid drug desensitization (RDD) for platinum-based chemotherapy is generally successful; however, real-life data on desensitization outcomes and patterns of immediate hypersensitivity reactions (HSRs) remain limited and heterogeneous.
- This study demonstrates a high overall success rate for RDD (94.1%). The success rate without breakthrough reactions was 85.6% in the overall platinum cohort, with no statistically significant differences among platinum agents, including carboplatin (85.0%), oxaliplatin (87.3%), and cisplatin (84.2%).
- Notably, HSRs to oxaliplatin were observed significantly more frequently in male patients compared with other platinum agents.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 27.0 (SPSS Inc., Chicago, IL). The normality of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Non-normally distributed continuous variables were compared using the Mann–Whitney U test. Normally distributed continuous variables were compared using Student's t-test. Categorical variables were analyzed using the Pearson chi-square test or Fisher's exact test, as appropriate. Data are presented as medians (minimum-maximum) for continuous variables and as numbers (percentages) for categorical variables. Risk factors associated with the development of BTRs were evaluated using univariate regression analyses followed by multivariate models. All results are reported with 95% confidence intervals. A P value <0.05 was considered statistically significant.

RESULTS

A total of 2,131 patients received chemotherapy during the study period, of whom 105 (5.0%) experienced platinum-induced immediate HSRs. Among these patients, 75 (71.4%) were female, and the mean age was 61.3±10.3 years. The demographic and clinical characteristics of the study cohort are summarized in Table 1.

Carboplatin was the most frequently implicated platinum agent, identified in 56 (53.3%), patients followed by oxaliplatin in 35 (33.3%) patients and cisplatin in 14 (13.3%) patients.

Table 1. Demographic and clinical characteristics of patients with and without BTRs during rapid drug desensitization with platinum agents

Variables, n (%)	All patients (n = 105)	Patients with BTRs (n = 40)	Patients without BTRs (n = 65)	*P* value
Age at diagnosis (years), mean (± SD)	61.3±10.3	61.7±12.7	61.0±8.9	0.745
Sex				
Male	30 (28.6)	11 (27.5)	19 (29.2)	0.849
Female	75 (71.4)	29 (72.5)	46 (70.8)	
BMI, median, (min–max)	26.3 (16.7–55.1)	25.7 (18.6–36.7)	26.6 (16.7–55.1)	0.266
Obesity (BMI ≥30 kg/m²)	29 (27.6)	9 (22.5)	20 (30.8)	0.357
Other drug allergy diagnosis*	16 (15.2)	8 (20.0)	8 (12.3)	0.287
Comorbidity†	50 (47.6)	22 (55.0)	28 (43.1)	0.235
Hypertension	33 (31.4)	15 (37.5)	18 (27.7)	0.293
Antihypertensive treatment††				
Beta-blocker	4 (15.4)	2 (18.2)	2 (13.3)	0.426
ACE inhibitor/ARB	15 (57.7)	5 (45.5)	10 (66.7)	
Beta-blocker and ACE inhibitor/ARB	1 (3.8)	0 (0.0)	1 (6.7)	
Other	6 (23.1)	4 (36.4)	2 (13.3)	
CVD, n (%)	8 (7.6)	6 (15.0)	2 (3.1)	0.051
Family history of drug allergies, n (%)	7 (6.7)	1 (2.5)	6 (9.2)	0.248
Type of chemotherapy, n (%)				
Monotherapy	2 (1.9)	1 (2.5)	1 (1.5)	1.000
Combination therapy	103 (98.1)	39 (97.5)	64 (98.5)	
Culprit chemotherapeutic agent, n (%)				
Cisplatin	14 (13.3)	4 (10.0)	10 (15.4)	0.330
Carboplatin	56 (53.3)	25 (62.5)	31 (47.7)	
Oxaliplatin	35 (33.3)	11 (27.5)	24 (36.9)	
Time to index reaction (minutes), median (min–max)	30.0 (2.0–180.0)	20.0 (5.0–180.0)	30.0 (2.0–180.0)	0.884
Cycle of index reaction, median (min–max)	5.0 (1.0–20.0)	6.0 (1.0–16.0)	5.0 (1.0–20.0)	0.303
Total cumulative chemotherapy dose (mg), median (min–max)	250.0 (37.5–720.0)	290.0 (80.0–700.0)	240.0 (37.5–720.0)	0.376
Index reaction severity (Brown's classification), median (min–max)				
Mild	26 (24.8)	7 (17.5)	19 (29.2)	0.365
Moderate	73 (69.5)	30 (75.0)	43 (66.2)	
Severe	6 (5.7)	3 (7.5)	3 (4.6)	
Skin test positivity with the culprit drug, n (%)	33 (31.4)	14 (35.0)	19 (29.2)	0.690
Number of chemotherapy cycles with RDD, median (min–max)	3.0 (1.0–17.0)	4.0 (1.0–17.0)	3.0 (1.0–12.0)	0.081
Number of chemotherapy cycles without BTRs	3.0 (0.0–16.0)	2.5 (0.0–16.0)	3.0 (1.0–12.0)	0.198

*Cetuximab, iron supplement, Sinovac vaccine (inactivated SARS-CoV-2 virus), proton pump inhibitor, and granulocyte colony-stimulating factor therapy, NSAID, antibiotic

†Asthma, hypertension, cardiovascular disease

††Percentages calculated among patients with hypertension

BTRs: breakthrough reactions, SD: standard deviation, min: minimum, max: maximum, BMI: body mass index, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, CVD: cardiovascular disease, RDD: rapid drug desensitization, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, NSAID: non-steroidal anti-inflammatory drug

Index reactions occurred at a median of 5 chemotherapy cycles (range: 1.0–20.0). According to Brown's[10] classification, index reactions were mild in 26 (24.8%) patients, moderate in 73 (69.5%) patients, and severe in 6 (5.7%) patients. The most common clinical manifestations of index reactions were cutaneous symptoms (80 patients, 76.2%); respiratory (61 patients, 58.1%); cardiovascular (27 patients, 25.7%); neurological (17 patients, 16.2%); gastrointestinal (11 patients, 10.5%); fever (9 patients, 8.6%); and back pain (2 patients, 1.9%). Skin testing was performed in 84 patients (80.0%), of whom 33 (39.2%) had positive results. SPT was positive in 7 of 84 patients (8.3%). Among patients with negative prick test results (n = 77), IDT yielded positive results in 27 (33.7%) patients (Table 1).

A total of 430 chemotherapy administrations were performed using RDD; the median number of procedures per patient was 3 (range: 1–17). Overall, 40 (38.1%) patients experienced a total of 62 (14.4%) BTRs among all desensitization procedures. BTRs occurred at a median cycle of 2.0 (range: 1.0–16.0) and most frequently at the 16th step of the desensitization protocol (range: 1.0–20.0). Among the 62 BTRs, 49 involved cutaneous symptoms, 10 involved respiratory symptoms, and 14 involved cardiovascular symptoms. Epinephrine administration was required in 4 BTRs, and no fatalities occurred. Overall, 414 of 430 (94.1%) desensitization procedures were successfully completed.

Analysis stratified by platinum agent showed that index reactions occurred at median cycles of 4.0 (range: 2.0–10.0) for cisplatin, 6.0 (range: 1.0–20.0) for carboplatin, and 5.0 (range: 1.0–14.0) for oxaliplatin, with no statistically significant difference among the three agents (P = 0.157). The proportion of desensitization procedures completed without BTRs was similar among carboplatin (226/266, 85.0%), oxaliplatin (110/126, 87.3%), and cisplatin (32/38, 84.2%) (P = 0.800) (Figure 1). Skin test positivity rates by culprit agent were 33.3% (4/14) for cisplatin, 31.8% (14/43) for carboplatin, and 53.5% (15/35) for oxaliplatin, with no statistically significant differences among groups (P = 0.118). A significant difference in sex distribution according to the culprit platinum agent was observed: HSRs were more frequent in males receiving oxaliplatin (20 patients, 57.1%) than in males receiving cisplatin (1 patient, 7.1%) or carboplatin (9 patients, 16.1%) (P < 0.001). The distribution of malignancies differed among platinum agents, with gastrointestinal malignancies accounting for a higher proportion of cases in the oxaliplatin group (34/35, 97.2%) than in the carboplatin (2/56, 3.5%) and cisplatin (1/14, 7.1%) groups (P < 0.001) (Table 2). Desensitization characteristics and BTR outcomes, stratified by culprit platinum agent, are summarized in Table 3.

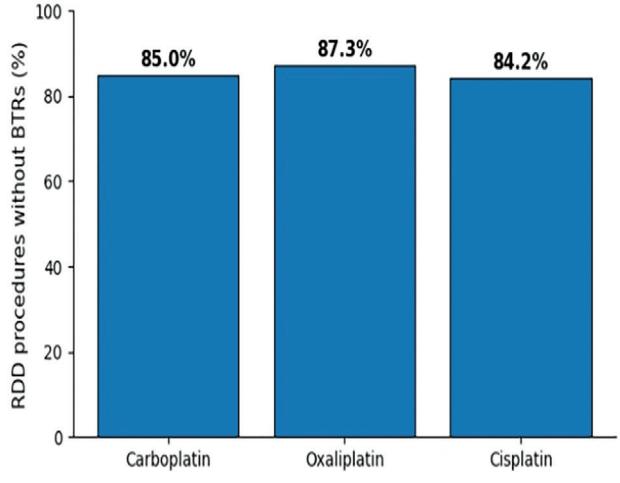


Figure 1. Breakthrough reaction-free desensitization rates by platinum agent

RDD: rapid drug desensitization, BTRs: breakthrough reactions

Potential risk factors for BTRs, including age, sex, type of chemotherapy, body mass index, history of other drug allergy, atopy, hypertension, culprit platinum agent, index reaction severity, skin test positivity, and the total number of desensitizations, were evaluated using univariate and multivariate logistic regression analyses. In univariate analysis, atopy [odds ratio (OR): 4.62, 95% confidence interval (CI): 1.03–20.7; P = 0.046], skin test positivity (OR: 3.69, 95% CI: 1.33–10.2; P = 0.012), and total number of desensitizations (OR: 1.18, 95% CI: 1.01–1.37; P = 0.034) were associated with an increased risk of BTRs. However, none of these variables remained statistically significant in the multivariate model. Detailed results are presented in Supplementary Table S1.

DISCUSSION

Current literature supports the safe continuation of platinum-based chemotherapy through RDD, with success rates approaching 98.7%; however, data directly comparing outcomes among different platinum agents are limited.[3,6,7] Consistent with these data, our study demonstrated a high overall desensitization completion rate of 94.1%, confirming the effectiveness and safety of RDD in a real-life clinical setting and demonstrating comparable success rates for carboplatin, oxaliplatin, and cisplatin.

Previous studies have shown that cutaneous symptoms are the most frequent and earliest manifestations of platinum-induced HSRs across all platinum agents, followed by respiratory symptoms, while cardiovascular involvement, although less common, is associated with greater severity.[15,16] In our cohort, index reactions most commonly presented with cutaneous symptoms, followed by respiratory and cardiovascular manifestations. In the study by Gorgulu Akin et al.,[7] HSRs occurred at a median of the fifth infusion, with significant differences in reaction onset according to the specific platinum agent, occurring at a median of 6 cycles for carboplatin and 3 cycles for both cisplatin and oxaliplatin. In our cohort, index HSRs occurred after a median of five chemotherapy cycles. Although the median cycle number at reaction onset was similar across platinum agents (6 for carboplatin, 4 for cisplatin, and 5 for oxaliplatin), no statistically significant difference in reaction timing was observed. Although carboplatin HSRs are generally reported to occur after a higher number of treatment cycles, the earlier onset observed in our cohort may be explained by our status as a tertiary referral center, where close collaboration with oncologists and heightened awareness of chemotherapy-related HSRs facilitate earlier recognition and referral.[3,13]

The sensitivity of skin testing to platinum drugs varies among studies, with an overall reported sensitivity of approximately 66%.[3]

Table 2. Baseline demographic and clinical characteristics of patients according to culprit platinum agent

Variables, n (%)	Cisplatin (n = 14)	Carboplatin (n = 56)	Oxaliplatin (n = 35)	*P* value
Age at diagnosis (years), median (min–max)	61.0 (42.0–70.0)	61.0 (36.0–86.0)	63.0 (34.0–81.0)	0.489
Sex				
Male	1 (7.1)	9 (16.1)	20 (57.1)	**<0.001**
Female	13 (92.9)	47 (83.9)	15 (42.9)	
BMI, median (min–max)	27.0 (22.0–37.6)	27.9 (16.6–55.1)	25.3 (17.3–36.8)	0.164
Obesity (BMI ≥30 kg/m²)	4 (28.6)	19 (33.9)	6 (17.1)	0.218
History of other drug allergies	4 (28.6)	7 (12.5)	5 (14.3)	0.320
Drug allergy type				
NSAID	0 (0.0)	1 (14.3)	2 (40.0)	
Antibiotic	1 (25.0)	2 (28.6)	3 (60.0)	0.361
Others*	3 (75.0)	4 (57.1)	0 (0.0)	
Comorbidity†	6 (42.9)	26 (46.4)	18 (51.4)	0.834
Hypertension	4 (28.6)	16 (28.6)	13 (37.1)	0.672
Antihypertensive treatment††				
Beta-blocker	1 (25.0)	2 (16.7)	1 (10.0)	
ACE inhibitor/ARB	3 (75.0)	6 (50.0)	6 (60.0)	0.796
Beta-blocker and ACE inhibitor/ARB	0 (0.0)	1 (8.3)	0 (0.0)	
Other	0 (0.0)	3 (25.0)	3 (30.0)	
CVD	0 (0.0)	5 (8.9)	3 (8.6)	0.513
Family history of drug allergy	13 (92.9) 1 (7.1)	52 (92.9) 4 (7.1)	33 (94.3) 2 (5.7)	0.962
Type of malignancy				
Gynecologic cancers	11 (78.7)	38 (67.8)	1 (2.8)	
Head and neck tumors	2 (14.2)	1 (1.7)	0	**< 0.001**
Gastrointestinal malignancies	1 (7.1)	2 (3.5)	34 (97.2)	
Lung cancer	0	10(17.8)	0	
Others**	0	5 (8.9)	0	
Type of mutation				
HER/neu	1 (16.7)	1 (5.6)	1 (25.0)	
TP53	4 (66.7)	13 (72.2)	0 (0.0)	0.098
Others##	1 (16.7)	4 (22.2)	3 (75.0)	
Type of chemotherapy				
Monotherapy	2 (14.3)	0 (0.0)	0 (0.0)	**0.001**
Combination therapy	12 (85.7)	56 (100.0)	35 (100.0)	
Time to index reaction (minutes), median (min–max)	30.0 (2.0–110.0)	20.0 (3.0–80.0)	30.0 (5.0–180.0)	0.118
Cycle of index reaction, median (min–max)	4.0 (2.0–10.0)	6.0 (1.0–20.0)	5.0 (1.0–14.0)	0.157
Index reaction severity (Brown's classification), median (min–max)				
Mild	6 (42.9)	11 (19.6)	9 (25.7)	
Moderate	8 (57.1)	40 (71.4)	25 (71.4)	0.275
Severe	0 (0.0)	5 (8.9)	1 (2.9)	
Skin test positivity with the culprit drug	4 (33.3)	14 (31.8)	15 (53.5)	0.118

*Cetuximab, iron supplement, Sinovac vaccine (inactivated SARS-CoV-2 virus), proton pump inhibitor, and granulocyte colony-stimulating factor therapy

†Asthma, hypertension, cardiovascular disease

††Percentages calculated among patients with hypertension

**Skin tumors, hematolymphoid malignancies, ocular tumors, and breast cancer

##EGFR, c-KIT, KRAS, BRCA, PD-L1 expression, mismatch repair deficiency, microsatellite instability, and PMS2 loss

min: minimum, max: maximum, BMI: body mass index, NSAID: non-steroidal anti-inflammatory drug, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, CVD: cardiovascular disease, HER/neu: human epidermal growth factor receptor 2, TP53: tumor protein p53, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, EGFR: epidermal growth factor receptor, c-KIT: KIT proto-oncogene, receptor tyrosine kinase, KRAS: Kirsten rat sarcoma viral oncogene homolog, BRCA: breast cancer gene, PD-L1: programmed death-ligand 1

Table 3. Desensitization characteristics and breakthrough reaction outcomes according to platinum agent

Variables, n (%)	Cisplatin (n = 14)	Carboplatin (n = 56)	Oxaliplatin (n = 35)	*P* value
Total RDD procedures	38 (8.8)	266 (61.9)	126 (29.3)	**<0.001**
Chemotherapy cycles with RDD per patient, median (min–max)	2.0 (1.0–9.0)	4.0 (1.0–17.0)	3.0 (1.0–10.0)	0.119
Number of patients with BTRs	4 (29.6)	25 (44.6)	11 (31.4)	0.330
Chemotherapy cycles without BTRs per patient, median (min–max)	1.5 (0.0–9.0)	3.0 (0.0–16.0)	3.0 (0.0–9.0)	0.159
RDD procedures completed without BTRs	32 (84.2)	226 (85.0)	110 (87.3)	0.800
Cutaneous BTR symptoms	7 (63.6)	31 (55.4)	12 (63.2)	0.660
Respiratory BTR symptoms	1 (9.1)	6 (10.7)	3 (15.8)	0.780
Cardiovascular BTR symptoms	2 (18.2)	10 (17.9)	2 (10.5)	0.790
Febrile BTR symptoms	0 (0.0)	5 (8.9)	2 (10.5)	0.940
Anaphylaxis events during BTRs	0 (0.0)	4 (7.1)	0 (0.0)	0.270

RDD: rapid drug desensitization, BTRs: breakthrough reactions

The diagnostic sensitivity of skin testing to platinum agents differs according to the specific compound. In contemporary studies, carboplatin has consistently demonstrated the highest skin test sensitivity, reported in approximately 60–70% of patients, whereas oxaliplatin and cisplatin show lower and more heterogeneous sensitivities, generally ranging from 30–60% and 20–50%, respectively.[1,11,12,17,18] In our cohort, skin test positivity rates were 31.8% for carboplatin, 53.5% for oxaliplatin, and 33.3% for cisplatin. Oxaliplatin showed higher positivity rates, consistent with known variability in oxaliplatin-associated HSRs. The lower carboplatin skin test positivity observed in our study may be explained by the use of lower IDT concentrations, as the predictive value of skin testing is known to be concentration dependent.[19] Although platinum-induced HSRs are generally considered IgE-mediated, the low rate of positive skin tests in our cohort suggests that non-IgE-mediated mechanisms may also contribute. Pathways such as cytokine release or complement activation may be involved, particularly in patients undergoing RDD who have negative skin tests. Because acute-phase cytokine markers, including interleukin-6, were not routinely measured in our study, we were unable to further delineate the relative contributions of these mechanisms.

Previous platinum desensitization studies have reported that 71.0–75.8% of procedures were completed without BTRs.[6,7] In our study, approximately 85% of desensitization procedures were completed without BTRs, indicating a relatively lower rate of BTRs compared with previously published data. When stratified by platinum agent, desensitization procedures were completed without BTRs in 85.0% of carboplatin administrations, 87.3% of oxaliplatin administrations, and 84.2% of cisplatin administrations, with no statistically significant differences among agents. The higher reaction-free completion rate observed in our study may be attributable to the use of a 20-step desensitization protocol, which allows for more gradual dose escalation. Previous studies and current EAACI recommendations support increasing the number of desensitization steps in high-risk patients, particularly those receiving platinum agents, to improve tolerability and reduce BTRs.[1,4,5] Previous studies have reported that RDD is successfully completed in 94% to 98.7% of procedures.[5,7] Consistent with this range, our study demonstrated a similarly high overall completion rate: 414 of 430 desensitization procedures (94.1%) were successfully completed. From a clinical perspective, our findings indicate that desensitization outcomes do not differ meaningfully among platinum agents, supporting RDD as a safe and practical approach that enables patients with HSRs to continue essential chemotherapy.

Although germline BRCA1/2 mutations have been reported as independent risk factors for carboplatin HSRs, particularly in patients receiving repeated cycles, comparative analyses of mutation frequencies across different platinum agents remain limited.[20] In our cohort, the frequency of BRCA1/2 mutations did not differ significantly among patients treated with cisplatin, carboplatin, or oxaliplatin; this suggests that BRCA-related genetic susceptibility may not account for inter-agent differences in hypersensitivity patterns. Notably, sex-related differences were observed with respect to the culprit platinum agent. Kim et al.[17] previously reported a male predominance among patients experiencing oxaliplatin HSRs, with males constituting 54.2% of affected cases. In line with these findings, our study identified a significant difference in the sex distribution of HSRs among patients treated with platinum-based agents, with reactions observed more frequently in male patients receiving oxaliplatin (57.1%) than in those treated with cisplatin (7.1%) or carboplatin (16.1%). This pattern is considered to be related both to the significantly higher prevalence of gastrointestinal malignancies in the oxaliplatin-treated cohort and to existing epidemiological evidence demonstrating a higher incidence of gastrointestinal cancers in males.[21]

Study Limitations

The limitations of this study include its retrospective design, which inherently limits causal inference, and the potential for incomplete documentation and referral bias. Another limitation is that serum tryptase measurements during index or BTRs were not routinely available. In addition, the relatively small number of patients receiving cisplatin may have limited the statistical power for agent-specific comparisons. The strengths of this study include its relatively large real-life cohort, the

comprehensive evaluation of three commonly used platinum agents within the same clinical setting, and the standardized assessment of index reactions, skin testing, and desensitization outcomes, using predefined, risk-adapted protocols and a uniform premedication regimen applied across all procedures.

CONCLUSION

This study demonstrates a high overall success rate of RDD (94.1%). The success rate without BTRs in the overall platinum cohort was 85.6%, with comparable success rates for carboplatin (85.0%), oxaliplatin (87.3%), and cisplatin (84.2%). HSRs to oxaliplatin were observed more frequently in male patients compared with reactions to other platinum agents.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Hacettepe University Ethics Committee (approval number: SBA 25/917, date: 09.12.2025).

Informed Consent: Owing to the retrospective study design, informed consent was waived.

Footnotes

Authorship Contributions

Concept: H.K.,E.D., M.C., Design: H.K., K.Ç., E.H, Data Collection or Processing: H.K., E.D., Analysis or Interpretation: H.K., E.D., Literature Search: H.K.,K.Ç., E.H. Writing: H.K.,Ç.T., A.P.U., G.K., A.F.K.

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Supplementary Table S1. https://d2v96fxpocvxx.cloudfront.net/d18681b3-da48-42d0-9b05-c9e02fb8192c/content-images/add714ec-6985-4279-90ce-73fc11e42dd2.pdf

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Review

Respiratory Emergencies in Disasters: A Narrative Review

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ABSTRACT

Disasters cause a wide spectrum of respiratory injuries and affect hundreds of millions of people each year. Because the respiratory system is in continuous contact with the external environment, it is among the most vulnerable systems in disaster settings. Silica- and asbestos-containing dust released from earthquake debris, fine particulate matter from wildfire smoke, mold spores in flood-damaged interiors, ash and acidic gases from volcanic eruptions, toxic industrial chemicals released during chemical incidents, barotrauma from explosions, and biological or pandemic threats each trigger acute and chronic respiratory diseases through distinct mechanisms. This narrative review addresses respiratory emergencies associated with natural and human-made disasters, the underlying pathophysiological mechanisms, diagnostic and management approaches, vulnerable populations, and the influence of climate change on the rising burden of disaster-related respiratory disease. Evidence was synthesized from PubMed/MEDLINE, Web of Science, and Scopus, supplemented by official reports from the Emergency Events Database, the World Health Organization, and the United Nations Office for Disaster Risk Reduction. Available data indicate that acute respiratory infections are major causes of morbidity and mortality in disaster settings across all age groups. Furthermore, patients with chronic respiratory diseases face an increased risk of exacerbations, while the management of acute respiratory distress syndrome remains a significant challenge, particularly in resource-limited environments. Disaster preparedness planning must prioritize respiratory emergencies and strengthen response protocols for vulnerable groups.

KEYWORDS: Disasters, acute respiratory distress syndrome, earthquakes, wildfires, pandemics, climate change

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INTRODUCTION

Disasters are events that exceed a community's coping capacity, require external assistance, and produce severe consequences for human life and health systems.[1] According to the Emergency Events Database (EM-DAT) classification, disasters are grouped into natural disasters (including geophysical, hydrological, meteorological, climatological, and biological subtypes) and technological (human-made) disasters.[2] Each year, recorded disaster events affect millions of people, cause substantial mortality and morbidity, and impose a heavy burden on healthcare systems.[3]

Between 1995 and 2022, a mean of 398 natural disasters per year was recorded, with a cumulative death toll of 918,198.[4] In 2023 alone, disaster-related mortality reached 86,473, exceeding the two-decade average, largely driven by the February 6, 2023 Kahramanmaraş earthquake sequence in Türkiye and Syria, which claimed 56,683 lives, affected 18 million people, and caused USD 42.9 billion in economic losses.[5]

The respiratory system is uniquely exposed in disaster settings. The lungs maintain continuous contact with the environment and serve as the primary surface for inhaled particulates, toxic gases, and biological agents.[6] Silica- and asbestos-containing dust from collapsed structures, fine particulate matter (PM2.5) in wildfire smoke, mold spores proliferating in flood-

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damaged interiors, irritant gases released in chemical incidents, and pressure waves generated by explosions cause upper and lower airway injuries, acute bronchospasm, pneumonia, and acute respiratory distress syndrome (ARDS) through distinct mechanisms.[7] A systematic review of 47 studies on earthquake-induced tsunamis demonstrated that crowded evacuation centers increase the incidence of acute respiratory infections, which rank among the most frequently reported post-disaster illnesses.[8]

The Sendai Framework for Disaster Risk Reduction 2015–2030, endorsed by 187 UN member states, explicitly identifies protection of health infrastructure and continuity of health services as integral to disaster preparedness.[9] However, disaster protocols specific to respiratory diseases remain underdeveloped. This review addresses respiratory emergencies associated with natural and human-made disasters, the underlying pathophysiological mechanisms, diagnostic and management approaches, vulnerable populations, and the influence of climate change.

METHODS-LITERATURE SEARCH STRATEGY

This narrative review draws on a comprehensive literature search of PubMed/MEDLINE, Web of Science, and Scopus, completed in March 2026. Search terms combined respiratory- and disaster-related vocabulary using Boolean operators, including respiratory emergencies, inhalation injury, ARDS, chronic obstructive pulmonary disease (COPD) exacerbation, asthma exacerbation, mechanical ventilation, mass casualty, earthquake, wildfire, flood, hurricane, volcanic eruption, tsunami, chemical disaster, blast lung, pandemic, displaced populations, and climate change. The review focused on publications from 2015-2026, with selected seminal references retained from earlier periods. Official reports from EM-DAT, the World Health Organization, and the United Nations Office for Disaster Risk Reduction were consulted as primary sources for disaster epidemiology.

Main Points

- The respiratory system is a primary target across virtually all disaster types, with mechanisms ranging from particulate inhalation and toxic gas exposure to barotrauma and viral aerosol transmission.
- Crowded evacuation centers and disrupted health infrastructure substantially increase the burden of acute respiratory infections and tuberculosis after natural disasters.
- Wildfire-derived fine particulate matter (PM2.5) appears to be more toxic to the respiratory system than urban PM2.5 of equivalent concentration.
- Point-of-care ultrasound, pulse oximetry, and capnography are pragmatic, field-deployable tools that should be embedded in disaster respiratory triage protocols.
- Children, the elderly, pregnant women, patients with chronic respiratory disease, and displaced populations bear a disproportionate share of disaster-related respiratory burden.

CLASSIFICATION OF DISASTERS AND GENERAL RESPIRATORY EFFECTS

The EM-DAT database contains more than 27,000 recorded disaster events, the majority of which are of natural origin, with floods and storms appearing most frequently.[2] Biological disasters—including epidemics and pandemics—are classified within the natural disaster category in EM-DAT.

Each disaster type affects the respiratory system through distinct mechanisms, making disaster-specific clinical planning necessary. Earthquakes generate acute inhalation injury through dust containing silica and asbestos released during structural collapse. Wildfires produce complex, PM2.5-dominated smoke that directly damages the airway epithelium. Floods and hurricanes create conditions for biological contamination, particularly mold, which triggers exacerbations of asthma and COPD. Industrial chemical disasters release highly toxic gases, such as chlorine, ammonia, and phosgene, causing mass inhalation injuries.[7]

The post-disaster respiratory burden is substantial. The systematic review of 47 earthquake-induced tsunami studies cited above identified acute respiratory infections as the most frequently reported post-disaster illness group, with crowded evacuation centers, exposure to high pathogen loads, adverse climate, and inadequate vaccination coverage as the principal risk factors.[8] Recent evaluations following the Kahramanmaraş earthquake have demonstrated that dust clouds rising from collapsed buildings can spread across wide geographic areas within hours, with silica and asbestos content posing both acute inhalation hazards and long-term pneumoconiosis risk.[10,11] A contemporary review of natural disasters and respiratory health similarly highlights that heatwaves, wildfires, hurricanes, floods, earthquakes, and volcanic eruptions each gives rise to distinct but serious respiratory complications.[7]

RESPIRATORY EMERGENCIES BY DISASTER TYPE

Earthquakes

Earthquakes cause abrupt and widespread damage to the built environment and rapidly generate large volumes of airborne particulate matter. The respiratory consequences span a wide clinical spectrum, ranging from the acute phase to long-term sequelae, and include inhalation of dust and particulates, acute respiratory infections, exacerbation of pre-existing respiratory disease, thoracic trauma, and pulmonary thromboembolism.[12]

Dust released from collapsed structures may contain high concentrations of silica, asbestos, and other toxic constituents. Measurements performed in Hatay after the February 6, 2023, Kahramanmaraş earthquakes—conducted during the active demolition phase and representing peak rather than time-weighted average exposures—recorded mean respirable and total dust concentrations of 30.84 mg/m^3 and 33.66 mg/m^3, respectively, far exceeding international occupational exposure limits. Scanning electron microscopy (SEM) of debris samples identified fibrous particles consistent with the morphology of asbestos; however, definitive mineralogical confirmation requires further analytical methods beyond SEM.[11] Given Türkiye's well-documented pre-existing environmental and

occupational asbestos burden, these findings warrant serious attention to the long-term risk of mesothelioma and lung cancer among both survivors and rescue workers.[13]

Beyond particulate exposure, deteriorating shelter conditions, compromised sanitation, and stress-related immunosuppression substantially increase the post-earthquake burden of respiratory infections. A retrospective study of 1,122 patients after the Kahramanmaraş earthquake found significant increases in hospitalization for pneumonia and COPD exacerbations,[14] while a systematic review following the 2011 Great East Japan earthquake identified pneumonia as the most frequent post-disaster respiratory disease.[15] A multiplex reverse transcription quantitative polymerase chain reaction study from Gaziantep tent cities (n = 830) identified rhinovirus (20%), *Streptococcus pneumoniae* (12.9%), respiratory syncytial virus A/B (12.1%), and *Haemophilus influenzae* type b (10.9%) as the dominant respiratory pathogens, providing pathogen-level data from the Kahramanmaraş aftermath.[16] A multi-center observational study of adults admitted to intensive care after the same earthquake further documented the burden of severe respiratory infection requiring critical care support in the affected region.[17]

Güleç Balbay et al.[12] comprehensively reviewed the respiratory effects of earthquakes, identifying inhalation injury, respiratory infections, exacerbation of pre-existing disease, thoracic trauma, and pulmonary and venous thromboembolism as the principal complications, with the quality of building infrastructure emerging as a key determinant of both injury severity and infection risk.

Thoracic trauma is a frequently overlooked complication that is associated with mortality. Imaging in survivors trapped under rubble after Kahramanmaraş most commonly identified thoracic injuries—rib fractures, pulmonary contusion, pneumothorax, hemothorax, and pulmonary thromboembolism.[18] The earthquake-specific injury pattern differs from non-earthquake trauma. Prolonged entrapment precipitates crush syndrome, characterized by hypovolemia, hyperkalemia, and myoglobinuria; reperfusion injury after rescue can, in turn, progress to ARDS. Long-bone fractures increase the risk of fat embolism. Crush-related immobility and hypercoagulability further elevate the risk of pulmonary thromboembolism, which may evade detection during the acute phase.[12,18] Taken together, these findings underline the need for systematic evaluation of thoracic trauma, pulmonary contusion, and thromboembolic complications alongside inhalation injury in earthquake medicine.

Wildfires

Wildfires have become more frequent, severe, and prolonged over the past decade, under the influence of climate change. Wildfire smoke is a complex mixture of chemicals, including PM2.5, carbon monoxide (CO), ozone, nitrogen oxides, benzene, and various volatile organic compounds.[19] Wildfire-specific PM2.5 elicits stronger oxidative and inflammatory responses than urban PM2.5 at equivalent concentrations, reflecting a distinct toxic profile.[20]

Mechanistically, wildfire PM2.5 inhalation causes lung injury by inducing oxidative stress, systemic inflammation, disruption of airway epithelial integrity, and increased susceptibility to infection. Sustained exposure increases the risk of developing COPD, accelerates disease progression, and is associated with lung cancer and increased mortality.[19,20]

A study of more than six million emergency department visits demonstrated that each 1 $\mu g/m^3$ increase in wildfire smoke PM2.5 was associated with a 1.6% rise in asthma-related visits, 0.4% in COPD, and 0.4% in bronchitis, with effects markedly stronger than those of urban PM2.5.[21] A systematic meta-analysis of wildfire smoke exposure reported a 7% increase in overall health risk, a 9% increase in emergency department visits, and a 4% increase in hospitalizations, with respiratory disease and COPD risks rising by 7% and asthma by 11%.[22] In pediatric populations, wildfire smoke exposure has been associated with substantially increased asthma-related emergency department visits, and fine particles in California wildfire smoke have been linked specifically to pediatric respiratory hospitalizations.[23] In older adults with COPD, increased hospitalization and mortality have been consistently reported.[20]

The January 2025 Los Angeles (LA) wildfires offered a recent and stark illustration of the urban-interface respiratory threat. Within the most affected census tracts, daily mean PM2.5 reached 101.7 $\mu g/m^3$ at the downtown LA regulatory monitor, with concomitant elevations in nitrogen dioxide (NO_2) concentrations. Preliminary analyses of healthcare utilization documented increases of more than 35% in cardiovascular and respiratory telehealth visits among exposed populations.[24]

Wildfires also affect first-response personnel. A systematic review of 26 studies in firefighters and other responders found adverse respiratory effects in 24 studies, including decreased lung function, airway dysfunction, and increased respiratory symptoms.[25] Occupational wildfire smoke exposure has been shown to adversely affect lung function, reinforcing the need for respiratory protection as a standard component of wildfire response.

Floods and Hurricanes

Floods and hurricanes are among the most frequent and widely impactful natural disasters globally. Their respiratory health consequences arise through three principal mechanisms: aspiration injury, deterioration of indoor air quality due to mold and biological contamination, and an elevated risk of respiratory infection in crowded evacuation conditions.[7]

Drowning and near-drowning events produce the most acute respiratory complications. A cohort of 144 near-drowning patients reported acute respiratory failure on presentation in 54%, although early bacterial aspiration pneumonia did not independently determine mortality and was generally manageable with standard supportive care.[26] The pathophysiology of aspiration differs by water type: freshwater dilutes and inactivates pulmonary surfactant, whereas hyperosmolar seawater induces fluid shift into the alveolar space and disrupts the alveolar-capillary barrier, with both ultimately producing surfactant dysfunction and impaired gas exchange.[27,28] Aspiration of contaminated water further predisposes individuals to polymicrobial infection. A systematic meta-analysis identified Gram-negative bacteria as

the principal pathogens, with *Aeromonas* species, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* among the most frequently isolated organisms; severe cases may progress to ARDS, requiring intensive care support.[29]

Rapid mold growth in flood-damaged interiors poses an additional acute and long-term respiratory hazard. The Houston-3H study, conducted after Hurricane Harvey in 2017, documented a significant increase in upper-airway allergic symptoms among exposed individuals and found strong associations between exposure to contaminated water and mold and the occurrence of multiple allergic manifestations.[30] Measurements in New Orleans after Hurricanes Katrina and Rita found markedly higher airborne mold concentrations in severely water-damaged homes than in lightly damaged dwellings, with endotoxin and fungal glucan levels comparable to those in agricultural settings.[31] A large cohort study of more than 11 million adults aged ≥65 years documented post-flood increases of 4.6% in all-cause emergency department visits, 6.9% in hospitalizations, and 8.3% in respiratory hospitalizations specifically.[32]

In addition, power outages following hurricanes pose an underrecognized threat to patients receiving home oxygen or domiciliary ventilation. Sandy (2012) and Maria (2017) provided clinical exemplars, and population-level data confirm significantly increased hospitalization risk in oxygen-dependent COPD patients during outages.[33]

Crowded evacuation centers and temporary shelters create conditions favorable for outbreaks of respiratory infection in the aftermath of floods and hurricanes. Influenza, tuberculosis (TB), and other droplet-transmitted pathogens spread more readily in densely populated indoor settings, with concurrent malnutrition, sleep deprivation, and chronic stress further weakening immune responses.[7,8] The combination of deteriorating shelter conditions, sanitation breakdown, and reduced access to health services amplifies the burden. These findings highlight the need to place respiratory health at the center of flood and hurricane response plans and to pre-configure infection control protocols in evacuation centers.

Volcanic Eruptions

Volcanic eruptions simultaneously release multiple respiratory irritants-ash particles, sulfur dioxide (SO_2), hydrogen sulfide (H_2S), hydrogen chloride (HCl), and CO-with respiratory effects varying by particle size, crystalline silica content, and gas concentration.[34] Volcanic ash induces airway injury through oxidative stress, inflammatory cytokine release, and impaired mucociliary clearance; the presence of cristobalite increases the risk of silicosis.[35]

Epidemiological evidence consistently associates acute exposure to volcanic emissions with increased respiratory morbidity. A recent scoping review of the global burden of volcanic exposure identified cough, sputum production, dyspnea, chest tightness, and wheeze as the principal symptoms, with significant increases in emergency department visits for asthma and COPD exacerbations. Chronic exposure has been linked to silicosis, pneumoconiosis, and lung cancer; respirable volcanic particles may cross the alveolocapillary barrier and contribute to systemic cardiovascular and cerebrovascular disease.[34]

The 2014–2015 Holuhraun eruption in Iceland provided a detailed picture of mass exposure to SO_2. In Reykjavik, approximately 250 km from the eruption site, a registry study showed significant increases in daily asthma medication use after the eruption began and significant rises in primary care and emergency utilization on high-SO_2 days.[36] Volcanic smog from Kilauea adversely affected respiratory symptoms and lung function in nearby Hawaiian populations, with high-exposure areas showing marked increases in cough prevalence.[37] The 2021 Cumbre Vieja (Tajogaite) eruption on La Palma, the first major eruption in a densely populated European setting in decades, has provided the most contemporary dataset: the Icelandic Volcanoes and Respiratory Health cohort study of 1,002 participants documented respiratory symptom patterns and pulmonary function changes during and after eruptive activity, establishing a framework for short-, medium-, and long-term respiratory follow-up.[38] These data demonstrate that the respiratory effects of volcanic emissions extend far beyond the immediate eruption zone.

Taken together, the evidence supports the use of appropriate respiratory protective equipment by responders, the systematic pre-planning of early evacuation for at-risk populations, close clinical follow-up of patients with chronic respiratory disease, and the establishment of long-term surveillance programs that capture both acute and chronic exposure scenarios.

Chemical Disasters

Chemical disasters involve the uncontrolled release of toxic substances through industrial or transport accidents, or by deliberate dissemination. Among toxic industrial chemicals (TICs), chlorine, ammonia, phosgene, and H_2S are the principal respiratory threats. These substances affect different anatomic regions depending on their water solubility: highly soluble agents—ammonia and HCl—rapidly damage the upper airways; chlorine, with intermediate solubility, affects both upper and lower airways; phosgene and nitrogen oxides, with low solubility, reach the lower airways and alveoli and produce severe pulmonary edema hours after exposure.[39]

Chlorine gas is among the most commonly encountered TICs in industrial accidents. Its intermediate solubility causes conjunctival irritation, laryngospasm, bronchospasm, and pulmonary edema.[39] Phosgene accounted for more than 80% of all chemical casualties in World War I and remains widely produced today (approximately 12 million metric tons annually) for use in the manufacture of plastics, pesticides, and pharmaceuticals. Its hallmark feature—a prolonged, asymptomatic latency followed by refractory pulmonary edema and ARDS—poses substantial diagnostic challenges in mass-casualty scenarios.[40]

The August 4, 2020 Beirut Port explosion dramatically illustrated the respiratory impact of industrial chemical disasters. The detonation of approximately 2,750 tons of ammonium nitrate produced one of the largest non-nuclear explosions of the modern era, injuring more than 6,000 people and killing 220 people.[41] Inhalation of nitric oxide and NO_2 gases caused

ARDS, diffuse distal airway inflammation, pulmonary edema, and methemoglobinemia.[41,42] Severe exposure produced fibrous bronchiolar obstruction lasting for weeks and reactive airway dysfunction syndrome.[41]

Medical response to chemical disasters rests on early airway management, lung-protective ventilation strategies, active airway suctioning, and respiratory physiotherapy. Identification of the agent is critical for both treatment and decontamination, but is often dependent on clinical presentation and exposure circumstances. Critical gaps in chemical disaster preparedness include rapid overflow of triage capacity, secondary exposure risk to healthcare workers, and the potential for systemic biochemical injury to develop before clinical findings emerge. Chemical disaster response, therefore, requires agent-specific antidote protocols, respiratory protection standards for first responders, and realistic mass-exposure exercises performed in concert.[43]

Blast Injuries and Blast Lung

Blast injuries arise in military, terrorist, and industrial settings and result from a distinct injury mechanism. Explosions injure the respiratory system through four mechanisms: (1) primary blast injury from direct effects of the supersonic pressure wave; (2) secondary injury from penetrating debris; (3) tertiary injury from victim displacement; and (4) quaternary injury from burns and toxic smoke inhalation.[44]

Primary blast lung injury (PBLI) occurs because the gas-filled lung is the organ most susceptible to damage from pressure waves. The supersonic pressure wave disrupts the alveolar–capillary membrane, producing interstitial and alveolar hemorrhage, pulmonary contusion, pneumothorax, pneumomediastinum, and arterial gas embolism. The incidence of blast lung ranges from 6–11% in open-air military explosions to over 90% in enclosed-space terrorist attacks, reflecting amplification of the pressure wave.[44,45] A key feature of PBLI is the relative paucity of external findings in the early hours despite the potential for rapid progression to ARDS over subsequent hours; most cases require mechanical ventilation and intensive care.

A multi-center study of mass casualty blast events identified blast lung as the strongest independent predictor of severe injury, with severe injury 18.8 times more likely in cases with documented blast lung.[46] No specific treatment protocol exists for PBLI; management is largely adapted from ARDS protocols, with lung-protective ventilation as the cornerstone.[45] A comprehensive review of combat-related ARDS literature emphasized that most evidence derives from retrospective data, that standardized blast-specific management protocols are still under development, and that systematic data on long-term pulmonary function in survivors remain insufficient.[47]

Biological Disasters and Pandemics

Biological disasters include epidemics and pandemics caused by intentional or accidental mass dissemination of pathogenic microorganisms. The severe acute respiratory syndrome (SARS) (2003), H1N1 (2009), Middle East respiratory syndrome (MERS) (2012), and coronavirus disease-2019 (COVID-19) (2019) outbreaks in the twenty-first century have demonstrated the devastating impact of biological threats on modern health systems, with the respiratory system as the primary target and acute respiratory failure and ARDS as the leading causes of death.[48,49]

The COVID-19 pandemic exposed the respiratory burden of biological disasters at an unprecedented scale. With more than 770 million confirmed cases globally, a substantial proportion of patients admitted to intensive care have developed acute hypoxemic respiratory failure requiring invasive mechanical ventilation. COVID-19 ARDS exhibited distinct pulmonary vascular dysregulation, with gas exchange impairment not consistently correlating with respiratory system compliance—a finding that revealed a pathophysiological profile separate from classical ARDS.[50]

Health system strain during the pandemic peaked with respect to intensive care capacity and ventilator supply. In a study of 625 U.S. hospitals, 63% issued at least one capacity alert during the pandemic; among those, 63% reported emergency department crowding, 61% reported intensive care unit (ICU) capacity overflow, and 12% reported ventilator shortages.[51] These data underscore the need to position ventilators as strategic preparedness resources and to address capacity inequities across countries.[51,52]

The long-term respiratory effects of COVID-19 extend the burden of the disaster well beyond the acute phase. A systematic review and meta-analysis of 3,066 discharged patients found residual abnormalities on chest computed tomography (CT) in approximately half of patients, with ground-glass opacity (44.1%) as the most common finding, and impaired diffusing capacity of the lungs for carbon monoxide observed in 34.8%. Post-COVID pulmonary fibrosis has been recognized as a distinct long-term phenotype requiring structured follow-up.[53]

The cumulative lessons of SARS, MERS, and COVID-19 define the core components of biological disaster preparedness: early warning and transparent reporting; rapid expansion of ICU capacity; stockpiling of respiratory protective equipment; and infection-control protocols for healthcare workers. Countries with prior outbreak experience were reported to have implemented faster containment measures during the COVID-19 pandemic.[48,54,55]

Displaced Populations

Displaced populations include those forced into temporary shelters and refugee camps following earthquakes, floods, conflict, or climate-related disasters. In addition to disaster-related respiratory risks, these groups face distinct environmental hazards: crowded and poorly ventilated indoor spaces, biomass fuel smoke exposure, malnutrition, and limited access to health services.[56,57] The burden of respiratory infectious diseases is markedly elevated in refugee populations, with upper respiratory tract infections among the most frequently reported complaints.[58]

Türkiye, which hosts the world's largest refugee population, provides one of the most informative settings for understanding

the respiratory burden among displaced populations. A national review of infectious disease patterns among more than 3.5 million Syrian refugees in Türkiye reported that 1,299,209 cases of respiratory tract infection and 108 active TB cases were identified and treated in temporary shelters between 2012 and 2016.[59] More recently, a multi-center retrospective analysis of TB patterns across Türkiye demonstrated higher rates of cavitary TB (50.9% vs. 28.9%; $P = 0.002$) and greater immunosuppression among migrant populations compared with non-migrants, although overall drug resistance rates remained similar.[60] A recent study from northwestern Ethiopia documented a TB prevalence of 7.6% in internally displaced populations, with prolonged camp residence and limited healthcare access as principal risk factors.[61] Evidence from armed conflict settings further supports this pattern, with conflict-associated rises in TB notifications, reductions in treatment success, and increased risk of TB spread to non-conflict regions through mass displacement.[62]

Biomass fuel smoke exposure is a major environmental contributor to chronic respiratory disease in displaced populations. Combustion of wood, dung, and crop residues for heating and cooking generates indoor air concentrations of PM2.5, CO, and polycyclic aromatic hydrocarbons. Chronic exposure to biomass smoke has been associated with more than a 2.5-fold increase in COPD risk.[63,64] Biomass exposure has been linked to acute lower respiratory tract infections and asthma-like symptoms in children and to chronic bronchitis and COPD in adults.[65] A systematic review of interventions to reduce respiratory infection burden in refugees and migrants found that arrival vaccination is effective in reducing secondary infections and outbreaks, although controlled evidence remains limited.[57]

Comprehensive care for displaced populations, therefore, requires reframing shelter design and ventilation standards through a respiratory health lens, integrating routine TB screening into disaster health services, reducing biomass smoke exposure, and implementing early post-arrival vaccination programs. The respiratory burden of displaced populations remains insufficiently addressed in disaster medicine.

The respiratory emergencies associated with each disaster type, principal exposures, and clinical syndromes are summarized in Table 1.

DIAGNOSIS AND MANAGEMENT

Diagnosis and management of respiratory emergencies in disaster settings face distinct challenges: resource constraints, high patient volumes during mass-casualty incidents, and inadequate medical infrastructure. Meeting these challenges requires pre-positioned diagnostic tools and clinical decision protocols tailored to the field.

Point-of-care ultrasound (POCUS) has become an increasingly valuable bedside tool. POCUS detects pneumothorax, pleural effusion, pulmonary consolidation, and pulmonary edema with high diagnostic accuracy and significantly shortens the time to diagnosis for patients with dyspnea compared with conventional radiography.[66] Pre-hospital lung ultrasonography performed by paramedics has demonstrated technical feasibility and moderate-to-high agreement with expert interpretation.[67]

Peripheral oxygen saturation (SpO_2) remains the primary monitoring tool in disaster settings owing to its low cost, non-invasive nature, and ease of use. A pre-hospital SpO_2 ≤90% supports triage to hospital admission and independently predicts in-hospital mortality and length of stay.[68] In CO poisoning, however, standard pulse oximetry yields misleading values; non-invasive pulse CO-oximetry that measures carboxyhemoglobin can serve as a first-line screen, but its sensitivity is approximately 65%, and arterial blood gas analysis

Table 1. Respiratory emergencies by disaster type: principal exposures, clinical syndromes, and pathophysiological mechanisms

Disaster type	Principal respiratory exposure	Principal clinical syndrome	Pathophysiological mechanism
Earthquake	Silica, asbestos, structural dust, debris smoke	Acute inhalation injury, pneumonia, COPD/asthma exacerbation, pulmonary thromboembolism	Particulate inhalation, mucosal injury, inflammation, hypercoagulability
Wildfires	PM2.5, CO, ozone, volatile organic compounds	Asthma/COPD exacerbation, ARDS, CO poisoning	Oxidative stress, bronchospasm, alveolar injury
Floods and hurricanes	Mold spores, aspiration, contaminated water	Respiratory tract infection, asthma exacerbation, aspiration pneumonia	Biological contamination, allergen amplification, surfactant disruption
Volcanic eruptions	Ash particles, SO_2, H_2S, silica	Acute bronchitis, reactive airways disease, pneumonia	Irritant gas exposure, reactive airway response
Chemical disasters	Chlorine, ammonia, phosgene, hydrogen sulfide	Toxic inhalation injury, pulmonary edema, ARDS	Direct mucosal injury, alveolar injury
Blast/terrorism	Pressure wave, combustion gases, secondary particulates	Blast lung, pulmonary contusion, pneumothorax	Barotrauma, alveolar rupture, gas embolism
Biological disasters and pandemics	Pathogenic microorganisms, aerosols	Viral pneumonia, ARDS, respiratory failure	Viral infection, cytokine storm, immune dysregulation
Displaced populations	Inadequate ventilation, crowding, biomass fuel smoke	ARI, influenza, tuberculosis, pneumonia outbreaks	Droplet/aerosol transmission, malnutrition

Biological disasters are categorized as natural disasters in the EM-DAT classification

EM-DAT: Emergency Events Database, ARI: acute respiratory infection, ARDS: acute respiratory distress syndrome, CO: carbon monoxide, COPD: chronic obstructive pulmonary disease, H_2S: hydrogen sulfide, PM2.5: fine particulate matter, SO_2: sulfur dioxide.

remains necessary for confirmation.[69] When intubation is required, end-tidal CO_2 monitoring is the gold standard for tube placement verification and ventilation management; pre-hospital capnography has been shown to predict mortality and transfusion requirements, guiding triage.[70]

Portable chest radiography enables on-site imaging where fixed radiology infrastructure is unavailable and was shown during the pandemic to be a reliable alternative for the detection of pneumothorax, consolidation, and pleural effusion in critically ill patients.[71] Arterial blood gas analysis supports the diagnosis of ARDS through calculation of PaO_2/FiO_2 ratio and assessment of acid–base status; the Berlin 2012 definition remains the standard, with the 2024 American Thoracic Society/ESICM update broadening the framework to include high-flow oxygen therapy.[72] Laboratory infrastructure requirements limit applicability in resource-constrained settings. Clinical scoring systems partially address this gap: NEWS2 has shown high prognostic value (area under the curve 0.89) in prehospital mass-casualty triage, while CRB-65—which does not require laboratory parameters—remains a pragmatic option for pneumonia severity assessment in resource-limited settings.[73,74] CT offers superior diagnostic value for blast lung and complex thoracic trauma but is limited by its requirement for fixed installations.[75]

The principal diagnostic tools for respiratory emergencies in disaster settings are summarized in Table 2. Protocols adapted to available infrastructure and personnel can substitute for standard hospital management; oxygen concentrators, simple continuous positive airway pressure devices, and oral antibiotics may be lifesaving.[76] The speed and nature of intervention directly determine outcomes. In chemical inhalation injury, early bronchodilator therapy and humidified oxygen form the foundation of management; in CO poisoning, high-flow oxygen should be initiated immediately. In cyanide toxicity and other chemical exposures, pre-positioned agent-specific antidote protocols are critical.[39,43,69] For aspiration pneumonia and respiratory tract infections, region-specific resistance patterns should guide early empirical antibiotic therapy.[29]

Triage and ventilator allocation are among the most critical challenges during mass respiratory failure events. When ventilator demand exceeds capacity, probability of survival, expected duration of ventilation, and underlying disease status are recommended as triage criteria, and allocation should be coordinated at the regional rather than institutional level.[77] Respiratory support should follow a stepped approach from nasal cannula and high-flow oxygen therapy to non-invasive and invasive mechanical ventilation, with pre-positioned contingency protocols for oxygen-dependent patients. In low- and middle-income countries, mechanical ventilation has been associated with crude mortality of 36–72% and a high risk of iatrogenic complications.[78]

ARDS represents the most severe respiratory presentation in disaster settings and requires a specialized approach. Lung-protective ventilation is the cornerstone, with tidal volumes of 4–8 mL/kg predicted body weight, plateau pressures below 30 cmH_2O, and driving pressures below 14 cmH_2O.[79] Prone positioning for at least 12 hours per day in moderate-to-severe ARDS has been shown, with high-quality evidence, to reduce mortality; high-flow nasal oxygen and neuromuscular blockade may have additional roles in selected patients.[80]

Respiratory protective equipment is a critical component of disaster response, both to protect healthcare workers from occupational exposure and to prevent respiratory injury in affected communities. Equipment selection varies by disaster type, particulate concentration, toxic gas profile, and duration of exposure. N95/FFP2 filtering facepiece respirators are recommended for earthquake and structural-collapse scenarios with high particulate loads and provide protection against dust, silica, and asbestos.[81] In wildfires, N95/FFP2 respirators protect against PM2.5 in smoke, but are inadequate for CO and volatile organic compounds, necessitating separate monitoring

Table 2. Diagnostic tools for respiratory emergencies in disaster settings

Diagnostic tool	Condition assessed	Strengths	Limitations
Lung POCUS	Pneumothorax, pleural effusion, consolidation, pulmonary edema	Rapid, radiation-free, repeatable	Requires training
Pulse oximetry (SpO_2)	Hypoxemia, oxygen requirement screening	Inexpensive, simple, continuous monitoring	Misleading in CO poisoning
Pulse CO-oximetry	Carbon monoxide poisoning	Critical in fire/blast scenarios	Expensive, limited stock
End-tidal CO_2 ($EtCO_2$)	Airway confirmation, ventilation monitoring	Gold standard for tube placement	Requires intubation
Portable chest radiography	Pneumonia, pneumothorax, contusion	Widely used	Radiation; requires portable equipment
Arterial blood gas analysis	Type of respiratory failure, pH, PaO_2/FiO_2	Acid–base and oxygenation assessment	Requires laboratory infrastructure
Clinical scores (CRB-65, NEWS2)	Pneumonia severity, mass casualty triage	Rapid triage, minimal training	CRB-65 preferable in resource-limited settings
Chest CT	Blast lung, ARDS, pulmonary embolism, complex trauma	Very high sensitivity	Requires fixed installation

ARDS: acute respiratory distress syndrome, CO: carbon monoxide, CRB-65: confusion, respiratory rate, blood pressure, age ≥65 years, CT: computed tomography, $EtCO_2$: end-tidal carbon dioxide, NEWS2: National Early Warning Score 2, PaO_2/FiO_2: arterial oxygen partial pressure/fraction of inspired oxygen, POCUS: point-of-care ultrasound; SpO_2: peripheral oxygen saturation

for CO.[19] During volcanic eruptions, N95-equivalent masks have demonstrated filtration efficiency above 89% against volcanic ash.[82] In chemical disasters involving chlorine, ammonia, phosgene, or H_2S, full-face self-contained breathing apparatus or chemical, biological, radiological, and nuclear protection is required.[43] In biological and pandemic scenarios, FFP2/N95 respirators, combined with eye protection, are a standard component of infection control.[83] Disaster planning must determine equipment needs by disaster type and stockpile equipment strategically.

Effective disaster respiratory management requires field-deployable diagnostic capacity, ventilation protocols adapted to resource-constrained settings, pre-configured triage systems, and strategic stockpiling of respiratory protective equipment, all integrated within a comprehensive preparedness framework.

VULNERABLE POPULATIONS

Disaster-related respiratory risks affect entire populations, but specific biological, physiological, and socioeconomic factors place certain groups at disproportionate risk. Children, older adults, pregnant women, patients with chronic respiratory disease, and socioeconomically disadvantaged communities are the most vulnerable groups. Preparedness planning must therefore incorporate strategies tailored to these populations.

Children are biologically more susceptible to air pollutants and disaster-related respiratory threats than adults. Lung development continues from birth to adolescence, and PM2.5 exposure during this period not only triggers acute respiratory infections and asthma exacerbations but also may permanently constrain lung function development.[84] Elevated weight-adjusted minute ventilation and immature immune responses further increase pediatric vulnerability. Wildfire-related PM2.5 has been shown to increase pediatric respiratory hospitalizations more than urban PM2.5 of equivalent concentration.[23] Prenatal exposure to air pollutants is also linked to adverse respiratory outcomes, with PM2.5 exposure during pregnancy adversely affecting lung development and elevating respiratory disease risk in adulthood.[84]

Older adults are particularly vulnerable in disaster settings due to reduced respiratory reserve, decreased respiratory muscle strength, multimorbidity, and social isolation. Increased post-disaster hospitalization and mortality have been consistently documented in older patients with COPD and asthma.[14,33] Power outages pose a critical and distinct threat to advanced-stage COPD patients on home oxygen or domiciliary mechanical ventilation; large epidemiological studies have demonstrated a significantly increased risk of hospitalization among oxygen-dependent COPD patients during outages.[33]

Pregnant women face heightened respiratory risk in disaster settings, both for themselves and for the developing fetus. Exposure to air pollutants and extreme climate events increases the risk of preterm birth and low birth weight. PM2.5 exposure during pregnancy, particularly in the second trimester, has been shown to significantly increase the risk of preterm birth, with first-trimester exposure associated with reduced birth weight.[85] A systematic review conducted in the United States found that hurricanes, floods, and tropical cyclones have been consistently linked to adverse perinatal outcomes.[86]

Low socioeconomic status has emerged as an independent determinant of disaster-related respiratory risk. Disadvantaged communities are geographically closer to climate-related disasters, face barriers in accessing health services and protective equipment, and contend with inequitable post-disaster reconstruction. World Bank data indicate that 80% of the 7.3 billion people globally exposed to unsafe PM2.5 concentrations live in low- and middle-income countries, where disaster-related respiratory injuries are reported to be more severe.[87]

CLIMATE CHANGE AND THE INCREASING DISASTER BURDEN

Climate change is fundamentally transforming the frequency, severity, and geographic distribution of disasters, with corresponding increases in the societal burden of respiratory disease. In 2023, the global mean surface temperature reached 1.45 °C above the pre-industrial baseline, breaking all previous records. This warming has been directly linked to Canada's record-breaking wildfire season, devastating floods in the Horn of Africa, and lethal heatwaves across the Northern Hemisphere. The 2024 Lancet Countdown report documented that 10 of the 15 tracked health indicators reached alarming new records in the most recent year of data.[88] The European Lancet Countdown report showed that, in a survey of 185 European cities, 48% identified exacerbations of respiratory disease as the second most common climate-related health concern.[89]

The most direct effect of climate change on respiratory health occurs through wildfires. Shifts in temperature and precipitation patterns are increasing both the frequency and severity of wildfires, with implications for global respiratory health.[20] The January 2025 LA wildfires demonstrated the potential for such events to expand into densely populated urban areas, with documented increases in cardiovascular and respiratory healthcare utilization.[24]

The respiratory impact of climate change extends beyond wildfire smoke. Rising CO_2 concentrations increase both the quantity and the allergenicity of plant pollen. In North America, the pollen season has advanced by approximately 20 days, and pollen concentrations have risen by 21%.[90] Thunderstorms with elevated humidity can fragment pollen grains into thousands of smaller particles that reach the lower airways, triggering severe asthma exacerbations (thunderstorm asthma) through osmotic shock and microaerosol formation; the frequency of such extreme weather events is rising with climate change.[91] Higher temperatures elevate ground-level ozone, accelerated post-flood mold growth exacerbates atopic respiratory disease, and heatwaves produce high concentrations of ozone and particulate matter that increase mortality in patients with chronic respiratory disease.[88,89]

Low- and middle-income countries bear a disproportionate share of the climate-related disaster burden. Limited climate adaptation capacity results in more severe respiratory injury, earlier collapse of health infrastructure, and greater difficulty in protecting vulnerable populations. Strategies for disaster risk reduction and health system strengthening must therefore be integrated into climate adaptation policy. While the Sendai Framework provides direction, current implementation lags

substantially behind the rising burden of climate-related respiratory emergencies.

CONCLUSION

Disasters—from earthquakes and pandemics to wildfires and chemical incidents—target the respiratory system through a broad range of mechanisms, and each disaster type produces acute and chronic respiratory injury via distinct pathophysiological pathways. This review demonstrates that respiratory emergencies represent a universal threat across disaster types, that vulnerable populations bear a disproportionate share of the risk, and that climate change is steadily increasing the disaster-related respiratory burden.

Three priorities emerge for the field. First, research must address persistent gaps in long-term respiratory follow-up of disaster survivors, the development of disaster-specific clinical protocols, and the inclusion of underrepresented geographic regions in the evidence base.

Second, preparedness planning must position respiratory health more centrally, with pre-stockpiled respiratory protective equipment, pre-configured triage and ventilator allocation frameworks, and strengthened diagnostic capacity at the field level. Third, in the Turkish context, the lessons of the Kahramanmaraş earthquake—from dust exposure to refugee respiratory health—should inform the integration of respiratory specialists into national disaster response architecture.

Meeting the rising burden requires a multidisciplinary agenda uniting respiratory physicians, disaster medicine specialists, public health policymakers, and climate scientists.

Footnotes

Authorship Contributions

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

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Letter to the Editor

Tobacco Industry and Cannabis: A New Public Health Challenge for Türkiye

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DEAR EDITOR,

As is well known, the "Regulation on Cannabis Cultivation and Control" was published in the Official Gazette on January 31, 2026.[1] However, it has long been recognized that the tobacco industry has had a close interest in cannabis production since the early 1970s. Companies have viewed inhalable or smokable cannabis products both as a threat to conventional cigarettes and as an opportunity to develop new products.[2] By the 2000s, tobacco companies began to engage more closely with cannabis producers, investing in them and even acquiring these companies outright.[3-7] To date, the largest investments in the cannabis sector have been made by British American Tobacco (BAT) and Philip Morris International (PMI). The companies' regarding cannabis use are as follows: BAT focuses on both recreational and medical use; PMI focuses on medical and wellness products; Altria focuses on recreational use; and Imperial Brands focuses on medical cannabis. BAT, which acquired TEKEL in Türkiye in 2008, demonstrates exceptionally high production capacity and activity in the cannabis sector and is actively pursuing production across a broad geographic area, with a particular emphasis on the European market.

The fundamental motivations behind tobacco companies' investments in cannabis production and/or acquisitions of cannabis companies include the global decline in the volume of traditional tobacco products such as cigarettes, the synergies created by the similar infrastructure of tobacco and cannabis companies, the frequent co-use of tobacco and cannabis, and the desire of tobacco companies to portray themselves as "responsible" and "public health-conscious" entities.

Today, tobacco companies are implementing policies involving executive appointments, capital investments, and product diversification in relation to cannabis-producing companies.[3,8,9] The objectives of the tobacco industry's integration model with cannabis companies are to offset corporate losses caused by declining cigarette use worldwide, achieve high profit margins through research and development, and convert technological patents developed for cannabis consumption into economic gains.

The tobacco industry is currently shifting from producing traditional tobacco products, such as cigarettes and cigars, to newer products, including electronic cigarettes, heated tobacco products, oral nicotine products, and nicotine pouches. Cannabis consumption products will soon be added to this portfolio. Contract farming to secure a reliable raw material

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supply, the rapid adaptability of cigarette machines to cannabis production, and biosynthetic production of non-plant-derived cannabis will increase the profit margins of tobacco companies, which are currently declining. Restrictions on cannabis production and use are being liberalized worldwide, often under the pretext of "medicinal cannabis use," thereby preparing the ground for tobacco companies' future new products. However, it is known that cannabis use disorder exists in 29% of individuals using cannabis for medicinal purposes; as of 2023, the global prevalence of cannabis use among the 15–64 age group was 4.6%, while it was 8.4% in Europe and 17.4% in North America.[10-12] In regions of the Americas where non-medicinal cannabis use is legal, particularly among young adults, the use of high-tetrahydrocannabinol cannabis has been associated with increased hospital admissions, psychiatric disorders, and suicide attempts.[11]

Preventing addiction is easier and more humane than controlling or treating it. Although cannabis use in Türkiye has increased in recent years, it has not yet become as widespread as the use of cigarettes or other tobacco products. However, the alliance between tobacco and cannabis companies poses the danger of turning Türkiye into a country similar to those in North America, where cannabis use has become widespread and may become even more common in the near future. Physicians and public health advocates must take a stand in defense of the right to health by recognizing this new face of addiction.

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Letter to the Editor

Comparative Clinical Outcomes of Nintedanib and Pirfenidone in Idiopathic Pulmonary Fibrosis: A Five-year Real-life Study

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DEAR EDITOR,

We read with great interest the article by Yanalak and Yazıcı[1] entitled "Comparative Long-term Effects of Nintedanib and Pirfenidone in Idiopathic Pulmonary Fibrosis: A Real-life Study with Five-year Follow-up." The authors should be congratulated for providing valuable five-year real-world data comparing the long-term outcomes of the two currently approved antifibrotic therapies in idiopathic pulmonary fibrosis (IPF). The availability of long-term real-world follow-up remains relatively limited in the literature; therefore, studies such as this provide important evidence that complements randomized clinical trials.[1]

The aim of this letter is to highlight selected methodological considerations that may influence the interpretation of survival outcomes in real-world comparative studies. We would like to emphasize that baseline disease severity should be carefully considered when interpreting survival differences. In the present study, patients receiving pirfenidone had higher gender-age-physiology (GAP) scores and more extensive radiological involvement at baseline, both of which are well-established predictors of mortality in IPF.[2] Therefore, the observed differences in mortality may partially reflect baseline disease severity rather than treatment effect alone. Another important issue is treatment switching during follow-up. A considerable proportion of patients crossed over between antifibrotic therapies, which reflects routine clinical practice and increases the real-world relevance of the study. However, such treatment changes may introduce bias in long-term outcome assessment. Future studies incorporating time-dependent survival models may provide additional insight into the independent effects of antifibrotic therapies.[3]

In addition, because survival was a primary outcome, we believe that more robust survival analysis methods would further strengthen the interpretation of the findings. Kaplan and Meier[4] survival curves with log-rank testing would improve visualization of time-to-event differences between groups. Furthermore, multivariable Cox[5] proportional hazards regression models could help adjust for key baseline confounders such as GAP score and radiological extent. Alternatively, propensity score-based approaches (matching or weighting) may reduce selection bias inherent in observational cohort studies.[6,7]

Overall, this study provides valuable long-term real-world evidence supporting individualized antifibrotic treatment strategies in IPF. Future prospective multicenter studies with more homogeneous baseline characteristics and advanced survival methodologies will further clarify the comparative effectiveness of nintedanib and pirfenidone.

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Letter to the Editor

Artificial Intelligence in Respiratory Medicine: Epistemic Authority, Trust and Responsibility in Practice and in Training

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DEAR EDITOR,

We read with interest the review by Karan and Elbek[1], which surveys artificial intelligence (AI) across medicine and calls for ethical and regulatory frameworks. Such frameworks are enacted in two places at once: at the bedside, and in training.

One example lies close to respiratory practice.[1] When 120 pulmonologists interpreted 50 pulmonary function cases, their pattern recognition matched American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines in 74.4% and their diagnoses were correct in 44.6%; task-specific, rule-based software matched the patterns in 100%-unsurprisingly, since it encodes those guidelines-but diagnosed correctly in 82%.[2] In that dataset the software was reliable where rules were explicit, yet fallible where judgment began. Generative models encode no such rule set, and their fluency carries no comparable warrant. Beyond accuracy, our concern is with the justification of reliance on AI and with clinical responsibility.

A framework one of us has proposed rests on three pillars: *epistemic authority* (where a model's authority ends), *calibrated trust* (reliance proportioned to demonstrated reliability, not fluency), and an *architecture of responsibility* assigned before deployment.[3] It presumes a user able to recognize error-an assumption weakest in training. Surveys of medical students report widespread use alongside limited confidence in appraising output;[4,5] learners consult these tools about what they do not yet understand, so those likeliest to rely on them may be least able to catch mistakes.

It terms the resulting hazard an *epistemic placebo*: the unearned reassurance of confident prose.[3] A model's reading of a flow-volume loop arrives in the cadence of a competent report and reads exactly as a correct interpretation does-whether or not it is right.

Three measures follow, in clinic and classroom alike. First, classify tasks by risk: by consequence for the patient in practice, and by *formative risk* in teaching, because asking a model to produce the differential removes the very reasoning the exercise is meant to develop. Second, treat trust calibration as a trainable, examinable skill; automation bias is documented among experienced clinicians,[6] and there is no evidence that learners, who have less clinical experience to draw on, are any less prone to it. Tracings carrying seeded AI errors, checked against the 2022 ERS/ATS technical standard,[7] make the placebo an object of study. Third, assign responsibility explicitly-including our own: when teachers use AI without declaring it, yet penalize learners for doing so, the inconsistency itself becomes the lesson, and it is learned more thoroughly than anything taught in a session on professionalism.[8]

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Regulation governs systems; education forms those who use them. Clinicians trained to critically appraise their sources and take responsibility for outcomes will utilize these tools rather than be led by them.

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Letter to the Editor

Reply: Artificial Intelligence in Respiratory Medicine: Epistemic Authority, Trust and Responsibility in Practice and in Training

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DEAR EDITOR,

We thank the authors for their insightful letter regarding our review on artificial intelligence (AI) in medicine. We strongly agree with their premise that the macro-level ethical and regulatory frameworks we discussed must be actualized directly at the bedside and within clinical training programs, and we are pleased to witness these discussions arise more and more in the field.

In our review, we highlighted the black-box nature of AI models, pointing out that the internal reasoning behind an AI system's outputs often cannot be readily interpreted even by experts.[1] The letter excellently articulates the clinical manifestation of this opacity: the "epistemic placebo" generated by fluent but potentially inaccurate language models.[2] As the authors astutely point out, using the shared example of pulmonary function test interpretations: while rule-based models encode established guidelines, generative models lack such explicit rule sets. In evaluating AI applications for complex respiratory conditions such as interstitial lung diseases or obstructive syndromes, robust biostatistical and methodological scrutiny is of utmost importance to differentiate true diagnostic utility from mere generative linguistic confidence.

Furthermore, our article emphasized that the integration of AI into medicine is profoundly shaped by neoliberal logic, which prioritizes cost-effectiveness, performance-based metrics, and output targets over collective well-being.[1] This systemic pressure trickles directly and indirectly down to medical education. When clinical and educational environments demand high efficiency, the unearned reassurance provided by generative AI becomes a highly attractive, yet perilous, shortcut for overworked residents and students. If trainees consult these tools for complex physiological and pathological mechanisms or differential diagnoses they do not yet fully comprehend, they risk profound deskilling and automation bias, causing them to become copycats of whichever AI model they use. This process risks exacerbating the individualization of responsibility that neoliberal frameworks often promote, blaming the individual trainee for a structural failure in the educational architecture rather than the system that produces it.

Therefore, the framework proposed in the letter–epistemic authority, calibrated trust, and an architecture of responsibility–is a vital addition to modern medical education.[2] We fully support the practical recommendations provided.

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Ensuring that AI contributes to justice, inclusivity, and patient safety requires transparent clinical workflows and educational environments that model explicit accountability. When the faculty uses AI transparently and teaches the methodological limits of these tools to their trainees, a culture of critical appraisal is passed down. We share the conviction that clinicians and trainees must be equipped to rigorously appraise their sources, ensuring that we utilize these powerful tools to advance health outcomes rather than being led blindly by them.

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