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The metastatic journey and the uniqueness of the pulmonary system

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Abstract:

The lungs are among the most frequent sites of distant dissemination of malignancy, a phenomenon driven by the organ's unique physiological properties and complex molecular interactions. This paper provides a comprehensive review of the biological mechanisms underlying pulmonary metastasis and explores their direct implications for surgical management, specifically pulmonary metastasectomy (PM). The metastatic journey is analyzed through the lens of three evolving models of tumorigenesis: the stochastic model, the cancer stem cell model, and the cellular plasticity model. Central to this dissemination is the epithelial-mesenchymal transition (EMT), a dynamic process in which tumor cells acquire a hybrid phenotype that facilitates invasion, intravasation, and immune evasion. The lung's susceptibility is attributed to its receipt of the entire cardiac output, its dense capillary network, and its establishment of pre-metastatic niches. These niches, modulated by inflammatory responses and extracellular matrix remodeling, create a permissive microenvironment for disseminated tumor cells (DTCs) to undergo colonization or to enter states of dormancy. Clinically, the efficacy of PM is rooted in these biological realities. The necessity for radical R0 resection and systematic lymphadenectomy is supported by routes of hematogenous and lymphatic spread. Furthermore, the debate between traditional thoracotomy and minimally invasive surgery (MIS) is framed by the biological challenge of radiologically occult nodules that may require bimanual palpation for identification. A comparative perspective on colorectal carcinoma, renal cell carcinoma, sarcomas, and germ cell tumors illustrates how histological behavior dictates surgical timing and the integration of systemic therapies. While advances in immunotherapy and molecular targeting offer hope, the heterogeneity of metastatic disease and the protective nature of the pulmonary microenvironment remain significant barriers. This review underscores that future therapeutic success necessitates a multidisciplinary approach targeting both tumor-intrinsic drivers and extrinsic niche factors. Ultimately, a deeper synthesis of metastasis biology and surgical principles is essential to refine therapeutic algorithms and improve long-term survival for patients with secondary pulmonary malignancies.

Keywords:

Epithelial-mesenchymal transition, metastasectomy, pre-metastatic niche, pulmonary metastasis, thoracic surgery, tumor biology

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Introduction

The lungs are among the most common destinations for metastatic spread. Pulmonary metastases frequently arise from extrapulmonary sites due to hematogenous, lymphatic, or transcoelomic spread.^[1–3] It is commonly accepted that circulating tumor cells enter the lungs via the venous circulation and are trapped in the pulmonary parenchyma due to the filtering function of the lungs. This idea is complex and, for most clinicians, often difficult to comprehend. The process involves a dynamic and complex sequence in which healthy cells are transformed into cancerous cells, leading to uncontrolled proliferation, immune evasion, resistance to programmed cell death, promotion of angiogenesis, acquisition of invasive capabilities, survival in the bloodstream, and the establishment of malignant growths in distant organs [Fig. 1].^[4–8] This paper seeks to clarify the metastatic journey by concentrating on the complex processes of primary tumor formation and metastasis and by examining how distinct characteristics of the pulmonary system lead to a greater prevalence of metastases than in other body regions, thereby aiding clinicians' understanding of the fundamental mechanisms underlying metastasis.

Pulmonary Metastases and Metastasectomy

Approximately 30% of patients diagnosed with a malignancy will eventually develop pulmonary metastases. These secondary lesions frequently originate from carcinomas of the colon and rectum, kidney, breast, prostate,

and oropharynx. Furthermore, certain tumors such as choriocarcinoma, osteosarcoma, soft tissue sarcoma, testicular germ cell tumors, Ewing sarcoma, and thyroid carcinoma exhibit a preferential metastatic affinity for the lungs. Pulmonary metastasectomy has emerged as a well-established therapeutic intervention that substantially improves long-term survival for patients with lung metastases from solid tumors, and currently represents a significant proportion of the clinical workload in thoracic surgery departments. The pillars of this surgical approach include radical resection to ensure negative surgical margins and adequate lymphadenectomy. The primary objective is to achieve complete resection of all metastatic foci while maximizing the preservation of the lung parenchyma. Consequently, while limited resections, primarily wedge resections, are the standard treatment for peripheral lesions, centrally located tumors may require anatomical resections such as segmentectomy or lobectomy and, in exceptionally rare cases, pneumonectomy.^[9]

Surgical indications are determined through a case-specific evaluation by a multidisciplinary team. The conventional criteria for intervention include the effective control of the primary malignancy, the absence of extrapulmonary metastatic disease, and the technical feasibility of achieving a complete resection of all pulmonary lesions. Additionally, the patient must be a suitable surgical candidate with an acceptable risk profile and preserved physiological reserve. While the presence of multiple metastases is not an absolute contraindication, having three or more nodules is recognized as a significant prognostic factor that may increase the risk of mortality by 33%. Nonetheless, surgi-

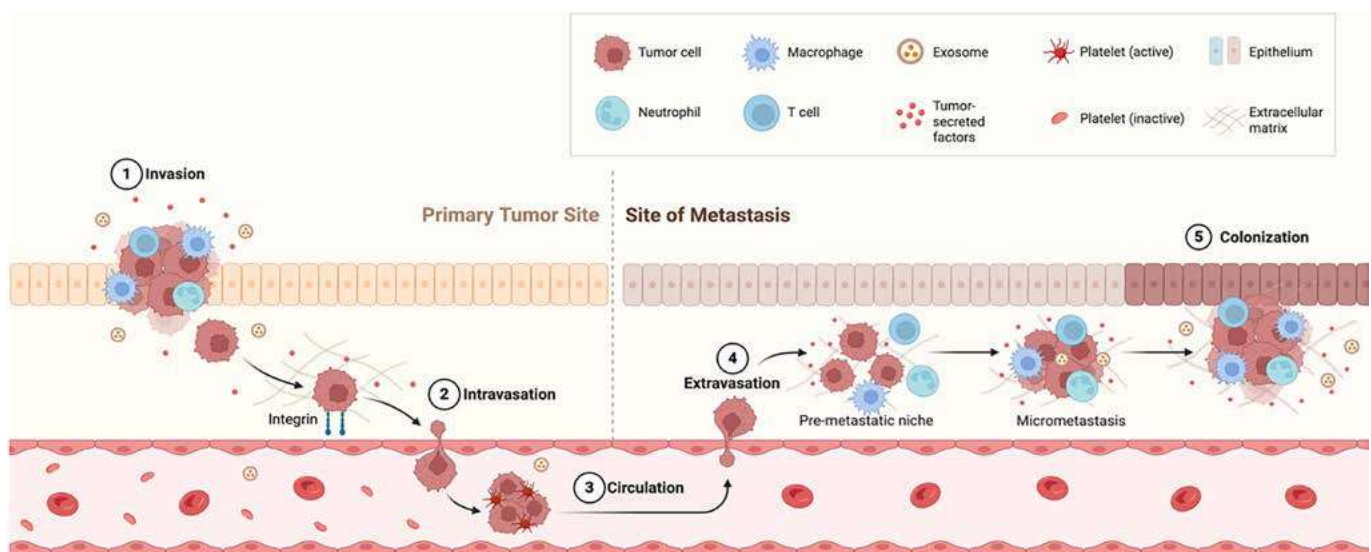


Figure 1: Overview of metastatic cascade

cal intervention should remain a viable consideration for appropriate patients presenting with two to four lesions.^[10]

The optimal surgical approach, comparing traditional thoracotomy with minimally invasive surgery (MIS), remains subject to debate. Thoracotomy provides the advantage of bimanual palpation of the entire lung, facilitating the identification of occult nodules not detected by preoperative imaging, which occurs in 18% to 36% of cases according to various studies.^[11,12] Conversely, MIS is often the preferred modality for medically eligible patients due to its association with shorter recovery periods, fewer postoperative complications, and superior quality of life. MIS is particularly beneficial in reducing pleural adhesions, an important consideration for patients who may require subsequent metastasectomies.

Maintaining an adequate surgical margin is essential to reduce the risk of local recurrence, particularly in wedge resections. Current evidence recommends a surgical margin of more than 10 mm and a tumor size-to-margin ratio of less than 1.7. Furthermore, because intrathoracic lymph node (LN) involvement is a poor prognostic indicator, routine LN sampling or formal dissection is recommended during the procedure. Finally, an aggressive surgical approach, including redo surgery for recurrent metastases, is justified under similar clinical

indications when complete resection is feasible and the patient maintains adequate functional status.^[9]

The surgical strategies and prognostic considerations outlined above underscore the clinical complexity of managing secondary pulmonary lesions. However, the efficacy of these interventions is fundamentally rooted in the biological behavior of the primary malignancy. Understanding the mechanisms of tumorigenesis and the pathways of metastasis facilitates a comprehensive grasp of the disease, thereby enabling the more precise formulation of therapeutic algorithms. In this context, determining the surgical modality for metastasectomy, for example, whether to include lymph node dissection, is of paramount clinical importance. Consequently, a deeper exploration into the molecular drivers of primary tumor development and the intricate biological cascades that govern metastatic dissemination is essential to further refine these surgical paradigms.

Formation of the Primary Tumor

Numerous factors, including chemically driven carcinogenesis, viral infections, changes in epigenetic patterns, and somatic mutations, contribute to cancer development. Our present understanding of how healthy cells are converted into cancerous ones is guided by three distinct models [Fig. 2].^[13]

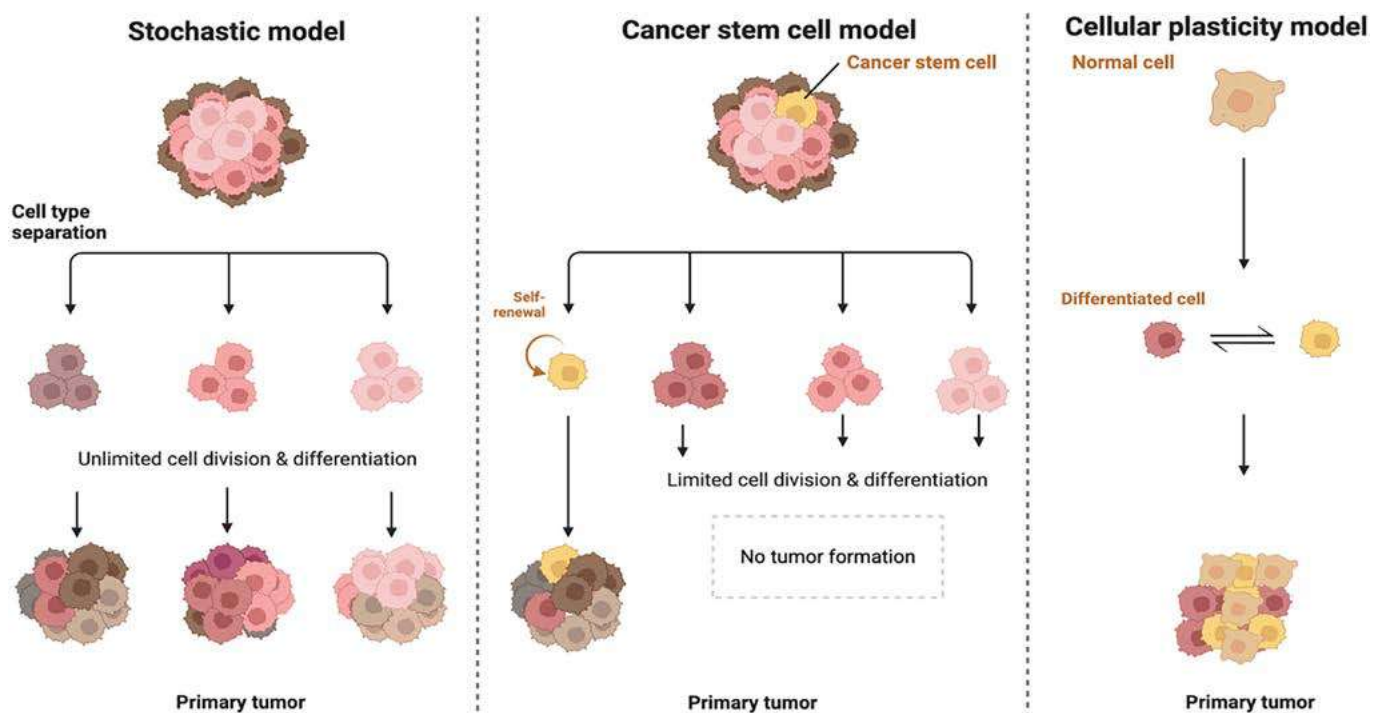


Figure 2: Schematic illustration for the models of tumorigenesis

The stochastic tumorigenesis model suggests that cancer arises due to random genetic mutations and alterations that accumulate in normal cells over time. This model assumes that every cell in the body has some probability of developing cancer-causing mutations; essentially, it treats cancer development as a matter of chance. The key features of the stochastic model are:

- **Random Mutations:** In this model, the genetic mutations that lead to cancer are unexpected events that can occur during cell division or DNA replication, or in response to environmental factors such as radiation or chemicals. These mutations can affect genes responsible for cell cycle regulation, DNA repair, and other critical cellular processes.
- **No Specific Cell Type:** In contrast to the cancer stem cell model, the stochastic model does not posit a distinct stem-like cell population; rather, it proposes that any normal cell may acquire oncogenic mutations and undergo malignant transformation.
- **Gradual Progression:** Tumorigenesis in the stochastic model is gradual and progressive. A single cell accumulates multiple mutations over time, eventually leading to uncontrolled cell growth and tumor development.
- **Heterogeneity:** Tumors formed under the stochastic model often exhibit genetic and phenotypic heterogeneity, as the mutations can vary between individual cancer cells within the same tumor.^[14,15]
- **Tumor Heterogeneity:** This model also accounts for the genetic and phenotypic heterogeneity of tumors. Differentiated cancer cells within the tumor are derived from CSCs and may have varying degrees of genetic mutations and aggressiveness.
- **Target for Therapy:** The CSC model suggests that targeting and eliminating CSCs should be a priority in cancer therapy, as they are the driving force behind tumor growth and recurrence. Developing treatments that specifically target CSCs is an ongoing area of research.^[16]

The recently proposed cellular plasticity model challenges the traditional cancer stem cell (CSC) paradigm by positing that CSCs do not arise from a fixed cell of origin. Instead, it suggests that normal cells possess intrinsic plasticity, enabling epigenetic and phenotypic reprogramming in response to internal or external stimuli. This plasticity facilitates the acquisition of CSC characteristics and contributes to mutational accumulation and intratumoral heterogeneity.^[17] These models are not mutually exclusive, and individual tumors may exhibit features of both to varying extents. Tumorigenesis is therefore a heterogeneous and multifactorial process, differing across cancer types and patients, and remains an active area of oncologic investigation.^[18]

Molecular Biology of Metastasis

Conversely, the cancer stem cell (CSC) model postulates that tumor growth and progression are driven by a small subpopulation of stem-like cells capable of self-renewal and differentiation into diverse cancer cell lineages. The key characteristics of this model include:

- **Hierarchical Organization:** The CSC model suggests that tumors are hierarchically organized, with a small population of CSCs at the apex. CSCs can divide to produce more CSCs (self-renewal) and can differentiate into non-CSC cancer cells that constitute the bulk of the tumor.
 - **Specific Cell Type:** Unlike the stochastic model, the CSC model posits the existence of specific cells (CSCs) that initiate and sustain tumorigenesis. These cells are believed to be more resistant to conventional cancer treatments, such as chemotherapy and radiation therapy.
- Cancer metastasis, the dissemination of malignant cells from a primary tumor to distant organs, remains a major challenge in oncology, with fewer than 0.01% of primary tumor cells ultimately forming macrometastases at secondary sites.^[19] Clinically established organ-specific metastasis models demonstrate that metastatic organ tropism is nonrandom and is strongly influenced by the microenvironment of secondary sites.^[20]
- The timing at which a primary tumor acquires metastatic potential remains poorly defined. Although metastatic dissemination was traditionally attributed to microenvironmental stresses such as hypoxia and nutrient deprivation, emerging evidence in HER2-positive breast cancer indicates that tumor cell dissemination may occur prior to clinical detectability of the primary lesion, with circulating tumor cells capable of seeding distant metastases.^[21,22] The detection of circulating tumor cells prior to clinical identification of a primary tumor challenges conventional models of metastasis. Among metastatic sites, the lung is the most frequently involved, underscoring

the need to elucidate the molecular mechanisms governing pulmonary metastasis to advance cancer biology and inform targeted therapeutic strategies.^[23]

Formation of the Pre-metastatic Niche: Central to the process of lung metastasis is the formation of a specific microenvironment known as the premetastatic niche. This tissue-specific niche is created by genetic mutations and epigenetic changes in primary tumor cells and promotes altered intercellular communication among cell types.^[24] Additionally, the release of signaling mediators such as cytokines, chemokines, exosomes, and growth factors enhances microenvironmental responses, creating a favorable environment for metastatic cells.^[25]

Epithelial-Mesenchymal Transition (EMT): Epithelial-mesenchymal transition (EMT) is a key mechanism in lung metastasis, whereby cancer cells lose epithelial characteristics and acquire mesenchymal traits, resulting in increased motility and invasiveness. This process is regulated by transcription factors including Snail, Slug, Twist, and ZEB1.^[26] Only a subset of cancer cells can intravasate and survive within the circulation; successful metastasis requires the acquisition of stem cell-like properties and invasive capabilities.^[27] This transformation is mediated by epithelial-mesenchymal transition (EMT), characterized by loss of epithelial polarity and cell-cell junctions with concurrent acquisition of mesenchymal migratory and invasive properties.^[28,29] During EMT, a subset of cells adopts a hybrid epithelial/mesenchymal (E/M) phenotype, co-expressing epithelial and mesenchymal markers. These cells retain limited cell-cell adhesion mediated by E- and N-cadherin, albeit weaker than in fully epithelial cells. In contrast, cells with a predominantly mesenchymal phenotype, key drivers of metastasis, exhibit actin and vimentin-rich cytoskeletal structures that enhance migratory and invasive capacities.^[30] Complete mesenchymal transition is not required for metastatic competence; instead, a hybrid epithelial/mesenchymal (E/M) state is pivotal. EMT constitutes a reversible phenotypic continuum, in which mesenchymal traits promote invasion, whereas metastatic colonization often requires epithelial reversion via mesenchymal-epithelial transition (MET).^[31,32] Cells exhibiting EMT-MET plasticity can undergo EMT or MET and adapt to changes in the microenvironment. Furthermore, hypotheses suggest that cells with EMT-MET plasticity have a higher potential for tumor initiation and metastasis than cells at either end of the EMT spectrum.^[33]

The hybrid epithelial/mesenchymal (E/M) phenotype is associated with enhanced metastatic capacity, increased tumor-initiating potential, therapeutic resistance, and poor prognosis, and is linked to resistance to antiestrogen therapies and elevated programmed death-ligand 1 (PD-L1) expression.^[34,35] Cells undergoing partial EMT adopt an intermediate phenotype, co-express epithelial and mesenchymal traits, and often migrate collectively while retaining cell-cell adhesions. Figure 3 illustrates the EMT spectrum, which varies *in vivo* according to tissue context, epithelial differentiation, junctional organization, basal adhesion, and EMT regulatory mechanisms.^[36]

Hybrid epithelial/mesenchymal (E/M) cells promote an immunosuppressive microenvironment by recruiting myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and tumor-associated M2 macrophages (TAMs) through secretion of cytokines and chemokines, including IL-8.^[37] These immunoregulatory effects are further amplified by impaired caspase-dependent apoptosis and reduced antigen-presenting capacity, both of which are characteristic features of hybrid epithelial/mesenchymal (E/M) cells.

Extracellular Matrix Reconstruction and Vascular Invasion: Metastatic cells must penetrate the extracellular matrix (ECM) to invade neighboring tissues and blood vessels. Matrix metalloproteinases (MMPs) play an essential role in ECM remodeling. These enzymes are regulated by various signaling pathways, such as TGF- β .^[38] Cancer cells undergoing EMT enter the bloodstream via intravasation with the help of cell surface adhesion molecules such as integrins and selectins. Signaling pathways such as PI3K/AKT and MAPK contribute to the invasion process.^[39]

Primary tumor cells may enter the circulation either as single cells or through collective migration, processes that differ in cellular morphology and underlying molecular mechanisms. Regardless of the invasion mode, dissemination enables tumor cells to detach from the primary site and intravasate into the bloodstream. Emerging anti-invasive strategies target cytoskeletal components, such as vimentin, to disrupt intermediate filament assembly; altered vimentin phosphorylation impairs cellular mechanical properties. However, further investigation is required to determine whether targeting intermediate filaments can effectively inhibit metastatic progression.^[40]

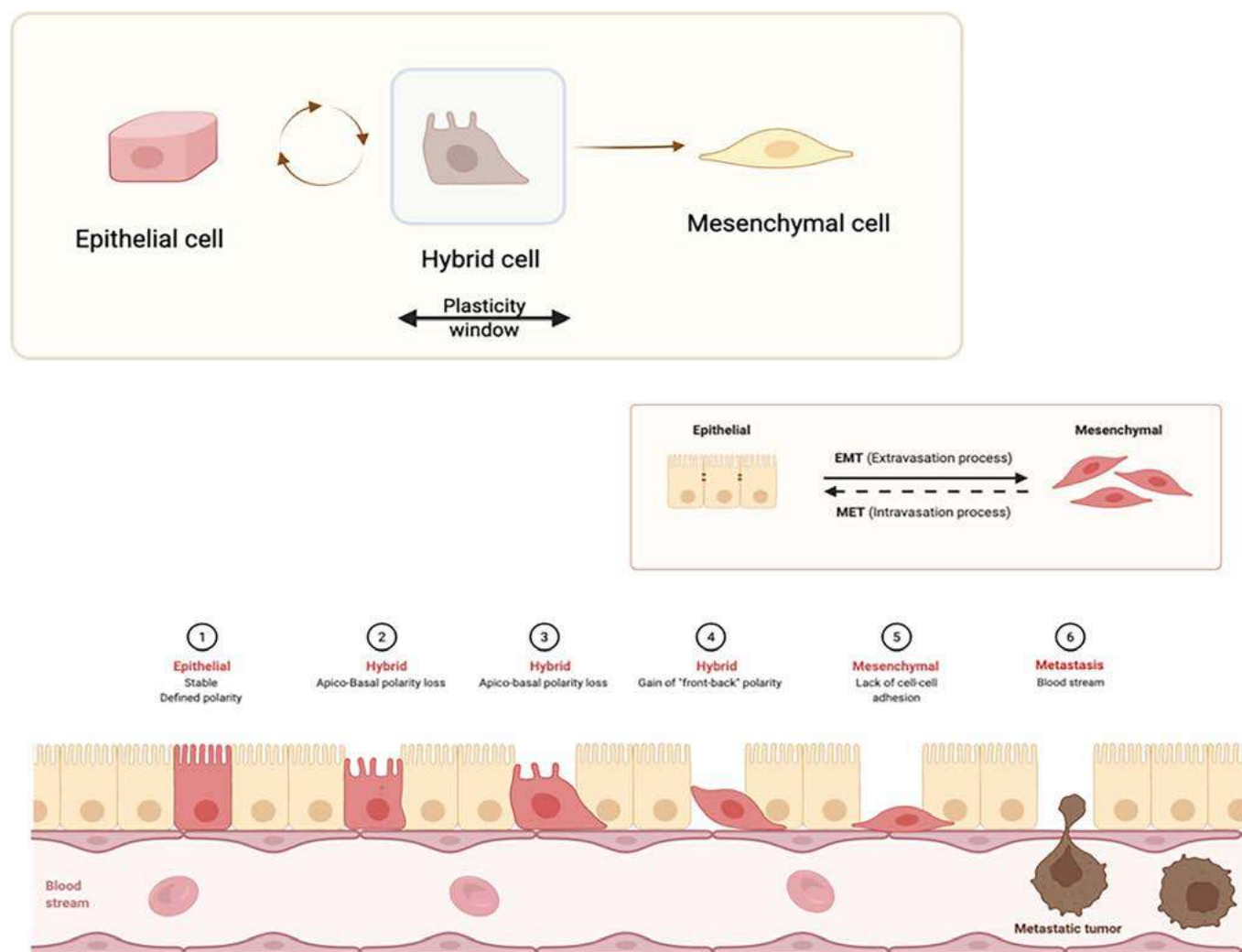


Figure 3: EMT (epithelial-mesenchymal transition) and MET (mesenchymal-epithelial transition). EMT and MET orchestrate dynamic and reversible changes involving a range of intermediate epithelial-mesenchymal phenotypes. Fully developed epithelial cells are characterized by apical-basal polarity, lateral cell-cell connections such as adherens junctions, gap junctions, tight junctions, and connections to the basement membrane. In contrast, mesenchymal cells exhibit anteroposterior polarity, lack cell-cell adhesion and move independently when detached from the basement membrane

Intravasation and Immune Modulation: Following intravasation, most circulating tumor cells are eliminated by hemodynamic shear stress and immune surveillance; fewer than 0.01% successfully extravasate at distant sites. Vascular invasion may occur via active or passive mechanisms; in passive invasion, the majority of cells undergo apoptosis. This attrition has been attributed to unfavorable microenvironmental conditions, including hypoxia-induced nutrient deprivation and the structurally leaky nature of tumor-associated vasculature.^[41,42]

Conversely, during active intravasation, cells utilize the process of chemotaxis to migrate toward blood vessels, controlled by gradients of nutrients and growth factors.^[43] These cells degrade the ECM and basement mem-

brane and actively invade blood vessels via intravasation. These cancer cells form bonds with platelets as they circulate, allowing them to withstand shear stress.^[42,43]

Arrest and Extravasation: To establish metastatic lesions, cancer cells must undergo extravasation, a multistep process involving endothelial adhesion at secondary sites, disruption of the endothelial barrier, and transendothelial migration into surrounding tissues.^[44] During circulation, cancer cells are mechanically arrested within pulmonary microvessels before migrating into the lung parenchyma, a process mediated by adhesion molecules including ICAM-1, VCAM-1, and E-selectin, as well as chemokines and cytokines such as CXCL12 and IL-8.^[45]

Immune Modulation: Cancer cells evade immune-mediated destruction through multiple mechanisms, including the creation of an immunosuppressive microenvironment via secretion of soluble factors such as VEGF, IL-10, TGF- β , prostaglandin E₂, and Fas ligand. Additionally, downregulation of antigen-presenting machinery, particularly the expression of the major histocompatibility complex (MHC), enables escape from immune surveillance. Circulating tumor cells may also be shielded by platelet cloaking, which protects them from T-cell and natural killer cell-mediated cytotoxicity, while platelet-to-tumor transfer of MHC molecules further contributes to immune evasion.^[17] Moreover, during multiple stages of T-cell activation, the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death-1/programmed death-ligand 1 (PD-1/PD-L1) immune checkpoint pathways negatively regulate T-cell function, thereby fostering an immunosuppressive microenvironment and promoting tumor progression.

PD-1/PD-L1-mediated immune evasion is primarily driven by tumor PD-L1 overexpression, which engages PD-1 on activated T cells and inhibits PI3K/AKT and Ras/MEK/ERK signaling, while CTLA-4 binding to CD80/CD86 suppresses costimulatory signals essential for T-cell activation and proliferation.^[46]

Angiogenesis: Angiogenesis represents a principal route of tumor dissemination, as newly formed tumor-associated vessels are structurally abnormal, exhibiting hyperplasia, excessive branching, and increased permeability. These defects facilitate vascular leakage and enable tumor cells to escape from the primary tumor.^[47] Primary tumors remain localized while the angiogenic switch is inactive; its delayed activation, occurring months to years after tumor initiation, reactivates tumor growth, sustains proliferation, and enables dissemination to secondary sites. Accordingly, clinically quiescent tumors or micrometastases may persist in a dormant state until angiogenesis is triggered.^[48]

In addition to hematogenous spread, cancer cells may disseminate via lymphatic and perineural routes. Lymphatic spread typically involves initial seeding of regional lymph nodes followed by distant organ metastasis, a process critically regulated by factors such as vascular endothelial growth factor (VEGF) and angiopoietin-2.^[14,49] Overexpression of VEGF-C or VEGF-D promotes tumor-associated lymphangiogenesis, thereby facilitating cancer cell dis-

semination.^[50] Perineural dissemination involves tumor spread along neural axons and the surrounding perineural sheath and has been documented in multiple malignancies, including breast, pancreatic, prostate, colorectal, and head and neck cancers.^[51] Perineural spread is initiated within a specialized peripheral microenvironment composed of neural cells, inflammatory infiltrates, extracellular matrix, vasculature, and immune components, which collectively facilitate metastatic progression.^[52]

Dormancy in Micrometastasis: Following extravasation, many disseminated cancer cells fail to develop into macrometastases and instead persist as solitary cells or small micrometastatic clusters that enter a state of quiescence. Metastatic dormancy is characterized by cell cycle arrest and may result from inadequate growth factor signaling, activation of metastasis suppressor genes (cytostatic dormancy), failure to initiate angiogenesis (angiogenic dormancy), or sustained immune-mediated control (immunologic dormancy).^[53-55] Cell-cycle arrest represents a double-edged strategy, as quiescence may render conventional therapies, particularly those targeting rapidly proliferating cells, ineffective. Dormant micrometastatic cells may either persist in quiescence or re-enter active proliferation. Although modulation of pathways such as AXL/Gas6 can induce dormancy, the durability of this suppression is uncertain. Accordingly, strategies that promote dormancy and prevent macrometastatic outgrowth primarily delay disease progression rather than provide curative benefit.^[56]

What Makes the Pulmonary System Unique?

The lung is the most common site of metastasis, owing to the distinctive features of the pulmonary system. It receives the entire cardiac output, contains the densest capillary network in the body, and represents the first capillary bed encountered by much of the lymphatic drainage before venous return. In addition, its extensive network of thin alveolar-capillary membranes readily traps circulating tumor cells. Collectively, these characteristics create a permissive microenvironment for metastatic seeding and growth in the lung.^[57] Although several metastatic routes to the lung exist, hematogenous dissemination is the predominant pathway. The growth of pulmonary metastases depends on an adequate blood supply, and the lung's dual circulatory system, pulmonary and bronchial, acting independently or in combination, provides a vascular milieu that may facilitate metastatic establishment and progression.^[58,59]

Multiple malignancies, including breast, melanoma, and colorectal cancers, release soluble factors and extracellular vesicles that remodel the pulmonary microenvironment and establish pre-metastatic niches. Murine models show that these niches, marked by immune and inflammatory cell recruitment, organ-specific chemoattractants, growth factors, and extracellular matrix remodeling, create permissive conditions for tumor cell extravasation, colonization, and metastatic outgrowth.^[60,61]

After entering the circulation, disseminated tumor cells (DTCs) extravasate through the pulmonary endothelium into the lung parenchyma, where pre-metastatic niche mechanisms support colonization. Hypoxia-induced lysyl oxidases promote collagen crosslinking, enhancing myeloid cell adhesion and niche formation. In parallel, chemokines released by alveolar type II cells recruit neutrophils that facilitate colonization of leukotriene B4 receptor 2 (LTB4R2)-positive DTCs, suppress CD8⁺ T-cell activation, and promote metastatic outgrowth through secretion of cathepsin G and neutrophil elastase, which degrade the tumor-suppressive factor thrombospondin-1 (TSP1).^[62-64]

After colonization, disseminated tumor cells (DTCs) adapt to the pulmonary microenvironment with support from $\alpha 4$ integrin-expressing macrophages, which activate pro-survival AKT signaling. Metastatic outgrowth is further promoted by angiogenesis driven by bone marrow-derived endothelial progenitor cells or by VEGF-induced VEGFR2 activation in the lung endothelium. Although natural killer (NK) cells are central to tumor immunosurveillance, hypoxia-driven CCL2 secretion recruits granulocytic myeloid cells, thereby establishing an immunosuppressive niche that impairs NK cell maturation and cytotoxicity.^[60]

Pre-existing pulmonary inflammation, such as that induced by cigarette smoke exposure, may further facilitate metastasis. Inflammatory mechanisms implicated in this process include activation of the ubiquitin-CXCR4 axis, upregulation of E-selectin in lung tissue, NF- κ B activation in airway epithelial cells, increased CCL2 expression, and enhanced macrophage infiltration within the pulmonary microenvironment.^[65,66]

Further studies are needed to clarify the complex interactions between the host microenvironment, immune system, and lung structure that could also impact prognosis and therapeutic approaches.^[67]

Clinical Implications of Metastasis Biology: The Underlying Mechanisms at the Core of Metastasectomy

The physiological and molecular characteristics of the pulmonary system render it a highly permissive environment for metastatic seeding, primarily due to its dense capillary network and role as the first major capillary bed for lymphatic and venous return. Beyond simple mechanical trapping of tumor cells, the lung actively facilitates colonization through the establishment of pre-metastatic niches. These niches, driven by soluble factors, extracellular matrix remodeling, and the recruitment of immunosuppressive myeloid cells, suppress anti-tumor immunity (such as NK-cell and CD8⁺ T-cell activity) and promote pro-survival signaling. Furthermore, the lung's dual circulatory system and inflammatory triggers, including cigarette smoke, exacerbate this susceptibility by enhancing vascularization and chemoattractant expression.^[24,25,31,32]

From a clinical perspective, these biological mechanisms provide a profound rationale for the surgical principles of pulmonary metastasectomy. The predominantly hematogenous pathway of dissemination explains the necessity for radical and complete resection of all detectable nodules to achieve oncological control. The involvement of the lymphatic system and recruitment of inflammatory cells into the lung parenchyma underscore the paramount importance of lymph node dissection and sampling, since intrathoracic lymph node involvement directly indicates systemic disease progression and poor prognosis. Moreover, the recognition that the pulmonary microenvironment can harbor radiologically occult disseminated tumor cells (DTCs) justifies the surgical debate between thoracotomy and MIS, in which bimanual palpation may be required to address the biological reality of multifocal seeding. Ultimately, the transition from tumor biology to surgical intervention reflects a comprehensive strategy to disrupt the permissive milieu and improve patient prognosis through precise anatomical and oncological clearance.

Clinical Application of Pulmonary Metastasectomy

The clinical application of pulmonary metastasectomy is fundamentally dictated by the interplay between tumor histology and the receptive biology of the lung. In contemporary thoracic practice, PM is most frequently indicated for colorectal carcinomas, sarcomas (both soft-tissue

sarcomas and osteosarcomas), renal cell carcinomas, and selected head-and-neck tumors or germ-cell tumors. These malignancies typically exhibit a focal colonization pattern, in which disseminated tumor cells (DTCs) utilize the lung's dense capillary network for mechanical entrapment but remain relatively localized within the parenchyma. For these patients, surgical intervention serves as a critical tool to physically disrupt the pro-survival AKT signaling and angiogenic support provided by the pulmonary microenvironment, offering substantial long-term survival benefits that systemic therapies alone may not achieve.^[41–43]

In contrast, certain secondary pulmonary malignancies are traditionally excluded from surgical consideration due to their distinct biological behavior or extreme sensitivity to systemic agents. Hematological malignancies (e.g., Hodgkin and non-Hodgkin lymphomas) and highly chemosensitive tumors, such as small-cell lung cancer, are managed with systemic therapies because their diffuse molecular signaling renders local surgical excision ineffective. Furthermore, diffuse clinical patterns, such as lymphangitic carcinomatosis or miliary metastases, represent a biological state in which the permissive microenvironment has been entirely subverted. In these scenarios, the recruitment of immunosuppressive myeloid cells and the widespread remodeling of the extracellular matrix occur throughout the organ, rather than at discrete foci, rendering radical R0 surgical resection anatomically and biologically impossible. Even in cases where the disease remains localized and biologically amenable to resection, the patient's physiological reserve must be considered; for those deemed to have prohibitive surgical risk, nonoperative techniques, such as radiofrequency ablation or stereotactic body radiation therapy, may be preferred to maintain local control.^[68]

When comparing these two groups through the lens of tumor biology, the distinction becomes clear: the surgical group comprises tumors that exploit the lung's vascular and mechanical features to establish isolated, often chemoresistant niches that can be surgically removed. Conversely, the non-surgical group encompasses malignancies that either utilize the lung's lymphatic and immune-suppressive frameworks to achieve systemic infiltration or possess a molecular vulnerability that is more effectively addressed via pharmacological disruption. Ultimately, the decision to proceed with metastasectomy is a clinical judgment about whether the disease remains a series of localized biological events or has transitioned into a systemic state that transcends the boundaries of surgical clearance.

Comparative Clinical Perspectives on Surgically Manageable Pulmonary Metastases

A comparative analysis of secondary pulmonary malignancies originating from renal cell carcinoma, germ cell tumors, colorectal carcinoma, and sarcomas further demonstrates how these specific biological characteristics govern the strategic implementation of pulmonary metastasectomy. While all four malignancies disseminate hematogenously and utilize the lung's dense capillary network as a primary site for secondary colonization, their clinical management is governed by distinct histological behaviors and sensitivities to systemic therapy. Sarcomas and RCC represent a category in which surgical intervention is of paramount importance. Due to their relative resistance to conventional chemotherapy, radical resection often serves as the only definitive modality for achieving long-term survival or cure.^[69,70] In these cases, the pulmonary microenvironment acts as a critical battleground where the physical elimination of chemoresistant niches is essential. Conversely, GCTs represent a unique biological paradigm characterized by extreme sensitivity to cisplatin-based regimens. In this context, metastasectomy is typically reserved as a post-chemotherapy adjunctive measure to address residual masses, facilitating the differentiation between necrotic tissue, mature teratoma, and viable malignancy.^[71]

From a procedural perspective, colorectal carcinoma introduces an additional layer of biological complexity, as it more commonly disseminates via the lymphatic system, in contrast to the predominantly hematogenous spread observed in sarcomas and RCC. This has necessitated a shift in surgical philosophy for CRC, where formal lymphadenectomy or systematic sampling is strongly advocated due to the profound prognostic implications of occult nodal involvement.^[72] While the objective of achieving an R0 resection remains the universal gold standard across all groups, the technical approach varies; for instance, the aggressive pursuit of repeat metastasectomies is particularly common in young GCT and sarcoma patients to manage the high rate of recurrence.^[71] Ultimately, the transition from primary tumor biology to surgical practice across these four groups reflects a tailored oncological strategy. For GCT, surgery is both a diagnostic and curative completion of systemic treatment. On the other hand, for sarcomas and RCC, it is the primary pillar of local control. For CRC, it is a multidisciplinary step integrated into a broader systemic and potentially multi-organ metastatic framework.^[72]

Treatment Goals and Future Direction

Although significant progress has been made in understanding the mechanisms underlying cancer growth and spread, it remains difficult to elucidate the metastasis process due to its complex nature. However, despite the success of immunotherapy in certain primary tumors, no uniformly effective treatment for metastatic disease has yet been established.^[73,74]

Therapies targeting early metastatic drivers, including metabolic, angiogenic, and EMT-related pathways, have thus far shown limited clinical efficacy. Greater therapeutic promise may lie in combinatorial approaches, particularly integrating immunotherapy with metabolic inhibition. However, the development of personalized or targeted treatments for metastatic disease remains challenging due to the paucity of actionable mutations and pronounced tumor heterogeneity.^[17,75–77] Notably, disseminated tumor cells (DTCs) that colonize the lung may enter dormancy, presenting a potential therapeutic window to reduce recurrence. Although the molecular regulation of dormancy is increasingly understood, accumulating evidence underscores a critical role for the local microenvironment. These observations highlight the multifactorial nature of cancer dormancy and the need to target both tumor-intrinsic and microenvironmental determinants in therapeutic strategies.^[78,79]

Conclusion

In conclusion, metastatic cancer remains a complex and challenging process responsible for the majority of cancer-related deaths. While our understanding of the mechanisms underlying metastasis has grown significantly in recent years, effective treatments for metastatic disease remain elusive. The unique characteristics of the pulmonary system, including its extensive blood supply, dense capillary network, and thin membrane structure, make the lungs particularly susceptible to metastatic colonization. The formation of pre-metastatic niches in the lungs, driven by factors released from primary tumors, supports the establishment and growth of disseminated tumor cells.

Future advances in the treatment of metastatic disease will require a comprehensive understanding of these complex, interacting processes. Multi-targeted therapeutic approaches addressing multiple aspects of the meta-

static cascade are likely necessary. Some promising areas for further research and therapeutic development include:

- Targeting the formation of pre-metastatic niches.
- Disrupting tumor cell dormancy or preventing reactivation.
- Enhancing anti-tumor immune responses.
- Inhibiting angiogenesis and vascular remodeling.
- Developing combination therapies that address both cancer cell-intrinsic and microenvironmental factors.

Additionally, a better understanding of the molecular and genetic drivers of metastasis may enable personalized treatment approaches for individual patients and tumor types.

While significant challenges remain, ongoing research into the intricacies of the metastatic process continues to uncover new potential therapeutic targets and strategies. Ultimately, improving outcomes for patients with metastatic disease will require continued collaboration between researchers and clinicians to translate mechanistic insights into effective clinical interventions. With further advances in our understanding of pulmonary metastasis, there is hope that more effective treatments can be developed to prevent and combat this lethal aspect of cancer progression.^[18,66,67]

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Diagnostic yield of CT-guided needle biopsy for subsolid pulmonary nodules: Correlation with postoperative pathology

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Abstract:

BACKGROUND AND AIM: Subsolid pulmonary nodules (SSNs), encompassing pure ground-glass nodules (pGGNs) and part-solid nodules (PSNs), may represent a spectrum of pulmonary adenocarcinoma. Accurate preoperative diagnosis is essential to guide treatment decisions and avoid unnecessary surgeries. This study aimed to evaluate the diagnostic performance of computed tomography-guided transthoracic core needle biopsy (CT-TNB) in SSNs, with correlation to final surgical pathology.

METHODS: This retrospective cohort study included 41 SSNs from 40 patients who underwent CT-TNB followed by surgical resection between 2012 and 2022. Radiological and histopathological characteristics were evaluated. Descriptive statistics and diagnostic performance metrics were calculated using Python.

RESULTS: Of the 41 SSNs, 13 (31.7%) were pGGNs and 28 (68.3%) were PSNs. CT-TNB diagnosed 36 nodules (87.8%) as adenocarcinoma, four (9.8%) as atypical epithelial cells, and one (2.4%) as benign pathology. Final pathology revealed 28 (68.3%) invasive adenocarcinomas (IA), 10 (24.4%) minimally invasive adenocarcinomas (MIA), one adenocarcinoma in situ, one atypical adenomatous hyperplasia, and one breast cancer metastasis. CT-TNB demonstrated 97.6% sensitivity and 100% positive predictive value (PPV) for malignancy. For invasive carcinoma (MIA or IA), sensitivity was 94.7%, with 100% specificity and PPV.

CONCLUSIONS: CT-TNB demonstrates high diagnostic accuracy for SSNs and correlates reliably with postoperative pathology. It remains a valuable tool for preoperative assessment when performed by experienced teams using core needle techniques.

Keywords:

Adenocarcinoma, lung, needle biopsy, subsolid nodules

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Introduction

Subsolid pulmonary nodules (SSNs) are a distinct category of lung lesions characterized by a ground-glass opacity component on computed tomography (CT), allowing visualization of bronchial and vascular structures. Based on radiological appearance, they are classified as pure ground-glass nodules (pGGNs) or part-solid nodules (PSNs). Although less prevalent than solid nodules, SSNs carry a higher probability of malignancy and often represent a spectrum of pulmonary adenocarcinoma, including atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (IA).^[1,2]

Management of SSNs is challenging due to their variable growth patterns and overlapping benign and malignant features. While some resolve spontaneously, others progress slowly and may develop invasive components, particularly in PSNs.^[3,4] Risk factors for malignancy include larger nodule size, a solid component, spiculated margins, and pleural retraction.^[1]

Given their heterogeneity, the management of SSNs poses significant diagnostic and therapeutic challenges. Accurate preoperative diagnosis is critical to guide treatment decisions and avoid unnecessary surgical resections.^[5] Computed tomography-guided transthoracic needle biopsy (CT-TNB) is a minimally invasive procedure widely used for tissue diagnosis. Although it has demonstrated high diagnostic accuracy and safety in the evaluation of pulmonary nodules, concerns persist regarding its diagnostic yield in SSNs, particularly in smaller or predominantly ground-glass lesions.^[6,7]

The present study aimed to evaluate the diagnostic performance of CT-TNB in patients with subsolid pulmonary nodules who subsequently underwent surgical resection.

Materials and Methods

Study design and population

This retrospective cohort study was derived from a medical specialty thesis conducted at our institution and included adult patients who underwent surgical resection for SSNs between 2012 and 2022. Eligible patients were identified through a systematic review of surgical and histopathology records (n=4497). Cases in-

volving non-parenchymal surgeries, resection of masses larger than 3 cm, purely solid nodules, non-oncological procedures, or incomplete data were excluded. Among the 86 patients with a total of 92 resected SSNs identified in the thesis cohort, a subset of 41 nodules that had undergone preoperative CT-TNB was selected for inclusion in the present study [Fig. 1]. In cases where multiple nodules were excised from the same patient, each nodule was evaluated independently.

Data collection

Demographic and clinical data, including age, sex, smoking history, comorbidities, and family history of malignancy, were obtained from the hospital information management system. Radiological assessments were based on the most recent preoperative thoracic CT scans, with additional imaging studies reviewed when available. Nodule characteristics, including location, size, shape, borders, internal structure, and relationship to adjacent bronchial, vascular, and pleural structures, were evaluated. All CT-TNBs were performed using a core needle. Data on diagnostic outcomes and post-procedural complications were recorded. Patient epicrisis and post-procedural chest radiographs were reviewed to assess for complications. Histopathological diagnoses were determined by an experienced pulmonary pathologist blinded to radiological findings. Classification of lesions was performed according to the 2021 World Health Organization Classification of Lung Tumors.^[8]

TNB technique

All patients underwent a clinical evaluation, including medical history and hematological testing. Eligibility required an International Normalized Ratio (INR) <1.5 and a platelet count $>50 \times 10^9/L$, confirmed within five days. Antiplatelet and anticoagulant agents were discontinued per guidelines: nonsteroidal anti-inflammatory drugs (NSAIDs) and clopidogrel five days, heparin six hours, rivaroxaban one day, and dabigatran/edoxaban three days before the procedure. Biopsies were performed by four board-certified interventional radiologists (8–20 years of experience) under CT guidance (Siemens Somatom) with an 18- or 20-gauge coaxial needle. Planning used non-contrast chest CT reconstructed at 3-mm intervals, following standardized protocols to optimize trajectory and minimize risk. Pulmonary vessels, fissures, and effusion-associated targets were avoided. Patient positioning was individualized based on operator judgment and anatomical considerations.

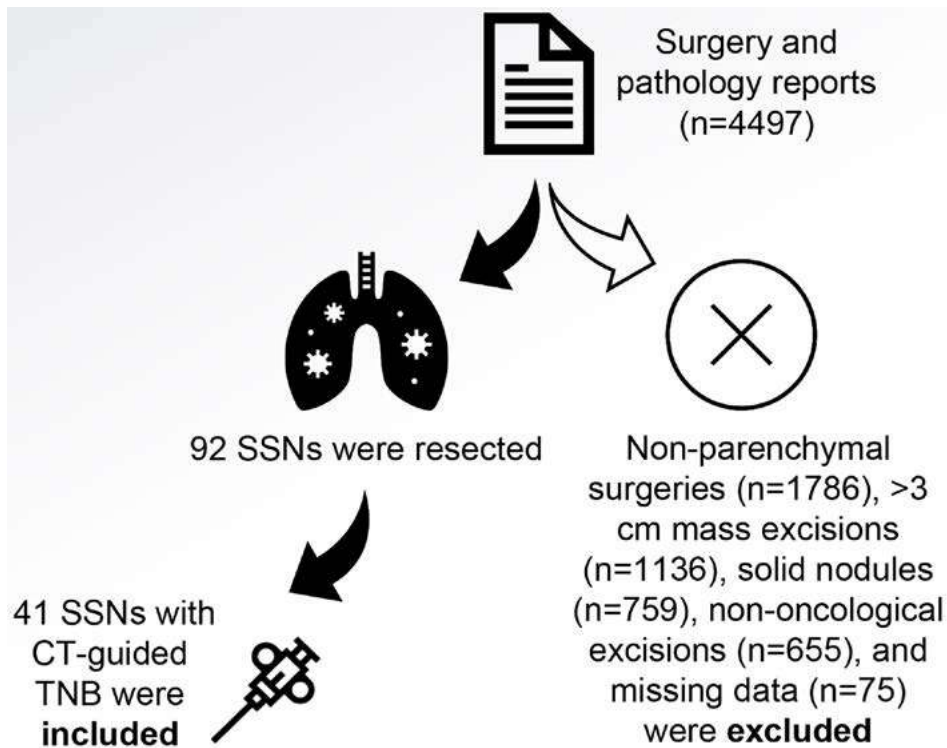


Figure 1: Flow chart of the study

SSNs: Subsolid pulmonary nodules, TNB: Transthoracic needle biopsy

Statistical analysis

All statistical analyses were conducted using Python version 3.13 (Python Software Foundation, Wilmington, DE, USA). Descriptive statistics were applied to summarize demographic and radiological features. Continuous variables were reported as mean±standard deviation (SD) or median with range, and categorical variables as counts and percentages. Diagnostic accuracy metrics, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated using the scikit-learn library. To provide a measure of precision for these estimates, particularly given the study's sample size, 95% confidence intervals (CIs) were calculated for each metric using the Clopper-Pearson exact method. Data management and summary statistics were performed with pandas and numpy, while confusion matrices were created using matplotlib and seaborn.

Ethical considerations

This study is derived from the medical specialty thesis of the first author. It was approved by Hacettepe University Non-interventional Clinical Research Ethics Committee (Approval Number: 2023/03-01, Date: 21.02.2023) and conducted in accordance with the ethical principles out-

lined in the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

Artificial intelligence-based tools (ChatGPT, OpenAI, San Francisco, CA, USA) were used exclusively to improve the clarity, fluency, and grammar of the manuscript text. All content generated with artificial intelligence (AI) assistance was critically reviewed, revised, and approved by the authors, who take full responsibility for the final version.

Results

The study included 40 patients (23 males, 17 females) with a mean age of 61.5±9.6 years (range: 27–75). One patient underwent CT-TNB for two different nodules at separate time points. All SSNs included in the study were incidentally detected. Baseline characteristics of the patients are detailed in Table 1.

Of the 41 nodules evaluated with CT-TNB, 13 (31.7%) were classified as pGGNs and 28 (68.3%) as PSNs. The most frequent location was the right upper lobe (39.0%), followed by the left upper lobe (31.7%), left lower lobe (17.1%), right lower lobe (9.8%), and right middle lobe (2.4%). The me-

Table 1: Baseline characteristics of the patients

Characteristics	n	%
Total number of patients	40	
Male	23	57.5
Female	17	41.5
Age at diagnosis (mean±SD) (years)	61.5±9.6	
Smoking status		
Active smoker	10	25.0
Former smoker	20	50.0
Never smoker	10	25.0
Comorbidities		
Hypertension	21	52.5
Malignancy	18	45.0
Lung cancer	2	5.0
Other cancers	16	40.0
Diabetes mellitus	15	37.5
Coronary artery disease	6	15.0
COPD	4	10.0
Others	25	62.5
Family history of cancer	12	30.0

SD: Standard deviation, COPD: Chronic obstructive pulmonary disease

dian longest diameter of the nodules was 17 mm (range: 10–30 mm). Detailed radiological characteristics are presented in Table 2. A total of 22 nodules (53.7%) were biopsied immediately after detection, whereas 19 nodules (46.3%) were biopsied after a follow-up period of at least three months. Among those followed radiologically with serial CT, the median follow-up duration was 27 months (range: 4–105). The 19 nodules under surveillance exhibited diverse progression patterns: 16 showed a size increase of >2 mm/year, nine demonstrated increased density, five showed growth in the solid component, and three developed a new solid component [Fig. 2]. Among those with diameter progression, the median volume doubling time was 460 days (range: 168–5918). The surgical procedure was lobectomy in 36 nodules (87.8%), wedge resection in four (9.8%), and segmentectomy in one (2.4%).

On CT-TNB, 36 nodules (87.8%) were diagnosed as adenocarcinoma, four (9.8%) as atypical epithelial cells, and one (2.4%) as benign pathology. Postoperative pathological diagnoses included 28 (68.3%) IA, 10 (24.4%) MIA, one (2.4%) metastasis, one (2.4%) AIS, and one (2.4%) AAH. A confusion matrix illustrating the correlation between preoperative biopsy and postoperative pathological diagnoses is shown in Figure 3. The nodule that yielded a benign result on preoperative biopsy was a PSN located in the right lower lobe, with a maximum diameter of 10 mm and a solid component of 4 mm, exhibiting spiculated and irregular margins. It was ultimately diagnosed as IA after surgical resec-

Table 2: Radiological characteristics of subsolid nodules

Characteristics	n	%
Total number of nodules	41	
SSN subtype		
pGGN	13	31.7
PSN	28	68.3
Longest diameter, median (range), mm	17 (10–30)	
Lesion-pleura distance, median (range), mm	12 (0–55)	
Location		
Right upper lobe	16	39.0
Right middle lobe	1	2.4
Right lower lobe	4	9.8
Left upper lobe	13	31.7
Left lower lobe	7	17.1
Border		
Indistinct	36	87.8
Spiculated	5	12.2
Shape		
Irregular	28	68.3
Oval	7	17.1
Round	5	12.2
Lobulated	1	2.4
Internal structure		
Air bronchogram	17	41.5
Air bubble or cyst	7	17.1
Vascular sign	28	68.3
Bronchial sign	15	36.6
Pleural contact	16	39.0
Pleural retraction	23	56.1

SSN: Subsolid nodule, pGGN: Pure ground-glass nodule, PSN: Part-solid nodule

tion. The four nodules interpreted as atypical epithelial cells on CT-TNB were later diagnosed as AAH, AIS, IA, and breast cancer metastasis, respectively. Among the 36 nodules diagnosed as adenocarcinoma on CT-TNB, 10 were confirmed as MIA and 26 as IA.

The sensitivity and PPV of CT-TNB for diagnosing malignancy were 97.6% (95% CI: 87.1–99.9) and 100% (95% CI: 91.2–NA), respectively. Specificity and NPV for malignancy could not be calculated, as the surgically resected cohort contained no confirmed benign lesions. The sensitivity, specificity, PPV, and NPV of CT-TNB for identifying invasive carcinoma (MIA or IA) were 94.7% (95% CI: 82.3–99.4), 100% (95% CI: 29.2–NA), 100% (95% CI: 90.3–NA), and 60% (95% CI: 14.7–94.7), respectively.

No complications were observed in 40 (97.6%) of the biopsy procedures. However, one 52-year-old male patient with comorbidities that increased the risk of hemorrhagic complications, including multiple myeloma, chronic kidney disease, hypertension, and coronary artery disease, died due to biopsy-related hemorrhage.

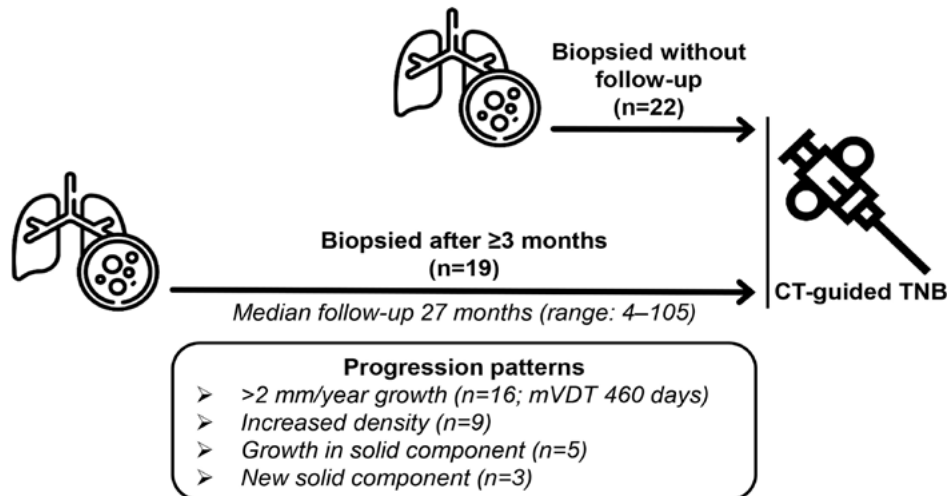


Figure 2: Timeline and progression patterns of subsolid nodules undergoing computed tomography-guided biopsy
TNB: Transthoracic needle biopsy, mVDT: Median volume doubling time

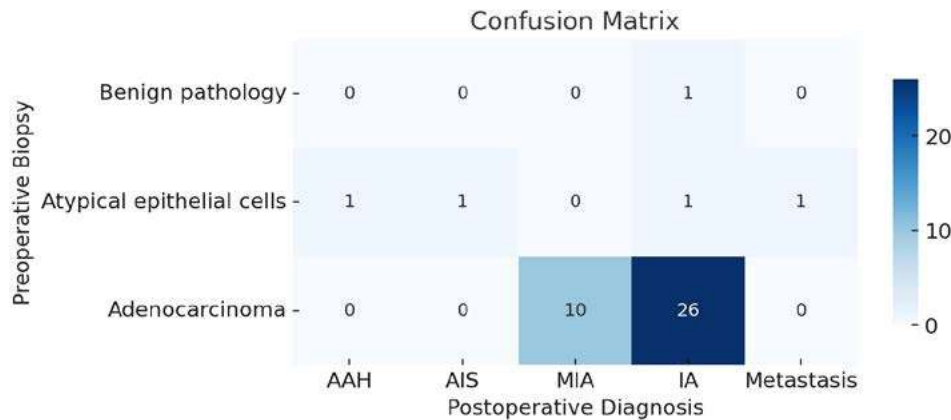


Figure 3: Confusion matrix showing the correlation between preoperative biopsy results and postoperative pathological diagnoses of subsolid nodules
AAH: Atypical adenomatous hyperplasia, AIS: Adenocarcinoma in situ, MIA: Minimally invasive adenocarcinoma, IA: Invasive adenocarcinoma

Discussion

This study evaluated the diagnostic performance of CT-TNB in SSNs, with correlation to final surgical pathology. Our findings demonstrate that CT-TNB provides high diagnostic accuracy in this population, with a sensitivity of 97.6% and a PPV of 100% for malignancy. For predicting invasive adenocarcinoma (IA or MIA), the sensitivity was 94.7%, and the specificity and PPV remained at 100%.

Our results are consistent with the existing literature. The robust performance of CT-TNB for SSNs, including both PSNs and GGNs, has been increasingly recognized. Kim et al.^[6] performed a systematic review and meta-analysis involving 744 SSNs and demonstrated pooled sensitivity

and specificity of 90% and 99%, respectively, for percutaneous TNB. Comparable accuracy across solid and subsolid nodules has also been highlighted by Yun et al.,^[9] who reported similar sensitivity, specificity, and predictive values for both lesion types, suggesting that the presence of ground-glass components does not inherently compromise diagnostic accuracy. Another study using propensity score matching showed that ground-glass and solid nodules yield similar diagnostic and safety outcomes in CT-TNB, further reinforcing our findings.^[10]

The slightly higher sensitivity in our study may be attributable to the exclusive use of core needle biopsies and a relatively experienced interventional team, consistent with Kim et al.'s^[6] observation that core needle biopsies

trend toward higher diagnostic yield than fine-needle aspiration. This preference for core biopsy is further supported by a study on nodules smaller than 1 cm, which found that using aspiration alone was a significant independent risk factor for diagnostic failure.^[11]

Kiranantawat et al.^[7] reported sensitivities ranging from 88.6% to 95.6%, with 100% specificity in SSNs, regardless of nodule size or ground-glass opacity proportion. Their findings support our observation that CT-TNB is reliable even for small or predominantly ground-glass lesions. High diagnostic accuracy for small lesions (≤ 20 mm) has also been reported by Li et al.,^[12] who achieved an overall accuracy of 93.5% and a sensitivity of 90.4%, and by Choi et al.^[11] for nodules < 1 cm, with a sensitivity of 93.1% and accuracy of 95.0%. However, it is worth noting that Huang et al.^[13] found that diagnostic accuracy was significantly lower for small nodules (≤ 15 mm) at 83.7% compared to 96.8% for larger nodules (> 15 mm), suggesting that lesion size can still pose a challenge.

Tsai et al.^[14] explored the ability of CT-guided core biopsy to predict predominant histologic subtypes in adenocarcinoma and reported a 64% concordance rate with surgical pathology. Our findings complement this by demonstrating a strong correlation between CT-TNB and postoperative histology in both MIA and IA cases. However, in four cases initially diagnosed as atypical epithelial cells, the final pathology ranged from AAH to metastasis, indicating limitations in sampling accuracy and the need for careful interpretation of atypical findings. Such indeterminate results are not uncommon; Borelli et al.^[15] reported a nondiagnostic biopsy rate of 18% in their cohort, with subsequent analysis revealing that 66.7% of these nondiagnostic cases were ultimately malignant. They also identified lesions ≤ 20 mm and a final benign diagnosis as risk factors for nondiagnostic results, which underscores the complexities of biopsying smaller SSNs or those with subtle malignant foci. The challenge of accurately targeting the solid component of PSNs during biopsy has been highlighted by Halpenny et al.,^[16] who found that inadequate targeting may lead to underestimation of invasiveness. In our study, the single false-negative case involved a PSN with spiculated and irregular margins that yielded a benign biopsy result but was later confirmed as IA. This reinforces the importance of precise radiologic-pathologic correlation and targeting strategies during CT-TNB.

Complication rates in our cohort were lower than those reported in several studies. A large meta-analysis reported a pooled overall complication rate for CT-guided core biopsy of 38.8% and a major complication rate of 5.7%.^[17] Overall complication rates were also significantly higher for core biopsy compared to fine-needle aspiration, highlighting a trade-off between increased diagnostic yield and procedural risk associated with core biopsies. Lee et al.^[18] found that SSNs were associated with a significantly higher incidence of pulmonary hemorrhage compared to solid nodules (29.7% vs. 8.9%, $p < 0.001$). This observation is supported by a study that reported comparable diagnostic accuracy between lesion types; however, the incidence of hemorrhage on post-biopsy follow-up CT was significantly higher in part-solid lesions compared to solid lesions, despite no significant difference in rates of symptomatic major hemorrhage or pneumothorax.^[9] Although only one patient in our series experienced a major complication, the outcome was fatal, underscoring the need for careful preprocedural evaluation, particularly in patients with comorbidities. Azour et al.^[19] emphasized that lesion- and patient-related variables significantly impact both diagnostic yield and safety outcomes and advocated for tailored procedural planning. Several studies have identified specific risk factors for complications: Huang et al.^[13] identified longer needle path length from pleura to lesion, lower lobe location, and obstructive lung function as risk factors for pneumothorax, while longer needle path, smaller lesions, and non-pleural contact were associated with pulmonary hemorrhage. Li et al.^[12] found that for small (≤ 20 mm) lesions, a lesion-pleural distance ≥ 21 mm and a needle-pleural angle $\geq 51^\circ$ were significant risk factors for pneumothorax, with the former also being a risk for bleeding. Furthermore, An et al.^[10] noted an increased incidence of significant pneumothorax with small lesion size, deep lesion location, and traversing an interlobar fissure, and interestingly reported that post-biopsy hemorrhage may be a protective factor for pneumothorax. In contrast to these single-center findings, the meta-regression did not identify significant risk factors for complications specifically for core biopsy procedures, which may reflect heterogeneity across pooled studies or limitations in the granularity of data available for meta-regression.^[17]

A primary limitation of our study is the selection bias inherent in its design. By exclusively including patients who underwent both CT-TNB and subsequent surgical resection, our cohort is enriched with nodules that were highly

suspicious for malignancy, leading to a high prevalence of cancer in the final pathology. This design was chosen to ensure a definitive histopathological gold standard for every case but prevents the inclusion of true-negative cases (i.e., patients with a benign biopsy who were correctly managed with surveillance). Consequently, our calculated specificity and PPV of 100% are likely inflated and do not reflect the performance of CT-TNB in a broader, unselected population of patients with SSNs. Furthermore, this makes a meaningful calculation of the negative predictive value impossible. A study incorporating a control group of biopsied SSNs with benign final diagnoses confirmed by long-term follow-up would be necessary to establish the true specificity and NPV of the procedure. Other limitations of our study include its retrospective design and single-center setting, which may limit generalizability. Additionally, the small sample size limited our statistical power and, importantly, precluded any meaningful subgroup analyses, such as comparing the diagnostic performance of CT-TNB between pGGNs and PSNs or evaluating the impact of lesion size on accuracy. Future studies should focus on assessing how variables such as lesion-pleural distance, needle trajectory, and consolidation ratio within SSNs affect diagnostic accuracy and complication profiles. Moreover, integration of radiomics or AI-based biopsy guidance systems could enhance lesion targeting and reduce false-negative rates, especially in complex PSNs.

Conclusion

Computed tomography-guided transthoracic needle biopsy provides high diagnostic accuracy in the evaluation of SSNs, with strong correlation to final surgical pathology. While the procedure is generally safe, clinicians should remain vigilant for hemorrhagic complications, especially in patients with multiple comorbidities. Our findings reinforce the value of CT-TNB in preoperative planning, particularly when performed by experienced teams using core needle techniques, and contribute to the growing body of evidence supporting its role in the management of SSNs.

Ethics Committee Approval

The study was approved by the Hacettepe University Non-interventional Clinical Research Ethics Committee (No: 2023/03-01, Date: 21/02/2023).

Informed Consent

Informed consent was waived due to the retrospective nature of the study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Use of AI for Writing Assistance

Artificial intelligence-based tools (ChatGPT, OpenAI) were used solely to enhance the clarity, fluency, and grammar of the manuscript. The authors critically reviewed and edited all AI-assisted text, accepting full responsibility for the final content.

Author Contributions

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Clinical significance of the DECAF score in acute exacerbations of chronic obstructive pulmonary disease

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Abstract:

BACKGROUND AND AIM: The prognosis of chronic obstructive pulmonary disease (COPD) depends on the frequency and severity of exacerbations. The DECAF score (dyspnea, eosinopenia, consolidation, acidemia, and atrial fibrillation) is a cost-effective tool used to predict exacerbation outcomes. This study examines its relationship with six-month mortality following COPD exacerbations (ECOPD).

METHODS: Patients (n=260) hospitalized at our center between December 15, 2021 and June 15, 2022 due to ECOPD were evaluated prospectively. Patients were classified into low-risk (DECAF score <2) and moderate-high-risk (DECAF score ≥2) groups. Patients who died within six months were compared with survivors in terms of their demographic and clinical characteristics. Independent risk factors associated with mortality were identified using logistic regression analysis.

RESULTS: The study included 260 patients, 78.8% of whom were male, with a median age of 67 years. The moderate-high-risk group comprised 43.5% (n=113) of patients, and the low-risk group comprised 56.5% (n=147). Patients with a DECAF score ≥2 had a significantly higher six-month mortality rate (p=0.022). Regression analysis showed that mortality risk increased with the presence of congestive heart failure (CHF), higher blood urea nitrogen (BUN) levels, longer hospital stay, and lower hematocrit percentage and body mass index (BMI) values. However, the DECAF score did not emerge as an independent risk factor for six-month mortality following ECOPD.

CONCLUSIONS: Clinical parameters including BMI, length of hospital stay, hematocrit, BUN levels, and the presence of CHF can be used to determine six-month mortality risk in patients hospitalized due to ECOPD. However, the DECAF score was not found to be an independent predictor of six-month mortality.

Keywords:

DECAF score, exacerbations of chronic obstructive pulmonary disease, mortality

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Introduction

As a result of systemic responses to abnormal airway and parenchymal inflammation, chronic obstructive pulmonary disease (COPD) presents as a systemic disease with various extrapulmonary consequences.^[1] COPD ranks as the third most common cause of mortality worldwide and causes approximately 3 million deaths each year. Low- and middle-income countries account for more than 90% of the global mortality burden. The prognosis of COPD depends on exacerbations resulting from physiological deterioration and increased airway inflammation. Exacerbations increase hospitalization rates and admissions to healthcare services.^[2] Determining the severity of exacerbations and managing them attacks play an important role in the follow-up of patients with COPD. There is a growing body of evidence for determining prognosis in stable COPD; however, there remains a clinical need for practical scoring systems that can be used to predict mortality risk in patients hospitalized due to exacerbations of COPD (ECOPD).

Consequently, Steer et al.^[3] developed the DECAF (dyspnea, eosinopenia, consolidation, acidemia, and atrial fibrillation) score, which consists of five parameters, to predict in-hospital mortality risk in patients hospitalized with ECOPD. According to this easily applicable scoring system, 0–1 points indicate low risk, 2 points indicate moderate risk, and 3–6 points indicate high risk. It has been shown that in-hospital mortality risk increases with higher scores.^[4] There are also studies demonstrating that the DECAF score is an effective and cost-effective tool for predicting mortality, disease severity, and the possibility of early discharge in patients with COPD.^[5,6] The DECAF score facilitates accurate prognostic assessment by identifying low-risk patients eligible for home care or early discharge, as well as high-risk patients requiring intensive management. The aim of this study was to evaluate the clinical significance of the DECAF score in predicting six-month mortality risk following ECOPD in hospitalized patients.

Materials and Methods

This prospective cohort study adhered to the principles outlined in the Declaration of Helsinki and received ethical approval from the Clinical Research Ethics Committee of the Keçiören Training and Research Hospital (Approval Number: 2012-KAEK-15/2433, Date: 23.11.2021).

Written informed consent was obtained from each participant in accordance with ethical standards. The clinical and demographic characteristics of 260 patients hospitalized at our center between December 15, 2021 and June 15, 2022 due to ECOPD were evaluated prospectively. Patients with previously documented airway obstruction confirmed by pulmonary function test (PFT) (post-bronchodilator forced expiratory volume in one second to forced vital capacity ratio [FEV₁/FVC] <70%, indicating persistent airflow limitation) and a smoking history of at least 20 pack-years and/or biomass exposure were included in the study.

The exclusion criteria were metastatic malignancy with a life expectancy of less than one year, a diagnosis of asthma, severe neurological or psychiatric disorders impairing effective communication, and the requirement for invasive mechanical ventilation and/or sedative-hypnotic therapy in a level III intensive care unit.

The following demographic and clinical data of the study group were recorded: age, sex, smoking history, body mass index (BMI), occupation, comorbidities, exposures (asbestosis, biomass), electrocardiography (ECG) findings, arterial blood gas results (obtained within the first three days of hospitalization), complete blood count, pulmonary function test results, blood urea nitrogen (BUN), albumin levels, C-reactive protein (CRP), creatinine levels, chest radiograph findings, echocardiography results, history of Coronavirus Disease 2019 (COVID-19) infection, vaccination status (COVID-19, pneumococcal, influenza vaccines), length of hospital stay, and in-hospital mortality.

Patients with a positive COVID-19 polymerase chain reaction (PCR) test from a nasal or oronasal swab at any time before hospitalization were considered to have a history of COVID-19 infection.

Hemoglobin concentrations below 12 g/dL in women and below 13 g/dL in men were defined as anemia.^[7] According to the 2016 World Health Organization (WHO) definition, hemoglobin levels >16.5 g/dL in men and >16 g/dL in women were classified as polycythemia.^[8]

Treatment adherence was evaluated using the Morisky–Green–Levine Scale (MGLS), a self-administered tool consisting of four dichotomous (yes/no) questions. Medication adherence was considered high if all responses

were “no,” moderate if one or two responses were “yes,” and low if three or four responses were “yes”.^[9] Approval from Donald E. Morisky^[9] was obtained for use of this questionnaire. This scale was validated in Turkish by Yılmaz et al.^[10] in 2004.

The number of emergency department visits, hospitalizations, and intensive care unit (ICU) admissions due to COPD exacerbations within one year and six months before and after enrollment was recorded. Patients with more than two emergency department admissions in the previous year were considered frequent exacerbators.

The extended Medical Research Council (eMRC) dyspnea scale was used to assess the degree of dyspnea.^[4] Patients were classified into groups A, B, and E according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) assessment tool.^[1]

The DECAF score was calculated as the sum of the points listed below:

Dyspnea

- eMRCD 5a (too breathless to leave the house unassisted but independent in washing and/or dressing) – 1 point,
- eMRCD 5b (breathlessness severe enough to prevent leaving the house unaided and requiring assistance with washing and dressing) – 2 points.

Eosinopenia

- Eosinophils $<0.05 \times 10^9/L$ – 1 point.

Consolidation

- Presence of consolidation – 1 point.

Acidemia

- Moderate or severe acidemia (pH <7.3) – 1 point.

Atrial fibrillation

- Atrial fibrillation, including a history of paroxysmal atrial fibrillation – 1 point.

A total score of 0–1 points was considered low risk, and 2–6 points were considered moderate-high risk.^[5]

Statistical method

The demographic and clinical data of patients who died or survived within six months following ECOPD were

compared using SPSS Statistics version 21 for Windows (IBM, New York, USA). The distribution of variables was evaluated using visual and analytical methods. Variables with compatible histograms and probability plots were considered normally distributed when the p-value in the Kolmogorov-Smirnov test was >0.05 . Descriptive statistics for normally distributed variables were presented as mean $\pm$ standard deviation (SD). The significance of differences in means between groups was assessed using the Student's t test. Descriptive statistics for other numerical variables were presented as medians with interquartile ranges (IQR), and nominal variables were expressed as numbers and percentages. The Mann-Whitney U test was used to evaluate differences in median values, while the Pearson chi-square test or Fisher's exact test was applied to compare nominal variables.

Multiple logistic regression analysis was performed to determine independent risk factors for six-month mortality following ECOPD. Variables with a p-value <0.10 were included in the model. Among variables that were highly correlated with each other, clinically significant variables were selected. Model fit was assessed using the Hosmer-Lemeshow test. Final model results were obtained using the backward variable elimination method. As the aim of the study was to determine the odds of factors affecting six-month mortality after exacerbation (a binary outcome at a single time point), logistic regression analysis was preferred over Cox proportional hazards modeling. In addition, the small number of deaths may have violated the proportional hazards assumption. Results were considered statistically significant when the p-value was <0.05 .

Statistical power was calculated using the final sample size, observed mortality ratios in the moderate-high-risk group (DECAF score ≥ 2), and a significance level of 0.05. The estimated power of the study was 0.63.

Results

The study group comprised 260 consecutive patients, 78.8% (n=205) of whom were male, with a median age of 67 years (IQR: 15). According to the DECAF score, 56.5% (n=147) of patients were in the low-risk group (score <2), and 43.5% (n=113) were in the moderate-high-risk group (score ≥ 2). Examination of DECAF score components showed that 33.8% had eMRC 5a dyspnea, 15% had eMRC 5b dyspnea, 43.5% had eosinopenia, 40.8%

had consolidation, 7.3% had acidemia, and 8.5% had atrial fibrillation or flutter. In-hospital mortality occurred in five patients. All in-hospital deaths (n=5) occurred in patients with a DECAF score ≥ 2 , and this finding was statistically significant ($p=0.015$). However, because the number of in-hospital deaths was low, further statistical analyses to determine clinical factors associated with in-hospital mortality could not be performed. Six-month mortality after ECOPD was higher in patients with a DECAF score ≥ 2 (6.8% vs. 15.7%, $p=0.022$).

The 255 discharged patients were divided into two groups: the mortality group (patients who died within six months after ECOPD, n=27) and survivors. The clinical and demographic characteristics of these groups were compared. The proportion of patients with a moderate-high risk DECAF score (≥ 2) was significantly higher in the than in the survivor group (39.9% vs. 63%, $p=0.022$). Median BMI was significantly lower in the mortality group (21.8 kg/m² vs. 26.15 kg/m², $p<0.001$). Length of hospital stay (13 days vs. 10 days, $p=0.001$), rate of intensive care unit admission (25.9% vs. 10.1%, $p=0.025$), and length of ICU stay (17 days vs. 9 days, $p=0.039$) were also higher in the mortality group. The groups were similar with respect to GOLD stages and inhaler medication adherence assessed by the MGLS (Table 1).

When comorbidities were compared, only congestive heart failure (CHF) was significantly more frequent in the mortality group (29.6% vs. 5.7%, $p<0.001$). The groups were similar in terms of other comorbidities, including benign prostatic hyperplasia, lung cancer, extrathoracic malignancies, diabetes mellitus, hypertension, coronary artery disease, and pulmonary thromboembolism. No statistically significant difference was observed between groups in dyspnea severity assessed by the mMRC score ($p=0.246$). The rate of type 2 respiratory failure was 50.4% in the survivor group and 55.6% in the mortality group ($p=0.615$).

Comparison of laboratory findings showed that anemia was significantly more common in the mortality group (59.3% vs. 23.7%, $p<0.001$). Mean hemoglobin, hematocrit, and albumin levels were lower, while median BUN levels were significantly higher in the mortality group ($p<0.001$, $p<0.001$, $p<0.001$, and $p=0.009$, respectively) (Table 2). When echocardiographic findings were examined, the ejection fraction (EF) was lower (57.5% vs. 60%, $p=0.003$) and systolic pulmonary artery pressure (sPAP)

Table 1: Comparison of demographic and clinical characteristics between groups

	Survivors (n=228) Median (IQR)		Mortality group (n=27) Median (IQR)		p
	n	%	n	%	
Sex (male)	177	77.6	24	88.9	0.176
Age (years)	14	66	15	72	0.096
BMI (kg/m ²)	8.6	26.15	5.3	21.8	<0.001
ICU admission	23	10.1	7	25.9	0.025
Length of hospital stay					
Length of ward stay (days)	6	10	9	13	0.001
ICU stay (days) (n=30)	6	9	24	17	0.039
GOLD stage					0.260
B	119	52.2	11	40.7	
E	109	47.8	16	59.3	
Smoking status					0.524
Current smoker	70	30.7	8	29.6	
Former smoker	124	54.4	17	63	
Never smoker	34	14.9	2	7.4	
Exposure history					
Biomass exposure	89	39	10	37	0.840
Asbestos exposure	142	62.3	17	63	0.945
Occupational exposure	162	71.1	17	63	0.385
Treatment adherence (MGLS)					
Low	35	15.4	4	14.8	0.643
Moderate	81	35.5	12	44.4	
High	112	49.1	11	40.7	
Vaccination status					
COVID-19	220	96.5	27	100	1.00
Influenza	85	37.3	11	40.7	0.726
Pneumococcal	92	40.4	12	44.4	0.682
Hospital admissions in previous year					
≥ 2 emergency visits	146	64	20	74.1	0.301
≥ 1 ward hospitalization	91	39.9	16	59.3	0.054
≥ 1 ICU hospitalization	50	21.9	6	22.2	0.972
History of COVID-19 infection	65	28.5	3	11.1	0.053
DECAF score					0.022
<2	137	60.1	10	37	
≥ 2	91	39.9	17	63	

BMI: Body mass index, GOLD: Global Initiative for Chronic Obstructive Lung Disease, ICU: Intensive care unit, MGLS: Morisky–Green–Levine Scale

was higher in the mortality group (38.5 mmHg vs. 35 mmHg, $p=0.048$) (Table 2). The FEV₁/FVC value was significantly lower in the mortality group, whereas other respiratory function test parameters were statistically similar between groups (Table 2).

Variables with a p-value <0.10 in univariate analyses were included in the logistic regression model for mor-

Table 2: Comparison of laboratory findings between groups

	Survivors (n=228) Median (IQR) Mean±SD	Mortality Group (n=27) Median (IQR) Mean±SD	p
CBC values			
HGB (g/dL)	14.35±2.26	12.6±2.4	<0.001
Hematocrit (%)	44.68±6.87	39.3±7.1	<0.001
Thrombocyte count (10 ³ /μL)	258 (112.50)	241(184)	0.845
Eosinophils (10 ³ /μL)	0.08 (0.21)	0.03 (0.16)	0.565
Biochemical parameters			
Albumin (g/L)	36.51±5.08	33±4.4	<0.001
Creatinine (mg/dL)	0.90 (0.33)	0.97 (0.53)	0.617
BUN (mg/dL)	16 (8)	22 (18)	0.009
CRP (mg/L)	29.5 (120)	51 (109)	0.225
Anemia			
HGB <12 g/dL for females <13 g/dL for males	54 (23.7)	16 (59.3)	<0.001
Polycythemia			
HGB>16 g/dL for females >16.5 g/dL for males	45 (19.7)	2 (7.4)	0.118
Arterial blood gas analysis			
pH	7.42 (0.08)	7.42 (0.10)	0.812
pO ₂ (mmHg)	57 (22.75)	55.6 (25.20)	0.440
pCO ₂ (mmHg)	44.55 (17.3)	46.7 (16)	0.321
Echocardiography (n=222)			
EF (%)	(n=198) 60 (0)	(n=24) 57.5 (8.75)	0.003
sPAP (mmHg)	(n=198) 35 (13)	(n=24) 38.5 (19)	0.048
Pulmonary function tests			
FEV ₁ (L)	0.95 (0.51)	0.810 (0.51)	0.153
FEV ₁ (%)	34.5 (19)	32 (22)	0.444
FVC (L)	1.7 (0.89)	1.45 (0.74)	0.201
FVC (%)	49 (23.75)	46 (19)	0.614
FEV ₁ /FVC (%)	58 (16)	52 (14)	0.026

Data were expressed as % (n), median (interquartile range, IQR), or mean± standard deviation (SD), as appropriate for data type and distribution. BUN: Blood urea nitrogen, CRP: C-reactive protein, EF: Ejection fraction, FEV₁: Forced expiratory volume in the first second, FVC: Forced vital capacity, HGB: Hemoglobin, sPAP: Systolic pulmonary artery pressure

tality (Table 3). BMI, hematocrit, BUN, and CHF were identified as independent risk factors for six-month mortality after ECOPD. In contrast, DECAF risk groups were not found to be clinical predictors of six-month mortality (odds ratio [OR]: 0.432, confidence interval [CI]: 0.117–1.586, p=0.206) (Table 3).

The final model was constructed using the backward elimination method. The Hosmer-Lemeshow test indicated an acceptable model fit for the final model (p=0.396). In

this model, six-month mortality risk increased with lower hematocrit and BMI values (p=0.016 and p=0.001, respectively). Higher BUN levels, longer hospital stay, and the presence of CHF were also identified as predictors of six-month mortality (p=0.008, p=0.047, and p=0.007, respectively) (Table 4). In this logistic regression analysis, CHF showed the strongest association with six-month mortality, with an odds ratio of 6.041 (CI: 1.650–22.131).

Discussion

Exacerbations are the most important cause of mortality and morbidity in COPD, as they reduce quality of life, accelerate the decline in lung function, and lead to frequent hospitalizations.^[1] Therefore, effective and reliable clinical tools for determining mortality risk after ECOPD are essential. Many scoring systems, such as DECAF, CURB-65 (Confusion, urea, respiratory rate, blood pressure, age), BAP-65 (blood urea nitrogen, altered mental status, pulse, age), PSI (Pneumonia Severity Index), PEARL (previous admissions, eMRC, age, right ventricular failure, left ventricular failure), PLR (platelet-to-lymphocyte ratio), and NLR (neutrophil-to-lymphocyte ratio), have been developed and investigated to address this clinical need. Recent studies have reported that the DECAF score is more effective in predicting 30- and 90-day mortality than the CURB-65, PSI, and BAP-65 scores.^[11–13] However, our study, which evaluated multiple demographic and clinical confounders simultaneously, revealed contrasting results for longer-term mortality.

It has also been reported that the DECAF score predicts in-hospital mortality related to ECOPD with high sensitivity and specificity.^[5,12,13] In-hospital mortality rates among patients with ECOPD range from 4.4% to 25%.^[14–16] Due to the exclusion of patients admitted to the level 3 ICUs, the in-hospital mortality rate in the present study was 1.9%. Nevertheless, all in-hospital deaths occurred in patients with a DECAF score ≥2.

Previous studies have highlighted the DECAF score as a cost-effective tool for predicting disease severity and guiding early discharge decisions in patients with COPD. However, a meta-analysis evaluating studies on these scoring systems indicated a high risk of bias associated with the DECAF score.^[17] In our study, although the proportion of patients with DECAF scores ≥2 was significantly higher in the mortality group in univariate analyses, regression analyses demonstrated that the DECAF score

Table 3: Initial regression analysis model

Variable	B	SE	Wald	Odds ratio	95% CI	p
ICU admission vs. ward	0.122	0.841	0.021	1.130	0.218-5.868	0.885
Length of hospital stay (days)	0.069	0.038	3.269	1.072	0.994-1.155	0.071
BMI (kg/m ²)	-0.171	0.068	6.321	0.843	0.737-0.963	0.012
Hct (%)	-0.101	0.043	5.364	0.904	0.830-0.985	0.021
BUN (mg/dL)	0.084	0.031	7.614	1.088	1.025-1.155	0.006
Albumin (g/L)	-0.074	0.058	1.618	0.928	0.828-1.041	0.203
DECAF score	-0.084	0.664	1.601	0.432	0.117-1.586	0.206
FEV ₁ /FVC ratio	-0.008	0.030	0.063	0.992	0.935-1.053	0.801
CHF	1.736	0.721	5.799	5.676	1.381-23.319	0.016
Ward hospitalization in previous year	0.179	0.628	0.081	1.196	0.349-4.095	0.775
sPAP (mmHg)	0.021	0.020	1.026	1.021	0.989-1.062	0.311
History of COVID-19 infection	-1.428	0.803	3.158	0.240	0.050-1.158	0.076

Hosmer–Lemeshow test p value=0.934. B: Beta coefficient, SE: Standard error, CI: Confidence Interval, BMI: Body mass index, BUN: Blood urea nitrogen, CHF: Congestive heart failure, FEV₁/FVC: Forced expiratory volume in 1 second to forced vital capacity ratio, Hct: Hematocrit, sPAP: Systolic pulmonary artery pressure

Table 4: Final regression analysis model

Variable	B	SE	Wald	Odds ratio	95% CI	p
Length of hospital stay (days)	0.068	0.034	3.855	1.071	1.001–1.145	0.047
BMI (kg/m ²)	-0.201	0.060	11.019	0.818	0.727–0.921	0.001
Hct (%)	-0.102	0.042	5.762	0.903	0.831–0.982	0.016
BUN (mg/dL)	0.074	0.028	7.148	1.076	1.020–1.136	0.008
CHF	1.799	0.662	7.381	6.041	1.650–22.131	0.007
History of COVID-19 infection	-1.392	0.737	3.570	0.249	0.059–1.053	0.059

Hosmer–Lemeshow test p value=0.396. B: Beta coefficient, SE: Standard error, CI: Confidence Interval, BMI: Body mass index, BUN: Blood urea nitrogen, CHF: Congestive heart failure, Hct: Hematocrit

could not predict six-month mortality after ECOPD. Instead, the regression analysis emphasized the importance of BMI, length of hospital stay, hematocrit, BUN levels, and the presence of CHF, parameters that have also been incorporated into other prognostic scoring systems.

Recent evidence has shown that the risk of moderate and/or severe exacerbations is higher in patients with low BMI.^[18,19] Similar to our study, Zhang et al.^[20] examined 890 patients hospitalized for COPD exacerbations and found a significant negative correlation between one-year mortality and body mass index.

The relationships between biochemical markers and clinical outcomes in COPD have been investigated in numerous studies. Hemoglobin abnormalities, including anemia and polycythemia, are common in COPD and have been associated with increased symptoms, poorer quality of life, reduced exercise capacity, higher hospitalization rates, and increased mortality.^[21–25] In addition, in-hospital, 30-day, six-month, and one-year mortality rates have been reported to be significantly higher in anemic patients hospitalized for ECOPD.^[24,25] These findings indicate that

anemia is not only an important marker of long-term survival but also a risk factor for short-term mortality in severe ECOPD. In our study, anemia was significantly more common in the mortality group, whereas the prevalence of polycythemia was similar between groups.

Inflammatory responses in COPD accelerate proteolysis, leading to hypoalbuminemia and increased BUN levels. BUN is associated with neurohumoral activity, cardiorenal function, and catabolic state. Therefore, elevated BUN levels have been linked to poor prognosis in patients with ECOPD.^[26,27] In the present study, elevated BUN was identified as an independent predictor of six-month mortality after ECOPD. Our results also demonstrated that longer hospital stay was associated with six-month mortality. Similarly, Gunen et al.^[28] reported that in-hospital mortality in ECOPD increases with prolonged hospitalization. Comorbidities have been emphasized as important components in the follow-up of patients with COPD, particularly cardiovascular comorbidities, which are significant predictors of one-year mortality after an exacerbation.^[1,29] In the present study, among multiple comorbidities analyzed,

only CHF emerged as an independent risk factor for six-month mortality after ECOPD. Patients with CHF had sixfold higher odds of six-month mortality after ECOPD compared with those without CHF after adjustment for potential confounders. However, the wide confidence interval suggests limited precision, likely reflecting the small number of cases.

As a limitation of this study, its single center design means that the results may not reflect regional differences. Additionally, data regarding smoking history, exposures, occupation, medication adherence, comorbidities, and hospitalization history were largely based on patient self-report. Therefore, recall bias should be considered when interpreting these subjective data. Although the study provides important preliminary information on the DECAF score with a longer follow-up period than previous studies, the statistical power was moderate, which may have limited the ability to detect smaller effect sizes.

Conclusion

In conclusion, although the proportion of patients with medium-high risk DECAF scores (≥ 2) was significantly higher in the mortality group, logistic regression analysis for six-month mortality identified length of hospital stay (days), BMI (kg/m^2), hematocrit (%), BUN (mg/dL), and the presence of CHF as independent risk factors. A key strength of this study is that the clinical significance of the DECAF score was evaluated alongside numerous clinical and demographic variables that may influence mortality, including treatment adherence, vaccination status, history of COVID-19 infection, and hospital admissions in the preceding year. Furthermore, unlike studies focusing on shorter-term outcomes, the present study demonstrated that the DECAF score was not an independent factor of six-month mortality. If these preliminary findings are confirmed in large, multicenter studies, they may contribute to the development of future artificial intelligence-based models for predicting mortality after ECOPD.

Ethics Committee Approval

The study was approved by the Keçiören Training and Research Hospital Clinical Research Ethics Committee (No: 2012-KAEK-15/2433, Date: 23/11/2021).

Informed Consent

Written informed consent was obtained from the participants.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

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Psychometric properties of the Turkish version of the "Functional Assessment of Chronic Illness Therapy-Fatigue Scale" in patients with chronic obstructive pulmonary disease

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Abstract:

BACKGROUND AND AIM: Chronic obstructive pulmonary disease (COPD) is frequently associated with fatigue, which negatively affects quality of life. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale is widely used to assess fatigue; however, its psychometric properties have not yet been established in Turkish patients with COPD. This study aimed to evaluate the reliability and preliminary construct validity of the Turkish version of the FACIT-F scale in patients with COPD.

METHODS: A total of 135 patients with a confirmed diagnosis of COPD (mean age 66.55±9.11 years) participated in the study. Internal consistency was assessed using Cronbach's alpha, and test-retest reliability was evaluated using the intraclass correlation coefficient (ICC). Exploratory factor analysis (EFA) was conducted to examine the factorial structure of the scale. Construct validity was assessed through correlation analyses with related clinical and functional measures. Known-group comparisons were performed according to disease severity.

RESULTS: Cronbach's alpha for the Turkish FACIT-F scale was $\alpha=0.945$, and the ICC was 0.954. The scale showed strong correlations with the Piper Fatigue Scale ($r=-0.725$ to -0.820) and the COPD and Asthma Fatigue Scale ($r=-0.760$). Moderate correlations were observed with the modified Medical Research Council dyspnea scale ($r=-0.489$), the COPD Assessment Test ($r=-0.588$), the Center for Epidemiologic Studies Depression Scale ($r=-0.501$), and St. George's Respiratory Questionnaire scores ($r=-0.437$ to -0.652). Factor analysis confirmed a one-factor structure, with factor loadings ranging from 0.605 to 0.879.

CONCLUSIONS: The Turkish version of the FACIT-F scale is a reliable and psychometrically sound instrument for assessing fatigue in patients with COPD. Its use in clinical and rehabilitation settings may facilitate systematic evaluation of fatigue severity and support individualized patient management.

Keywords:

Chronic obstructive pulmonary disease, fatigue, psychometric properties, reliability, quality of life, validity

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent and progressively worsening airflow limitation resulting from an abnormal inflammatory response of the lungs to noxious particles or gases.^[1] Recognized as a major public health concern worldwide, COPD affects approximately 12.64% of individuals over the age of 40 based on fixed-ratio diagnostic criteria.^[2] The disease typically develops from chronic airway inflammation, commonly manifesting as chronic bronchitis, along with alveolar destruction known as emphysema.^[1,2] Patients with COPD frequently present with respiratory symptoms such as dyspnea, chronic cough, and increased sputum production, as well as extrapulmonary manifestations including fatigue, musculoskeletal pain, psychological distress, and reduced muscle strength.^[3,4] The coexistence of these symptoms substantially impairs physical functioning and perceived health status.^[5]

Fatigue is defined as a persistent and overwhelming sense of tiredness or lack of energy that is disproportionate to physical activity and not relieved by rest.^[6] In patients with COPD, fatigue is recognized as the second most common and burdensome symptom after dyspnea. Epidemiological studies report that the prevalence of fatigue in this patient group varies considerably, ranging from 17% to 95%.^[7] This symptom exerts a substantial negative impact on patients' physical capacity, activity participation, and overall quality of life, often resulting in increased reliance on others.^[7-9] Furthermore, fatigue has been associated with poorer clinical outcomes, including a heightened risk of acute exacerbations and increased mortality rates in patients with chronic respiratory conditions.^[10]

Considering the rising awareness of fatigue as a critical symptom in patients with COPD, the development and application of concise, feasible, and psychometrically robust measurement tools for assessing fatigue in this population have become increasingly important.^[11]

A wide range of instruments has been used to assess fatigue in patients with COPD, including unidimensional, multidimensional, and disease-specific scales.^[12] These instruments include the Brief Fatigue Inventory,^[13] the Identity-Consequence Fatigue Scale,^[14] the Fatigue Impact Scale,^[15] the Multidimensional Fatigue Inventory,^[16]

the Checklist Individual Strength,^[17] the Fatigue Severity Scale,^[18] the Piper Fatigue Scale,^[19] the Manchester COPD Fatigue Scale,^[20] and the COPD and Asthma Fatigue Scale.^[21] Among these, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale is one of the most frequently used measures.^[11]

The psychometric properties of patient-reported outcome measures cannot be assumed to be universally stable across different cultural, linguistic, and clinical contexts. Cultural norms, language structure, health beliefs, and symptom expression can substantially influence how individuals perceive, interpret, and report subjective experiences such as fatigue.^[22,23] Therefore, even when an instrument has demonstrated strong psychometric performance in its original language or in other populations, re-evaluation within a new cultural context is essential to ensure measurement accuracy, conceptual equivalence, and clinical interpretability.^[24]

In addition to cultural considerations, disease-specific characteristics further justify renewed psychometric evaluation. The FACIT-F scale was originally developed for oncology populations, in which fatigue is often driven by mechanisms such as cancer-related anemia, systemic inflammation, and treatment-related side effects.^[25,26] In contrast, fatigue in COPD arises from distinct and multifactorial mechanisms, including persistent dyspnea, sleep disturbances, reduced physical activity, skeletal muscle dysfunction, and chronic systemic inflammation.^[27,28] These differences may influence both the severity and functional impact of fatigue, underscoring the importance of examining whether the FACIT-F scale retains its structural validity and measurement properties in patients with COPD.^[29]

The 13-item FACIT-F scale is a widely used instrument designed to assess multiple dimensions of fatigue in patients with chronic illnesses.^[11,12] Although it has been frequently applied in populations with COPD, the psychometric properties of its Turkish adaptation have not yet been evaluated. Accordingly, this study aimed to assess the psychometric properties, specifically the reliability and preliminary construct validity, of the Turkish version of the FACIT-F scale in a population with COPD. It was hypothesized that the Turkish version would demonstrate high internal consistency, strong test-retest reliability, and construct validity consistent with findings reported in other patient populations.

Materials and Methods

Research design and ethical considerations

This methodological cross-sectional study was conducted between April 2023 and October 2024 at the Department of Chest Diseases, İzmir Katip Çelebi University Faculty of Medicine, İzmir, Türkiye. The Turkish version of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale was obtained from the official FACIT.org website, and formal permission for its use in psychometric evaluation was granted. Ethical approval for the study protocol was obtained from the İzmir Katip Çelebi University Non-invasive Clinical Research Ethics Committee (Approval Number: 0383, Date: 22.09.2022). All study procedures were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to data collection.

Participants and procedure

Individuals aged 40 years and older with a confirmed clinical diagnosis of COPD, verified by a respiratory specialist in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria,^[1] were included in the study. Participants were required to be clinically stable for at least three months and fluent in Turkish. Exclusion criteria included the presence of coexisting systemic, cardiovascular, neurological, or musculoskeletal conditions; other pulmonary diseases; or cognitive impairments that could interfere with comprehension or task completion.^[11]

Demographic and clinical characteristics, including age, sex, educational level, employment status, body mass index, disease duration, and pulmonary function test results, were recorded. To assess test-retest reliability, the FACIT-F scale was re-administered one week after the initial assessment.

Outcome measures

In this study, a standardized methodology for scale validation was applied in accordance with established guidelines.^[24] Sociodemographic data (age, sex, educational level, and employment status) and clinical information (body mass index, disease duration, and pulmonary function test results) were collected. To evaluate construct validity, participants completed the Turkish versions of several validated instruments in addition to the FACIT-F scale.^[11] These instruments included the Piper

Fatigue Scale,^[30] the COPD and Asthma Fatigue Scale,^[31] the modified Medical Research Council (mMRC) Dyspnea Scale,^[32] the COPD Assessment Test (CAT),^[33] the St. George's Respiratory Questionnaire (SGRQ),^[34] and the Center for Epidemiologic Studies Depression Scale (CES-D).^[35] Test-retest reliability of the FACIT-F scale was assessed by re-administering the instrument to participants one week after the initial evaluation. All data collection procedures were performed by an experienced and qualified physiotherapist.

FACIT-F Scale: The FACIT-F is a 13-item self-administered questionnaire developed to assess multiple dimensions of fatigue. It was originally designed for use in patients with cancer-related anemia.^[36] The scale evaluates both the intensity of fatigue (items 1–4 and 7) and its impact on daily functioning (items 5–6 and 8–13). Each item is scored on a five-point Likert scale ranging from 0 to 4, yielding a total score between 0 and 52, with higher scores indicating lower fatigue severity.^[11]

Piper Fatigue Scale: This 22-item instrument assesses the subjective experience of fatigue across four domains: behavioral/severity, affective meaning, sensory perception, and cognitive/mood status.^[30] Each item is rated on a 0–10 scale. The total score is calculated by averaging item responses, with higher mean scores indicating greater perceived fatigue.

COPD and Asthma Fatigue Scale: This fatigue-specific instrument consists of 12 items and was developed to assess fatigue levels in patients with COPD and asthma.^[31] Items are rated on a five-point Likert scale. The total raw score ranges from 12 to 60 and is converted to a standardized 0–100 scale using a predefined formula, with higher scores indicating greater fatigue severity.

mMRC Dyspnea Scale: The modified Medical Research Council (mMRC) Dyspnea Scale is a brief, five-point measure used to assess the degree of breathlessness experienced during daily physical activities. Patients rate their dyspnea from 0 (no breathlessness) to 4 (very severe dyspnea), based on the level of exertion required to provoke symptoms. This scale is used as a practical indicator of functional respiratory impairment.^[32]

COPD Assessment Test: The CAT is an eight-item questionnaire designed to assess the health status of patients with COPD.^[33] It captures symptoms such as dyspnea,

cough, and sputum production, as well as broader health concerns including sleep quality and fatigue. Each item is scored from 0 to 5, yielding a total score between 0 and 40, with higher scores indicating more severe symptoms and poorer quality of life.

St. George's Respiratory Questionnaire: The SGRQ is a disease-specific instrument developed to evaluate health-related quality of life in patients with chronic respiratory diseases.^[34] It consists of 50 items across three domains: respiratory symptoms, activity limitations, and the overall impact of the disease. Each domain is scored separately, and a total score ranging from 0 (no impairment) to 100 (maximum impairment) is calculated.

CES-Depression Scale: The CES-D is a 20-item instrument designed to assess the frequency and severity of depressive symptoms in the general population. Respondents indicate how often they experienced each symptom during the preceding week using a four-point Likert scale (0–3). Total scores range from 0 to 60, with higher scores reflecting greater depressive symptom burden. In most research settings, a score of 16 or higher is considered indicative of clinically relevant depressive symptomatology.^[35]

Statistical analysis

There is no universally accepted consensus regarding the minimum sample size required for validation studies; however, a commonly cited recommendation is to include 2–20 participants per item.^[37,38] Given that the FACIT-F scale comprises 13 items, the inclusion of 135 participants exceeded these recommendations and was considered sufficient for reliability analyses and exploratory factor analysis. However, this sample size may be considered borderline for more advanced psychometric procedures, such as confirmatory factor analysis or subgroup-based validity testing.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test in conjunction with visual inspection of histograms. Descriptive statistics were presented as means and standard deviations for variables with a normal distribution, and as medians with interquartile ranges (25th–75th percentiles) for variables that did not meet normality assumptions. Categorical variables were summarized as frequencies and percentages.

Internal consistency of the FACIT-F scale was evaluated using Cronbach's alpha coefficient, with values greater than 0.70 considered indicative of acceptable reliability.^[39] Intra-rater reliability for both total scale scores and individual items was assessed using the intraclass correlation coefficient (ICC) based on a two-way random-effects model with absolute agreement. ICC values greater than 0.90 were interpreted as indicating excellent reliability.^[40]

To explore the factorial structure of the scale, exploratory factor analysis (EFA) was conducted to evaluate the underlying dimensional structure of the FACIT-F scale. A minimum explained variance threshold of 60% was considered supportive of a unidimensional structure. Prior to EFA, the suitability of the data for factor analysis was assessed.

Concurrent validity was examined using Pearson or Spearman correlation coefficients, depending on the distributional characteristics of the variables. Ninety-five percent confidence intervals (CIs) were calculated for all relevant estimates. To assess convergent validity, it was hypothesized that FACIT-F scores would demonstrate moderate to strong correlations with other fatigue-related instruments, disease severity indices, dyspnea scales, depression measures, and quality-of-life assessments.

The interpretation of correlation magnitude followed established thresholds: negligible ($|r| \leq 0.10$), weak ($|r| = 0.10–0.39$), moderate ($|r| = 0.40–0.69$), strong ($|r| = 0.70–0.89$), and very strong ($|r| \geq 0.90$).

Known-group validity was assessed according to disease severity based on the GOLD stage using the independent samples *t* test. A *p*-value < 0.05 was considered statistically significant.

Results

A total of 155 patients with a confirmed diagnosis of COPD were screened for participation. After applying the inclusion and exclusion criteria, 20 individuals were excluded, resulting in a final sample of 135 participants. Demographic and clinical characteristics of the cohort are summarized in Table 1. The sample was predominantly male (81.5%), with a mean age of 65.55 years and a mean body mass index (BMI) of 24.77 kg/m². Most participants had completed primary education (52.6%) and were retired (59.3%). Regarding disease severity, the

Table 1: Characteristics of the patients

Variables (n=135)	Mean±SD or Median (IQR)
Age, years	65.55 ± 9.11
Body mass index, kg/m ²	24.77 ± 5.06
Disease duration (years)	10.66 ± 7.88
Pulmonary function test	
FEV ₁ , %	55.18 ± 7.46
FVC, %	60.50 ± 7.8
FEV ₁ /FVC	52.7 ± 11.37
mMRC, points	2.4 ± 1.34
CAT score, 0-40	22.61 ± 9.86
St. George's respiratory questionnaire	
Symptoms, 0-100	48.12 ± 20.39
Activity, 0-100	67.48 ± 22.10
Impact, 0-100	37.14 ± 21.78
Total score, 0-100	56.88 ± 21.33
Emergency department visits (last year)	0 (0/2)
Hospitalizations (last year)	0 (0/1)
Smoking history (pack-years)	47.75 ± 21.46
FACIT-F, 0-52	33.99 ± 17.22
Piper fatigue scale	
Behavioral, 0-10	4.32 ± 2.71
Affective, 0-10	4.30 ± 2.49
Sensory, 0-10	4.17 ± 1.62
Cognitive, 0-10	4.14 ± 1.91
Total score, 0-10	4.30 ± 2.22
COPD and asthma fatigue scale	58.84 ± 26.51
CES-D Depression Scale, 0-60	21.77 ± 10.04
	n (%)
Male sex	110 (81.5)
COPD stage	
Stage 1	5 (3.7)
Stage 2	50 (37.0)
Stage 3	55 (40.7)
Stage 4	25 (18.5)
Smoking status	
Current smoker	31 (22.9)
Ex-smoker	88 (65.2)
Never smoked	16 (11.9)
Education level	
Primary School	71 (52.6)
High School	46 (34.1)
University	18 (13.3)
Employment status	
Working	34 (25.2)
Not working	21 (15.5)
Retired	80 (59.3)

Data presented as mean±standard deviation, median (25th-75th interquartile range), or percentage (%) SD: Standard deviation, IQR: Interquartile range, FEV₁: Forced expiratory volume in one second, FVC: Forced vital capacity, mMRC dyspnea scale: Modified Medical Research Council Dyspnea Scale, CAT: COPD assessment test, COPD: Chronic obstructive pulmonary disease

majority were classified as GOLD stage 3 (40.7%) or stage 2 (37.0%), with a mean disease duration of 10.66 years.

Test-retest reliability analysis demonstrated excellent temporal stability, with an intraclass correlation coefficient of 0.954 for the total FACIT-F score and item-specific ICC values ranging from 0.807 to 0.966 (Table 2). Internal consistency was also high, as indicated by Cronbach's alpha coefficient of 0.945. Item-deletion analysis showed minimal variation, with alpha values remaining between 0.935 and 0.944, supporting the retention of all items in the scale. Exploratory factor analysis supported a unidimensional structure of the FACIT-F scale. Factor loadings ranged from 0.605 to 0.879, indicating strong item-factor associations. The single-factor structure explained 52.4% of the total variance (Table 2).

Construct validity analyses are presented in Table 3. No significant correlations were observed between the total FACIT-F score and variables such as age, BMI, or disease duration ($p>0.05$). However, weak correlations were identified with percent predicted forced expiratory volume in one second (%FEV₁) ($r=0.385$, $p=0.001$), frequency of emergency department visits in the previous year ($r=-0.350$, $p<0.001$), and number of hospitalizations ($r=-0.308$, $p=0.001$). Moderate inverse correlations were observed between the FACIT-F score and both the mMRC dyspnea scale ($r=-0.489$, $p<0.001$) and the CAT score ($r=-0.588$, $p<0.001$), supporting convergent validity.

Strong negative correlations were found between the FACIT-F score and both the total and subscale scores of the Piper Fatigue Scale (ranging from -0.725 to -0.820, $p<0.001$), as well as with the COPD and Asthma Fatigue Scale ($r=-0.760$, $p<0.001$). Additionally, moderate correlations were observed with the CES-D Scale ($r=-0.501$, $p<0.001$) and with SGRQ domain scores ($r=-0.437$ to -0.652, $p<0.001$). Known-group validity analysis demonstrated that FACIT-F scores were significantly lower in patients classified as GOLD stages 3 and 4 (Table 4).

Discussion

The present study evaluated the psychometric properties of the Turkish adaptation of the FACIT-F scale in patients with COPD. The findings indicate that the Turkish version of the FACIT-F demonstrates excellent internal consistency, high test-retest reliability, and a well-supported unidimensional factor structure. Col-

Table 2: Intra-rater reliability, Cronbach's α values if item deleted, and factor loadings for each item of the FACIT-F scale

	Intra-rater reliability [ICC (95% CI)]	Internal consistency (Cronbach α if item deleted)	Factor loading
Item 1	0.924 (0.872–0.954)	0.936	0.820
Item 2	0.950 (0.882–0.958)	0.935	0.831
Item 3	0.966 (0.928–0.976)	0.936	0.821
Item 4	0.942 (0.880–0.957)	0.940	0.771
Item 5	0.946 (0.826–0.951)	0.935	0.830
Item 6	0.954 (0.918–0.974)	0.935	0.879
Item 7	0.847 (0.661–0.901)	0.940	0.767
Item 8	0.913 (0.814–0.944)	0.940	0.761
Item 9	0.907 (0.765–0.948)	0.944	0.605
Item 10	0.809 (0.741–0.935)	0.942	0.657
Item 11	0.931 (0.839–0.950)	0.941	0.701
Item 12	0.823 (0.641–0.905)	0.940	0.784
Item 13	0.807 (0.670–0.911)	0.939	0.740
Total score	0.954 (0.687–0.965)	0.936	0.835

FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue, ICC: Intraclass correlation coefficient, CI: Confidence interval

Table 3: Construct validity analysis of the Turkish version of the FACIT-F scale

Variables	FACIT-fatigue	
	r	p
Age	-0.033	0.774
Body mass index	0.006	0.901
Disease duration	0.005	0.964
Number of emergency department visits	-0.350	<0.001
Number of hospitalizations	-0.308	0.001
FEV ₁ %	0.385	0.001
mMRC	-0.489	<0.001
CAT score	-0.588	<0.001
Piper fatigue scale		
Behavioral	-0.788	<0.001
Affective	-0.807	<0.001
Sensory	-0.766	<0.001
Cognitive	-0.725	<0.001
Total score	-0.820	<0.001
COPD and asthma fatigue scale	-0.760	<0.001
CES-D depression scale score	-0.501	<0.001
St. George's respiratory questionnaire		
Symptoms	-0.561	<0.001
Activity	-0.437	<0.001
Impact	-0.652	<0.001
Total score	-0.611	<0.001

r represents Pearson's or Spearman's correlation coefficient. Bold values indicate statistically significant correlations. FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue, FEV₁: Forced expiratory volume in one second, mMRC dyspnea scale: Modified medical research council dyspnea scale, CAT: COPD assessment test

lectively, these findings provide preliminary evidence supporting the construct validity and strong reliability of the Turkish version of the FACIT-F scale for assessing fatigue in patients with COPD.

Table 4: Group comparisons for known-group validity

Variables (n=135)	Stage 1–2	Stage 3–4	p*
FACIT-F (0–52)	38.16±16.41	31.23±18.54	<0.001

Data are presented as mean±standard deviation. *: Independent samples t-test. FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue

Fatigue perception is influenced by cultural, social, and contextual factors, which may affect how individuals interpret and respond to patient-reported outcome measures.^[22,41] Accordingly, even well-established fatigue instruments may exhibit variations in factor structure or item functioning across different cultural settings.^[24] In this context, the unidimensional structure and strong psychometric performance of the Turkish version of the FACIT-F scale suggest that it captures a coherent fatigue construct within the cultural framework of Turkish patients with COPD.^[29,42] Originally developed for oncology populations,^[25] the FACIT-F scale has since been widely applied across multiple chronic conditions, including neurological, rheumatologic, and hematologic disorders.^[43–45] The psychometric findings of the present study are consistent with previous validation studies in these populations, further supporting the robustness of the FACIT-F framework across diverse cultural and clinical contexts. In particular, the test–retest reliability coefficient (ICC=0.95) closely aligns with values reported in prior research, ranging from 0.90 to 0.95,^[11,46,47] supporting the scale's temporal stability. It should also be noted that a substantial proportion of the study sample had a low level of education, which could potentially influence patients' comprehension of self-reported questionnaires. To mitigate this potential limitation, all assessments

were administered via face-to-face interviews by trained physiotherapists, ensuring standardized explanations of items without altering their original meaning.

The strong negative correlations observed between the Turkish FACIT-F and other fatigue measures—including the Piper Fatigue Scale and the COPD and Asthma Fatigue Scale—further support the scale's convergent validity. Moderate correlations with the mMRC Dyspnea Scale and the CAT were also consistent with prior findings in COPD cohorts.^[7,48] These results highlight that, although fatigue overlaps with dyspnea and overall disease burden, it remains a distinct and multidimensional construct encompassing both physical and emotional components. The moderate association observed between fatigue and depressive symptoms, as measured by the CES-D, is also in line with growing evidence demonstrating the close relationship between psychological distress and fatigue severity in COPD.^[7]

Interestingly, the present findings support emerging evidence suggesting that general disease impact measures, such as the CAT, may partially capture fatigue-related aspects of COPD.^[49] However, the FACIT-F scale provides a more comprehensive and condition-relevant assessment of fatigue and its impact on daily functioning and overall well-being. The unidimensional factor structure identified in this study further supports the conceptualization of fatigue in COPD as a single underlying construct influenced by multiple interrelated factors, including dyspnea, sleep disturbances, and psychological strain.

The lack of association between fatigue and demographic variables such as age or body mass index is also consistent with findings from previous systematic reviews.^[7] This suggests that fatigue severity is driven primarily by disease-related and psychosocial mechanisms rather than by general demographic or anthropometric characteristics. Consequently, incorporating fatigue assessment into comprehensive COPD management may enable clinicians to better address symptom clusters that affect daily functioning and quality of life. Correlations with demographic and clinical variables should be interpreted cautiously and are presented for exploratory purposes rather than as definitive evidence of construct validity.

From a clinical perspective, the Turkish adaptation of the FACIT-F scale represents an important addition to the assessment tools available to Turkish-speaking healthcare

providers. Its brevity, strong psychometric properties, and disease relevance make it suitable for use in both research and clinical settings, facilitating early identification of fatigue-related limitations and supporting personalized rehabilitation strategies. Furthermore, the cultural and linguistic adaptation enhances accessibility and measurement accuracy, ensuring that contextual nuances are appropriately reflected in patient self-reports.

Limitations and directions for future research

Several limitations of this study should be acknowledged. Although exploratory factor analysis supported a unidimensional structure, confirmatory factor analysis could not be conducted because of sample size constraints and should be addressed in future research. First, the cross-sectional design limits the ability to draw causal inferences regarding the relationships between fatigue and other clinical variables. Second, the absence of objective measures of physical performance, such as the six-minute walk test or actigraphy, restricts the ability to link subjective fatigue assessment with physiological indicators. Third, data were collected from a single tertiary care center, and the demographic characteristics of the sample may not fully represent the broader COPD population in Türkiye, potentially limiting external validity and generalizability of the findings. In addition, a substantial proportion of participants had a low level of education, which may have influenced comprehension of self-reported questionnaires. This potential limitation was mitigated by administering all assessments through face-to-face interviews conducted by trained physiotherapists, ensuring standardized explanations without altering the original meaning of the items.

Moreover, the study sample was predominantly male, which may further limit generalizability given known sex-related differences in fatigue perception among patients with COPD. Most participants were classified as GOLD stage II–III; therefore, the psychometric properties of the FACIT-F scale may differ in patients with milder or more advanced disease stages. Additionally, medication use was not systematically recorded or controlled for, although pharmacological treatments may influence fatigue severity and other related outcomes.

Although depressive symptoms were evaluated, other psychosocial factors, such as anxiety, social support, or sleep quality, were not assessed and should be explored in future studies. Finally, longitudinal research with

larger and more heterogeneous samples is needed to evaluate the responsiveness of the FACIT-F scale to rehabilitation or pharmacological interventions and to support more comprehensive psychometric validation.

Conclusion

Despite these limitations, the use of a culturally adapted fatigue assessment tool may facilitate more individualized rehabilitation planning and enhance symptom-focused management in clinical COPD practice.

In summary, the Turkish version of the FACIT-F scale demonstrates strong reliability and preliminary evidence of construct validity for assessing fatigue in patients with COPD. These findings provide clinicians and researchers with a culturally appropriate and psychometrically sound instrument for evaluating the multifaceted impact of fatigue in Turkish populations. Broader use of this scale may improve clinical monitoring, support individualized rehabilitation strategies, and contribute to more comprehensive symptom management in chronic respiratory care.

Ethics Committee Approval

The study was approved by the İzmir Katip Çelebi University Non-invasive Clinical Research Ethics Committee (No: 0383, Date: 22/09/2022).

Informed Consent

Written informed consent was obtained from all participants prior to data collection.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

Concept – N.S., İ.N.; Design – N.S., İ.N. Supervision – B.T., E.F., M.O.T. Resource – B.T., E.F., M.K., İ.N.; Materials – N.S.; Data Collection and/or Processing – N.S.; Analysis and/or Interpretation – N.S., B.T., İ.N.; Literature Review – B.T., E.F., M.K., İ.N., M.O.T.; Writing – N.S., B.T., İ.N.; Critical Review – M.K., E.F., M.O.T., İ.N.

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Turkish validation of the "Test of Adherence to Inhalers Questionnaire" in patients with asthma and chronic obstructive pulmonary disease

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Abstract:

BACKGROUND AND AIM: This study aimed to evaluate the validity, reliability, and diagnostic accuracy of the Turkish version of the Test of Adherence to Inhalers (TAI), a widely used tool for assessing inhaler adherence in patients with asthma and chronic obstructive pulmonary disease (COPD).

METHODS: This cross-sectional study included 100 patients with asthma (n=50) or COPD (n=50) who were followed in outpatient clinics between February and May 2024. Adherence was assessed using the TAI-10 and TAI-12 questionnaires and the Morisky Medication Adherence Scale-8 (MMAS-8). Internal consistency was evaluated using Cronbach's alpha coefficients. Construct validity was examined using Spearman correlation analysis, and diagnostic accuracy was assessed using receiver operating characteristic (ROC) curve analysis.

RESULTS: The mean age was significantly higher in the COPD group than in the asthma group (70.9±8.3 vs. 48.0±17.3 years, p<0.001). The groups differed significantly in gender distribution, comorbidities, smoking status, symptom burden, and exacerbation history (all p<0.05). TAI and MMAS-8 did not differ significantly between asthma and COPD patients. The Turkish TAI demonstrated good internal consistency (Cronbach's α=0.836 for TAI-10 and 0.826 for TAI-12) and strong correlations with MMAS-8 scores (r=0.917 and r=0.902; p<0.001). Both versions showed high diagnostic accuracy for identifying non-adherence (area under the curve=0.892 and 0.876), with optimal cut-off values of ≤45 for TAI-10 and ≤47 for TAI-12, respectively.

CONCLUSIONS: The Turkish versions of TAI-10 and TAI-12 are valid and reliable instruments with high diagnostic accuracy for assessing inhaler adherence in patients with asthma and COPD.

Keywords: Asthma, chronic obstructive pulmonary disease, Test of Adherence to Inhalers, Turkish validation

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Introduction

Medication nonadherence is a major barrier to the effective management of chronic diseases. The World Health Organization has highlighted poor adherence as a serious global health problem affecting approximately half of patients with chronic illnesses. In chronic respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD), suboptimal adherence to inhaled therapies is associated with more frequent exacerbations, worse disease control, higher hospitalization rates, and even increased mortality.^[1,2] Studies indicate that up to 50% of patients with asthma or COPD do not use their inhalers as prescribed due to factors such as poor inhaler technique, complex treatment regimens, cognitive impairment, as well as low health literacy.^[3,4] Moreover, patients' beliefs about medications, perceptions of their disease, and the lack of perceived immediate benefit from inhaled therapy may further reduce adherence. Recognizing and addressing these multifactorial determinants of nonadherence is essential to enhance therapeutic success and reduce the healthcare burden associated with poorly controlled chronic airway diseases.^[5] Clinical practice guidelines for asthma and COPD accordingly emphasize the need to assess and improve adherence at every opportunity.^[6,7] However, simply asking patients whether they use their inhalers often leads to overestimation of adherence; therefore, more reliable assessment methods are necessary. Several self-report questionnaires are available to assess medication adherence. Although the Morisky Medication Adherence Scale (MMAS-8) is the most widely used, other tools have also been developed, including questionnaires specific to inhaler therapy, such as the Medication Adherence Report Scale for Asthma (MARS-A), the Adherence to Asthma Medication Questionnaire (AAMQ).^[8-12] The Turkish version of the MMAS-8, previously validated by Oğuzülgen *et al.*,^[13] is a reliable tool for assessing medication adherence in patients with asthma and chronic obstructive pulmonary disease. Until the development of the TAI in 2016, there was no instrument specifically tailored to the unique challenges of inhaler therapy, such as device technique and routine use, which may differ from oral medication regimens. To address this gap, a Spanish research group developed the Test of Adherence to Inhalers (TAI) questionnaire. The TAI is a self-reported adherence tool created specifically for patients with asthma and COPD. This questionnaire has been

used to assess inhaler adherence among patients with asthma and chronic obstructive pulmonary disease in both clinical practice and research settings. It provides a structured approach to evaluating adherence related to inhaler use. However, despite its applicability, a validated Turkish version of the scale is not yet available. The original validation study of the TAI in Spain, conducted in more than 900 patients, demonstrated that the TAI is a reliable and homogeneous questionnaire for identifying nonadherence and differentiating behavioral patterns of nonadherence. The TAI showed good internal consistency (Cronbach's α ~0.87) and test-retest reliability (intraclass correlation coefficient [ICC] ~0.88) in the original cohort, and it moderately correlated with objective electronic inhaler usage monitoring data. Notably, that study found that patients with COPD were more likely to exhibit good adherence than patients with asthma (49% vs. 28% prevalence of good adherence) and tended to have more "unconscious" (unintentional) nonadherence, whereas patients with asthma more often showed erratic or deliberate nonadherence.^[14,15] Given the proven utility of the TAI in international settings, a validated Turkish version could greatly assist clinicians in Türkiye in evaluating inhaler adherence and identifying barriers in their patients. Therefore, we aimed to translate the TAI questionnaire into Turkish and evaluate its validity and reliability in a sample of patients with asthma and COPD.

Materials and Methods

Ethical approval

The study was approved by the İzmir Katip Çelebi University Non-interventional Clinical Research Ethics Committee (Approval Number: 0111-0112, Date: 21.03.2024). The study was conducted in accordance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki (2013 revision) and the Declaration of Istanbul (2018). Written informed consent was obtained from all participants. Permission to use the original version of the TAI was obtained via e-mail from the original author.

Study design and patients

This cross-sectional validation study was conducted in a tertiary pulmonology clinic in Izmir. Patients diagnosed with asthma or COPD who were receiving inhaled maintenance therapy were recruited from outpatient clinics between February and May 2024.

Sample size estimation was performed using OpenEpi (v3.01) with a 95% confidence level and 80% power, resulting in a required sample size of 50 subjects per group (asthma and COPD). Accordingly, we aimed to enroll a total of 100 patients, including both asthma and COPD cases, to ensure an adequate sample size for statistical analyses.

The inclusion criteria were age ≥ 18 years, a confirmed physician diagnosis of asthma or COPD according to standard guidelines, and current use of at least one inhaler medication for ≥ 3 months. Patients with cognitive impairment or any language barrier preventing completion of the questionnaire were excluded.

Data collection

After providing informed consent, each participant completed a questionnaire package under supervision. This included: (1) the 10-item TAI (self-administered by the patient) and the additional 2-item TAI section (completed by the clinician) in their Turkish-translated form; (2) the 8-item MMAS-8, a validated self-report measure of general medication adherence; and (3) a demographic and clinical questionnaire capturing age, sex, smoking history, comorbid conditions, disease duration, current respiratory symptoms, history of recent exacerbations, and the types of inhaler devices used. Patients were instructed on how to answer the TAI and Morisky questionnaires and were informed that the data would be used solely for research purposes to encourage honest responses. A researcher was available to clarify any questions during survey completion. Because the study had a cross-sectional design, the test-retest reliability was not assessed. The TAI consists of a 10-item patient questionnaire and an optional 2-item clinician questionnaire. Each of the 10 patient items is scored from 1 (poor adherence) to 5 (good adherence), yielding a total score ranging from 10 to 50. This total score allows classification of the patient's adherence level as good (50 points), intermediate (46–49), or poor (≤ 45). The two additional clinician-rated items (each scored 1 or 2) assess the patient's knowledge of the inhaler regimen and inhalation technique. These items help identify the pattern of nonadherence—whether it is sporadic (erratic timing of doses), deliberate (intentional omission), or unconscious (unwitting improper use).

Data analysis and statistical methods

Translation of TAI

The TAI questionnaire was translated and culturally adapted into Turkish following internationally accepted

guidelines for cross-cultural scale validation. First, two independent bilingual translators (fluent in English and Turkish) translated the original English version of the TAI (derived from the Spanish version) into Turkish. Discrepancies between the two translations were resolved by consensus, resulting in an initial Turkish version. Next, this version was back-translated into English by a different bilingual translator who was not involved in the first step, to verify fidelity to the original meaning. An expert committee including pulmonologists reviewed the translations to ensure that the Turkish wording was clear, conceptually equivalent to the original, and culturally appropriate. A small pilot test was then conducted in which the draft Turkish TAI was administered to five patients with asthma or COPD to evaluate the clarity and interpretability of the items. Based on patient feedback, minor wording refinements were made to improve clarity. The final Turkish version of the TAI was thus obtained without altering the core content of the original items. The final version is presented in Table 1.

Reliability and validity analysis

We evaluated the internal consistency reliability of the Turkish TAI using Cronbach's alpha coefficient for the 10-item patient domain (TAI-10) and for all 12 items (TAI-12). An alpha value ≥ 0.7 was considered acceptable, with ≥ 0.8 indicated good internal consistency. Test-retest reliability was not formally assessed in this study due to the cross-sectional design; therefore, patients completed the TAI only once, and all items were required to be answered. To assess concurrent validity, we examined the correlation between TAI scores and Morisky scale scores, as the Morisky scale is an established measure of adherence behavior. Because the TAI score (10–50) and the Morisky MMAS-8 score (0–8) are ordinal, Spearman's rank correlation coefficient (ρ) was used to evaluate their association. Correlation strength was interpreted as follows: $\rho \geq 0.7$, strong; 0.4–0.69, moderate; and < 0.4 , weak correlation. Additionally, adherence scores were compared across groups to evaluate known-groups validity. We hypothesized that adherence might differ between patients with asthma and those with COPD, as well as according to other clinical characteristics. Mean TAI and Morisky scores were compared between disease groups (asthma vs. COPD) using the Student's *t* test for normally distributed variables or the Mann-Whitney *U* for non-normally distributed variables. Differences in adherence scores were also examined according to sex, presence of comorbidities, current smoking status, presence of uncontrolled symptoms at the time

Table 1: Turkish version of the Test of Adherence to Inhalers (TAI) questionnaire

No	Question in English	Translation (Turkish)	Scoring
Patient domain			
1	During the last 7 days, how many times did you forget to take your usual inhalers?	Son 7 gün içinde, inhalerinizi almayı kaç kez unuttunuz? Her zaman (1) – Yarısından fazla (2) – Yaklaşık yarısı kadar (3) – Yarısından az (4) – Hiç (5)	1–5
2	Do you ever forget to take your inhalers?	İnhalerinizi almayı unuttuğunuz olur mu? Her zaman (1) – Çoğunlukla (2) – Bazen (3) – Nadiren (4) – Asla (5)	1–5
3	When you feel well, do you stop taking your inhalers?	Kendinizi iyi hissettiğinizde inhaler kullanmayı bırakır mısınız? Her zaman (1) – Çoğunlukla (2) – Bazen (3) – Nadiren (4) – Asla (5)	1–5
4	When you are on vacation or during the weekend, do you stop taking your inhalers?	Tatilde veya hafta sonu olduğunda inhaler kullanmayı bırakır mısınız? Her zaman (1) – Çoğunlukla (2) – Bazen (3) – Nadiren (4) – Asla (5)	1–5
5	When you feel nervous or sad, do you stop taking your inhalers?	Sinirli veya üzgün olduğunuzda inhaler kullanmayı bırakır mısınız? Her zaman (1) – Çoğunlukla (2) – Bazen (3) – Nadiren (4) – Asla (5)	1–5
6	Do you stop taking your inhalers because you are afraid of side effects?	Yan etkilerinden korktuğunuz için inhaler kullanmayı bırakır mısınız? Her zaman (1) – Çoğunlukla (2) – Bazen (3) – Nadiren (4) – Asla (5)	1–5
7	Do you stop taking your inhalers because you think they are ineffective?	İnhalerlerin hastalığınızı tedavi etmekte faydasız olduğunu düşündüğünüz için kullanmayı bırakır mısınız? Her zaman (1) – Çoğunlukla (2) – Bazen (3) – Nadiren (4) – Asla (5)	1–5
8	Do you take fewer inhalations than those prescribed by your doctor?	Doktorunuzun önerdiğinden daha az inhalasyon yaptığınız olur mu? Her zaman (1) – Çoğunlukla (2) – Bazen (3) – Nadiren (4) – Asla (5)	1–5
9	Do you stop taking your inhalers because you believe they interfere with your daily or working life?	İnhalerlerin günlük yaşamınızı veya işinizi etkilediğini düşündüğünüz için kullanmayı bırakır mısınız? Her zaman (1) – Çoğunlukla (2) – Bazen (3) – Nadiren (4) – Asla (5)	1–5
10	Do you stop taking your inhalers because you have difficulty paying for them?	Maddi nedenlerle inhalerlerinizi almakta zorlandığınız için kullanmayı bırakır mısınız? Her zaman (1) – Çoğunlukla (2) – Bazen (3) – Nadiren (4) – Asla (5)	1–5
Sağlık Profesyoneli Alanı (Healthcare Professional Domain)			
11	Does the patient remember the prescribed regimen (dose and frequency)?	Hasta, kendisine reçete edilen dozu ve kullanım sıklığını hatırlıyor mu? Hayır (1) – Evet (2)	1–2
12	Is the patient's inhaler technique correct? (assessment of inhalation technique)	Hastanın inhaler cihazını kullanma tekniği nasıldır? Kritik hatalarla (1) – Kritik hata olmadan (2)	1–2

of the visit, disease duration (dichotomized by the median), history of ≥ 1 exacerbation in the previous year, and type of inhaler device (e.g., dry powder inhaler vs. metered-dose inhaler). Categorical variables (e.g., sex differences between asthma and COPD groups or the proportion of adherent vs. nonadherent patients) were analyzed using the chi-square test or Fisher's exact test when expected cell counts were small. A two-tailed p-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

A total of 100 patients were enrolled, including 50 patients with asthma and 50 with COPD. The mean age of patients with asthma was 48.0 ± 17.3 years, whereas the mean age of patients with COPD was 70.9 ± 8.3 years ($p < 0.001$). Overall, 48% of the study population were

male. Among all participants, 68% had at least one comorbidity. Regarding smoking status, 35% were current smokers, 37% were former smokers, and 28% were never smokers. In terms of inhaler device use, 71% of patients were using dry powder inhalers and 29% were using metered-dose inhalers. Significant differences between asthma and COPD patients were observed in terms of sex distribution ($p < 0.001$), presence of comorbidities ($p = 0.010$), smoking status ($p < 0.001$), presence of symptoms ($p = 0.022$), and history of exacerbations ($p < 0.001$).

Adherence scores and group comparisons

No significant difference was observed between the asthma and COPD groups in terms of TAI and Morisky scale scores ($p = 0.252$ and $p = 0.442$, respectively). Similarly, no statistically significant differences in adherence (according to both scales) were found according to sex, presence of comorbidities, smoking status, presence of symptoms, disease duration, history of exacerbations, or type of inhaler device (Table 2).

Table 2: Comparison of TAI and MMAS-8 scores between patients with asthma and chronic obstructive pulmonary disease (COPD)

Parameter	Asthma (n=50)	COPD (n=50)	p
TAI-10 total score (mean±SD)	45.6±6.8	44.2±7.1	0.252
TAI-12 total score (mean±SD)	54.7±8.2	53.1±8.4	0.262
MMAS-8 total score (mean±SD)	6.5±1.2	6.3±1.4	0.442
Adherence level (according to TAI or MMAS-8), n (%)			
High adherence	41 (41%)	39 (39%)	0.731
Moderate adherence	37 (37%)	36 (36%)	0.864
Low adherence	22 (22%)	25 (25%)	0.590

TAI-10: Test of Adherence to Inhalers (10-item version), TAI-12: Test of Adherence to Inhalers (12-item version), SD: Standard deviation, MMAS-8: Morisky Medication Adherence Scale (8-item version)

Reliability of the Turkish TAI

The internal consistency reliability of the Turkish version of the TAI was satisfactory. Cronbach's alpha coefficient was 0.836 for the 10-item patient domain (TAI-10) and 0.826 for the full 12-item version (TAI-12), indicating good internal consistency for both versions of the scale. All items were required to be answered, and no missing responses were observed.

Validity of the Turkish TAI

In this study, only the linguistic validity of the TAI questionnaire was assessed. The original English version was translated into Turkish and then back-translated by two bilingual translators. The translated version was reviewed by two pulmonologists and a linguist to ensure clarity, conceptual equivalence, and cultural appropriateness. Only linguistic validation was performed in this study; no additional statistical analyses of construct or criterion validity were conducted.

In our study, a strong positive correlation was observed between the TAI-10 and TAI-12 scores and the Morisky score ($r=0.917$ and $r=0.902$, respectively; $p<0.001$) [Fig. 1]. The reliability coefficients of the TAI-10 and TAI-12 scales were Cronbach's $\alpha=0.836$ and $\alpha=0.826$, respectively. In the receiver operating characteristic (ROC) analysis, both TAI-10 and TAI-12 demonstrated excellent discrimination in identifying nonadherent patients, with area under the curve (AUC) values of 0.892 (95% confidence interval [CI]: 0.83–0.95; $p<0.001$) and 0.876 (95% CI: 0.80–0.94; $p<0.001$), respectively. The optimal cut-off values determined using the Youden index were ≤ 45 for TAI-10 and ≤ 47 for TAI-12, yielding sensitivities of 84% and 82%, and specificities of 86% and 84%, respectively [Fig. 2].

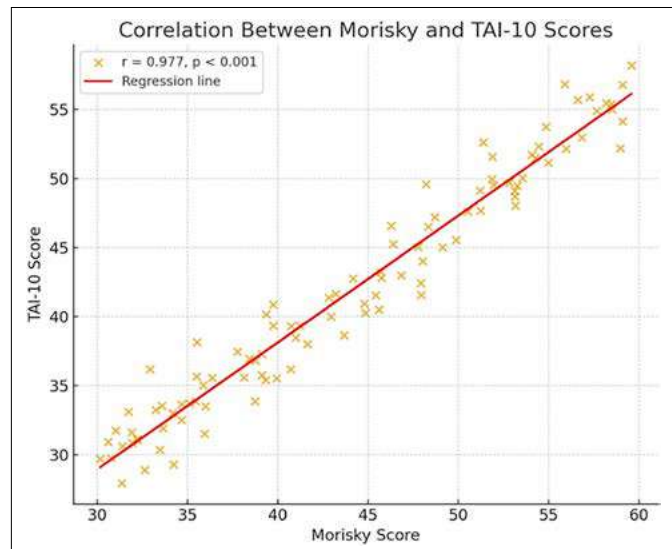


Figure 1: Correlation between the Morisky Medication Adherence Scale (MMAS) score and the Test of Adherence to Inhalers (TAI) scores

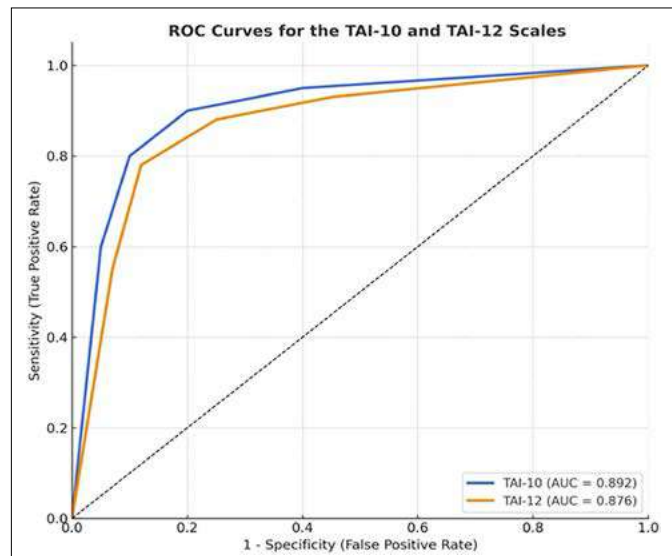


Figure 2: Receiver operating characteristic (ROC) curves illustrating the diagnostic performance of the Test of Adherence to Inhalers-10 (TAI-10) and the Test of Adherence to Inhalers-12 (TAI-12) scales in identifying nonadherent patients

Discussion

In this study, the Turkish version of the Test of Adherence to Inhalers demonstrated good reliability, strong validity, and high diagnostic performance in assessing inhaler adherence among patients with asthma and chronic obstructive pulmonary disease. One of the key findings was the high internal consistency reliability of the Turkish version of the Test of Adherence to Inhalers, with Cronbach's $\alpha=0.836$ for the 10-item TAI and 0.826 for the full 12-item scale. This level of reliability indicates good ho-

mogeneity of the items and is comparable to that reported in the original Spanish validation (Cronbach's $\alpha \approx 0.86$).^[14] Similarly, other language versions of the TAI have reported α values in the range of 0.82–0.87, confirming that the questionnaire consistently maintains good reliability across diverse populations.^[16] Another important result of our study was the very strong positive correlation between TAI scores and the 8-item Morisky Medication Adherence Scale ($r=0.917$ for TAI-10 and $r=0.902$ for TAI-12), supporting the convergent validity of the TAI as a measure of inhaler adherence. This correlation is notably higher than those observed in some previous validation studies using different reference standards. For instance, the original Spanish study found only a weak correlation with electronic inhaler monitoring ($\rho=0.29$), and an Iranian (Persian) version reported a moderate correlation with a general medication adherence scale ($r=0.61$).^[14,16] The stronger association observed in our study may reflect the use of another self-report instrument (MMAS-8) as the comparator, indicating that the TAI captures adherence behaviors in line with existing patient-reported measures while also providing inhaler-specific insights that general scales such as the MMAS-8 may overlook. The TAI also demonstrated excellent diagnostic accuracy in identifying nonadherent patients in our sample. The area under the receiver operating characteristic curve was 0.892 for the 10-item TAI and 0.876 for the 12-item TAI, indicating a favorable balance between sensitivity and specificity for detecting adherence problems. In practical terms, these AUC values approach the “excellent” range for diagnostic tools and suggest that the Turkish TAI can reliably distinguish adherent from nonadherent inhaler users. Notably, our AUC values were higher than those reported in the original Spanish validation study, which found an AUC of approximately 0.70 when electronic dose counter data were used as the reference criterion.^[14] This discrepancy could be due to differences in the gold standard definition of adherence. Our use of the MMAS-8 (a self-report classification) may have led to greater concordance with the TAI, whereas the Spanish study's objective electronic monitoring likely represented a more stringent benchmark. Nonetheless, the high AUC observed in our study underscores the value of the TAI as a screening tool for nonadherence. We also observed that the TAI can classify the nature of a patient's nonadherence, consistent with the design of the instrument. The original developers of the TAI described three patterns of inhaler nonadherence—erratic (inconsistent forgetfulness), deliberate (intentional nonuse), and unwitting

(incorrect technique or lack of understanding)—based on two additional clinician-completed items. Our Turkish translation retains these items, enabling clinicians not only to measure adherence levels but also to identify the predominant type of nonadherence. This has direct implications for tailored interventions, such as educational support for “unwitting” nonadherers or behavioral reminders for “erratic” nonadherers.

Importantly, we found no significant differences in TAI-measured adherence scores across various patient subgroups. Adherence levels were similar between patients with asthma and those with COPD, with neither disease group demonstrating higher TAI scores. This finding is consistent with the intended use of the instrument in both asthma and COPD populations. The TAI was originally developed and validated in a combined asthma/COPD cohort, and our results confirm that it performs similarly regardless of diagnosis. We also did not observe any significant effect of gender on adherence in our sample, as men and women had comparable TAI scores. Likewise, patients with comorbid chronic conditions had adherence scores similar to those without comorbidities, and the presence of respiratory symptoms (as reflected by dyspnea severity or level of asthma control) did not significantly influence TAI results. Notably, neither smoking status nor the type of inhaler device used (e.g., dry powder inhaler vs. metered-dose inhaler) was associated with differences in adherence according to the TAI. Overall, these findings suggest that poor adherence is a widespread challenge that cuts across demographic and clinical categories. This observation is consistent with previous studies indicating that nonadherence to inhaled therapy is widespread and not limited to specific subgroups. For example, a recent validation study in COPD patients reported no relationship between TAI-defined adherence and the number of comorbidities or baseline symptom scores.^[17] The lack of subgroup differences in our study reinforces the notion that all patients with asthma or COPD, regardless of their clinical profile, should be considered for adherence assessment. Good or poor inhaler use cannot be reliably predicted solely on factors such as sex, symptom burden, or disease type. Our results are broadly consistent with previous validation studies of the TAI conducted in other languages and populations, which further supports the credibility of the Turkish TAI. Since its introduction in Spain, the TAI has undergone cross-cultural adaptation in numerous

countries and is now available in more than 20 languages, including Spanish, Portuguese (European and Brazilian), several Arabic dialects (e.g., Saudi Arabian and Egyptian Arabic), Chinese, Persian, and others.^[18] A Malaysian study conducted in patients with asthma reported Cronbach's $\alpha=0.871$ and test-retest ICC=0.832, values very close to those observed in our study. That study also demonstrated high sensitivity (>85%) and specificity of the TAI when benchmarked against pharmacy refill data.^[19] The Persian version of the TAI, validated in patients with COPD, reported extremely high internal consistency ($\alpha=0.986$) together with an excellent test-retest reproducibility. However, its concurrent validity with a general medication adherence scale was only moderate, possibly due to the use of a different comparator or the smaller sample size in that study.^[16] Despite minor differences across studies, these validation efforts conducted in Europe, Asia, or the Middle East support the TAI as a reliable self-report tool for assessing inhaler adherence. Collectively, the literature indicates that patients from diverse cultural contexts can understand and respond to the TAI in a similar manner, making it a broadly applicable instrument for evaluating inhaler adherence. It is also noteworthy that none of these studies identified fundamental limitations in the questionnaire's utility. On the contrary, many authors recommend the TAI as a preferred tool for assessing inhaler adherence in clinical practice. The widespread adoption of the TAI across multiple languages, including the Turkish version evaluated in our study, further highlights its practicality and clinical relevance.

This study has several limitations. First, due to its cross-sectional design, we were unable to assess causality or the temporal stability of TAI scores. Test-retest reliability was not evaluated; therefore, measurement consistency over time remains unknown. Although we found a strong correlation with the MMAS-8, no objective adherence measure (e.g., electronic monitoring or pharmacy data) was used, which may introduce self-report bias. Construct validity was not analyzed, and TAI scores were not correlated with clinical outcomes such as symptom control or exacerbation history. Additionally, our sample included only patients with asthma and COPD, which limits the generalizability of the findings to other respiratory conditions. Finally, as this is the first validation study of the TAI in Turkish, no prior local reference standard exists beyond the MMAS-8, and subtle cultural factors may influence the interpretation of some items.

Future studies should evaluate the test-retest reliability of the Turkish TAI, examine its relationship with clinical outcomes, and assess its validity against objective adherence measures. Studies with larger sample sizes and interventional designs may further clarify its structure and clinical utility.

Conclusion

In conclusion, the Turkish version of the TAI is a valid and reliable tool for assessing inhaler adherence in patients with asthma and COPD. It enables the identification of adherence levels as well as potential patterns of nonadherence, supporting its usefulness in both clinical practice and research. Routine use of the TAI may facilitate early detection of nonadherence and help guide targeted interventions to improve disease management.

Ethics Committee Approval

The study was approved by the İzmir Katip Çelebi University Non-interventional Clinical Research Ethics Committee (No: 0111-0112, Date: 21/03/2024).

Informed Consent

Written informed consent was obtained from all participants.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Use of AI for Writing Assistance

Artificial intelligence tools were used for the preparation of figures.

Author Contributions

Concept – M.Y.Y., M.O.T., S.G., Ç.C.Ö., M.K.S., C.M., B.S.; Design – M.Y.Y., M.O.T., S.G., Ç.C.Ö., M.K.S., C.M., B.S.; Supervision – M.Y.Y., M.O.T., S.G., Ç.C.Ö., M.K.S., C.M., B.S.; Resource – M.Y.Y., M.O.T., S.G., Ç.C.Ö., M.K.S., C.M., B.S.; Materials – M.Y.Y., M.O.T., S.G., Ç.C.Ö., M.K.S., C.M., B.S.; Data Collection and/or Processing – M.Y.Y., M.O.T., S.G., Ç.C.Ö., M.K.S., C.M., B.S.; Analysis and/or Interpretation – M.Y.Y., M.O.T., S.G., Ç.C.Ö., M.K.S., C.M., B.S.; Literature Review – M.Y.Y., M.O.T., S.G., Ç.C.Ö., M.K.S., C.M., B.S.; Writing – M.Y.Y., M.O.T., S.G., Ç.C.Ö., M.K.S., C.M., B.S.; Critical Review – M.Y.Y., M.O.T., S.G., Ç.C.Ö., M.K.S., C.M., B.S.

Peer-review

Externally peer-reviewed.

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The impact of nutritional status and body mass index on lung function, functional capacity, and mortality in lung transplant candidates: A retrospective single-center study

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Abstract:

BACKGROUND AND AIM: Lung transplantation is an important treatment option for patients with end-stage lung diseases, and outcomes may be influenced by nutritional status. This retrospective cohort study of 210 lung transplant candidates aimed to examine the associations of the Nutritional Risk Index (NRI), body mass index (BMI), and biochemical markers with functional capacity, lung function, BODE index, mortality, intensive care unit (ICU) duration, and survival.

METHODS: This retrospective cohort study included 210 lung transplant candidates who were treated at a tertiary-level specialized training and research hospital between 2016–2023. The study collected biochemical measurements, Pulmonary Function Test (PFT), Six-Minute Walk Test (6MWT), bone scans, and nutritional status data. It also assessed post-transplant ICU duration and albumin levels.

RESULTS: Severe malnutrition was prevalent (approximately 46%) across all patient groups, including those listed for transplantation, those who underwent transplantation, and those who died while awaiting. Severe malnutrition was significantly associated with lower values of BMI, FVC%, FEV₁, and FEV₁/FVC ($p < 0.01$). NRI was strongly correlated with these parameters and post-transplant survival ($r = 0.85$, $p < 0.001$). Unlike BMI and albumin when considered alone, NRI remained an independent predictor of survival in multivariable linear regression analysis ($p < 0.01$). Patients with hypoalbuminemia showed reduced 6MWT performance and lower NRI scores ($p < 0.05$). Post-transplant ICU stay was prolonged in patients with severe malnutrition; however, waiting list mortality was not significantly associated with NRI after adjustment.

CONCLUSIONS: The NRI is a simple and effective nutritional screening tool for lung transplant candidates and predicts lung function and survival better than BMI or albumin alone. Routine pre-transplant nutritional optimization guided by NRI may improve post-transplant outcomes.

Keywords: Lung transplantation, nutrition, nutritional risk index

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Introduction

Lung transplantation is the definitive therapy for various end-stage lung diseases, but it is complicated by high morbidity and mortality.^[1] Although significant advances have been made in lung transplantation, the median survival remains approximately 6 years, notably lower than in recipients of other solid-organ transplants. Therefore, identifying risk factors associated with poor prognosis in lung transplantation may help mitigate transplant-related risks.^[2,3] Malnutrition exacerbates complications, prolongs hospital stays, and impairs survival, particularly in patients experiencing extended waiting times before transplantation.

Nutrition goals in the pre-transplant phase include optimizing the patient's nutritional status and addressing nutrition-related symptoms arising from organ failure. Relative contraindications to nutritional care include class I obesity (body mass index (BMI) 30–34.9 kg/m²), low BMI (<17 kg/m²), cachexia, malnutrition, uncontrolled diabetes, and osteoporosis. The nutritional needs of lung transplant candidates are diverse, requiring individualized recommendations tailored to best meet each patient's needs.^[4–6]

The impact of BMI in predicting lung transplant outcomes was first highlighted by Plöchl's report of increased intensive care unit mortality in lung transplant recipients with BMIs in the lowest quartile.^[7] Given risk factors such as advanced age and disease severity, lung transplant candidates are more vulnerable to malnutrition, which predisposes them to imbalances in energy, protein, and other essential nutrients. Malnutrition is a known major risk factor leading to adverse outcomes in chronic diseases and can negatively affect protein/energy balance, physical function, and clinical outcomes.^[8,9] Therefore, identifying potentially modifiable risk factors such as malnutrition may help offset some of the morbidity and mortality associated with lung transplantation.

No standardized malnutrition screening tool exists for lung transplant candidates. An ideal screening tool would enable the identification of patients at risk of malnutrition and facilitate the improvement of their nutritional status. The Nutritional Risk Index (NRI)—calculated from easy-to-obtain variables (serum albumin and weight relative to ideal body weight)—provides a practi-

cal, objective metric. The NRI has the potential to classify nutritional risk based on an individual's score. Chohan *et al.*^[1] proposed that the NRI could serve as an effective tool for identifying malnutrition in lung transplant candidates, potentially aiding in the prediction of both pre- and post-transplant outcomes.

NRI, given its simplicity and prior evidence of its predictive capability, was investigated in this study for its prognostic value, alongside BMI and biochemical markers, for functional and survival outcomes in lung transplant candidates.

Materials and Methods

The study population consisted of patients evaluated at a tertiary-level lung transplantation center between 2016 and 2023. The inclusion criteria were as follows. Patients aged 18–65 years with end-stage lung disease who were actively listed for lung transplantation, received oral nutrition, and had no severe psychiatric illness were included in the study. Patients who were removed from the waiting list, were pregnant or lactating, had severe psychiatric illness, received enteral nutrition via PEG or JEG, or had missing data were excluded.

Of 228 patients, 210 met the inclusion and exclusion criteria and were included in the retrospective cohort study. Ethics committee approval for this study was obtained from Ethics Committee of Koşuyolu High Specialisation Training and Research Hospital (Approval Number: 2023/04/671, Date: 28.02.2023).

Data collection

Study data were collected by the researcher from the hospital archive and the hospital information management system. After obtaining ethics committee approval, eligible patients were identified from the Lung Transplant Clinic database. 15 November 2023 was designated as the inclusion cut-off date, and patients on the waiting list at that time were followed for an additional 30 days. The study population consisted of patients registered between 08 December 2016 and 09 November 2023. A total of 210 patients entered the transplant list on these dates and met the inclusion and exclusion criteria. 73 patients died while waiting on the list, 86 patients were transplanted, and 51 patients remain on the current waiting list.

Table 1: Patients' age, waiting time for transplantation, and clinical values

Variables	Mean±SD	Median (25p-75p)
Waiting time (day)	264.01±285.61	160 (70–367)
Age (year)	46.42±13.4	50 (37–57)
BMI (kg/m ²)	23.03±4.22	23.5 (20–26)
6MWT (m)	275.39±141.06	297 (190–381)
FVC (%)	44.39±17.62	41.6 (33–52)
FEV ₁ (%)	36.83±19.51	32 (21–49.35)
FEV ₁ /FVC (%)	72.94±24.47	78 (54–90)
NRI	83.06±9.71	83.12 (76.1–90.78)
Post-transplant NRI	70.12±13.96	74.2 (64.38–78.2)
BODE index	5.97±1.93	6 (5–7)
Post-transplant ICU stay (days)	9.68±9.83	6 (3.5–13)
Post-transplant survival (day)	753.2±879.87	151.5 (18–1650)

SD: Standard deviation, BMI: Body mass index, 6MWT: Six-minute walk test, FVC: Forced vital capacity, FEV₁: Forced expiratory volume in one second, NRI: Nutritional risk index, BODE: Body mass index, airflow obstruction, dyspnea, and exercise, ICU: Intensive care unit.

For all patients, biochemical data, pulmonary function test (PFT) results, six-minute walk test (6MWT) data, bone mineral density (BMD) measurements and immunonutrition reporting status, height (cm), and weight (kg) on the date they entered the list were retrospectively reviewed. The duration of post-transplant intensive care unit hospitalisation, albumin values routinely checked at the first-month follow-up of patients who survived the first month after transplantation, and patients' L-glutamine reporting status were retrieved from the hospital information management system. It was ensured that L-glutamine supplementation had been reported at least 30 days prior. Glutamine supplementation between 15-30 g was reported for patients in whom immunonutrition was recommended, as recommended in the literature.^[10]

Nutritional assessment

Nutritional status was determined using the Nutritional Risk Index (NRI), calculated as:

$$\text{NRI} = (1.519 \times \text{serum albumin [g/L]}) + (41.7 \times \text{current weight / ideal body weight})$$

Patients were classified as severely malnourished (NRI < 82), moderately malnourished (NRI 82–92), mildly malnourished (NRI 92–98), or no risk (>98).^[11]

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation or median (25th–75th percentile), and categorical variables as number and percentage. Normality was assessed using the Kolmogorov–Smirnov

test. Categorical variables were analyzed using the chi-square or Fisher's exact test, as appropriate. For continuous variables, one-way ANOVA with Tukey post-hoc test or non-parametric tests (Kruskal–Wallis and Mann–Whitney U tests) were applied, depending on the data distribution. Associations between continuous variables were evaluated using Spearman's rank correlation analysis. Variables included in regression analyses were determined a priori based on clinical evidence from previous studies demonstrating associations between nutritional status and clinical outcomes. Survival time was treated as a continuous variable, and correlation and linear regression analyses were performed only for exploratory and associative purposes. A p-value of <0.05 was considered statistically significant.

Results

A total of 210 patients listed as candidates for lung transplantation were included in the study. The cohort comprised 72.9% male patients, with a mean age of 46.4 ± 13.4 years. The mean waiting time on the transplant list was 264.0±285.6 days. Baseline anthropometric, nutritional, respiratory, and clinical characteristics—including body mass index (BMI), NRI, BODE index, pulmonary function parameters, six-minute walk test (6MWT) performance, and post-transplant outcomes—are summarized in Table 1.

Patients were categorized into three groups according to current status: transplanted, deceased while on the waiting list, and still awaiting transplantation. Comparative analyses of demographic, clinical, and laboratory characteristics are presented in Tables 2–5.

Table 2: Distribution of patients according to their current status

Variables	On the list (n=51)	Transplanted (n=86)	Ex-listed (n=73)	p
Gender, n (%)				0.578 [†]
Female	13 (25.5)	21 (24.4)	23 (31.5)	
Male	38 (74.5)	65 (75.6)	50 (68.5)	
Diagnosis, n (%)				0.001 [†]
Obstructive lung disease	6 (11.8)	25 (29.1)	7 (9.9)	
Interstitial lung disease	24 (47.1)	36 (41.9)	49 (69.0)	
Suppurative lung disease	20 (39.2)	23 (26.7)	11 (15.5)	
Vascular lung disease	1 (2.0)	2 (2.3)	1 (1.4)	
Diabetes, n (%)				0.121 [†]
Yes	9 (17.6)	9 (11.1)	4 (5.8)	
No	42 (82.4)	72 (88.9)	69 (94.2)	
Bone status, n (%)				0.655 [†]
Normal	16 (57.1)	37 (47.4)	34 (51.5)	
Osteopenia/Osteoporosis	12 (42.9)	41 (52.6)	32 (48.5)	
Use of enteral nutritional supplements, n (%)				<0.001 [†]
Yes	8 (28.6)	24 (30.8)	15 (22.7)	
No	20 (71.4)	54 (69.2)	51 (77.3)	
NRI category, n (%)				0.711 [‡]
Severe malnutrition	23 (46.0)	40 (47.1)	30 (41.7)	
Moderate malnutrition	18 (35.3)	17 (20.2)	33 (46.5)	
Mild malnutrition	10 (19.6)	28 (32.9)	10 (13.7)	
No risk of malnutrition	<5%	<5%	<5%	

†: Chi-square test; ‡: Fisher's exact test was applied. NRI: Nutritional risk index.

Table 3: Clinical and demographic characteristics of patients according to NRI status

Variables	Severe malnutrition <82	Moderate malnutrition 82–92	Mild malnutrition 92–98	No risk >98	p
Gender, n (%)					0.682 [†]
Female	23 (24.7)	15 (20.5)	11 (33.3)	1 (12.5)	
Male	40 (43.0)	28 (38.4)	13 (39.4)	4 (50.0)	
Current status, n (%)					0.014 [†]
On list	24 (25.8)	16 (21.9)	10 (30.3)	6 (75.0)	
Transplant/Ex, n (%)	69 (74.2)	57 (78.1)	23 (69.7)	2 (25.0)	
Diagnosis					–
Obstructive lung disease	15 (16.1)	9 (12.3)	3 (9.1)	1 (12.5)	
Interstitial lung disease	30 (32.3)	30 (41.1)	9 (27.3)	3 (37.5)	
Vascular lung disease	18 (19.4)	11 (15.3)	7 (21.2)	2 (25.0)	
Indications for retransplantation	34 (36.6)	47 (65.3)	20 (60.6)	6 (75.0)	
Diabetes, n (%)					–
No	35 (37.6)	13 (18.1)	6 (18.2)	0 (0.0)	
Yes	4 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Bone status, n (%)					0.570 [†]
Normal	83 (92.2)	62 (87.3)	26 (83.9)	7 (87.5)	
Osteopenia/Osteoporosis	7 (7.8)	9 (12.7)	5 (16.1)	1 (12.5)	
Enteral product reporting, n (%)					0.029 [†]
Reported	42 (53.8)	28 (45.9)	14 (56.0)	3 (37.5)	
Not reported	27 (34.6)	11 (18.0)	6 (24.0)	3 (37.5)	

†: Chi-square test; NRI: Nutritional risk index.

The proportion of male patients did not differ significantly among the three groups ($p>0.05$). However, primary diagnoses varied significantly ($p<0.05$). Suppurative lung dis-

ease was more prevalent among patients who remained on the waiting list, whereas interstitial lung disease was less frequent in this group than in the transplanted and

Table 4: Comparison of laboratory and clinical characteristics of patients according to NRI status

Variables	Severe malnutrition <82	Moderate malnutrition 82–92	Mild malnutrition 92–98	No risk >98	p
Age (years)	43.0 (27–55)	54.0 (44–59)	51.0 (48–56)	55.0 (45.5–57)	<0.001 [¥]
Body weight (kg)	54 (46–64)	71 (65–78)	76 (66–83)	73 (65–75.5)	<0.001 ^Ω
BMI (kg/m ²)	19.6 (17–22)	25.0 (23.1–26.2)	27.0 (25–29)	29.0 (26.6–30.5)	<0.001 [¥]
Albumin (g/l)	38 (34–41)	40 (38–43)	43 (40–45)	41 (38–44)	<0.001 [¥]
Prealbumin (µg/mL)	17 (15–21)	21 (18–24)	22 (16.5–27)	20.5 (18–25)	0.014 [¥]
Creatinine (mg/dL)	0.62 (0.47–0.71)	0.73 (0.63–0.82)	0.76 (0.56–0.86)	0.68 (0.56–0.94)	<0.001 [¥]
Hemoglobin (g/dL)	13.1 (11.2–14)	14.2 (12.6–15.3)	14.9 (13.4–15.9)	14.25 (11.9–15.1)	<0.001 [¥]
Total cholesterol (mg/dL)	150 (127–195)	200 (167–221)	199 (166–227.5)	226 (196.5–270.5)	<0.001 ^Ω
Triglyceride (mg/dL)	86.5 (70–127)	120.5 (88–151)	122 (89–164)	137 (102–161)	0.001 [¥]
FVC (%)	37 (28–45)	43 (34–54)	47 (41–54)	50.5 (40–55.5)	0.003 [¥]
FEV ₁ (L)	0.81 (0.64–1.12)	1.17 (0.72–1.73)	1.25 (0.83–1.54)	1.15 (0.84–1.35)	0.003 [¥]
FEV ₁ (%)	24 (19–40)	38 (23–53)	42 (30–54)	45.5 (36–57)	<0.001 [¥]
FEV ₁ /FVC (%)	67.1 (47–86.3)	83.0 (56.1–95.5)	76.6 (53–86.4)	82.8 (77.5–88.5)	0.028 [¥]
6MWT (m)	270 (138–380)	312.5 (220–402)	295 (190–345)	262.5 (139–295)	0.163 [¥]
Post-transplant ICU stay (days)	322.5 (16.5–1675.5)	228.5 (34.5–1505.5)	132 (13–1846)	28 (8.5–1185)	0.850 [¥]

¥: Kruskal-Wallis Test; Ω: One-way analysis of variance applied. NRI: Nutritional risk index, BMI: Body mass index, FVC: Forced vital capacity, FEV₁: Forced expiratory volume in one second, 6MWT: Six-minute walk test, ICU: Intensive care unit.

Table 5: The relationship between NRI, nutritional status, functional capacity, and lung capacity

Variables	All group (N=210)	Patients on the waiting list (N=50)	Transplant patients (N=85)	Patients who died while on the waiting list (N=72)
BMI (kg/m ²)	0.810** (<0.001)	0.850** (<0.001)	0.856** (<0.001)	0.730** (<0.001)
Total protein (g/dL)	0.119 (0.100)	-0.158 (0.307)	0.113 (0.316)	0.294* (0.015)
Albumin (g/dL)	0.490** (<0.001)	0.453** (0.001)	0.489** (<0.001)	0.542** (<0.001)
Transplant albumin (g/dL)	-0.070 (0.593)	NA	-0.070 (0.593)	NA
Prealbumin (µg/mL)	0.272** (0.003)	0.132 (0.365)	0.442* (0.021)	0.456** (0.003)
6MWT (m)	0.052 (0.463)	0.159 (0.270)	-0.048 (0.668)	0.097 (0.433)
FVC (%)	0.269** (<0.001)	0.255 (0.074)	0.464** (<0.001)	0.065 (0.603)
FEV ₁ (L)	0.246** (0.001)	0.188 (0.196)	0.322** (0.004)	0.222 (0.072)
FEV ₁ (%)	0.391** (<0.001)	0.309* (0.029)	0.446** (<0.001)	0.425** (<0.001)
FEV ₁ /FVC (%)	0.176* (0.014)	0.070 (0.631)	0.136 (0.225)	0.228 (0.068)
Post-transplant NRI	0.520** (<0.001)	NA	0.520** (<0.001)	NA
BODE index	-0.317** (<0.001)	-0.472** (0.001)	-0.308** (0.005)	-0.263* (0.039)
Post-transplant ICU stay (days)	0.217* (0.048)	NA	0.217* (0.048)	NA
Post-transplant survival (days)	-0.099 (0.365)	NA	-0.099 (0.365)	NA

*:p<0.05, **:p<0.01. Values are presented as Spearman correlation coefficient (r) and p value. NRI: Nutritional risk index, BMI: Body mass index, 6MWT: Six-minute walk test, FVC: Forced vital capacity, FEV₁: Forced expiratory volume in one second, NA: Not available due to insufficient sample size, ICU: Intensive care unit.

deceased groups. The prevalences of diabetes mellitus and osteoporosis were similar across groups. Use of enteral nutritional products was significantly less frequent in transplanted patients than in the other groups (p<0.001). No statistically significant differences were observed in the distribution of malnutrition risk. Severe malnutrition was common across all groups, and fewer than 5% of patients were classified as well nourished (Table 3).

BMI demonstrated weak correlations with several nutritional and respiratory parameters — including pre-

albumin, forced vital capacity percentage (FVC%), forced expiratory volume in one second (FEV₁, L), and the FEV₁/FVC ratio — and a moderate correlation with FEV₁ (%). A very strong positive correlation was observed between BMI and NRI, whereas BMI showed a weak inverse correlation with the BODE index. BMI showed a weak association with post-transplant intensive care unit (ICU) length of stay but was not significantly correlated with post-transplant survival duration, white blood cell count, or albumin levels. In contrast, post-transplant survival time showed a mod-

erate positive correlation with total cholesterol levels and a strong positive correlation with NRI (Table 4).

NRI-based analyses revealed that patients with severe malnutrition had significantly lower BMI and worse pulmonary function parameters than those with mild or no malnutrition. Albumin concentrations decreased progressively with increasing malnutrition severity. Patients with severe malnutrition also had significantly lower creatinine levels than those with moderate or mild malnutrition. However, no significant differences were observed among malnutrition severity groups with respect to waiting time, post-transplant ICU stay, functional capacity, biochemical parameters other than albumin and creatinine, or post-transplant survival duration (Table 4).

Across the entire cohort, NRI was strongly positively correlated with BMI ($r=0.81$, $p<0.001$) and moderately correlated with albumin levels and with post-transplant NRI values. NRI also demonstrated positive associations with pulmonary function parameters and an inverse association with the BODE index. Detailed subgroup correlation analyses are presented in Table 5.

Comparison of nutritional status based on laboratory parameters

When nutritional status was evaluated by albumin levels, no significant differences were observed between the normal-albumin and low-albumin groups for BMI or pulmonary function parameters. However, patients with hypoalbuminemia exhibited significantly lower 6MWT performance and NRI values ($p<0.05$).

In analyses stratified by cholesterol levels, patients with moderate or severe hypocholesterolemia had significantly lower BMI and poorer pulmonary function compared with those with normal cholesterol levels. NRI values were significantly higher among patients with normal cholesterol concentrations ($p<0.001$).

Patients with low hemoglobin levels had significantly lower BMI and NRI values, as well as reduced functional capacity and impaired pulmonary function, compared with patients with normal hemoglobin levels.

Mortality was not significantly associated with either NRI or BMI. However, the observed post-transplant survival duration was significantly associated with albumin and urea levels, while its association with white blood cell count did not reach statistical significance. Overall,

regression analysis indicated a modest but statistically significant relationship between selected biochemical parameters and observed survival time.

Discussion

In the present study, the general characteristics, anthropometric measurements, biochemical findings, PFT, 6MWT, and bone density measurements of lung transplant candidates were compared according to their current clinical condition. The relationships among patients' NRI, post-transplant NRI, BMI, biochemical findings, post-transplant survival, ICU stay, PFT and 6MWT were investigated. In our study, 34.8% of the 210 patients listed for lung transplantation died while on the list. Similarly, in a study conducted in Japan, 37.7% of the patients listed for transplant died while awaiting transplantation. The main reason for the long waiting times and high mortality rates among patients on the waiting list is insufficient organ donation.^[12] In this study, the average waiting time for transplantation was 264.01 days. In the United States, the waiting time for patients listed in 2019 was reported to be an average of 90 days^[12] This difference can be attributed to an insufficient number of donors in our country. According to the data published by the Turkish Organ Transplantation Foundation on December 31, 2023, the number of patients waiting for organ transplantation is 32,018, while the total number of deceased donors is only 305.^[13]

End-stage respiratory failure is associated with impaired bone health, and osteoporosis and osteopenia are frequently observed in lung transplant candidates, with estimated prevalences reaching 60% and 50%, respectively.^[14] In our study, based on bone mineral density results, osteoporosis was detected in 27.3% of the patients and osteopenia in 50.6%. Osteoporosis is one of the significant causes of morbidity following lung transplantation, and the fractures resulting from it can significantly affect patients' life expectancy.^[15]

The 6MWT is widely used to assess the functional status of lung transplant patients and is part of the evaluation criteria for transplantation. Most evidence in the literature has examined the relationship between 6MWT and waiting-list mortality. Studies have shown that the functional exercise capacity measured by 6MWT is inversely related to mortality on the waiting list in lung transplant candidates.^[16–18] In our study, the median 6MWT for those on the list was 368.00, while for those who died while on the list, it

was 257.50. Consistent with the literature, the 6MWT was lower in patients who died while on the list ($p < 0.001$).

In lung transplantation, the nutritional status of the recipient is considered an indicator of post-transplant outcomes. The BMI of the recipient is one of the most practical and commonly used measurements in medical centers worldwide.^[19] The impact of BMI on lung transplant outcomes has been an active area of research; however, due to conflicting evidence in the literature, its effect on lung recipient survival remains controversial.^[19-21] The first study to report the relationship between BMI and survival in transplant recipients using a large national database was published by Lederer and colleagues in 2009.^[4] In a study screening over 5,900 patients from the database, being obese or underweight was associated with an increased risk of post-transplant mortality. Schwebel *et al.*^[22] used BMI and creatinine height index to assess nutritional status and reported that 72% of the lung transplant patient cohort was undernourished, which led to prolonged ICU stays. In this study, the average BMI of transplant candidates at the time of listing was 23.03 kg/m². BMI was associated with post-transplant ICU stay, but not with post-transplant survival. An inverse relationship with the BODE index was identified. In our study, BMI was found to have a moderate correlation with FEV₁ and a weak correlation with FVC and FEV₁/FVC. Waiting times for patients whose BMI is outside the desired range provide an opportunity to improve their overall health. These findings suggest that the waiting period may constitute a critical window for optimizing patients' nutritional status, which may, in turn, have implications for clinical outcomes, including post-transplant intensive care unit (ICU) length of stay.

One of the screening tools used to identify malnutrition is the NRI. A retrospective cohort study that screened 13,392 lung transplant patients assessed the effect of NRI on post-transplant mortality. FEV₁, FVC, and BMI were lower in patients with a low NRI. The five-year mortality rate was higher in patients with severe malnutrition than in those who were not malnourished. It was also reported that patients with severe malnutrition had longer hospital stays post-transplant.^[23] Similarly, patients with severe malnutrition had lower BMIs than the other three groups. The medians of FVC%, FEV₁ (lt), and FEV₁/FVC were significantly lower in those with severe malnutrition than in those with mild malnutrition, and all these values correlated with NRI. In our

study, we observed a very strong correlation between post-transplant survival and NRI ($r = 0.850$; $p < 0.001$). This finding suggests that malnutrition may be associated with post-transplant survival duration and influence post-transplant clinical outcomes.

A study investigating the independent relationship between pre-transplant hypoalbuminemia and higher post-transplant mortality found that hypoalbuminemia at the time of listing was associated with early post-transplant mortality (< 1 year)^[24] Hypoalbuminemia may directly contribute to poor outcomes post-transplant by promoting oxidative damage or platelet aggregation^[25] In this study, albumin levels were recorded at the time of listing. The median albumin value among patients who died while on the list was 38.70 (35–42), whereas that among patients still on the list was 41.00 (38–44); this difference was significant ($p = 0.035$). This difference may be due to hypoalbuminemia predisposing patients to infections and lung inflammation, thereby increasing mortality risk.

In coronary artery disease (CAD), cholesterol levels have been shown to be inversely related to all-cause mortality, and a U-shaped relationship has been observed between inflammation, malnutrition, and CAD-related deaths.^[26,27] In CAD and dialysis patients, the idea that malnutrition leads to lower cholesterol levels and higher mortality rates is being explored.^[26,28] In our study, those with moderate-to-severe low cholesterol had significantly lower BMI, FVC%, and FEV₁% compared with those with normal cholesterol levels. In patients with normal cholesterol levels, NRI was significantly higher than in those with mild or moderate-to-severe low cholesterol. The study concluded that low cholesterol, resulting from malnutrition, negatively affected lung capacity and NRI.

Glutamine is considered a conditionally essential amino acid due to its role in stress response and immune regulation.^[28,29] In the present study, 42.7% of patients reported using glutamine as an enteral nutritional supplement; however, no statistically significant association was observed between glutamine use and malnutrition risk.

This study has several limitations that should be considered when interpreting the findings. Its retrospective and single-center design may limit the generalizability of the results. In addition, the use of registry data may not accurately capture patients' nutritional status at the time of transplantation, and the lack of detailed dietary intake

records limits a comprehensive assessment of nutritional habits. Furthermore, immunonutrition use could not be objectively confirmed. Nevertheless, the study also has important strengths. The use of the NRI allowed for an objective evaluation of malnutrition, and the inclusion of multiple biochemical parameters enhanced the robustness of the findings. Moreover, anthropometric measurements were performed in a standardized manner by a dietitian, increasing the reliability of the data.

Conclusion

In conclusion, malnutrition is highly prevalent among lung transplant candidates and is closely associated with pulmonary function, biochemical parameters, and post-transplant outcomes. The NRI appears to be a practical and informative tool for identifying nutritional risk beyond BMI alone. Routine nutritional assessment during the waiting period may provide an opportunity to optimize patient status and potentially improve transplant-related outcomes.

Ethics Committee Approval

The study was approved by the Koşuyolu High Specialisation Training and Research Hospital Ethics Committee (No: 2023/04/671, Date: 28/02/2023).

Informed Consent

Informed consent was waived due to the retrospective nature of the study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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HRCT-assessed fibrosis burden predicts mortality better than pulmonary function decline in progressive pulmonary fibrosis

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Abstract:

BACKGROUND AND AIM: Progressive pulmonary fibrosis (PPF) is a clinically significant phenotype observed across fibrotic interstitial lung diseases (ILDs), characterized by pulmonary functional decline, radiologic progression, and worsening symptoms. While declines in forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) are widely used to define progression, the prognostic value of baseline radiologic fibrosis burden in real-world PPF cohorts remains incompletely defined. We aimed to evaluate the relationships among HRCT-derived fibrosis extent, pulmonary function decline, and overall survival in patients with PPF.

METHODS: In this retrospective single-center study, 99 patients with progressive fibrotic ILD who were followed between 2010 and 2019 were included. PPF was defined according to accepted criteria, including functional, radiologic, and symptomatic progression. The extent of fibrosis on HRCT was assessed by two independent radiologists using a semi-quantitative visual scoring method. Cox regression models were used to identify predictors of mortality.

RESULTS: Baseline HRCT fibrosis extent was independently associated with mortality. In a multivariable analysis adjusted for age, sex, smoking status, and diagnosis, each 1% increase in fibrotic involvement was associated with a 5% higher risk of death (HR 1.050, 95% CI 1.025–1.076; $p < 0.001$). In contrast, categorical declines in FVC or DLCO ($\geq 5\%$ or $\geq 10\%$) were not independently associated with survival. Baseline DLCO impairment and smoking history were also associated with reduced survival.

CONCLUSIONS: In patients with PPF, radiological fibrosis burden on HRCT outperformed conventional spirometric decline thresholds in predicting mortality. These findings support an integrated prognostic approach combining standardized HRCT quantification with longitudinal functional assessment to improve risk stratification and clinical decision-making in PPF.

Keywords:

Diffuse parenchymal lung diseases, high resolution computerized tomography, fibrotic interstitial lung diseases, progressive pulmonary fibrosis

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Introduction

Interstitial lung diseases (ILDs) comprise a heterogeneous group of disorders characterized by varying etiologies, clinical courses, and prognoses. Among them, idiopathic pulmonary fibrosis (IPF) represents the most aggressive fibrotic phenotype and is defined by the radiologic and histopathologic pattern of usual interstitial pneumonia (UIP).^[1] However, it has become increasingly recognized that a progressive fibrotic course is not exclusive to IPF. Several other fibrotic ILDs, including fibrotic hypersensitivity pneumonitis (fHP), connective tissue disease-associated ILDs (CTD-ILDs), and some idiopathic interstitial pneumonias, may also develop a similar progressive phenotype.^[2]

This clinical behavior has been defined as progressive pulmonary fibrosis (PPF) in the 2022 ATS/ERS/JRS/ALAT guideline, characterized by worsening respiratory symptoms, radiological progression, and/or pulmonary functional decline within a one-year period in patients with underlying fibrotic ILD.^[2] The development of PPF is associated with substantial deterioration in quality of life, progressive loss of lung function, and increased mortality. Consequently, early identification of patients at risk for PPF has become an important clinical objective. Functional parameters such as declines in forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) are widely used indicators of disease progression, and several threshold values have been proposed to define clinically meaningful deterioration.^[3–5] In addition, radiological progression and the extent of fibrotic involvement on high-resolution computed tomography (HRCT) provide important information regarding disease behavior.^[6]

Although both pulmonary functional decline and radiologic progression are recognized markers of disease worsening, the prognostic significance of baseline fibrotic burden on HRCT for predicting PPF has not been fully clarified. In this study, we retrospectively evaluated patients meeting the diagnostic criteria for PPF by analyzing pulmonary function parameters and HRCT findings to investigate whether the extent of fibrotic involvement on HRCT may provide additional prognostic information on disease progression.

Materials and Methods

This study was designed as a retrospective case-control study. The patient cohort consisted of individuals with

ILD who were followed at our center between January 1, 2010, and December 31, 2019. After approval for the study was obtained from the Ethics Committee of Pamukkale University (Approval Number: 60116787-020/72294, Date: October 27, 2020), patient data were analyzed. Our study was conducted in accordance with the Declaration of Helsinki. Patients were included if they demonstrated a PPF and had sufficient clinical data for analysis. Cases with incomplete medical records or those lacking serial HRCT or pulmonary function tests (PFTs) were excluded.

The data were obtained from the hospital's electronic medical records system. Survival data were obtained through the hospital information system and the national health system's mortality records. HRCT images and PFTs were performed in our outpatient clinic using the same standard equipment throughout the study period, ensuring consistency in data acquisition. As this was a retrospective study, HRCT and PFT assessments were performed according to the timing and clinical judgment of the treating pulmonologists. The time interval between radiologic and functional assessments was recorded for each patient and included in the analysis.

PPF was defined based on at least two of the following during follow-up:

1. Physiological evidence of disease progression (either of the following):
 - a. Absolute decline in FVC $\geq 5\%$ predicted within 1 year of follow-up,
 - b. Absolute decline in DLCO (corrected for Hb) $\geq 10\%$ predicted within 1 year of follow-up.
2. Radiologic evidence of fibrotic progression on HRCT, or
3. Documentation of worsening respiratory symptoms by the treating physician in the clinical notes.

The study population included patients with IPF, CTD-ILD, and fHP, as determined by a multidisciplinary team evaluation.

HRCT images were evaluated using a simplified semi-quantitative visual scoring system based on the method described by Goh et al.^[7] At each predefined anatomical level, the extent of fibrotic involvement was visually estimated to the nearest 5%, and the average of these estimates was used to determine global fibrosis. Reticulation grading was not performed; only the percentage of fibrotic

Table 1: Baseline demographic and clinical characteristics of the study population

Variable	Category	All patients	Censored	Exitus	p
Age	Mean±SD	66.97±9.84	66±10.87	68.34±8.1	0.313
	Median (IQR)	67 (62–74)	66 (60.75–73.25)	70 (62–75)	
	Min–max	34–86	34–86	47–83	
Sex, n (%)	Male	65 (65.66)	35 (60.3)	30 (73.2)	0.186
	Female	34 (34.34)	23 (39.7)	11 (26.8)	
Occupational exposure, n (%)	No risk	50 (50.51)	33 (56.9)	17 (41.5)	0.13
	Risk present	50 (49.49)	25 (43.1)	24 (58.5)	
Smoking status, n (%)	Never smoker	43 (43.43)	29 (50)	14 (34.1)	0.117
	Former smoker	56 (56.57)	29 (50)	27 (65.9)	
Rheumatologic disease, n (%)	No	78 (78.79)	43 (74.1)	35 (85.4)	0.178
	Yes	21 (21.21)	15 (25.9)	6 (14.6)	
Diagnosis, n (%)	CTD-ILD	34 (34.34)	24 (41.4)	10 (24.4)	0.155
	IPF	51 (51.52)	28 (48.3)	23 (56.1)	
	fHP	14 (14.14)	6 (10.3)	8 (19.5)	

SD: Standard deviation, CTD-ILD: Connective tissue disease–associated ILD, IPF: Idiopathic pulmonary fibrosis, fHP: Fibrotic hypersensitivity pneumonitis.

involvement was assessed. All HRCT scans were obtained at our center and met predefined standards for technical quality. Two experienced radiologists independently scored each scan while blinded to both clinical data and each other's evaluations. The interobserver agreement was calculated and found to be high, supporting the reliability and reproducibility of the visual scoring approach.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY). Continuous variables were presented as mean±standard deviation, and categorical variables as n (%). When parametric test assumptions were met, Student's t-test was used to compare two means; when parametric test assumptions were not met, the Mann-Whitney U test was used to compare independent groups. Furthermore, relationships between continuous variables were analyzed using Spearman or Pearson correlation analyses, and survival associations were assessed using Cox proportional hazards regression models. Comparisons of categorical variables, including those across multiple diagnostic subgroups, were performed using the chi-square test, with Fisher's exact test applied when appropriate. Interobserver agreement between the two thoracic radiologists for the visual fibrosis scores was assessed using the intraclass correlation coefficient (ICC). Statistical significance was defined as $p < 0.05$.

Results

A total of 99 patients diagnosed with PPF were included in the study. The baseline demographic and clinical characteristics are summarized in Table 1.

Interobserver agreement for visual HRCT fibrosis scoring was excellent, with an intraclass correlation coefficient (ICC) of 0.882, supporting the reproducibility of the semi-quantitative assessment method.

Kaplan–Meier survival analysis demonstrated significant differences across diagnostic subgroups (log-rank $p = 0.026$); patients with IPF exhibited the poorest survival among fibrotic ILD subtypes (Fig. 1, Table 2). Baseline pulmonary function parameters were also associated with survival: both baseline DLCO and baseline FVC showed significant differences in survival distributions ($p = 0.018$ and $p = 0.045$, respectively). In contrast, longitudinal declines in DLCO and FVC at predefined thresholds ($\geq 5\%$ and $\geq 10\%$) were not significantly associated with survival outcomes.

Among patients with available longitudinal data, declines in DLCO and FVC were frequently observed; however, these changes did not differ significantly between survival groups (Table 3) or across ILD subtypes (Table 4). Although a trend toward earlier decline was observed in patients with IPF, these differences did not reach statistical significance.

In univariate Cox regression analyses, smoking status, diagnostic subtype, baseline DLCO $\geq 80\%$ predicted, baseline FVC $\geq 80\%$ predicted, and HRCT-derived fibrosis extent were significantly associated with mortality (Table 5). In contrast, longitudinal declines in DLCO and FVC were not predictive of survival.

In multivariable models, HRCT fibrosis extent remained the only consistent independent predictor of mortality.

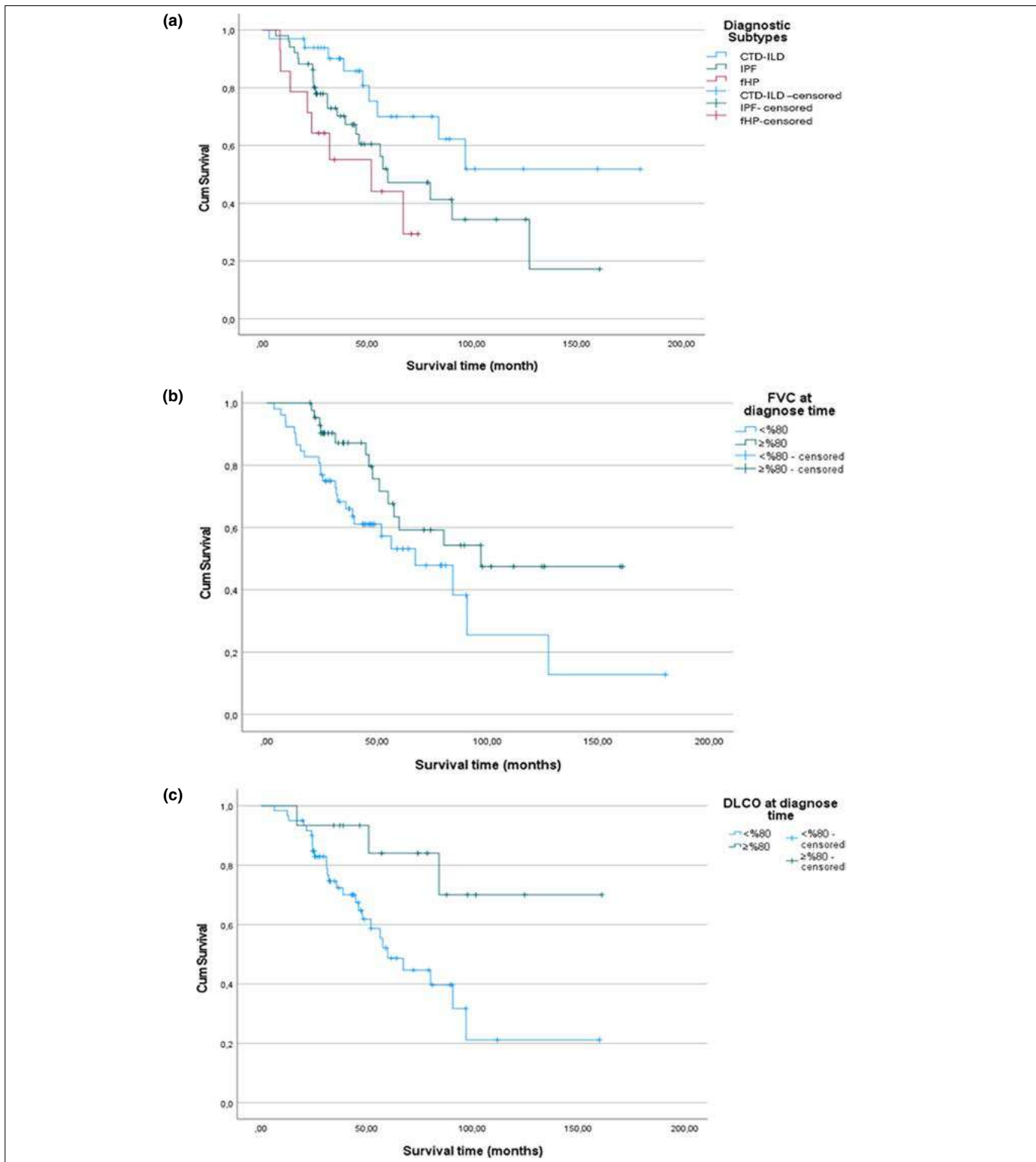


Figure 1: Kaplan–Meier survival curves according to diagnosis and baseline pulmonary function parameters. Kaplan–Meier survival curves showing overall survival according to (a) diagnostic subgroup, (b) baseline FVC status, and (c) baseline DLCO status. Survival differed significantly among fibrotic ILD subtypes, with patients with IPF showing poorer survival than those with CTD-ILD and fHP (log-rank $p=0.025$). Patients with impaired baseline DLCO had significantly different survival compared with those with preserved DLCO (log-rank $p=0.018$). Baseline FVC status was also significantly associated with survival outcomes (log-rank $p=0.045$). Tick marks indicate censored observations.

DLCO: Diffusing capacity of the lung for carbon monoxide, FVC: Forced vital capacity, ILD: Interstitial lung disease, IPF: Idiopathic pulmonary fibrosis, CTD-ILD: Connective tissue disease-associated ILD, fHP: Fibrotic hypersensitivity pneumonitis

Table 2: Survival analysis according to clinical variables and pulmonary function parameters

Variable	Total (n)	Event n (%)	Censored n (%)	Mean±SE (months)	%95 CI (Lower–Upper)	Log-rank p
Diagnostic subgroups						
CTD-ILD	34	10 (29.4)	24 (70.6)	118.31±14.64	89.62–147.00	0.026*
IPF	51	23 (45.1)	28 (54.9)	79.18±10.16	59.27–99.09	
fHP	14	8 (57.1)	6 (42.9)	45.76±7.21	31.61–59.9	
Baseline DLCO status						
<80	60	27 (45)	33 (55)	76.89±9.68	57.92–95.85	0.018*
≥80	15	3 (20)	12 (80)	130.38±15.22	100.55–160.21	
≥5% decline in DLCO						
No	18	7 (38.9)	11 (61.1)	64.51±9.53	45.83–83.18	0.329
Yes	47	18 (38.3)	29 (61.7)	97.9±10.34	77.63–118.18	
≥10% decline in DLCO						
No	27	12 (44.4)	15 (55.6)	71.66±9.67	52.7–90.62	0.189
Yes	37	13 (35.1)	24 (64.9)	102.39±11.77	79.32–125.46	
Baseline FVC						
<80	52	25 (48.1)	27 (51.9)	75.37±11.86	52.12–98.63	0.045*
≥80	43	14 (32.6)	29 (67.4)	104.67±11.04	83.02–126.31	
≥5% decline in FVC						
No	54	19 (35.2)	35 (64.8)	93.96±13.19	68.11–119.8	0.546
Yes	40	19 (47.5)	21 (52.5)	87.68±11.12	65.89–109.47	
≥10% decline in FVC						
No	66	23 (34.8)	43 (65.2)	95.48±12.61	70.77–120.18	0.359
Yes	28	15 (53.6)	13 (46.4)	81.57±12.6	56.88–106.27	

*p<0.05: Statistically significant, Kaplan Meier Survival Analysis. SE: Standard error, %95 CI: %95 Confidence interval, IPF: Idiopathic pulmonary fibrosis, DLCO: Diffusing capacity of the lung for carbon monoxide, FVC: Forced vital capacity.

Table 3: Longitudinal pulmonary function changes and their distribution by survival status

Variable	Category	All patients n (%)	Censored n (%)	Exitus n (%)	p
Baseline DLCO status	<80	61 (80.26)	33 (73.3)	28 (90.3)	0.067
	≥80	15 (19.74)	12 (26.7)	3 (9.7)	
≥5% decline in DLCO	No	18 (27.69)	11 (27.5)	7 (28)	0.965
	Yes	47 (72.31)	29 (72.5)	18 (72)	
≥10% decline in DLCO	No	27 (42.19)	15 (38.5)	12 (48)	0.451
	Yes	37 (57.81)	24 (61.5)	13 (52)	
Baseline FVC	<80	53 (55.2)	27 (48.2)	26 (65)	0.103
	≥80	43 (44.8)	29 (51.8)	14 (35)	
≥5% decline in FVC	No	54 (57.4)	35 (62.5)	19 (50)	0.229
	Yes	40 (42.6)	21 (37.5)	19 (50)	
≥10% decline in FVC	No	66 (70.2)	43 (76.8)	223 (60.5)	0.091
	Yes	28 (29.8)	13 (23.2)	15 (39.5)	

DLCO: Diffusing capacity of the lung for carbon monoxide, FVC: Forced vital capacity.

In Model 1, each 1% increase in fibrosis extent (Observer 1 – Scan 1) was associated with a 4.8% increase in the risk of death (HR 1.048, 95% CI 1.021–1.076; p<0.001). Similarly, in Model 2, fibrosis extent measured on the second scan remained independently associated with mortality (HR 1.082, 95% CI 1.037–1.129; p<0.001).

After adjustment for age, sex, smoking status, and diagnostic subtype, neither baseline FVC nor baseline DLCO,

and none of the predefined thresholds for longitudinal decline in these parameters, remained independently associated with mortality.

Discussion

In this study, we evaluated the clinical, functional, and radiological characteristics of 99 patients diagnosed with PPF and investigated factors associated with overall

Table 4: Distribution of baseline pulmonary function and longitudinal functional decline by ILD diagnostic subgroup

Variable	Category	CTD-ILD n (%)	IPF n (%)	fHP n (%)	p
Baseline DLCO status	<80	17 (70.8)	38 (88.4)	6 (66.7)	0.125
	≥80	7 (29.2)	5 (11.6)	3 (33.3)	
≥5% decline in DLCO	No	5 (25)	8 (22.2)	5 (55.6)	0.157
	Yes	15 (75)	28 (77.8)	4 (44.4)	
≥10% decline in DLCO	No	8 (40)	13 (37.1)	6 (66.7)	0.273
	Yes	12 (60)	22 (62.9)	3 (33.3)	
Baseline FVC	<80	17 (53.1)	28 (56)	8 (57.1)	0.956
	≥80	15 (46.9)	22 (44)	6 (42.9)	
≥5% decline in FVC	No	19 (59.4)	28 (57.1)	8 (57.1)	0.979
	Yes	13 (40.6)	21 (42.9)	6 (42.9)	
≥10% decline in FVC	No	20 (62.5)	38 (77.6)	9 (64.3)	0.297
	Yes	12 (37.5)	11 (22.4)	5 (35.7)	

CTD-ILD: Connective tissue disease-associated ILD, IPF: Idiopathic pulmonary fibrosis, fHP: Fibrotic hypersensitivity pneumonitis, DLCO: Diffusing capacity of the lung for carbon monoxide, FVC: Forced vital capacity.

Table 5: Cox proportional hazards regression analyses of factors associated with mortality in patients with fibrotic ILDs

Model	Variable	Wald	p	HR	95% CI (Lower–Upper)
Univariate	Age	0.724	0.395	1.014	0.982–1.047
	Sex (Female; Reference: Male)	2.913	0.088	0.547	0.273–1.094
	Smoking status (Present; Reference: Absent)	4.912	0.027*	2.124	1.091–4.137
	Diagnostic subtype (IPF; Reference: CTD-ILD)	3.852	0.05*	2.172	1.001–4.713
	Diagnostic subtype (IPF; Reference: fHP)	6.481	0.011*	3.537	1.337–9.354
	Baseline DLCO ≥80% (Present; Reference: Absent)	4.842	0.028*	0.258	0.077–0.863
	≥5% decrease in DLCO (Present; Reference: Absent)	0.940	0.332	0.645	0.265–1.566
	≥10% decrease in DLCO (Present; Reference: Absent)	1.689	0.194	0.591	0.268–1.306
	Baseline FVC ≥80% (Present; Reference: Absent)	3.899	0.048*	0.512	0.264–0.995
	≥5% decrease in FVC (Present; Reference: Absent)	0.444	0.505	1.243	0.656–2.354
	≥10% decrease in FVC (Present; Reference: Absent)	0.941	0.332	1.383	0.718–2.662
Model 1	HRCT fibrotic extent	15.953	<0.0001*	1.050	1.025–1.076
	Age	0.125	0.723	1.007	0.969–1.047
	Sex (Female; Reference: Male)	0.355	0.551	1.519	0.384–6.01
	Smoking status (Present; Reference: Absent)	1.813	0.178	2.484	0.661–9.341
	Diagnostic subtype (IPF; Reference: CTD-ILD)	0.103	0.748	1.176	0.436–3.174
	Diagnostic subtype (IPF; Reference: fHP)	3.557	0.059	3.181	0.956–10.586
Model 2	HRCT fibrotic extent	12.329	<0.0001*	1.048	1.021–1.076
	Age	0.899	0.343	1.023	0.976–1.072
	Sex (Female; Reference: Male)	0.071	0.790	1.381	0.129–14.81
	Smoking status (Present; Reference: Absent)	1.118	0.290	3.752	0.324–43.513
	Diagnostic subtype (IPF; Reference: CTD-ILD)	1.494	0.222	2.178	0.625–7.588
	Diagnostic subtype (IPF; Reference: fHP)	4.219	0.04*	5.212	1.078–25.194
	HRCT fibrotic extent	12.989	<0.0001*	1.082	1.037–1.129

*: $p < 0.05$ statistically significant. HR: Hazard ratio, CI: confidence interval, IPF: Idiopathic pulmonary fibrosis, CTD-ILD: Connective tissue disease-associated ILD, fHP: Fibrotic hypersensitivity pneumonitis, DLCO: Diffusing capacity of the lung for carbon monoxide, FVC: Forced vital capacity, HRCT: High-resolution computed tomography, ILD: Interstitial lung disease.

survival. A central finding of our analysis was that the extent of fibrotic involvement on baseline HRCT was independently associated with mortality. In both univariate and multivariate Cox regression models, each 1% increase in visually scored fibrotic extent was associated with an increased risk of death (multivariable HR 1.050, 95% CI 1.025–1.076; $p < 0.001$) and this association

remained significant after adjustment for age, sex, smoking status, and diagnosis. These findings highlight the critical prognostic role of radiological fibrosis burden in PF-ILD, suggesting that quantitative or semi-quantitative assessment of fibrosis on HRCT is a more robust predictor of survival than baseline pulmonary function parameters in our cohort. Conversely, declines in DLCO

and FVC of $\geq 5\%$ and $\geq 10\%$ were not significantly associated with mortality in either univariate and multivariate analyses. The observed effect size is clinically meaningful and supports the concept that radiological fibrosis burden captures irreversible structural lung damage more reliably than isolated spirometric measures.

In a recent multicenter analysis from the ILD-PRO registry, investigators reported that the extent of lung fibrosis on HRCT was a stronger predictor of disease progression than fibrotic pattern descriptors, such as a UIP pattern; however, the quantitative CT score did not provide additional prognostic information beyond clinical variables.^[8] Similarly, in CTD-ILD baseline HRCT fibrosis extent has been independently associated with mortality, reinforcing the concept that total fibrotic burden captures disease severity beyond functional decline alone.^[9] In our study, fibrotic burden on HRCT was quantified by two experienced thoracic radiologists who independently assessed scans while blinded to each other's evaluations, and their assessments showed high interobserver agreement. Although this approach ensured methodological rigor, we acknowledge that intercenter variability in image acquisition and reader interpretation may influence visual scoring in real-world settings. Rapid advances in deep learning and radiomics now provide more standardized, reproducible, and potentially more sensitive methods for quantifying fibrotic changes on HRCT. Recent studies suggest that AI-driven approaches may reduce observer dependency and enhance prognostic precision, particularly in heterogeneous diseases such as PPF.^[10,11] Therefore, while our findings support the prognostic value of expert visual scoring, we anticipate that future AI-based quantitative imaging tools could further refine and potentially surpass the accuracy of semi-quantitative methods, enabling more individualized risk stratification and treatment planning in PPF.

In our cohort, baseline fibrotic burden on HRCT emerged as a strong and independent predictor of mortality, whereas categorical declines in FVC or DLCO ($\geq 5\%$ or $\geq 10\%$) were not significantly associated with overall survival. Although this finding may appear to contrast with a substantial body of literature demonstrating the prognostic value of pulmonary function decline in PPF, it should not be interpreted as negating the clinical relevance of changes in FVC and DLCO. Although Kaplan-Meier analyses suggested that patients with baseline DLCO or FVC $< 80\%$ had significantly shorter

survival compared with those with higher values, these associations did not remain significant in multivariable Cox regression models. This discrepancy indicates that baseline pulmonary function is influenced by other clinical factors and radiological disease burden, and highlights that the extent of fibrosis on HRCT, a measure of structural lung damage, is a more robust independent predictor of mortality than baseline spirometric values. The 2022 ERS/ATS clinical practice guideline for PPF appropriately recognizes FVC and DLCO decline as a central criterion for defining disease progression and a key component of longitudinal assessment.^[2] Accordingly, our results should not be interpreted as diminishing the importance of FVC and DLCO in monitoring disease progression. Rather, they suggest that pulmonary function measures alone may not fully capture prognosis, and that the extent of fibrotic involvement on HRCT provides additional and potentially stronger prognostic information regarding survival.

Longitudinal changes in pulmonary function are influenced by multiple factors beyond fibrotic progression, including acute exacerbations, pulmonary hypertension, cardiac dysfunction, concomitant airway disease, and measurement variability, all of which may attenuate their prognostic signal in real-world heterogeneous cohorts.^[12-14] Pulmonary hypertension and left heart disease can reduce DLCO and FVC through mechanisms independent of parenchymal fibrosis, potentially confounding the relationship between functional decline and mortality.^[13,15] Furthermore, our cohort included not only patients with IPF but also individuals with fHP and CTD-ILD conditions characterized by distinct biological behaviors and variable physiological trajectories. The relatively limited sample size may have further reduced our statistical power to detect independent associations between functional decline and survival.

In contrast, the strong prognostic performance of quantitative HRCT fibrosis extent observed in our study underscores the central role of structural disease burden in determining outcomes in PPF. These findings suggest that while FVC and DLCO remain essential clinical tools, their prognostic utility is likely optimized when interpreted in conjunction with the extent of radiological fibrosis rather than used as standalone thresholds. An integrated, patient-level assessment combining imaging and lung function may therefore provide more accurate risk stratification, particularly in cohorts enriched for PPF.

In subgroup analyses, we observed that a $\geq 5\%$ decline in DLCO occurred more rapidly in patients with IPF, indicating a more aggressive disease course compared with other subtypes. Although patients with fHP experienced a $\geq 5\%$ decline in DLCO at a similar rate to those with CTD-ILD, the time to reach a 10% decline appeared shorter in the fHP group; however, this difference was not statistically significant. In our study, occupational or environmental exposures were identified in nearly half of the patients, suggesting that such exposures may negatively impact disease progression and survival. Smoking was found to have a significantly negative effect on survival across all patient groups ($p=0.027$), consistent with the literature and supporting its role in accelerating disease progression by increasing inflammation and tissue damage. These findings highlight the importance of thoroughly investigating exposures in patients diagnosed with ILD and of prioritizing smoking cessation efforts.

In the retrospective cohort study by Lee et al.,^[16] involving a one-year follow-up of 319 patients with IPF, a 10% decline in DLCO was emphasized as a significant prognostic marker for monitoring fibrotic progression. This study differs from ours in that it included all patients diagnosed with IPF, rather than only those with PPF. However, in patients with IPF and well-defined disease trajectories, such monitoring provides valuable insights into which parameters should be followed in clinical practice. Moreover, because IPF constituted the largest subgroup in our study, the finding that a 10% decline in DLCO is an important prognostic marker is relevant to our results.

In the study by Cen et al.,^[17] a baseline DLCO level of $<50\%$ and the presence of a UIP-like pattern on thoracic HRCT emerged as the variables most strongly associated with the development of PPF. The inclusion of patients with CTD-ILD in their cohort reflects a patient profile similar to that of our study. However, their approach was based on categorizing patients into those who developed PPF and those who did not, and directly comparing the clinical and radiological characteristics of these two groups. While our study does not include this exact stratification, the findings of Cen et al. suggest that parameters such as low DLCO and the presence of a UIP pattern may be valuable both diagnostically and in predicting progressive fibrotic behavior. In this respect, their findings are informative in identifying early markers relevant to the definition of PPF and are consistent with the results we obtained.

Although the time to 5% and 10% declines in FVC appeared shorter in patients with IPF than in those with CTD-ILD or fHP, the differences did not reach statistical significance. This trend, however, may still carry clinical relevance, as earlier functional deterioration in patients with IPF aligns with the known progressive nature of the disease. The lack of statistical significance might be partly attributable to a relatively small sample size, particularly in the fHP group, which may have limited statistical power to detect meaningful differences. Future studies with larger and more balanced subgroup populations are warranted to better clarify the trajectory of lung function decline across different ILD phenotypes.

In the study by Jang et al.,^[18] advanced age and low FVC were identified as independent predictors of mortality following the development of PPF in patients with non-IPF ILDs. This study is noteworthy because it evaluates factors influencing both the development of PPF and subsequent survival among patients with and without PPF. In contrast, our study did not find a statistically significant association between FVC and mortality. This discrepancy may be attributed to differences in patient profiles, follow-up durations, or assessment methodologies between the studies.

The demographic characteristics of our cohort are largely consistent with the literature. The mean age was 66.97 ± 9.84 years, with most patients being over 60 years old. This aligns with large-scale studies such as PROGRESS (68.4 ± 15.0 years)^[19] and ILD-PRO (median 68 years),^[20] which indicate that ILDs predominantly affect older individuals. Cellular senescence, telomere shortening, and genetic predispositions, including mutations in telomere-related genes such as TERT, TERC, RTEL1, and PARN, play significant roles in the development of fibrotic ILD.^[21,22] These mutations have been identified not only in IPF but also in other fibrotic ILD subtypes, such as nonspecific interstitial pneumonia (NSIP) and fHP. Notably, rare variants in genes such as TERT and TERC have been reported in 8–12% of patients with fHP and are associated with shortened telomere length.^[21]

The gender distribution showed a male predominance (65.7%). This ratio was more pronounced in the IPF (72.5%) and fibrotic HP (78.6%) subgroups, while the CTD-ILD group showed a balanced gender distribution. Although the PROGRESS study also reported

a higher male ratio, Nasser *et al.*^[19] described a slight female predominance (48.1%) but demonstrated that male sex was significantly associated with increased mortality risk. It is well established in the literature that males have a 1.5 to 2 times higher risk of developing IPF compared with females.^[23] Conversely, CTD-ILD is more common among younger, non-smoking women. Our study reflected this classic distribution, with male predominance in the IPF subgroup and female predominance in the CTD-ILD subgroup. Although male predominance was notable in the fHP group, the limited number of patients reduces the generalizability of this finding. In the real-life data study conducted by Nashatyreva *et al.*,^[24] no significant differences were reported between PF and PPF patient groups in terms of age, sex, symptom severity, or pulmonary function. Similarly, our study found no statistically significant differences in age or sex between the groups. However, among pulmonary function parameters, DLCO emerged as a significant predictor of mortality. Consistent with the findings of Nashatyreva *et al.*, cigarette smoking and a history of harmful occupational or domestic exposures were more frequently observed in the PPF group. Notably, our results suggest that occupational exposure may be associated with disease progression. Furthermore, shorter survival time was clearly associated with smoking, highlighting its detrimental impact on the disease course.

This study has several notable strengths. First, it was conducted in a well-characterized cohort of patients with PPF who were evaluated within a multidisciplinary framework, thereby increasing diagnostic accuracy and internal validity. Second, all HRCT scans used for semi-quantitative fibrosis assessment were obtained at a single center and were evaluated by experienced thoracic radiologists using a standardized visual scoring method, thereby minimizing variability related to imaging protocols and interpretation. The high interobserver agreement (ICC 0.882) further supports the reliability and reproducibility of our radiological assessments. Third, unlike many retrospective series that rely solely on baseline pulmonary function tests, our study incorporated both radiological fibrosis burden and longitudinal changes in DLCO and FVC, allowing a more comprehensive evaluation of structural and functional disease progression. Finally, by including three major fibrotic ILD subtypes (IPF, CTD-ILD, and fHP), our findings have broader applicability

across the spectrum of fibrotic lung diseases rather than being limited to IPF.

Our study also has important limitations that should be acknowledged. First, the relatively small sample size, particularly in the fibrotic HP subgroup, may have reduced statistical power and limited our ability to detect significant differences in the time to FVC and DLCO decline between diagnostic categories. This may partly explain why some clinically relevant trends did not reach statistical significance. Second, the retrospective design introduces potential sources of bias, including missing data, variability in follow-up duration, and heterogeneity in clinical management over time. Third, because this was a single-center study, our findings may not be fully generalizable to other populations or healthcare settings with different patient profiles or imaging practices. Fourth, although we used a validated semi-quantitative HRCT scoring system, visual assessment remains inherently subjective compared with fully automated quantitative or AI-based methods; thus, some degree of measurement variability is unavoidable. Finally, we did not systematically analyze genetic markers such as telomere length or fibrosis-related gene mutations, which could have provided additional prognostic insight and mechanistic context.

In this study, we demonstrate that the extent of fibrotic involvement on baseline HRCT is a robust and independent predictor of mortality in patients with PPF, outperforming conventional spirometric thresholds of FVC decline. Each incremental increase in visually scored fibrosis was associated with a significantly higher risk of death, underscoring the central role of radiological assessment in prognostic stratification. Although categorical declines in FVC and DLCO of $\geq 5\%$ and $\geq 10\%$ were not independently associated with mortality, DLCO, particularly when assessed longitudinally, remains clinically informative and should be interpreted alongside imaging findings rather than in isolation. Collectively, our results support an integrated approach in which early, standardized quantification of fibrotic burden on HRCT, combined with serial DLCO monitoring, can improve risk stratification, guide the timing of antifibrotic therapy, and facilitate more personalized follow-up strategies. Future multicenter studies incorporating quantitative imaging and genetic biomarkers are warranted to refine prognostic models and optimize management pathways for patients with fibrotic ILD.

Ethics Committee Approval

The study was approved by the Pamukkale University Ethics Committee (No: 60116787-020/72294, Date: 27/10/2020).

Informed Consent

Written informed consent was not required for this study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

Concept – N.Y., G.A.; Design – N.Y., G.A.; Supervision – G.A., E.U., F.U.; Resource – N.Y.; Materials – N.Y., G.A., H.G.Y., F.U.; Data collection and/or processing – N.Y., H.G.Y., F.U.; Analysis and/or interpretation – H.Ş.; Literature search – N.Y., G.A., F.U.; Writing – N.Y.; Critical review – G.A., E.U., F.U.

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Automated Versus Manual PSG Scoring: Evaluation of Somnolyzer in a Clinical Cohort

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Abstract:

BACKGROUND AND AIM: Manual polysomnography (PSG) scoring is time-consuming and subject to inter-scorer variability. Automated systems such as *Somnolyzer24X7* (*The Siesta Group Schlafanalyse GmbH, Vienna, Austria*) have been developed to improve efficiency and standardization, but real-world validation data remain limited. This study aimed to evaluate the performance of Somnolyzer in a clinical PSG cohort by comparing automated outputs with manual scoring by two independent human scorers.

METHODS: This methodological comparison study included 42 full-night diagnostic PSG recordings. Each study was scored independently by two experienced human scorers according to AASM criteria, and by Somnolyzer using automated analysis. Twenty-two PSG parameters were extracted, including sleep architecture measures, respiratory indices, and arousal indices. Agreement was assessed using intraclass correlation coefficients (ICC), and differences in PSG parameters across scoring methods were analyzed using the Friedman test with post-hoc comparisons.

RESULTS: Measures of sleep continuity and REM-related parameters did not differ significantly between scoring approaches (all $p > 0.05$). Significant differences were observed for N1 %, N2 %, and N3 % and for multiple respiratory indices (all $p < 0.05$). Somnolyzer showed excellent agreement with the human consensus for key respiratory parameters, including obstructive apnea index (ICC 0.97), apnea index (ICC 0.96), and apnea–hypopnea index (ICC 0.93). Agreement was also high for total sleep time (ICC 0.94), sleep efficiency (ICC 0.95), and REM percentage (ICC 0.90). Moderate agreement was observed for sleep stage proportions, whereas lower agreement was observed for the mixed apnea index and the arousal index.

CONCLUSIONS: Somnolyzer provides automated PSG scoring results that are largely consistent with expert manual scoring and may serve as a reliable first-pass analysis tool in clinical practice.

Keywords:

Automated sleep scoring, polysomnography, sleep staging, sleep scoring, Somnolyzer

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Introduction

Sleep staging remains a fundamental component of polysomnography (PSG) analysis and is still largely performed through manual scoring by trained technologists. Manual sleep staging involves visual inspection of overnight PSG recordings and may require up to two hours to score an eight-hour PSG recording.^[1] Despite standardized scoring criteria, sleep stage scoring remains susceptible to variability among scorers. Inter-scorer agreement between trained sleep technologists has been reported to range around 70–80%, while intra-scorer agreement is typically around 90%.^[2–4] In a large dataset including more than 2,500 scorers and over 3 million scoring decisions, the overall agreement for sleep staging was approximately 83%, with particularly low agreement for stages N1 and N3.^[2]

Recent advances in machine learning and deep learning have therefore aimed to automate sleep staging and provide more objective representations of sleep architecture.^[5] Over the years, several automated or semi-automated sleep scoring systems have been developed, including commercial platforms such as *Somnolyzer24X7* (The Siesta Group Schlafanalyse GmbH, Vienna, Austria),^[6–9] *Morpheus* by WideMed, Ltd. (Israel),^[9,10] and the *Michele Sleep Scoring System* (Cerebra, Winnipeg, Canada),^[11] to facilitate or partially automate the scoring process.

One of the early automated sleep staging systems developed to facilitate PSG scoring is Somnolyzer 24/7, which integrates automated signal processing and rule-based classification to emulate visual scoring according to the Rechtschaffen and Kales criteria.^[6,12] It was developed and validated using the multicenter Siesta database, which includes nearly 600 PSG recordings from healthy individuals and patients with sleep disorders. In validation studies, Somnolyzer achieved an epoch-by-epoch agreement of approximately 80% (Cohen's $\kappa=0.72$), comparable to inter-scorer agreement between human experts.^[6] These findings suggest that automated scoring can achieve a performance similar to that of manual scoring.

To the best of our knowledge, the performance of Somnolyzer has not yet been systematically evaluated in a Turkish PSG cohort. Given potential differences in patient characteristics, recording conditions, and scorer practices across sleep laboratories, external validation in diverse clinical populations is important to assess the generaliz-

ability of automated sleep staging systems. Therefore, the aim of the present study was to evaluate the performance of Somnolyzer in a Turkish clinical PSG dataset by comparing automated sleep stage classification with manual scoring performed by experienced human scorers.

Materials and Methods

Study design and participants

This methodological comparison study included 42 full-night diagnostic PSG recordings obtained in a sleep laboratory between 1 September and 15 October 2025. The number of recordings was determined by the availability of automated Somnolyzer analyses during the study period. Within this limit, all eligible full-night diagnostic PSG recordings were included consecutively without pre-selection. The final dataset comprised 42 PSG recordings from 42 individual patients, each contributing a single full-night study, with no repeated recordings. As the recordings were obtained during routine clinical practice, the study population represents a real-world cohort of patients referred for evaluation of suspected sleep disorders, including obstructive sleep apnea and related conditions. No additional inclusion or exclusion criteria were applied beyond the availability of a technically adequate full-night diagnostic PSG recording during the study period. All recordings were anonymized prior to analysis. Each PSG was scored independently by two human scorers blinded to each other's results and to the Somnolyzer output; Somnolyzer performed automated analysis.

The study protocol was approved by Başakşehir Çam and Sakura City Hospital Scientific Research Ethics Committee (Approval Number: 268, Date: 27.08.2025). The study was conducted in accordance with the principles of the Declaration of Helsinki. All PSG recordings were obtained as part of routine clinical care. Written informed consent for the use of clinical data for research purposes had been obtained from patients or their legal guardians at the time of the sleep study. No additional study-specific informed consent was required.

PSG recording and scoring

All studies consisted of standard attended overnight PSG recordings performed using routine clinical acquisition protocols. The recorded signals included electroencephalography (EEG: F3–M2, F4–M1, C3–M2, C4–M1, O1–M2, O2–M1), electrooculography (EOG), submental electromyography (EMG), electrocardiography (ECG), nasal airflow

(measured by a nasal pressure transducer and a thermistor), thoracic and abdominal respiratory effort (measured with belts), and pulse oximetry (SpO₂). Sleep staging and respiratory event scoring were performed according to the most recent version (Version 3.0) of the American Academy of Sleep Medicine (AASM) Scoring Manual. Respiratory events were defined as follows: Apnea was defined as a $\geq 90\%$ reduction in airflow from baseline lasting at least 10 seconds. Obstructive apnea was scored when respiratory effort persisted during the airflow reduction. Central apnea was scored when both airflow and respiratory effort were absent. Mixed apnea was defined as an apnea event beginning without respiratory effort and ending with the resumption of respiratory effort. Hypopnea was defined as a $\geq 30\%$ reduction in airflow lasting at least 10 seconds, associated with either $\geq 3\%$ oxygen desaturation or an arousal. An arousal was defined as an abrupt shift in EEG frequency lasting at least 3 seconds, preceded by at least 10 seconds of stable sleep. Both human scorers manually evaluated the recordings according to these criteria. Somnolyzer automatically generated sleep staging and scored respiratory events using its internal algorithm. Sleep staging was performed using 30-second epochs.

Data extraction

From each scoring output (Human scorer 1, Human scorer 2, and Somnolyzer), PSG parameters were extracted. These included measures of sleep continuity (total sleep time [TST], sleep onset latency [SOL], sleep efficiency [SE], and wake after sleep onset [WASO]); sleep architecture (N1, N2, N3, and rapid eye movement [REM] sleep percentages); respiratory event indices (central apnea index [CAI], obstructive apnea index [OAI], mixed apnea index [MAI], apnea index [AI], hypopnea index [HI], and apnea-hypopnea index [AHI]); positional respiratory indices (supine and non-supine AHI); and the arousal index.

Somnolyzer automated analysis

Automated analysis was performed using Somnolyzer software integrated within the Philips sleep analysis platform (Philips Respironics, Murrysville, PA, USA). The system automatically derives standard PSG parameters, including sleep architecture metrics and respiratory event indices, from recorded physiological signals. For the present study, Somnolyzer outputs were extracted from each recording and compared with manual scoring, which was performed independently by two experienced scorers according to the AASM criteria. Human consensus values were defined as the mean of the two manual scores and used as the reference for agreement analyses.

Statistical analysis

Continuous variables were assessed for normality using the Shapiro–Wilk test and visual inspection of distribution plots. As most variables were not normally distributed, continuous data are presented as median (minimum–maximum), and non-parametric tests are used for group comparisons. Comparisons among the three scoring approaches (Human scorer 1, Human scorer 2, and Somnolyzer) were performed using the Friedman test for repeated measures. When a significant overall difference was detected, Durbin–Conover pairwise post-hoc comparisons were conducted. Inter-scorer agreement was assessed using the Intraclass Correlation Coefficient (ICC), specifically the two-way random-effects model with absolute agreement [ICC(2,k)], following the classification of Shrout and Fleiss. ICC values were interpreted according to commonly accepted reliability thresholds, with values below 0.50 indicating poor agreement, 0.50–0.75 indicating moderate agreement, 0.75–0.90 indicating good agreement, and above 0.90 indicating excellent agreement. ICC results were also visualized using forest plots. All analyses were performed using R version 4.4.2. A two-sided P value < 0.05 was considered statistically significant.

Results

The analysis included 42 PSG recordings from 42 patients, of whom 33 (78.6%) were male; the mean age was 47.7 years. PSG parameters derived from the two human scorers and Somnolyzer are presented in Table 1. Measures reflecting overall sleep continuity and architecture, including TST, SE, SOL, WASO, REM latency, and REM %, did not differ significantly among the three scoring approaches (all pairwise comparisons, $p > 0.05$). In contrast, significant differences were observed for several sleep stage parameters. For N1%, N2%, and N3%, Human scorer 1 differed significantly from both Human scorer 2 and Somnolyzer, whereas no significant differences were observed between Human scorer 2 and Somnolyzer. Respiratory event indices differed consistently among scorers. CAI, OAI, AI, HI, and AHI differed significantly between scoring approaches (all $p < 0.001$). In most respiratory parameters, Somnolyzer produced values closer to Human scorer 2 than to Human scorer 1. Similar patterns were observed for positional metrics, including both supine and non-supine AHI (both $p < 0.001$).

The arousal index also differed significantly between scorers ($p < 0.001$). Human scorer 2 reported the highest

Table 1: Comparison of PSG parameters between two human scorers and Somnolyzer

Parameter	Human scorer 1	Human scorer 2	Somnolyzer	p
TST (min)	341 (152–460) ^a	341 (155–449) ^a	343 (154–449) ^a	0.10
SE (%)	79.9 (36.3–96.1) ^a	79.7 (37.1–97.4) ^a	79.8 (37.1–97.4) ^a	0.20
SOL (min)	18.5 (2–170) ^a	18.5 (1.5–170) ^a	17.5 (1.5–170) ^a	0.20
WASO (min)	65.3 (3.5–243) ^a	65 (3.5–242) ^a	68.3 (3.5–242) ^a	0.80
REM latency (min)	123 (58.5–384) ^a	111 (58–389) ^a	111 (58–389) ^a	0.40
N1 sleep (%)	3.70 (1.4–14.9) ^a	4.10 (1.6–14.5) ^b	4.10 (1.6–17.8) ^b	<0.001
N2 sleep (%)	68.1 (6.4–94.4) ^a	70.7 (47.9–96.8) ^b	70.2 (13.2–96.8) ^b	0.03
N3 sleep (%)	13.1 (0–31.8) ^a	7.3 (0–26.6) ^b	7.3 (0–26.5) ^b	<0.001
REM sleep (%)	16 (0–40) ^a	17 (0–40.7) ^a	17.1 (0–40.7) ^a	0.20
CAI (events/h)	0 (0–13.8) ^a	0 (0–14.4) ^a	0.2 (0–16.9) ^b	<0.001
OAI (events/h)	0.7 (0–76.8) ^a	0.25 (0–63.7) ^b	0.7 (0–76.5) ^a	<0.001
MAI (events/h)	0 (0–0.8) ^a	0 (0–1.5) ^a	0 (0–0.6) ^a	0.10
AI (events/h)	0.8 (0–77.4) ^a	0.3 (0–65.4) ^b	1.2 (0–77) ^a	<0.001
HI (events/h)	4.3 (0.3–68.8) ^a	7.65 (0–82.6) ^b	8.2 (0.7–71) ^c	<0.001
AHI (events/h)	7.35 (0.5–86.4) ^a	9.85 (0–82.8) ^b	11.6 (0.8–89.4) ^c	<0.001
Supine AHI (events/h)	11.6 (0–107) ^a	16.8 (0–89) ^b	19.7 (0–111) ^c	<0.001
Non-supine AHI (events/h)	2.55 (0–87.2) ^a	3.57 (0–87) ^b	5.43 (0–94.4) ^c	<0.001
Arousal index (events/h)	4.75 (0.4–49.5) ^a	18.3 (2.4–44.5) ^b	14.6 (5.5–69.3) ^b	<0.001

Overall p-values were calculated using the Friedman test. Values sharing the same superscript letter are not significantly different based on Durbin–Conover post-hoc pairwise comparisons. PSG: Polysomnography, TST: Total sleep time, SE: Sleep efficiency, SOL: Sleep onset latency, WASO: Wake after sleep onset, REM: Rapid eye movement, CAI: Central apnea index, OAI: Obstructive apnea index, MAI: Mixed apnea index, AI: Apnea index, HI: Hypopnea index, AHI: Apnea–hypopnea index.

Table 2: Inter-scorer agreement between human scorers and agreement between Somnolyzer and the human consensus across PSG parameters

Parameter	Human inter-scorer agreement			Somnolyzer vs. human consensus*		
	ICC	95% CI		ICC	95% CI	
		Lower	Upper		Lower	Upper
TST (min)	0.826	0.698	0.902	0.944	0.898	0.969
SE (%)	0.823	0.693	0.901	0.947	0.903	0.971
SOL (min)	0.991	0.982	0.995	0.841	0.724	0.911
WASO (min)	0.767	0.605	0.868	0.882	0.792	0.935
REM latency (min)	0.826	0.689	0.906	0.936	0.880	0.966
N1 sleep (%)	0.510	0.252	0.702	0.785	0.629	0.879
N2 sleep (%)	0.630	0.399	0.784	0.656	0.441	0.800
N3 sleep (%)	0.595	0.145	0.805	0.848	0.646	0.928
REM sleep (%)	0.714	0.528	0.835	0.904	0.829	0.947
CAI (events/h)	0.154	-0.159	0.437	0.655	0.444	0.798
OAI (events/h)	0.830	0.677	0.909	0.966	0.938	0.981
MAI (events/h)	0.279	-0.027	0.536	0.481	0.208	0.684
AI (events/h)	0.826	0.683	0.906	0.960	0.927	0.978
HI (events/h)	0.894	0.741	0.950	0.902	0.730	0.957
AHI (events/h)	0.971	0.948	0.984	0.925	0.796	0.967
Supine AHI (events/h)	0.769	0.604	0.871	0.841	0.690	0.917
Non-supine AHI (events/h)	0.965	0.936	0.981	0.932	0.853	0.966
Arousal index (events/h)	0.215	-0.077	0.488	0.493	0.209	0.696

*: Human consensus was defined as the mean score of the two independent human scorers. PSG: Polysomnography, ICC: Intraclass correlation coefficient, CI: Confidence interval, TST: Total sleep time, SE: Sleep efficiency, SOL: Sleep onset latency, WASO: Wake after sleep onset, REM: Rapid eye movement, CAI: Central apnea index, OAI: Obstructive apnea index, MAI: Mixed apnea index, AI: Apnea index, HI: Hypopnea index, AHI: Apnea–hypopnea index.

arousal index values, whereas Somnolyzer yielded intermediate values that were significantly higher than those of Human scorer 1 but not different from those of Human scorer 2 in post-hoc comparisons (Table 1).

Agreement between Somnolyzer outputs and the human consensus was generally high across most PSG parameters (Table 2; Fig. 1). For respiratory indices, Somnolyzer demonstrated excellent agreement with the human con-

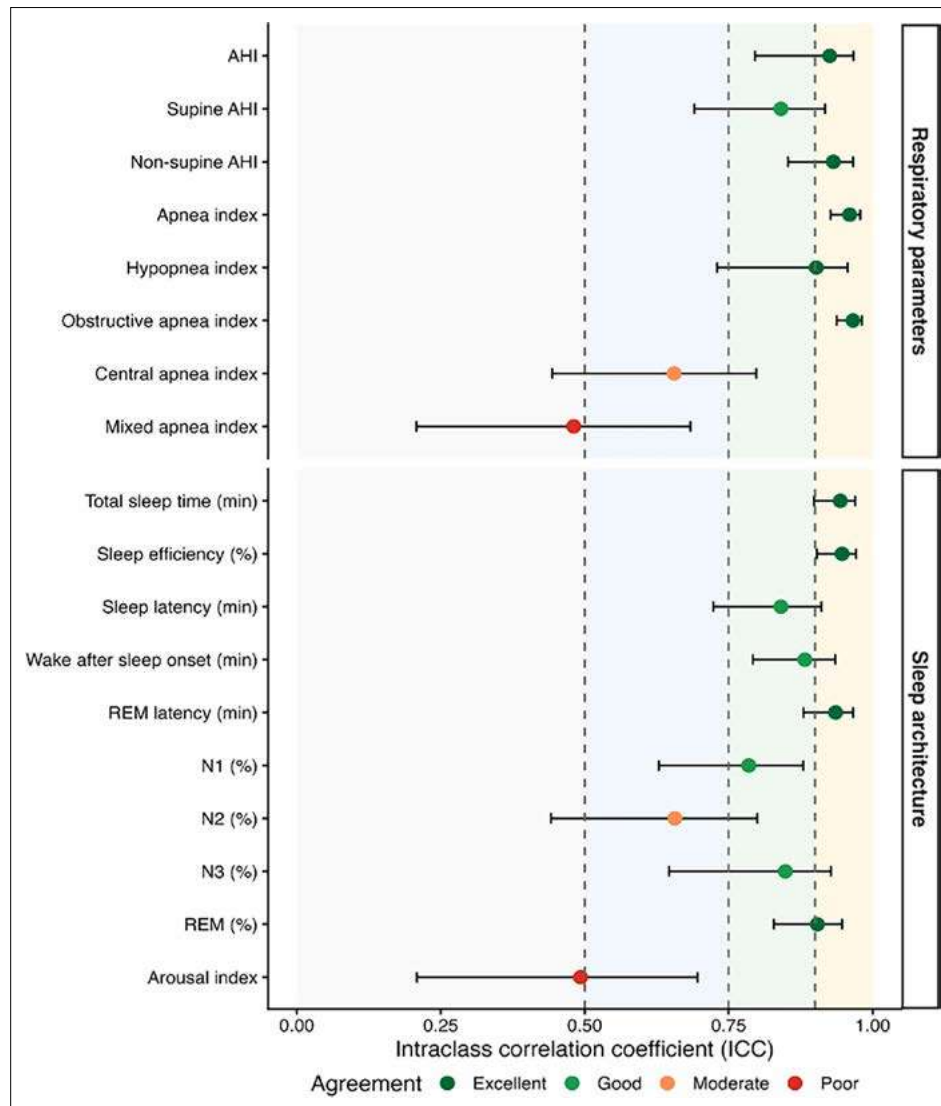


Figure 1: Agreement between Somnolyzer and the human consensus across PSG parameters. Forest plot of ICC and 95% CI. Dashed lines indicate ICC thresholds (0.50, 0.75, 0.90)

PSG: Polysomnography, ICC: Intraclass correlation coefficient, CI: Confidence interval

sensus, particularly for OAI (ICC 0.97, 95% CI 0.94–0.98), AI (ICC 0.96, 95% CI 0.93–0.98), AHI (ICC 0.93, 95% CI 0.80–0.97), and non-supine AHI (ICC 0.93, 95% CI 0.85–0.97). Agreement was also high for key sleep parameters, including TST (ICC 0.94), SE (ICC 0.95), REM latency (ICC 0.94), and REM% (ICC 0.90). Moderate agreement was observed for several sleep stage proportions, including N1% (ICC 0.78), N2% (ICC 0.66), and N3% (ICC 0.85). Lower agreement was observed for MAI (ICC 0.48) and arousal index (ICC 0.49) (Table 2).

Human inter-scorer agreement showed a broadly similar pattern, but was substantially lower for certain parameters, particularly for CAI (ICC 0.15, 95% CI -0.16–0.44)

and the arousal index (ICC 0.22, 95% CI -0.08–0.49). Notably, for several parameters, such as CAI and N3%, agreement between Somnolyzer and the human consensus exceeded that observed among human scorers. The distribution of ICC values across parameters is illustrated in the forest plot [Fig. 1].

Discussion

In this methodological comparison study, we evaluated the performance of an automated sleep-scoring system (Somnolyzer) against manual scoring performed by two experienced human scorers, using a clinical PSG dataset. Overall, Somnolyzer demonstrated high agreement with

the human consensus for most clinically relevant parameters, particularly respiratory indices and global sleep measures. Agreement was moderate for sleep stage proportions but lower for the MAI and the arousal index. These findings indicate that automated PSG scoring yields results largely consistent with expert manual scoring.

In the original validation study by Anderer et al.,^[6] Somnolyzer was developed and evaluated using the multicenter Siesta database, which included nearly 600 PSG recordings from both healthy individuals and patients with various sleep disorders. The system achieved an epoch-by-epoch agreement of approximately 80% with expert manual scoring (Cohen's $\kappa=0.72$), comparable to inter-scorer agreement between human experts. Our findings are consistent with this prior work, indicating that Somnolyzer yields results comparable to expert scoring and supporting its use in clinical sleep analysis. However, the studies differ in key aspects. While the original study focused on epoch-by-epoch agreement for sleep stage classification, our study assessed agreement across clinically derived PSG parameters, reflecting real-world clinical interpretation. This distinction is important because small epoch-level discrepancies may have limited impact on aggregated PSG variables used in clinical decision-making, such as sleep architecture percentages and respiratory indices. Sleep is a continuous neurophysiological process that is discretized into fixed 30-second epochs, making stage transitions inherently ambiguous, particularly between adjacent stages such as N1–N2 and N2–N3.^[4] Inter-scorer variability is therefore most pronounced during these transition periods and reflects interpretation of borderline epochs rather than true physiological differences.^[13] Consistent with this, N1 shows the lowest inter-scorer agreement.^[14] In contrast, respiratory indices demonstrate higher reliability, suggesting that variability in epoch-level staging does not necessarily translate into clinically meaningful differences in aggregated PSG metrics.

Consistent with these considerations, variability in specific respiratory indices was more pronounced in the present study. Human inter-scorer agreement was particularly low for CAI (ICC 0.15) and MAI (ICC 0.28), whereas agreement between Somnolyzer and the human consensus was modest (ICC 0.65 and 0.48 for CAI and MAI, respectively). This variability likely reflects the low frequency of these events, in which small absolute differences in counts can substantially affect agreement metrics. In addition, classification of respiratory events de-

pends on the interpretation of respiratory effort signals according to AASM criteria and may be influenced by signal quality and subtle variations in thoracoabdominal movement patterns.^[15] Mixed apneas, representing transitional events with both central and obstructive components, may further increase variability. Similar variability in respiratory event scoring across scorers and laboratories has been reported in previous studies.^[4,13] From a clinical perspective, these findings have direct implications for how differences between scoring approaches should be interpreted. Indices such as AHI, HI, and positional AHI differed systematically across scoring methods, with Somnolyzer generally yielding higher values, even when absolute differences were small, particularly in cases near diagnostic thresholds. Because AHI defines OSA severity, such differences may lead to reclassification across severity categories and influence treatment decisions, particularly in patients near diagnostic thresholds. These results indicate that observed differences reflect not only random variability but also systematic differences in event detection, highlighting the importance of careful interpretation in borderline clinical scenarios.

Lower agreement was also observed for the arousal index. Human inter-scorer agreement was low (ICC 0.22), and agreement between Somnolyzer and the human consensus remained moderate (ICC 0.49). This variability is consistent with previous studies showing that arousal scoring is inherently challenging. According to AASM criteria, cortical arousals are defined by transient EEG frequency shifts lasting at least 3 seconds, but their identification often requires interpretation of subtle and borderline EEG patterns.^[4,14,15] Arousals frequently occur near stage transitions, where distinguishing among brief awakenings, stage changes, and short cortical activations is difficult. In addition, because sleep staging discretizes a continuous physiological process into fixed 30-second epochs, scorers may differ in whether an epoch is classified as wakefulness or sleep. As a result, brief awakenings may be inconsistently classified, contributing to variability in the arousal index.

Taken together, these observations suggest that perfect epoch-by-epoch agreement may not be essential for reliable clinical interpretation of PSG recordings. This is consistent with the concept that sleep is a continuously evolving neurophysiological process, whereas conventional sleep staging represents a simplified framework imposed on its underlying dynamics.^[16,17] In the present study, Somnolyzer demonstrated good agreement with human scoring

for major sleep-stage proportions and excellent agreement for key respiratory indices; however, variability was primarily observed in scoring of central and mixed apneas.

Beyond earlier validation studies of rule-based automated systems such as Somnolyzer, more recent deep learning models have advanced automated sleep staging by learning directly from raw multichannel PSG signals and incorporating temporal context into classification.^[18] At the same time, growing evidence indicates that AI-based sleep research increasingly relies on multivariate and multimodal physiological data, reflecting a broader shift toward automated and data-driven PSG analysis,^[19] within which systems like Somnolyzer may represent an intermediate step between rule-based and fully data-driven approaches.

A key consideration in interpreting these findings is that manual PSG scoring, even when based on consensus between expert scorers, does not represent a true gold standard. Sleep staging and respiratory event scoring are subject to inherent inter-scorer variability, particularly in borderline or transitional epochs. Therefore, the reference used in this study should be viewed as an approximation of expert interpretation rather than an absolute ground truth. However, manual scoring remains the current clinical standard and the basis for diagnosis and treatment decisions in routine practice; thus, agreement with expert scoring serves as a clinically meaningful benchmark. In this context, the variability observed between human scorers further underscores the potential value of automated systems. Rather than reproducing an idealized gold standard, automated scoring may provide greater consistency and reproducibility, particularly for parameters prone to subjective interpretation.

Taken together, these findings support the implementation of automated scoring systems as first-pass analysis tools within clinical workflows. In this approach, the automated system performs an initial scoring of the PSG recording, which is subsequently reviewed and refined by an experienced clinician. This targeted review strategy can reduce scoring time while maintaining clinical accuracy by directing human attention to segments that are more prone to variability or uncertainty. In this context, automated systems such as Somnolyzer can enhance efficiency and standardization in routine sleep laboratory practice, supporting their integration into a hybrid human–AI scoring workflow.

Limitations

Several limitations of this study should be acknowledged. First, the sample size was relatively modest and derived from a single sleep laboratory, which may limit the generalizability of the findings to other clinical populations or recording environments. Second, the study evaluated agreement at the level of aggregated PSG parameters rather than performing an epoch-by-epoch comparison of sleep stage classification. While parameter-level agreement is highly relevant for clinical interpretation and reporting, epoch-level analyses may provide additional insights into the specific types of staging discrepancies between automated and manual scoring. Third, no subgroup analyses were performed based on patient characteristics or OSA severity. As agreement metrics may vary across different patient groups, this may have influenced the observed results. Fourth, the human consensus used as the reference standard was defined as the mean of two independent human scorers. Although this approach is commonly used in methodological validation studies, manual PSG scoring is subject to inter-scorer variability, as demonstrated by the relatively low agreement observed for certain parameters such as CAI and the arousal index in the present study. Consequently, the reference standard cannot be considered an absolute ground truth, but rather represents an approximation of expert consensus. Finally, the study focused on standard PSG parameters derived from routine clinical scoring and did not evaluate additional aspects of automated analysis such as signal quality detection, artifact handling, or performance in specific patient subgroups. Future studies incorporating larger datasets and more detailed epoch-level analyses may further clarify the strengths and limitations of automated PSG scoring systems in clinical sleep medicine.

Conclusion

In this clinical PSG dataset, the Somnolyzer automated scoring system demonstrated high agreement with expert manual scoring across most clinically relevant sleep and respiratory parameters. Agreement was particularly strong for respiratory indices and global sleep metrics, whereas lower agreement was observed for parameters known to show higher inter-scorer variability, such as arousal index and MAI. These findings suggest that automated scoring may provide a reliable first-pass analysis of PSG recordings and reduce scoring workload while maintaining clinical consistency.

Ethics Committee Approval

The study was approved by the Başakşehir Çam and Sakura City Hospital Scientific Research Ethics Committee (No: 268, Date: 27/08/2025).

Informed Consent

Written informed consent for the use of clinical data for research purposes had been obtained from patients or their legal guardians at the time of the sleep study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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AI-assisted tools were used for language editing and minor revisions. The authors take full responsibility for the content of the manuscript.

Author Contributions

Concept – D.A.Y., İ.Ç., A.B., S.Y., M.A.Ö.; Design – D.A.Y., İ.Ç., A.B., S.Y., M.A.Ö.; Supervision – D.A.Y., İ.Ç., A.B., S.Y., M.A.Ö.; Resource – D.A.Y., İ.Ç.; Materials – D.A.Y., İ.Ç.; Data Collection and/or Processing – İ.Ç., A.B.; Analysis and/or Interpretation – D.A.Y., A.B.; Literature Review – D.A.Y., İ.Ç., A.B., S.Y., M.A.Ö.; Writing – D.A.Y., İ.Ç., A.B.; Critical Review – S.Y., M.A.Ö.

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The management of exogenous lipoid pneumonia: A case series

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Abstract:

Exogenous lipoid pneumonia is a rare but serious respiratory condition caused by inhalation or aspiration of lipid-based substances. It often presents with nonspecific symptoms, such as cough, dyspnea, and fever, which can mimic infectious pneumonia and lead to diagnostic delays. Radiological imaging typically reveals ground-glass opacities, consolidations, or nodular lesions, particularly in the lower and middle lobes. Diagnosis is supported by a clinical history of exposure to specific oils or solvents, and confirmation often requires bronchoalveolar lavage demonstrating lipid-laden macrophages. Management includes cessation of exposure, supportive care, corticosteroids in selected cases, and treatment of secondary infections. This case series highlights three distinct clinical presentations of exogenous lipoid pneumonia—two involving fire-breathers and one related to occupational solvent exposure—emphasizing the importance of early recognition and tailored therapeutic strategies to prevent long-term complications.

Keywords:

Aspiration, fat-laden fluids, lipoid pneumonia

Introduction

Lipoid pneumonia is an uncommon condition resulting from the accumulation of lipids in the alveoli. Lipoid pneumonia is defined as a form of pneumonia resulting from the unintentional inhalation or aspiration of a lipid-containing fluid.^[1] The lipids in the respiratory system are categorized into two main categories based on their origin: exogenous lipoid pneumonia, derived from an external source, and endogenous lipoid pneumonia, originating

from an internal or idiopathic source.^[2,3] Exogenous lipoid pneumonia results from aspiration of fat-laden fluids or particles, whether deliberate or accidental.

Exogenous lipoid pneumonia results from the aspiration or inhalation of lipid-containing substances, most commonly mineral oils, animal fats, or plant-based oils.^[4,5] Traditional risk factors include the use of oil-based nasal drops, laxatives, occupational exposure to oily aerosols, and aspiration related to swallowing dysfunction

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or neurological disease.^[2,5,6] Recently, e-cigarette or vaping product use-associated lung injury (EVALI) has emerged as a novel and clinically relevant cause of exogenous lipid pneumonia.^[7,8] Propylene glycol and vegetable-sourced glycerine, particularly vitamin E acetate used as a diluent in vaping products, have been implicated in triggering an intense inflammatory response and lipid accumulation within alveolar macrophages.^[7,8] This emerging etiology has broadened the clinical spectrum of exogenous lipid pneumonia and has highlighted the importance of a detailed exposure history in affected patients.

Exogenous lipid pneumonia is an uncommon pulmonary condition resulting from the aspiration or inhalation of lipid-containing materials. Its nonspecific clinical manifestations and imaging findings often resemble those of infectious or other inflammatory lung diseases, making the diagnosis particularly challenging. Prompt identification and proper management are essential to avoid complications such as fibrosis or acute respiratory distress syndrome. This case series presents three patients with exogenous lipid pneumonia and outlines their clinical course, diagnostic evaluation, and treatment, emphasizing the crucial role of occupational exposure history in establishing the diagnosis.

Case 1

A 19-year-old male patient, employed as a fire-breather, presented to the emergency department with dyspnea, cough, and fever, which had emerged following multiple episodes of kerosene aspiration 2 weeks and 4 days prior. He had no known comorbidities and no history of tobacco use. Alcohol intake was 1–2 glasses per week. On admission to the emergency department, the pulse was 115 bpm with an oxygen saturation of 87%. Following administration of nasal oxygen at 3 L/min, oxygen saturation increased to 97%. The temperature was 38.3°C. Pulmonary auscultation revealed diminished breath sounds and coarse crackles at the right lung base. The laboratory findings exhibited the following abnormal values: white blood cell count: $23.69 \times 10^3/\mu\text{L}$ with neutrophilic predominance; C-reactive protein: 21 mg/L. The liver function tests were within normal parameters. Thoracic computed tomography (CT) revealed extensive consolidation and fluid-filled regions with intermittent air bronchograms in the right middle lobe [Fig. 1a]. The patient was brought to the chest diseases ward, where nasal oxygen was administered and antibiotic treatment with piperacillin-tazobactam 4.5 g (three times a day) and ciprofloxacin

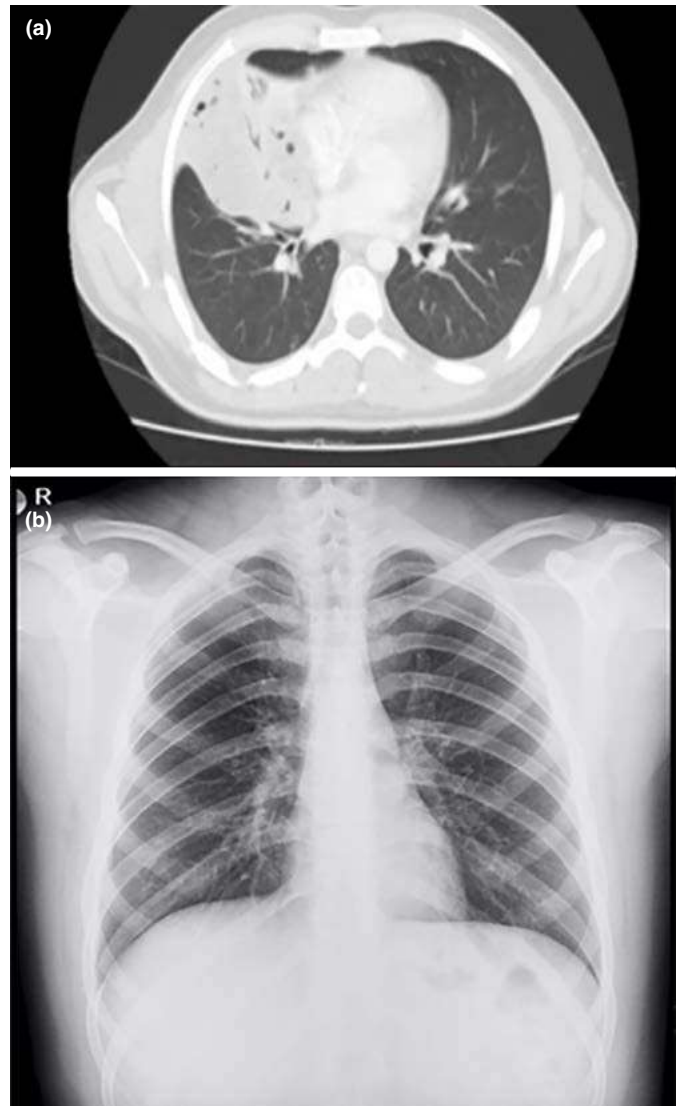


Figure 1: (a) CT shows consolidation in the right middle lobe. (b) Chest X-ray obtained after 1 year of follow-up revealed resolution of the consolidation

400 mg (two times a day) IV, together with supportive care, was commenced. A fiberoptic bronchoscopy (FOB) was scheduled. FOB revealed dense, dark-hued inflammatory mucoid secretions in the right main bronchus, which were aspirated, and bronchoalveolar lavage (BAL) was performed. No growth was observed in the bronchoalveolar lavage culture. Pathological examination demonstrated a pronounced inflammatory pattern and a significant presence of alveolar macrophages. Oil Red O staining revealed lipid-laden macrophages. On the tenth day of hospitalization, the patient, who exhibited improved symptoms and radiographic regression on chest X-ray (CXR), was discharged on outpatient antibiotic therapy. No sequelae were noted on the CXR performed during the initial year of follow-up [Fig. 1b].

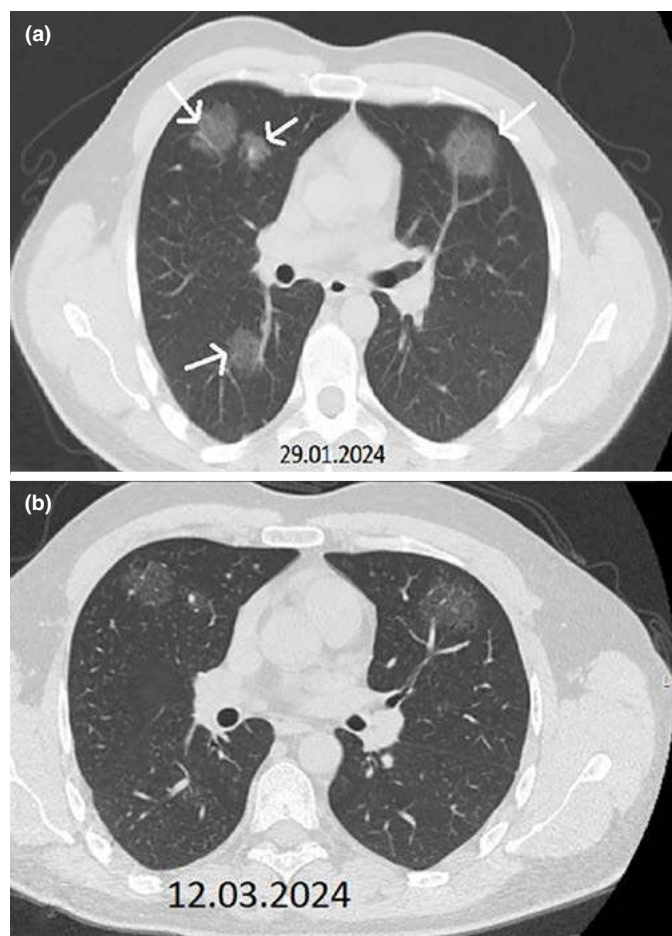


Figure 2: (a) CT scan shows asymmetric, scattered infiltrates with well-defined ground-glass opacities in both lungs. (b) Following cessation of exposure and medical treatment, resolution of the infiltrates was observed at 2 months

Case 2

A 31-year-old male patient was admitted to our outpatient clinic with complaints of cough and dizziness persisting for the past two months. No additional comorbidities were documented. The patient had a 10 pack-year smoking history. There was no record of alcohol consumption. No prior history or exposure to tuberculosis was noted. The patient's medical and family history revealed no significant findings. He was not taking any medication. It was discovered that, in his professional experience, he had engaged in laser cutting of metal and wood, as well as in painting with solvent-based epoxy and paint thinner, for six years. Pulmonary auscultation revealed bibasilar inspiratory crackles. Lung CT revealed nodular lesions and diffuse ground-glass opacities involving (suggestive of atypical pneumonia) both lungs [Fig. 2a]. Moxifloxacin 400 mg/day was prescribed for outpatient treatment for one week. One week later, the patient returned for a follow-up, although no clinical improve-

ment was noted. The patient, presenting with dizziness, was admitted to the Department of Chest Diseases with a provisional diagnosis of lipid pneumonia. FOB was offered, but the patient refused the procedure. Additionally, the presence of extensive ground-glass opacities prompted consideration of several alternative diagnoses, including e-cigarette or vaping product use-associated lung injury (EVALI), hypersensitivity pneumonitis, organizing pneumonia, and atypical or viral pneumonia. EVALI was considered unlikely due to the absence of any history of e-cigarette or vaping product use. Hypersensitivity pneumonitis was deemed less probable given the lack of relevant antigen exposure. Given the chronic occupational solvent exposure, systemic toxicity was also considered. The patient's fundoscopic examination and brain MRI were unremarkable. Consequently, ophthalmology and neurology consultations did not establish a diagnosis. The patient's radiological findings prompted an investigation into the presence of connective tissue disorders. Results for the ANA profile, complement levels, HLA B27, CCP, RF, anti-SS-A, anti-SS-B, anti-Jo-1, and anti-DS-DNA were all within normal limits. The rheumatology consultation concluded that the patient did not have an active rheumatological condition. Infectious etiologies were excluded based on negative microbiological studies and lack of clinical response to antimicrobial therapy. Diffusing capacity for carbon monoxide (DLCO) was measured. DLCO/VA was 71%. Pulmonary function tests (PFTs) showed an FEV₁ of 75%, an FVC of 76%, and an FEV₁/FVC ratio of 96%. Based on these findings and the clinical history, lipid pneumonia associated with chronic solvent exposure was considered the most likely diagnosis. The patient received methylprednisolone at a dosage of 16 mg per day for one month. He was provided with a protective mask appropriate for his profession. A notable beneficial response in PFT and DLCO was recorded at the one-month follow-up. Pulmonary function testing showed a DLCO/VA of 82%, FEV₁ of 87%, FVC of 92%, and an FEV₁/FVC ratio of 94%, findings suggestive of a mild restrictive ventilatory defect. A notable improvement in pulmonary function test results was observed prior to therapy. The complaint of dizziness has been recorded as resolved. A control non-contrast thoracic CT performed during the first month of treatment revealed a notable resolution in ground-glass opacities, which were diffusely distributed across all lobes of both lungs [Fig. 2b]. The patient's symptoms of dizziness and cough have subsided, and he is currently under surveillance and therapy.

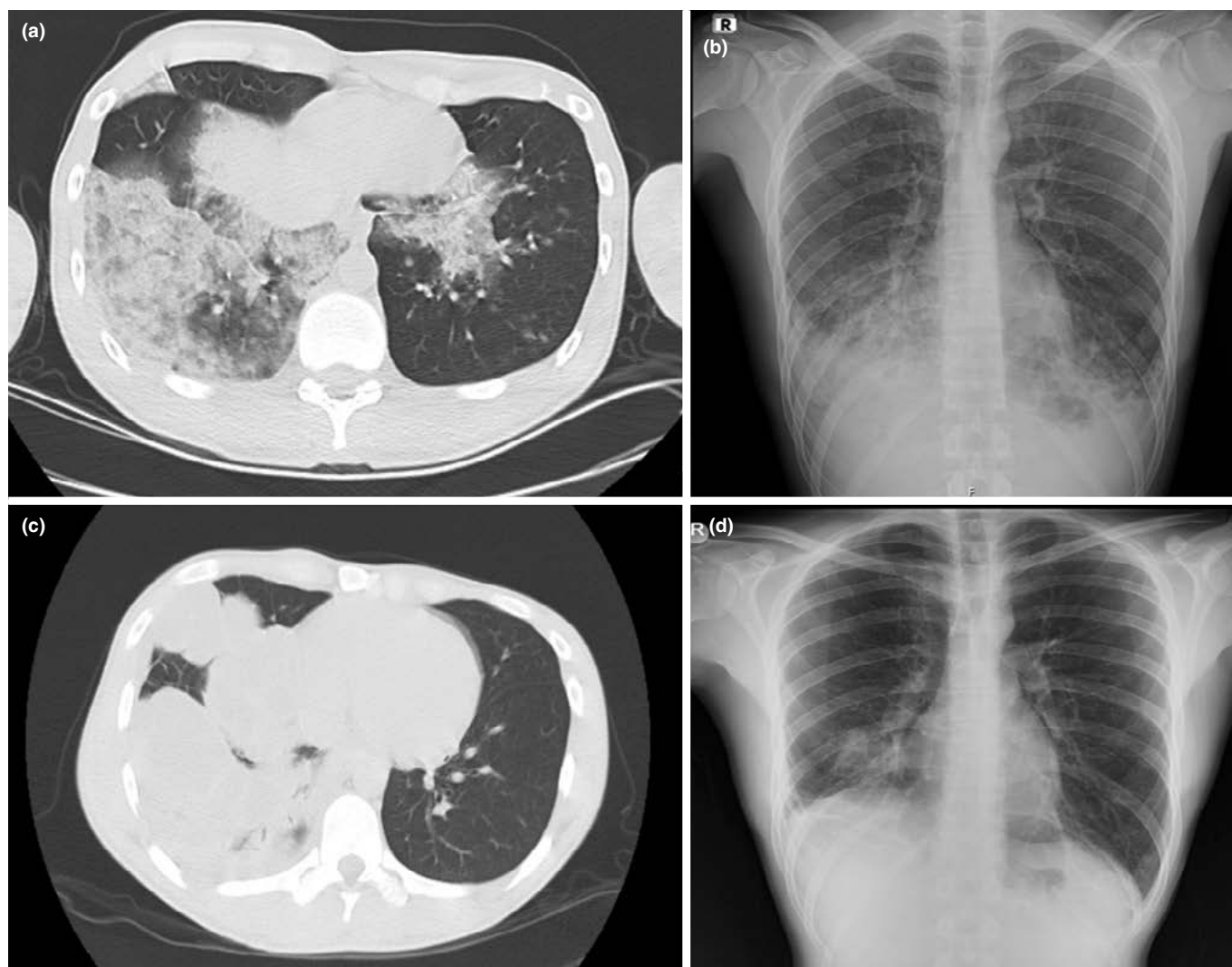


Figure 3: (a) CT scan shows extensive ground-glass opacities and consolidations in the lower lobes of both lungs. (b) Chest X-ray reveals bilateral lower lobe opacities, with denser consolidation more prominent on the right side. (c) On CT scan, pleural-based, well-defined, loculated collections are observed, consistent with homogeneous density increases compatible with pleural effusion; surrounding areas of consolidation are also noted. (d) Chest X-ray demonstrated significant resolution of the consolidated areas after treatment

Case 3

A 25-year-old male patient, employed as a fire breather, was admitted to the emergency department with complaints of dyspnea, cough, and fever that manifested 24 hours following the aspiration of approximately 75 ml of kerosene during an animation show for tourists. He had no recorded medical history; nonetheless, he was an active smoker with a smoking history of six pack-years. Upon admission to the emergency department, the Glasgow Coma Scale (GCS) score was 14; the pulse rate was 142 bpm; oxygen saturation on room air was approximately 85%, and with nasal oxygen at 6 L/min, the saturation was 92%. Physical examination revealed oropharyngeal hyperemia, reduced respiratory effort, and decreased breath sounds accompanied by coarse crackles at the bi-

lateral lung bases. Laboratory findings were remarkable for leukocytosis ($WBC\ 17.57 \times 10^3/\mu L$) with neutrophil predominance, an elevated CRP level of 180 mg/L, and a procalcitonin level of $2.52\ \mu g/L$. Thoracic CT revealed extensive ground-glass opacities and consolidations in the lower lobes of both lungs, as well as in the right middle lobe [Fig. 3a, b]. The patient was admitted to the pulmonology department and intravenous antibiotic therapy with piperacillin-tazobactam 4,5 g (three times a day) and ciprofloxacin 400 mg (two times a day) was commenced. During the patient's follow-up, the fever persisted. Following the detection of a dense right-sided pleural fluid collection on thoracic CT, the thoracic surgery department was consulted for drainage [Fig. 3c]. The antibiotic regimen was modified to meropenem (3 times 1 g) and ami-

kacin (2 times 1 g). The patient's overall condition shows partial improvement, and follow-up assessments are ongoing [Fig. 3d]. Both the clinical findings and radiological assessment, together with a history of acute kerosene aspiration, supported the diagnosis of lipid pneumonia. Histopathological confirmation was not pursued, as the clinical evidence was considered sufficient.

Discussion

The diagnosis of lipid pneumonia relies on radiological characteristics due to the inhalation or aspiration of fats and oily substances, the identification of lipid-laden macrophages in bronchoalveolar lavage fluid or lung tissue via Oil Red O or Sudan III, IV, or Sudan Black B staining, and the exclusion of other diseases that may account for the radiological anomaly.^[5] Lipid pneumonia was initially documented by Laughlen in 1925.^[9] Lipid pneumonia has been documented globally across all age demographics.^[10–12] Lipids are characterized as endogenous, exogenous, or idiopathic based on their source. The exogenous type is more prevalent and is linked to the administration of mineral oil for constipation relief with laxatives, particularly observed in the elderly.^[10]

Fire-breather's pneumonia represents a well-described but rare form of exogenous lipid pneumonia resulting from accidental aspiration of hydrocarbon-based fuels during fire-eating performances.^[5,13] Published case series typically involve young, otherwise healthy individuals presenting with acute respiratory symptoms shortly after exposure, accompanied by bilateral ground-glass opacities or consolidations on chest imaging, often with lower lobe predominance.^[5] Consistent with these reports, both of our fire-breather cases developed symptoms rapidly after exposure and demonstrated imaging findings consistent with acute inflammatory lung injury. However, compared with previously published series, the clinical course in our patients was relatively mild, possibly reflecting limited exposure volume, early recognition of symptoms, and prompt cessation of further exposure. Prior studies have suggested that the amount of aspirated hydrocarbon and the interval between exposure and diagnosis are key determinants of clinical severity, supporting this interpretation.^[5,14]

In contrast, the second case, related to chronic occupational exposure to solvents, represents a less frequently reported but clinically important cause of exogenous lipid pneumonia. Unlike the acute presentation observed in

fire-breather's pneumonia, this patient exhibited a more insidious onset, progressive respiratory symptoms, and more extensive radiological involvement. The novelty and relevance of this case lie in the prolonged low-dose inhalational exposure, which may lead to cumulative lipid deposition and sustained alveolar inflammation over time.^[4,5] Occupational exposure-related lipid pneumonia has been sporadically described in the literature, and such cases emphasize the importance of a detailed occupational history in patients with unexplained or slowly progressive pulmonary infiltrates.^[2,5]

In addition, the prevalence of electronic cigarette usage has increased rapidly in recent years, particularly among younger populations.^[15] A substantial proportion of patients with e-cigarette or vaping product use-associated lung injury (EVALI) reported by the Centers for Disease Control and Prevention (CDC) in 2019 demonstrated clinical, radiological, or pathological features consistent with lipid pneumonia.^[8,16] Accordingly, EVALI has been recognized as an emerging cause of exogenous lipid pneumonia, as lipid-containing substances—most notably vitamin E acetate used as a diluent in vaping products—are introduced into the lungs via inhalation, leading to lipid accumulation and inflammatory lung injury.^[7,8,16]

Although none of our patients reported e-cigarette use, the recent emergence of EVALI has further expanded the etiological spectrum of exogenous lipid pneumonia. EVALI represents a contemporary form of inhalational lipid-mediated lung injury, most commonly linked to vitamin E acetate, and reinforces the need to consider both traditional and modern sources of exogenous lipids in the differential diagnosis of compatible clinical and radiological presentations.^[7,8]

Conversely, the endogenous type is secondary to bronchial constriction or to pulmonary fat embolism, alveolar proteinosis, and lipid accumulation disorders. The idiopathic variant is an uncommon disease observed in smokers.^[17] Additional risk factors encompass neuromuscular problems, structural anomalies of the nasopharynx that increase the risk of aspiration, and increased occupational hazards among “fire breathers” who perform in circus or other entertainment acts. Two of our cases involved performers who practiced fire-breathing, while one patient presented with exogenous lipid pneumonia resulting from exposure to paint thinner during painting work. Mineral oil is the material most frequently associated with exogenous lipid

pneumonia; it is not degraded by pulmonary enzymes but is phagocytosed by alveolar macrophages. Lipid-laden alveolar macrophages induce a granulomatous response. Chronic inflammation may result in progressive lung fibrosis.^[4,6] Common signs of exogenous lipid pneumonia include fever, weight loss, cough, dyspnea, chest discomfort, and hemoptysis. Approximately 40% of lipid pneumonia patients have mild symptoms or are asymptomatic, complicating the diagnosis and resulting in frequent incidental findings.^[18] Conversely, substantial exposure to the detrimental substance may result in severe hypoxemic respiratory failure, potentially advancing to acute respiratory distress syndrome (ARDS).^[2] The predominant symptoms seen in our cases were dyspnea, cough, and fever. In our patients, symptoms and clinical status have been observed to vary from mild to severe.

In lipid pneumonia, the initial radiological abnormalities have been documented to manifest within minutes to hours. The intensity and duration of exposure to the harmful agent are associated with a diverse array of findings. These findings typically encompass pulmonary ground-glass opacities, a crazy paving pattern linked to alveolitis and interlobular septal thickening, consolidative foci, and/or lung nodules that may disappear within 2 weeks to many months.^[11,19] The lesions are often distributed bilaterally, may be segmental or lobar, and predominantly affect the middle and lower lobes.^[19] In our cases, as in the literature, the most commonly observed findings were ground-glass opacities and consolidation. Moreover, uncommon observations have also emerged, including severe toxic exposure potentially resulting from alveolar, bronchial, and/or vascular necrosis; multiple discrete and confluent nodules; abscesses; and air-fluid levels indicative of pneumatoceles associated with cavitating lung lesions, all indicative of fulminant disease.

The primary treatment for lipid pneumonia involves eliminating the causative agent, ensuring sufficient oxygen support with antimicrobial therapy for secondary bacterial infections, administering corticosteroids to suppress the inflammatory response in the lungs, and implementing additional supportive measures such as chest physiotherapy to aid in the drainage of tracheobronchial secretions.^[20] Moreover, it has been documented that the mechanical extraction of lipid constituents using bronchoscopy via bronchoalveolar lavage is advantageous in severe instances of lipid pneumonia.^[21] In one of our cases, tube drainage and abscess evacuation were per-

formed to mitigate exposure and inflammation resulting from pneumonia and abscess that were unresponsive to antibiotic therapy and from pneumothorax.

Conclusion

Exogenous lipid pneumonia is a serious clinical condition that can arise from various causes and present with different and variable radiological appearances depending on the cause. In patients presenting with atypical infiltrates on chest X-rays or CT scans, situations such as occupational exposures, inhalation of foreign or different substances either intentionally or accidentally, and the use of electronic cigarettes should definitely be inquired about in the patients' medical history. Radiological appearances can present in various forms, ranging from ground-glass infiltrates to consolidation and even ARDS. In patients, acute respiratory failure, cough, and fever may often be prominent. Bronchoalveolar lavage is helpful in diagnosis. Removal of the causative agent and treatments with steroids, antibiotics, bronchodilators, and an approach to acute respiratory failure are the first treatment interventions to consider.

Ethics Committee Approval

This is a case series, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent

All patients gave their written, signed informed consent, which is retained in their medical records, on admission to the hospital for the use of their medical information in scientific studies as long as their names remain anonymous.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

Concept – A.Y.; Design – A.Y., D.Ç., H.L., Ö.Y.; Supervision – A.Y.; Resource – A.Y.; Materials – A.Y.; Data Collection and/or Processing – A.Y.; Analysis and/or Interpretation – A.Y., D.Ç., H.L., Ö.Y.; Literature Review – A.Y.; Writing – A.Y., D.Ç., H.L., Ö.Y.; Critical Review – A.Y., D.Ç., H.L., Ö.Y.

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Vaping-triggered diffuse alveolar haemorrhage in a patient with advanced liver disease and severe coagulopathy: A causal inflection?

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Abstract:

Vaping-triggered diffuse alveolar haemorrhage (DAH) is rarely reported in the literature. We report the case of a 60-year-old man who presented to the emergency department with hemoptysis. He had a known history of chronic liver disease and presented with coagulopathy. He was an active smoker with a cumulative tobacco exposure of 12.5 pack-years and had been using nicotine-containing e-cigarettes for the past 10 months. Initial chest radiograph revealed bilateral infiltrates and high-resolution computed tomography (HRCT) of the thorax demonstrated bilateral, nodular, multifocal ground-glass opacities. Bronchoalveolar lavage (BAL) showed a progressively bloody return, consistent with diffuse alveolar haemorrhage (DAH). Coagulopathy was managed using targeted therapy guided by Rotational Thromboelastometry (ROTEM). Despite aggressive management, the patient succumbed to septic shock on the ninth day of admission. The pathogenesis of vaping-induced DAH may involve direct vascular injury from heated chemicals or an indirect mechanism via inflammatory cascades triggered by inhaled chemicals. In our patient with chronic liver disease complicated by coagulopathy, vaping triggered diffuse alveolar haemorrhage. This case highlights that vaping exposure may trigger DAH in patients with predisposing conditions such as severe coagulopathy due to chronic liver disease.

Keywords:

Bronchoscopy, diffuse alveolar haemorrhage, intensive care, respiratory failure, smoking, vaping

Introduction

E-cigarettes were initially developed as a smoking cessation tool. However, their popularity increased rapidly among

adolescents due to targeted marketing, the availability of flavored options, and the ease of access through online platforms. Over time, it became evident that ENDS (electronic nicotine delivery

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systems) are associated with various health-related hazards. There are several reported cases of EVALI (E-cigarette or vaping associated lung injury).^[1] However, vaping-triggered diffuse alveolar haemorrhage (DAH) is rarely reported in the literature.

Case Report

A 60-year-old male presented with an acute onset of cough and blood-tinged sputum. There was no history of fever, chest pain, orthopnea, or paroxysmal nocturnal dyspnea. There was no history suggestive of a connective tissue disease, such as joint pain, rash, myalgia, Raynaud's phenomenon, dry eye, or dry mouth. Travel and recreational drug use history were unremarkable. He had a 5-year history of chronic liver disease — non-alcoholic steatohepatitis (NASH). He was not taking any regular medications and did not report any drug intake in the past 2 months. He was an active smoker with a cumulative tobacco exposure of 12.5 pack-years and had been using nicotine containing e-cigarettes for the past 10 months.

On examination, he was conscious and oriented to time, place, and person. His vital signs were heart rate of 92 beats per minute, respiratory rate of 22 breaths per minute, and peripheral oxygen saturation (SpO₂) of 97 % on room air. Auscultation revealed fine end-inspiratory crepitations throughout both lung fields. The rest of the systemic examination was unremarkable.

Laboratory investigation revealed a hemoglobin level of 8.6 g/dl, a total leucocyte count of 10000/mm³, and a platelet count of 38000/mm³. Liver function tests showed a total bilirubin of 9.7 mg/dl and an international normalised ratio (INR) of 4.7. Serum creatinine was 1 mg/dl. The patient had a Child–Pugh score of 11 (Class C) and an estimated MELD 3.0 score of 34. Bedside 2D echocardiography showed a preserved left ventricular ejection fraction with no regional wall-motion abnormalities. The inferior vena cava (IVC) measured between 1.1 and 1.2 cm. Urinalysis did not reveal red blood cells.

The chest radiograph showed bilateral infiltrates [Fig. 1a]. The high-resolution computed tomography (HRCT) of the thorax showed bilateral, nodular, multifocal ground-glass opacities [Fig. 1b]. A nasopharyngeal swab for RT-PCR testing for H1N1, Influenza A, HMPV, and SARS COV-2 was negative. Sputum and blood cultures did not grow any pathogenic organisms.

Coagulopathy was addressed using ROTEM-guided targeted therapy. Despite correction of the coagulopathy, the patient's oxygen requirement progressively increased, and he eventually required 2 L/min of supplemental oxygen via nasal cannula to maintain an SpO₂ of 97%.

Autoimmune serologies, including antinuclear antibody, antineutrophil cytoplasmic antibodies (ANCA) — both cytoplasmic (c-ANCA) and perinuclear (p-ANCA) — were negative by indirect immunofluorescence. HIV screening using an immunochromatographic card test was non-reactive. A urinary drug screen for amphetamines, benzodiazepines, barbiturates, and cannabinoids was negative.

Flexible bronchoscopy, performed on day three, revealed blood clots at the carina [Fig. 1c]. Bronchoalveolar lavage (BAL) demonstrated a progressively bloody return, consistent with diffuse alveolar haemorrhage (DAH) [Fig. 1d]. Cytological examination of BAL fluid on hematoxylin and eosin-stained sections showed hemosiderin-laden macrophages [Fig. 1e]. Further confirmation of hemosiderin accumulation within the macrophages was achieved using Perls' Prussian blue stain, which specifically highlighted the hemosiderin pigment and demonstrated the presence of iron deposits [Fig. 1f]. BAL cultures were negative for infection. Despite correction of coagulopathy (INR less than 2), the patient's condition continued to deteriorate, with progressively increasing oxygen requirements, suggesting that correction of coagulation abnormalities alone did not fully reverse the pulmonary haemorrhage. A diagnosis of DAH secondary to coagulopathy in the context of chronic liver disease (non-alcoholic steatohepatitis, NASH) was made, with vaping identified as the likely trigger.

During the hospital stay, the patient developed a fever, septic shock, and acute kidney injury. Antibiotic therapy was escalated. Glucocorticoid therapy was planned after sepsis was controlled. The poor prognosis was explained to the patient's family. He required inotropic support to maintain blood pressure, and was started on continuous renal replacement therapy. The patient succumbed to septic shock on the ninth day of admission.

Discussion

E-cigarette or vaping product associated acute lung injury (EVALI) is a recognised complication of vaping.^[1] Electronic nicotine delivery systems typically consist of

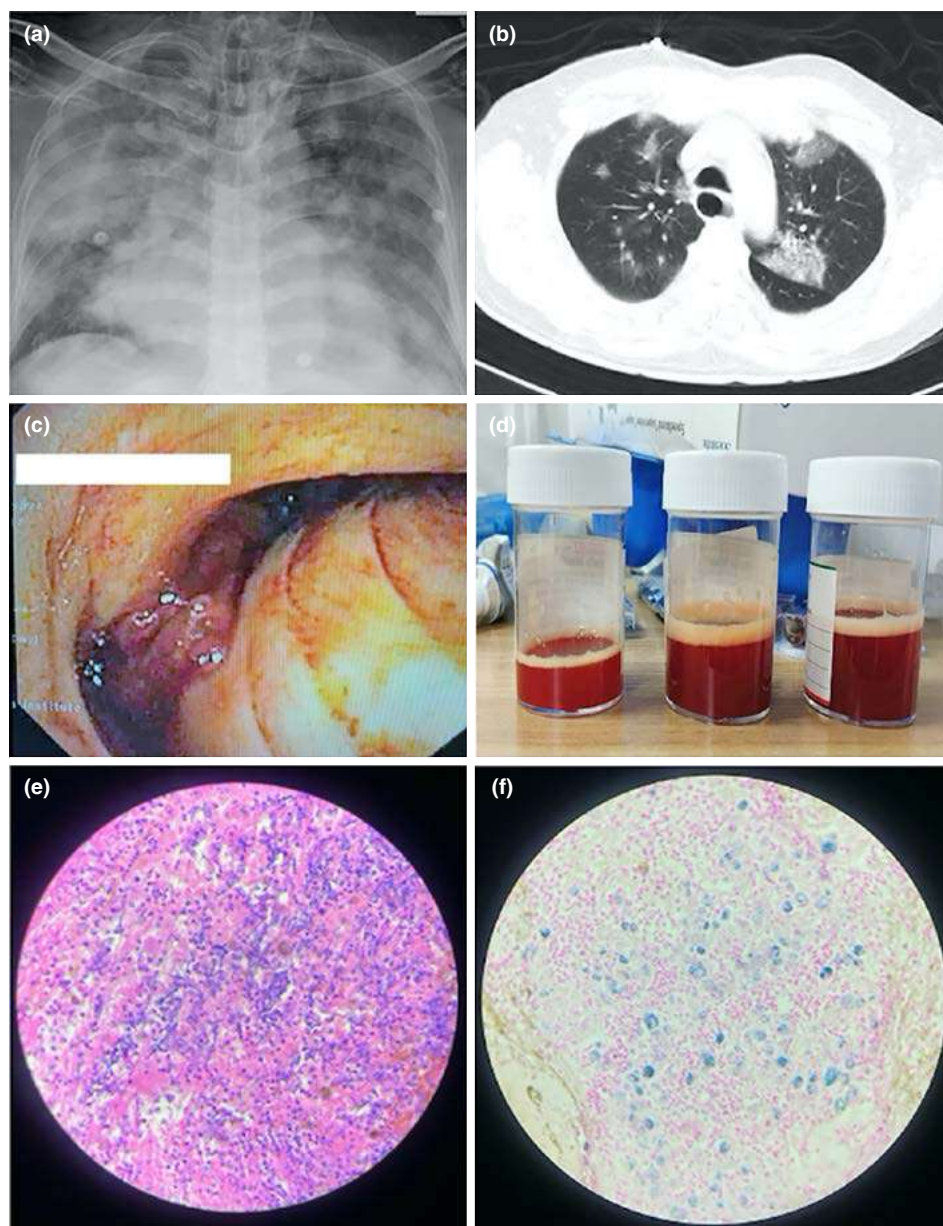


Figure 1: (a) Chest radiograph showed bilateral infiltrates. (b) The High resolution computed tomogram (HRCT) of thorax showing bilateral nodular, multifocal ground glass opacities. (c) Flexible bronchoscopy image showing blood clots at the carina. (d) Bronchoalveolar lavage (BAL) showing progressively bloody return consistent with diffuse alveolar haemorrhage (DAH). (e) BAL fluid showing hemosiderin-laden macrophages on the hematoxylin and eosin stained sections. (f) Perl's Prussian blue stain demonstrating the hemosiderin pigment

a cartridge containing a liquid, a chamber containing a heating element, and a battery-operated power source. E-cigarette liquid generally contains nicotine, propylene glycol, and added flavours. Vaping refers to using electronic cigarettes to vaporize nicotine and other flavoured liquids for inhalation.

EVALI is defined as the presence of bilateral lung opacities, the use of e-cigarettes within the previous 90 days,

the exclusion of infection, and the absence of an alternative diagnosis. The clinical spectrum of e-cigarette-associated pulmonary disease is varied, ranging from mild pulmonary symptoms without associated lung injury to life-threatening acute lung injury. Our patient met several of the diagnostic criteria proposed for E-cigarette or vaping-associated lung injury (EVALI), including recent vaping within 90 days, bilateral pulmonary opacities on imaging, and exclusion of infectious causes. However,

Table 1: Cases of vaping induced diffuse alveolar haemorrhage reported in literature

Authors	Year of publication	Age (years)	Gender	Symptom onset after initiation of vaping	Predominant vaping product	Treatment
Agustin et al. ^[3]	2018	33	Male	2 months	Nicotine	Steroids
Wilhite et al. ^[4]	2019	22	Male	Not known	THC	Steroids
Edmonds et al. ^[5]	2020	31	Female	4 years	Nicotine	Only cessation of vaping
Singh et al. ^[6]	2020	22	Male	3-4 years	THC	Steroids
Shehata et al. ^[7]	2020	61	Female	2 weeks	THC	Steroids
Villeneuve et al. ^[8]	2020	28	Female	1 month	Nicotine	Steroids and Rituximab
Suhling et al. ^[9]	2020	21	Male	2 years	Nicotine	Steroids
Hoekstra et al. ^[10]	2021	17	Male	Not known	Nicotine and Cannabis oil	Observation

the clinical and bronchoscopic findings were most consistent with diffuse alveolar haemorrhage as the predominant pathological manifestation, rather than with the more typical organizing pneumonia or diffuse alveolar damage patterns described in EVALI. Therefore, this case is best interpreted as vaping-associated DAH within the broader EVALI spectrum, occurring in a patient with significant underlying coagulopathy.

Although vaping can cause various forms of acute lung injury, vaping-triggered DAH is particularly rare. In a retrospective multicentre cohort of 160 EVALI cases, DAH was reported in only six (3.8%) cases.^[2] A PubMed search identified eight reported cases of DAH due to vaping (Table 1). Among these, four patients vaped only nicotine, three patients vaped only tetrahydrocannabinol (THC), and one patient vaped both nicotine and THC. All the patients except one was managed with steroids.^[3-10] One patient received Rituximab in addition to steroids.^[8] One patient improved only with smoking cessation as he was maintaining SpO₂ on room air.^[5] Our patient differed from previously reported cases by presenting with advanced liver disease and severe coagulopathy, suggesting that vaping exposure may act as a trigger in such patients.

In our case, several alternative causes of diffuse alveolar haemorrhage were systematically evaluated. Pulmonary–renal syndromes were considered unlikely because of the absence of hematuria or renal dysfunction at presentation and because autoimmune serologies, including ANA and ANCA, were negative. Infectious etiologies were excluded through negative microbiological testing of respiratory samples and blood cultures. Portal hypertension–related pulmonary vascular complications such as hepatopulmonary syndrome and portopulmonary hypertension were also considered; however, echocardiography demonstrated preserved cardiac function without evidence of pulmonary hypertension, and the clinical

presentation was not consistent with these conditions. These findings favored the diagnosis of DAH over other pulmonary complications of chronic liver disease.

The mechanism of vaping-induced DAH not fully understood and is proposed to be multifactorial. It may be due either to direct vascular injury from heated chemicals or to an inflammatory cascade triggered by the inhaled chemicals. In the present case, the patient had advanced chronic liver disease with significant coagulopathy (INR 4.7, thrombocytopenia). This likely created a vulnerable haemostatic environment within the pulmonary microvasculature. However, the temporal association with ongoing vaping exposure raises the possibility that inhaled chemical irritants may have acted as a trigger, potentially through direct endothelial injury or inflammatory activation. Thus, the clinical presentation may reflect a multifactorial process in which vaping exposure precipitated DAH in a patient with a pre-existing haemostatic vulnerability. There are no randomised controlled trials on the management of vaping-induced lung injury, so therapeutic regimens have not yet been confirmed. Currently, cessation of e-cigarette use and systemic glucocorticoid therapy are used in the management of vaping-induced DAH. Glucocorticoid therapy was planned, but its use was deferred in our patient due to the development of sepsis. The management focused primarily on correction of coagulopathy using targeted therapy, guided by rotational thromboelastometry (ROTEM), and supportive care.

Conclusion

This case highlights that vaping exposure may act as a potential trigger for diffuse alveolar haemorrhage in patients with predisposing conditions such as severe coagulopathy from chronic liver disease. Clinicians should consider a history of vaping when evaluating unexplained pulmonary haemorrhage in at-risk patients.

Ethics Committee Approval

This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent

Written informed consent was obtained from the patients relative.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Elevated neutrophil-to-lymphocyte ratio is associated with poor outcomes in patients with chronic thromboembolic pulmonary hypertension

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Dear Editor,

We read with great interest the article by Acet Öztürk et al.,^[1] entitled "Elevated neutrophil-to-lymphocyte ratio is associated with poor outcomes in patients with chronic thromboembolic pulmonary hypertension." The article provides valuable insights into prognostic determinants in chronic thromboembolic pulmonary hypertension (CTEPH) based on a long-term, real-world cohort. The authors are to be congratulated for their comprehensive evaluation of inflammatory markers alongside hemodynamic, imaging, and treatment-related variables within a multidisciplinary management framework.

A major strength of this study is the demonstration that the neutrophil-to-lymphocyte ratio (NLR), a simple and widely available inflammatory biomarker, is independently associated with

mortality in patients with CTEPH. This finding is particularly important given that current risk stratification in CTEPH largely relies on invasive hemodynamic measurements and advanced imaging modalities.^[2] The identification of NLR as an independent prognostic factor therefore provides a cost-effective and easily applicable tool that may enhance routine clinical risk assessment.

Another important contribution is the evaluation of baseline and longitudinal B-type natriuretic peptide (BNP) levels.^[1,2] The observed association of both initial BNP values and BNP trajectories during follow-up with mortality highlights the clinical importance of serial biomarker monitoring rather than relying solely on a single baseline measurement. This dynamic approach to risk assessment is consistent with the evolving understanding of pulmonary hypertension as a progressive and heterogeneous disease.

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The study also reinforces the well-established survival benefit of pulmonary endarterectomy (PEA). Patients treated with medical therapy alone exhibited a markedly higher risk of mortality than those who underwent surgical intervention. These findings are consistent with large registry data and previous multicenter studies, confirming that PEA remains the cornerstone of therapy in appropriately selected patients with CTEPH.^[3]

Importantly, the lack of significant differences in baseline echocardiographic and hemodynamic parameters between survivors and nonsurvivors suggests that resting measurements of pulmonary arterial pressure and vascular resistance may have limited prognostic value when considered in isolation.^[1,4] This observation further supports the integration of systemic inflammatory markers, such as NLR, into multidimensional risk stratification models. Although the retrospective, single-center design and limited sample size may restrict generalizability, these limitations are expected in rare disease research and do not diminish the clinical relevance of the findings. On the contrary, the study provides meaningful hypothesis-generating evidence that may guide future prospective, multicenter investigations. Overall, this well-conducted study adds significant value to the current literature by highlighting the prognostic role of NLR, emphasizing the importance of BNP dynamics, and reaffirming the survival benefit of surgical intervention in CTEPH. It also supports the potential integration of simple inflammatory biomarkers into future risk stratification strategies.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Methodological considerations on the association between eosinophilia and tuberculosis treatment duration

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Dear Editor,

We read with interest the article by Yayla et al.,^[1] entitled "The impact of eosinophilia on treatment duration in patients with newly diagnosed drug-sensitive pulmonary tuberculosis.". The authors address a relatively unexplored question; however, several methodological issues may affect the interpretation of the association between eosinophilia and treatment duration.

First, although the introduction describes eosinophilia and its possible antimycobacterial effects, the clinical rationale for why peripheral eosinophilia might influence tuberculosis treatment duration could be clearer.^[2] Conversely, the operational definitions of eosinophilia, particularly the absolute eosinophil count (AEC) threshold of ≥ 500 cells/ μ L, are discussed extensively in the introduction, although these would more appropriately belong in the Methods section.

The exclusion of patients with AEC ≥ 1500 cells/ μ L deserves consideration. Patients with more pronounced eosinophilia may

represent an important eosinophilic phenotype; excluding them may introduce selection bias and limit generalizability. Moreover, categorizing eosinophilia solely as present or absent using a threshold of 500 cells/ μ L may result in the loss of relevant information. In addition to categorical analysis, AEC could have been evaluated as a continuous variable using baseline, peak, or changes during treatment to assess a possible dose-response relationship between eosinophil levels and treatment duration.

Similarly, treatment duration was dichotomized as ≤ 6 months versus > 6 months for logistic regression. Although clinically intuitive, this approach discards information on actual treatment duration, which ranged from 6 to 9 months in both groups. Retaining treatment duration as a continuous or time-based outcome could provide additional information and avoid the limitations associated with dichotomization.

Potential confounding is also important. Treatment duration in pulmonary tuberculosis may be influenced by disease severity and treatment response. However,

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Table 1 does not include radiological parameters such as cavitation, bilateral involvement, or overall radiological extent. Microbiological indicators that may influence treatment prolongation are also not presented. The authors acknowledge the absence of baseline cavitary disease as a limitation. Nevertheless, because radiological severity may directly influence treatment duration, the lack of adjustment for these variables may substantially affect the observed association with eosinophilia.^[3]

Baseline characteristics could also be presented more comprehensively. Sex, despite differing significantly between the groups, is absent from Table 1. Several comorbidities included in the regression model are reported only in the text. Total bilirubin and other laboratory parameters relevant to treatment tolerability and duration are also not presented. A more complete baseline table would facilitate the assessment of group comparability and residual confounding.

Finally, although the results refer to univariate analysis, the complete results and criteria for multivariable variable selection are unclear. Age was excluded because it was not significant in the univariate analysis and was similarly distributed between the groups. Relying predominantly on univariate statistical significance may overlook clinically relevant confounders. Providing the full univariate analysis and a clearer explanation of the prespecified or clinically based variable-selection strategy would improve the transparency of the regression analysis.

In conclusion, the association between eosinophilia and shorter tuberculosis treatment duration is intriguing. However, possible selection bias resulting from the exclusion of marked eosinophilia, dichotomization of eosinophilia and treatment duration, incomplete adjustment for radiological and clinical determinants of treatment

duration, and limited reporting of the regression strategy should be considered when interpreting the findings. Further analyses treating eosinophil count as a continuous variable and incorporating major determinants of tuberculosis disease severity would strengthen the conclusions.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Reply to the letter to the editor: Methodological considerations on the association between eosinophilia and tuberculosis treatment duration

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We read with great interest the letter^[1] regarding our recently published article entitled “*The Effect of Eosinophilia on the Duration of Treatment in Patients With New-Case Drug-Sensitive Pulmonary Tuberculosis.*”^[2] We appreciate the author(s) for their valuable comments, rigorous methodological evaluation, and constructive feedback. Below, we address the specific points raised in their correspondence.

The reader correctly notes that patients with an absolute eosinophil count (AEC) ≥ 1500 cells/ μ L were excluded (n=5). Our primary rationale for this strict cutoff was to exclude severe hypereosinophilic syndromes, underlying secondary organ dysfunction, or severe adverse drug reactions (e.g., DRESS syndrome or drug-induced liver injury), which inherently complicate anti-tuberculosis (TB) treatment management and prolong therapy independently of *Mycobacterium tuberculosis* (MTB) clearance. Including

these rare, severe systemic cases would have introduced substantial confounding regarding treatment duration. Although we acknowledge that excluding these cases limits generalizability to extreme hypereosinophilic phenotypes, it was necessary to isolate the mild-to-moderate idiopathic/reactive eosinophilic response.

We agree that analyzing AEC as a continuous variable provides valuable insights into potential dose-response dynamics. In our preliminary data exploration, we observed that peak AEC levels within Group 2 varied widely, without a strict linear relationship with treatment shortening once the threshold of ≥ 500 cells/ μ L was exceeded. *In vitro* evidence demonstrates that eosinophil products, such as eosinophil peroxidase (EPO), exert direct mycobactericidal activity and induce MTB cell wall damage and lysis.^[2] Because national guidelines and clinical practice traditionally mandate

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a standard 6-month core regimen versus extended regimens (>6 months) based on clinical decision-making.^[3] Dichotomizing the outcome (≤ 6 months vs. extended >6 months) therefore aligned directly with real-world clinical endpoints. Nonetheless, we appreciate this suggestion and recommend that future prospective trials incorporate continuous modeling (e.g., restricted cubic splines) to evaluate potential nonlinear dose-response curves.

The author(s) rightly emphasize the critical role of baseline radiological severity (cavitation, bilateral involvement) and microbiological conversion dynamics in determining treatment duration.^[4] As explicitly acknowledged in our limitations section, the absence of detailed radiological scoring, such as baseline cavitation, was a limitation of our retrospective database design. In routine practice at our tertiary national reference center, treatment extension beyond 6 months is governed by a holistic assessment, including delayed sputum culture conversion, extensive cavitory lesions, and persistent clinical symptoms. Although we controlled for major clinical comorbidities, such as diabetes mellitus (DM), which strongly predicted prolonged treatment in our cohort (OR: 3.20), residual confounding from unmeasured radiological extent cannot be fully ruled out. Future prospective studies should systematically adjust for cavitory burden and 2-month culture conversion.

Regarding baseline variables, sex was included in both univariate and multivariate logistic regression models and showed no statistically significant association with prolonged treatment duration ($p=0.328$ and $p=0.340$, respectively). Although sex was omitted from the main summary table for brevity, the sex distribution (70.2% male in the control group vs. 89.1% in the eosinophilia group, $p=0.001$) was explicitly detailed in the Results section and controlled for during multivariate adjustment. Furthermore, metabolic and systemic comorbidities such as DM are well recognized to induce chronic subclinical inflammation and impair host immunity, frequently contributing to prolonged TB treatment.^[5] This further supports our multivariate approach to controlling for major metabolic confounders.

Our variable selection strategy for the final multivariable model employed a combined approach based on clinical relevance and automated backward stepwise selection. Variables known to influence TB clinical pathways (age, sex, comorbidities including DM and HT, and eo-

sinophilia status) were entered into the model.^[4,6] Age was excluded during backward elimination because it showed no univariate trend ($p=0.438$) and was closely matched across both cohorts (median, 43 vs. 45 years). Diabetes mellitus (OR: 3.20, 95% CI: 1.57–6.52; $p=0.001$) and the absence of eosinophilia (OR: 2.06, 95% CI: 1.14–3.71; $p=0.017$) remained robust independent predictors of treatment prolongation in the final parsimonious model.

In summary, we thank the author for highlighting these important methodological points. Although the limitations inherent in the retrospective design necessitate cautious interpretation, our findings provide an intriguing foundation suggesting that mild-to-moderate eosinophilia during drug-sensitive TB therapy may reflect an efficient host immune response rather than merely a drug reaction. We fully support the call for prospective, multicenter studies integrating radiological metrics and detailed cellular immunology to further validate these observations.

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