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Severe asthma and biologic therapies in children and adults

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Abstract:

Severe asthma is characterized by persistent symptoms or recurrent exacerbations despite appropriately delivered high-dose controller therapy, verified adherence, correct inhaler technique, and optimal management of comorbidities and relevant triggers, or by deterioration in control when treatment intensity is reduced. Although severe asthma affects only an estimated 3–10% of patients with asthma, it accounts for the majority of asthma-related morbidity and mortality. Biologic agents constitute an important treatment option for severe asthma, and responses to these therapies vary across endotypes, which are broadly classified as type 2–high or type 2–low. Approved biologic agents for asthma management target immunoglobulin E (IgE), interleukin-5 (IL-5), the interleukin-4 receptor (IL-4R), and thymic stromal lymphopoietin (TSLP). Selection of an appropriate biologic agent is guided by markers of type 2 inflammation, such as blood eosinophil counts, fractional exhaled nitric oxide (FeNO), and serum IgE levels. However, substantial overlap in clinical and inflammatory profiles among patients often complicates identification of the most suitable biologic therapy. This review synthesizes available data from randomized controlled trials and real-world studies evaluating the clinical efficacy of biologic agents in the current management of severe asthma and aims to provide a practical perspective by integrating key biomarkers into clinical decision-making.

Keywords:

Biologic therapies, biomarkers, endotype, severe asthma

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Introduction

Asthma is a chronic disorder characterized by persistent airway inflammation that can occur at any age and typically presents with symptoms such as cough, dyspnea, or chest tightness.[1] Symptom intensity varies over time, and airflow limitation may become persistent. Inhaled corticosteroids (ICS) remain the mainstay of asthma management, effectively reducing airway inflammation, improving symptom control, and preventing exacerbations. Difficult-to-treat asthma refers to asthma that remains uncontrolled despite treatment with medium- or high-dose ICS plus a second controller or maintenance oral corticosteroids (OCS), or that

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requires high-dose therapy to maintain symptom control and reduce exacerbations.[2] Inadequate asthma control may be associated with modifiable factors, including incorrect inhaler technique, poor treatment adherence, smoking, obesity, exposure to environmental or occupational allergens, or misdiagnosis.[1] In patients with suboptimal asthma control, the possibility of obstructive sleep apnea should be considered, and individuals should be evaluated accordingly.[3]

Low adherence to treatment is a key contributor to poor disease control in obstructive lung diseases. Suboptimal adherence may arise from incorrect use of inhaler devices, irregular use of controller medications, or limited perception of disease severity. Notably, during periods of heightened health threat, such as the coronavirus disease 2019 (COVID-19) pandemic, patients demonstrated temporary improvements in adherence, highlighting the critical role of patient education and illness awareness in optimizing asthma management.[4] Additionally, structured education on inhaler technique is of critical importance, and evidence indicates that training provided by physicians significantly improves inhaler use accuracy and associated clinical outcomes.[5] Although the type of inhaler device is often considered in clinical practice, recent evidence suggests that device selection alone does not substantially influence asthma outcomes.[6]

Severe asthma is defined as asthma that remains uncontrolled despite optimization of modifiable factors.[2] According to the Global Initiative for Asthma (GINA), severe asthma affects an estimated 3–10% of patients with asthma.[1] Among children with asthma, however, severe disease appears to be less common, with a reported prevalence of approximately 3%.[7] The prevalence of severe asthma varies substantially between countries. In a study conducted in the Netherlands, approximately 24% of adults with asthma required management at GINA Steps 4–5. Within the overall asthma population, an estimated 17% met the criteria for difficult-to-treat asthma, whereas a further 3.7% constituted the subgroup that remained uncontrolled despite documented good adherence and correct inhaler technique and were therefore classified as having severe asthma.[8] Severe asthma has been reported in 8.1% of patients with asthma in Denmark and 4.2% in Sweden.[9,10] These differences are attributed to heterogeneity in genetic and environmental factors. Additionally, the absence of a universally accepted and precise definition of asthma, along with the use of varying definitions and methodologies in epidemiological studies, complicates comparisons of prevalence data across studies.[1]

Endotypes of Asthma

Asthma can be broadly categorized into two major endotypes, each driven by distinct immunological pathways and exhibiting variable clinical responses to treatment.

Type 2 (T2)-High Endotype: Exposure to pollutants, viruses, or bacteria can render airway epithelial cells more fragile and increase their permeability to environmental factors, ultimately causing tissue injury.[11] As a result, epithelial cells secrete innate cytokines, referred to as alarmins, including thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25), and interleukin-33 (IL-33). Alarmins stimulate the differentiation of T helper 2 (Th2) cells and trigger activation of type 2 innate lymphoid cells (ILC2s). Both ILC2s and Th2 cells secrete several T2 cytokines, including interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13). IL-4 and IL-13 promote class switching in allergen-specific B cells, leading to immunoglobulin E (IgE) production. IgE subsequently binds to high-affinity FcεRI receptors on mast cells and basophils. Allergen-induced cross-linking of surface-bound IgE triggers degranulation and the release of pro-inflammatory mediators.[12] IL-4 further induces IgE production by B cells, whereas IL-5 promotes eosinophil maturation and differentiation. IL-13 upregulates inducible nitric oxide synthase expression in airway epithelial cells, resulting in increased fractional exhaled nitric oxide (FeNO) levels, and contributes to mucus hypersecretion and airway hyperresponsiveness.[13] Airway remodeling initiated by alarmins requires the expression of fibrogenic and angiogenic factors, leading to marked structural alterations in the bronchial walls and blood vessels. These changes result in airway narrowing and stiffening, which clinically manifest as airflow limitation and respiratory symptoms.[14] Biologic therapies primarily target the T2-high endotype. The immunopathogenesis of T2-high severe asthma and the biologics targeting this pathway are illustrated in Figure 1.

T2-Low Endotype: T2-low asthma is characterized by increased disease severity, airway remodeling, and poor responsiveness to anti-inflammatory therapy. The immunopathogenesis of this endotype involves several mechanisms, including intrinsic neutrophil abnormali-

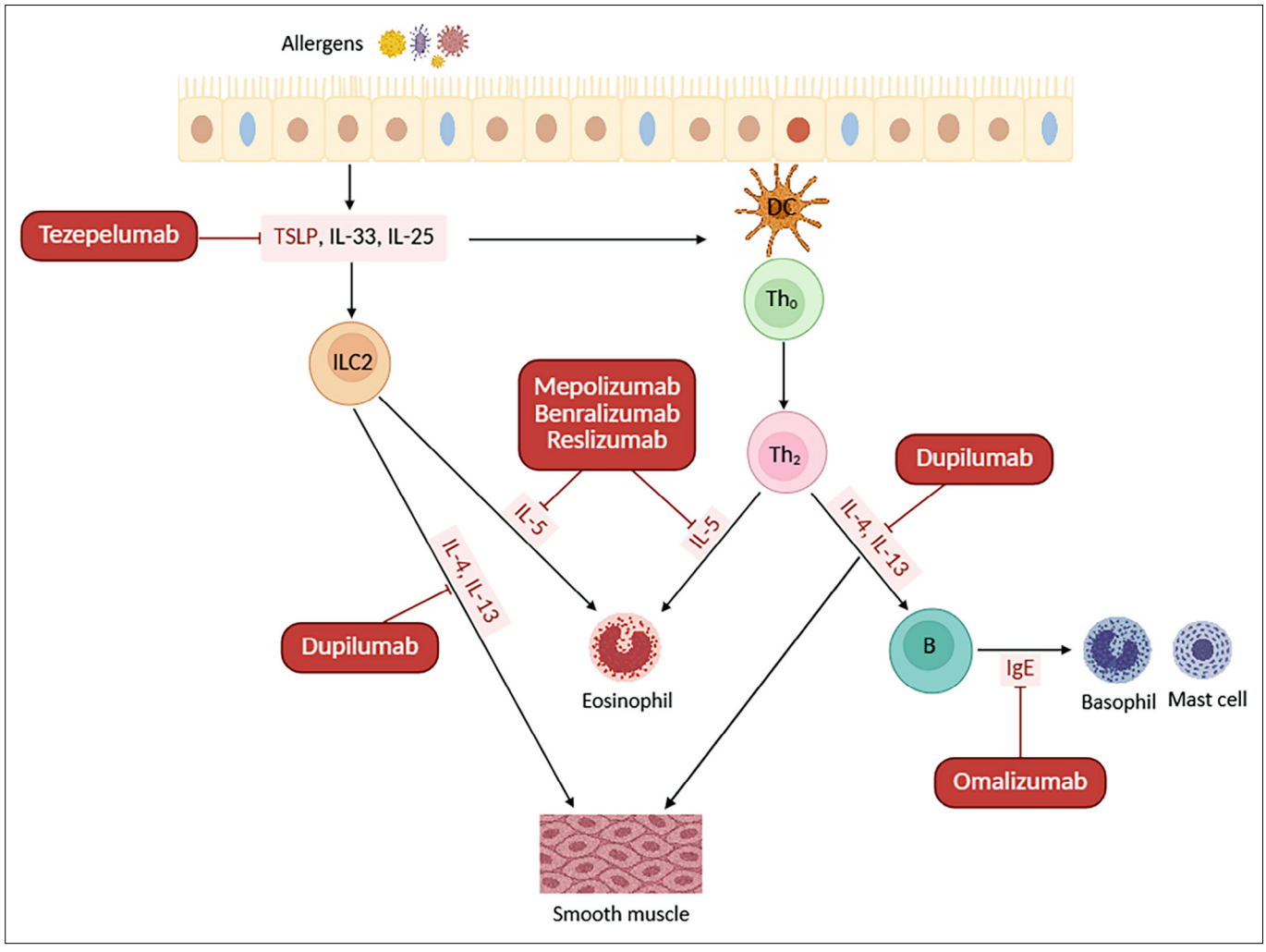

Figure 1: Type 2 (T2)-high severe asthma immunopathogenesis and specific biologic targets. In T2-high asthma, exposure to allergens, pollutants, or microbial agents stimulates the airway epithelium to release alarmins, including interleukin-33 (IL-33), IL-25, and thymic stromal lymphopoietin (TSLP). Dendritic cells (DCs) present these aeroallergens to naïve CD4⁺ T cells (Th0), promoting their differentiation into T helper 2 (Th2) cells. IL-4 is a critical cytokine driving this differentiation process. Activated Th2 cells, together with type 2 innate lymphoid cells (ILC2s), produce large amounts of type 2 cytokines, including IL-4, IL-5, and IL-13. In addition to promoting Th0-to-Th2 differentiation, IL-4 in combination with IL-13 plays a key role in inducing immunoglobulin E (IgE) class switching in B lymphocytes. IgE binds to the high-affinity FcεRI receptors expressed on mast cells and basophils. Upon re-exposure to the same allergen, cross-linking of these IgE molecules triggers the release of histamine, leukotrienes, and prostaglandins, leading to bronchoconstriction

ties, activation of inflammatory pathways, and engagement of the IL-17 axis.[14] Activation of T helper 1 (Th1) and T helper 17 (Th17) cells leads to elevated levels of interleukin-17A (IL-17A). Bronchial biopsies obtained from individuals with severe asthma demonstrated increased levels of Th17-associated cytokines, which mediate neutrophil recruitment to the airways.[15] Consequently, elevated IL-17 activity has been recognized as a distinct contributor to the development of severe asthma. T2-low asthma typically presents in adulthood and is frequently associated with factors such as obesity, aging, alterations in the lung microbiome, epithelial dysfunction, and gastroesophageal reflux disease.[11]

Biomarkers of Asthma Used in Clinical Practice

The ideal biomarker for asthma should accurately reflect the underlying pathophysiological mechanisms or therapeutic targets, exhibit high sensitivity and specificity, and be easily obtainable with minimal discomfort or risk. Additionally, it should be reproducible, cost-effective, practical, and safe, while providing valuable prognostic and pharmacodynamic information for disease monitoring.

Eosinophils

The extent of eosinophilic inflammation in blood and sputum correlated with disease activity in both atopic

and non-atopic asthma.[16] Blood eosinophil count (BEC) remains a valuable biomarker for differentiating asthma phenotypes and evaluating response to treatment.

Sputum eosinophils

Eosinophil counts in induced sputum provide valuable insight into asthma phenotypes and underlying disease mechanisms. A sputum eosinophil count of ≥2% suggests underlying eosinophilic airway inflammation.[1] Higher sputum eosinophil levels have been associated with an increased incidence of exacerbations and suboptimal disease control.[17]

Blood eosinophil count

An elevated BEC exceeding national or regional reference values may indicate type 2 asthma, although lower counts do not exclude this diagnosis. Blood eosinophil levels may also be elevated in non-asthmatic conditions, including parasitic infections, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis with nasal polyposis (CRSwNP), hypereosinophilic syndrome, and eosinophilic granulomatosis with polyangiitis (EGPA). In addition, BEC can be influenced by age, sex, timing of measurement (with afternoon values generally lower), geographic region, obesity, and atopy.[18] BEC ≥150/μL during treatment with high-dose ICS or maintenance OCS suggests the possibility of refractory type 2 inflammation.[1]

Fractional concentration of exhaled nitric oxide

Nitric oxide synthesis in airway epithelial cells is promoted by the cytokines IL-4 and IL-13. FeNO levels show a moderate correlation with sputum eosinophil counts and blood eosinophil levels and are typically elevated in type 2-high asthma.[19] FeNO may also be increased in non-asthmatic conditions, such as eosinophilic bronchitis, atopy, allergic rhinitis, and atopic dermatitis, while remaining normal in certain asthma phenotypes, including neutrophilic and obesity-associated asthma.[20] According to the GINA 2025 report, high FeNO levels are defined as >50 ppb in ICS-naïve patients, ≥25 ppb in patients treated with medium-dose ICS, and ≥20 ppb in those receiving high-dose ICS therapy.[1] In patients presenting with typical asthma symptoms, elevated FeNO levels may support a diagnosis of type 2 asthma; however, lower values do not exclude asthma.[1]

Serum total IgE

IgE synthesis is driven by interactions between Th2 lymphocytes and B cells, culminating in the stimulation of mast cells and basophils. Serum IgE levels do not consistently reflect asthma severity or treatment response. In addition to asthma, elevated total IgE levels may be observed in conditions such as allergic rhinitis, nasal polyposis, atopic dermatitis, parasitic infections, immunodeficiency syndromes, and allergic bronchopulmonary aspergillosis. Increased IgE levels may occasionally be associated with malignancies, smoking, or high environmental allergen exposure. Anti-IgE therapy may be considered in appropriately selected patients with asthma.[21]

Neutrophils

High levels of airway neutrophils are frequently observed in severe T2-low asthma phenotypes associated with activation of Th17 pathways. Although sputum examination may demonstrate marked neutrophilic inflammation, studies have reported inconsistent correlations between airway and peripheral blood neutrophil counts, highlighting the need for additional diagnostic assessments.[22]

Biologics in Severe Asthma

Severe asthma accounts for less than 10% of all asthma cases but contributes disproportionately to overall morbidity and healthcare costs.[8] Currently, four main classes of biologic agents are approved for the management of severe asthma, targeting IgE, IL-5, IL-4R, and TSLP (Table 1). These biologic therapies have been associated with substantial reductions in exacerbations, healthcare resource utilization (HCRU), and maintenance OCS requirements, along with improvements in patients' quality of life.[12]

Omalizumab

Omalizumab specifically targets the Fc region of IgE. By forming omalizumab–IgE complexes, it effectively reduces circulating free IgE levels.[23]

Omalizumab was approved by the United States (U.S.) Food and Drug Administration (FDA) in 2003 and was the first biologic agent developed for the targeted treatment of moderate-to-severe persistent asthma in adults and adolescents (≥12 years) who are sensitized to perennial aeroallergens and continue to have uncontrolled symptoms despite ICS therapy.[24] Approval by the European Medicines Agency (EMA) followed in 2005, extending its indication as add-on therapy for adolescents and adults (≥12 years) with severe allergic asthma that remains insufficiently controlled despite high-dose ICS plus a long-acting β2-agonist.[25] The approved use was

Table 1: Biologic therapies for severe asthma in children and adults

Biologic agent	Target	Indication	Biomarkers	Route of administration	Approved age		Biological effects
					FDA	EMA	
Omalizumab	IgE	Severe allergic asthma	IgE 30–1500 IU/mL[25]	Subcutaneous	≥6 years	≥6 years	Decreases circulating total IgE; Downregulates FcεRI receptors on basophils, mast cells, and dendritic cells
Mepolizumab	IL-5	Severe eosinophilic asthma	Eos ≥150 cells/μL before first administration or Eos ≥300 cells/μL in the previous year[38,44]	Subcutaneous	≥6 years	≥6 years	Blockade of IL-5/IL-5 binding
Benralizumab	IL-5Rα	Severe eosinophilic asthma	Eos ≥300 cells/μL[55]	Subcutaneous	≥6 years	≥18 years	Blockade of IL-5/IL-5R binding
Reslizumab	IL-5	Severe eosinophilic asthma	Eos ≥400 cells/μL[67]	Intravenous	≥18 years	≥18 years	Binds circulating IL-5 to prevent receptor engagement
Dupilumab	IL-4Rα	Severe eosinophilic asthma	Eos ≥150 cells/μL or FeNO ≥25 ppb[78]	Subcutaneous	≥6 years	≥6 years	Blockade of IL-4/IL-4Rα binding; Blockade of IL-13/IL-4Rα binding
Tezepelumab	TSLP	Severe asthma	T2-independent[83]	Subcutaneous	≥12 years	≥12 years	Blockade of TSLP/TSLPR binding

FDA: Food and drug administration, EMA: European medicines agency, Eos: Eosinophils, FeNO: Fractional exhaled nitric oxide, IgE: Immunoglobulin E, IL: Interleukin, IL-4Rα: Interleukin-4 receptor alpha, IL-5Rα: Interleukin-5 receptor alpha, TSLP: Thymic stromal lymphopoietin, T2: Type 2 inflammation, TSLPR: Thymic stromal lymphopoietin receptor.

subsequently expanded to include patients aged ≥6 years, with pediatric approval granted by the EMA in 2009 and by the FDA in 2016.[24,25]

Omalizumab is administered via the subcutaneous (SC) route at two- or four-week intervals. Dosing is adjusted according to patient weight and baseline total IgE levels, with authorized ranges of 30–1500 IU/mL across the European Union (EU) and 30–700 IU/mL in the U.S. Routine measurement of IgE levels during omalizumab therapy is unnecessary. Reassessment of clinical benefit is recommended after completion of an initial treatment period of approximately four to six months.[24]

Omalizumab is also approved and used in clinical practice for the management of CRSwNP, IgE-mediated food allergies, and chronic spontaneous urticaria.[24,25]

Randomized controlled trials (RCTs) have demonstrated that omalizumab treatment reduces the asthma exacerbation rate (AER) by 25–61%, improves disease-related quality of life, and decreases HCRU by 44%, while also allowing for a reduction in ICS doses.[23,26–28] Pediatric RCTs have shown approximately a 40% reduction in asthma exacerbation rates among children receiving omalizumab compared with those receiving placebo.[29,30] A large Cochrane review published in 2014, which included 25 RCTs involving both adults and children, demonstrated that omalizumab significantly reduced exacerbation frequency (by nearly 25%), lowered hospital admission rates, and facilitated reductions in inhaled ICS requirements.[31] Real-world data have consistently shown that omalizumab treatment is associated with fewer asthma exacerbations and reduced hospital attendance.[32] An integrated analysis combining data from clinical trials and seven years of real-world experience showed that omalizumab therapy in children with moderate-to-severe allergic asthma resulted in improved symptom control, reduced exacerbation rates, fewer hospital visits, and sustained reductions in inhaled corticosteroid use.[33]

Post-marketing surveillance has estimated the risk of anaphylaxis associated with omalizumab at approximately 0.2%, prompting the U.S. FDA to issue a boxed warning.[24]

The EXPECT study (The EXPOSURE in Pregnancy to Omalizumab), a prospective pregnancy registry including 250 women with asthma receiving omalizumab, demonstrated no increased incidence of major congen-

ital anomalies compared to matched controls.[34] Data derived from registries and post-marketing experience further support the absence of an increased risk of congenital anomalies, miscarriage, or preterm delivery.[12]

Mepolizumab

Mepolizumab inhibits the interaction between IL-5 and its receptor (IL-5Rα) on eosinophils, thereby suppressing eosinophil maturation in the bone marrow, reducing extracellular matrix deposition within the airway mucosa, and ultimately attenuating key pathophysiological mechanisms underlying eosinophilic asthma.[16]

Mepolizumab was approved in 2015 by both the U.S. FDA[35] and EMA[36] for the treatment of severe eosinophilic asthma (SEA) in individuals aged ≥12 years. The indication was subsequently expanded to include pediatric patients aged 6–11 years, with EMA approval granted in 2018 and FDA approval following in 2019.[35,36] Mepolizumab is indicated for patients with SEA who have experienced a specified number of asthma exacerbations in the previous year and have BEC above a locally defined threshold (e.g., ≥150 or ≥300/μL), with different cutoffs sometimes applied for patients receiving OCS.[1] The drug is administered via the SC route every four weeks, with a recommended dose of 40 mg for children aged 6–11 years and 100 mg for patients aged ≥12 years.[35,36] Mepolizumab is also approved for the treatment of CRSwNP, hypereosinophilic syndrome, and EGPA.

A multicenter, double-blind, placebo-controlled trial (Dose Ranging Efficacy And safety with Mepolizumab in severe asthma [DREAM]) evaluated three dosing regimens of mepolizumab and demonstrated a 39–52% reduction in the annual AER compared with placebo, along with a prolonged time to first exacerbation.[37] In the MENSA trial (MEpolizumab as adjunctive therapy iN patients with Severe Asthma), which evaluated both SC and intravenous (IV) mepolizumab versus placebo in adolescents and adults, treatment with mepolizumab resulted in a marked reduction in AERs across both routes of administration. In addition, increases in forced expiratory volume in 1 second (FEV_1) occurred rapidly after the first dose and were maintained over time.[38]

In an open-label, non-randomized study involving a small cohort of children aged 6–11 years, designed to assess mepolizumab bioavailability and optimal dosing, no safety signals were identified. Following treatment initiation, blood eosinophil levels declined in association with clinical improvement, whereas lung function parameters showed no significant change.[39] In the MUPPITS-2 trial (MEPolizumab adjUnct therapy in children and adolescents with severe eosInophilic aSthma), which enrolled participants aged 6–17 years, mepolizumab therapy resulted in an approximate 27% reduction in annual AERs compared to the placebo group.[40] However, this improvement was not accompanied by significant enhancements in pulmonary function or other clinical outcomes. The smaller reduction in exacerbation frequency compared to adult studies may reflect differences in the underlying pathophysiology of pediatric asthma.[41]

The COSMEX study (Long-term Safety and Efficacy of Mepolizumab in Patients with Severe Eosinophilic Asthma), which evaluated the long-term effects of mepolizumab, demonstrated that patients receiving mepolizumab experienced sustained reductions in AER and maintenance OCS use, along with improvements in FEV_1 and Asthma Control Questionnaire-5 scores.[42] Additionally, in this study, patients who discontinued mepolizumab for more than 12 weeks experienced a temporary deterioration in symptoms and FEV_1, which resolved rapidly after treatment reinitiation.[42] In the MUSCA study (Mepolizumab in Subjects with Severe Eosinophilic Asthma), mepolizumab produced an early and sustained improvement in FEV_1 compared with placebo and enhanced health-related quality of life (HRQOL) in patients with SEA.[43] In another study involving patients requiring daily OCS therapy, mepolizumab also conferred important clinical benefits, including reduced exacerbation rates, improved symptom control, and a substantial glucocorticoid-sparing effect.[44]

Real-world studies confirm the efficacy and safety profile of mepolizumab observed in clinical trials, particularly with respect to reductions in exacerbation rates, decreased systemic steroid use, improvements in FEV_1, and maintenance of favorable safety profile.[45,46]

A more favorable therapeutic response to mepolizumab has been associated with several clinical characteristics, including higher sputum eosinophil counts, the presence of comorbid CRSwNP, a history of frequent exacerbations at baseline, late-onset disease, lower body mass index, and the use of low-dose maintenance OCS.[47,48]

The most frequently reported adverse events associated with mepolizumab include respiratory tract infections,

headache, bronchitis, and worsening asthma symptoms. An increased incidence of herpes zoster has been observed in patients receiving mepolizumab compared with those receiving placebo.[49] Consequently, the U.S. FDA[35] recommends consideration of herpes zoster vaccination when clinically appropriate. The risk of parasitic infections associated with biologic agents targeting IL-5 and eosinophils remains uncertain. Nevertheless, a parasitic infection occurring during mepolizumab therapy has been reported previously in our clinic.[50]

Data on mepolizumab use during pregnancy are limited and are derived primarily from observational reports rather than interventional clinical studies. In this context, our clinical experience includes a patient who became pregnant while receiving mepolizumab; treatment was discontinued early in gestation, and the pregnancy resulted in a healthy term delivery.[51]

Benralizumab

Benralizumab targets IL-5Rα on eosinophils and basophils, leading to rapid and near-complete eosinophil depletion via antibody-dependent cell-mediated cytotoxicity. Benralizumab was approved in 2017 by the U.S. FDA for use in adults and adolescents (≥12 years) with SEA, and the indication was extended in 2024 to include children aged 6–11 years.[52] It was also approved in 2018 by the EMA for use in adults only, and the pediatric extension is currently under regulatory review.[53]

In pediatric patients aged 6–11 years weighing <35 kg, benralizumab is administered subcutaneously at a dose of 10 mg every four weeks for the first three doses, followed by maintenance dosing at eight-week intervals. In patients weighing ≥35 kg, as well as in adolescents and adults, benralizumab is administered subcutaneously at 30 mg every four weeks for the initial three doses, followed by maintenance treatment every eight weeks.[52]

Benralizumab is an option for patients with uncontrolled SEA and a BEC ≥300 cells/μL. In the SIROCCO study (Study of IL-5 Receptor α mAb in Patients with Severe Asthma) involving adolescents and adults, benralizumab improved pulmonary function, reduced AERs, and decreased OCS dependence in patients with moderate-to-severe asthma.[54] In the double-blind SIROCCO and CALIMA (Cytokine Antibody-mediated Inhibition of IL-5 in Patients with Moderate-to-Severe Asthma) trials, which enrolled adolescents and adults, comparison between benralizumab and placebo demonstrated a 17–40% reduction in exacerbation rates in patients with BECs below 300 cells/μL and a 28–51% reduction in those with BECs ≥300 cells/μL.[54,55] The ZONDA study (Zonal OCS Dose Reduction with Benralizumab in Severe Asthma), which included patients requiring maintenance OCS therapy, demonstrated that benralizumab enabled a 50% reduction in OCS dosage compared with placebo.[56]

Long-term evaluations extending up to five years demonstrated that benralizumab maintained favorable safety and tolerability profiles.[57] Long-term extension data also showed that the clinical benefits of benralizumab were maintained for nearly two years. During this period, approximately 50% of patients experienced no exacerbations, and the AER remained low at 0.56 events per patient-year in patients receiving benralizumab every eight weeks with baseline BEC ≥300 cells/μL. Improvements in lung function persisted, with mean increases in FEV_1 of 0.343 L and 0.364 L after one and two years of treatment, respectively, and gains in HRQOL were maintained.[58] Positive effects on HRQOL were also observed in the ANDHI study (Andalusia Severe Asthma Study with Benralizumab),[59] and real-world evidence further supports the efficacy and safety of benralizumab.[60,61]

Factors associated with enhanced clinical response to benralizumab include adult-onset asthma, a history of more than three exacerbations in the previous year, the presence of nasal polyps, higher baseline BEC, maintenance OCS use, and a pre-bronchodilator forced vital capacity (FVC) below 65% of the predicted value.[54,62]

In the TATE study (Trial of Benralizumab Pharmacokinetics, Pharmacodynamics, and Safety in Pediatric Patients with Severe Asthma), benralizumab demonstrated predictable pharmacokinetics in children aged 6–11 years, which were comparable to those observed in adolescents and adults. Treatment resulted in near-complete depletion of blood eosinophils. Exploratory analyses indicated numerical improvements in pulmonary function (FEV_1) and asthma symptom control, with the annualized exacerbation rate reduced by approximately 50% compared to baseline.[63] Adverse events were reported in 78.6% of participants; most were mild and consisted primarily of nasopharyngitis and local injection-site reactions. None of the adverse events led to treatment discontinuation or death.[63]

Reslizumab

Reslizumab is a monoclonal antibody targeting IL-5, resulting in reduced eosinophil levels in both the bloodstream and the airways. The U.S. FDA[64] and the EMA[65] approved IV reslizumab in 2016 for the treatment of SEA, administered at a weight-based dose of 3.0 mg/kg every four weeks. Reslizumab is indicated for adults (≥18 years) with a history of asthma exacerbations within the preceding year and baseline BECs of at least 400 cells/μL.[66] While some studies have demonstrated significant improvements in FEV_1 and asthma-related symptoms with reslizumab compared to placebo, others have failed to show a meaningful difference between reslizumab and placebo.[67,68] A recent real-world study demonstrated that reslizumab was effective in reducing exacerbation frequency and improving FEV_1 six months after treatment initiation.[69] Further studies are needed to elucidate the role of reslizumab in the mechanisms underlying airway remodeling in patients with asthma.

Dupilumab

Dupilumab inhibits both IL-4 and IL-13 signaling by binding to the IL-4 receptor α chain, which is a shared component of the receptor complexes for these cytokines. IL-4 promotes B-cell differentiation toward IgE production, whereas IL-13 contributes to airway smooth muscle contraction and upregulates enzymes involved in nitric oxide generation in bronchial epithelial cells, resulting in elevated FeNO levels.[70] Dupilumab received FDA[71] approval in 2018 for the treatment of SEA or OCS–dependent asthma in adolescents (≥12 years) and adults, followed by authorization from the EMA[72] in 2019 for the same population. Approval was later extended to include pediatric patients aged 6–11 years, with FDA approval granted in 2021 and EMA approval in 2022.[71,72] In addition to asthma, dupilumab is approved for the treatment of atopic dermatitis, CRSwNP, prurigo nodularis, and eosinophilic esophagitis.[71]

For pediatric patients aged 6–11 years, dupilumab is administered via SC injection at a dose of 100 mg every other week or 300 mg every four weeks for those weighing 15–30 kg, and 200 mg every other week for those weighing ≥30 kg. In this age group, for patients with concomitant moderate-to-severe atopic dermatitis, the dosing regimen includes an initial loading dose of 600 mg followed by 300 mg every four weeks for children weighing 15–30 kg, and an initial loading dose of 400 mg followed by 200 mg every other week for those weighing 30–60 kg.[71] In adolescents (≥12 years) and adults, dupilumab is administered via SC injection, starting with an initial loading dose of 400–600 mg, followed by a maintenance dose of 200–300 mg every two weeks. For patients with OCS–dependent asthma, comorbid moderate-to-severe atopic dermatitis, or adults with concomitant CRSwNP, the higher dose is recommended.[71]

In several RCTs, dupilumab was associated with lower annualized AERs, improved lung function and asthma control, and a favorable safety profile in patients with moderate-to-severe uncontrolled asthma.[70,73] Additionally, in adolescents (≥12 years) and adults with OCS-dependent severe asthma, dupilumab further reduced OCS requirements while lowering the rate of severe exacerbations and improving FEV_1.[74] A large real-world retrospective study, US ADVANTAGE (United States Assessment of Dupilumab Effectiveness in Asthma in a Real-World Setting) involving individuals aged ≥12 years with moderate-to-severe asthma, elevated baseline BEC, and common atopic comorbidities (allergic rhinitis, CRSwNP, and atopic dermatitis) demonstrated that dupilumab effectively reduced AER regardless of baseline exacerbation rate or BEC.[75]

The LIBERTY ASTHMA QUEST trial (Evaluation of Dupilumab in Patients with Uncontrolled, Moderate-to-Severe Asthma) demonstrated that dupilumab treatment improved pulmonary function and reduced markers of T2 inflammation in adolescents with inadequately controlled moderate-to-severe asthma.[76] In the VOYAGE trial (Efficacy and Safety of Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma), which enrolled children aged 6–11 years with poorly controlled moderate-to-severe asthma, add-on dupilumab therapy was associated with reductions in AERs and improvements in lung function and symptom control compared to placebo.[77] In the TRAVERSE (Long-Term Safety and Efficacy of Dupilumab in Patients with Asthma) open-label extension studies, long-term dupilumab therapy maintained a favorable safety profile.[78]

Dupilumab shows greater effectiveness in T2-high asthma, with factors associated with a favorable therapeutic response including a baseline BEC ≥300 cells/μL, elevated FeNO (≥50 ppb), and higher IgE levels (>167 IU/mL). These characteristics are also associated with more pronounced reductions in severe exacerbation rates and improved lung function and overall asthma control.

Table 2: Selection of biologic therapy in severe asthma[87]

Biomarker type	Biomarker value	Preferred biologic options
1. Blood eosinophils	≥1500 cells/μL (eosinophilic asthma)	• Anti–IL-5 • Anti–IL-5R
	≥300–1500 cells/μL (eosinophilic asthma)	• If allergic: Anti-IgE, Anti–IL-4Rα, Anti–IL-5, Anti–IL-5R, Anti-TSLP • If non-allergic: Anti–IL-4Rα, Anti–IL-5, Anti–IL-5R, Anti-TSLP
	≥150–299 cells/μL (eosinophilic asthma)	• If allergic: Anti-IgE, Anti–IL-4Rα, Anti-TSLP • If non-allergic: Anti–IL-4Rα, Anti-TSLP
	<150 cells/μL (non-eosinophilic asthma)	Proceed to FeNO evaluation
2. FeNO	≥25 ppb	• If allergic: Anti-IgE, Anti IL-4Rα, Anti-TSLP • If non-allergic: Anti IL-4Rα, Anti-TSLP
	<25 ppb	• If allergic: Anti-IgE, Anti-TSLP • If non-allergic: Anti-TSLP
3. Allergic sensitization (IgE-mediated)	Present	Omalizumab may be considered across phenotypes (if eligibility criteria are met)
4. Other considerations	Comorbidities (nasal polyposis, atopic dermatitis, ABPA, urticaria)	Selected biologics may provide additional benefit depending on comorbidity profile

Anti-IgE (omalizumab), anti–IL-4Rα (dupilumab), anti–IL-5 (mepolizumab, reslizumab), anti–IL-5R (benralizumab), and anti-TSLP (tezepelumab).
ABPA: Allergic bronchopulmonary aspergillosis.Biomarkers are not the sole determinants of biologic therapy selection and may be concurrently elevated in individual patients. Therefore, treatment decisions should be individualized based on clinical characteristics and comorbidities.

[79] Dupilumab demonstrates a favorable tolerability profile, with adverse events generally mild in nature, most commonly including localized injection-site reactions and transient elevations in eosinophil counts.[70]

Tezepelumab

Tezepelumab is a monoclonal antibody directed against TSLP. Approval was granted by the U.S. FDA[80] in 2021, followed by authorization from the EMA[81] in 2022, for use in adolescents (≥12 years) and adults with severe asthma, irrespective of T2 inflammatory status. Tezepelumab is administered as a 210 mg SC injection every four weeks.[80]

In pivotal clinical trials, tezepelumab significantly reduced asthma exacerbations by 56% compared to placebo in patients with severe asthma, independent of baseline BECs, and improved lung function (mean increase in FEV_1 of 130 mL), asthma control, and HRQOL over a 52-week treatment period.[82,83] Extension studies of tezepelumab in adolescents (≥12 years) and adults demonstrated sustained, clinically meaningful reductions in annualized AERs, with continued treatment providing persistent benefits compared to treatment discontinuation after two years.[84,85] In the SOURCE study (Steroid Reduction with Tezepelumab in Patients with Severe Asthma), which evaluated the effectiveness of tezepelumab in patients with OCS-dependent severe asthma, no significant reduction in OCS dose was observed compared to placebo; however, a beneficial effect was noted in participants with baseline BEC ≥150 cells/μL.[86]

Tezepelumab has demonstrated efficacy in both T2-high and T2-low asthma, with greater benefits observed in patients with higher baseline BEC and FeNO levels. The drug was generally well tolerated, with safety analyses indicating that adverse events were mostly mild in nature, most commonly nasopharyngitis and headache.[83]

Selection of Biologic Therapy

Direct comparative randomized controlled trials evaluating these biologic agents in severe asthma have not been conducted. Eligibility for biologic therapy varies across regions and countries and is influenced by regulatory approvals, local reimbursement policies, and treatment affordability. Criteria guiding the selection of patients for biologic therapy include age, the number of exacerbations in the preceding year, the need for maintenance OCS therapy, lung function parameters, and biomarker profiles such as BEC, FeNO, total serum IgE, and allergen-specific IgE (Table 2).[87] Comorbid conditions, including urticaria, nasal polyposis, and atopic dermatitis, should also be taken into consideration. Patient preference must always be respected, and individuals should be fully informed about dosing frequency and the route of administration.

Phenotypic characterization of exacerbations occurring during biologic therapy may be instrumental in optimizing treatment strategies and guiding decisions regarding switching between biologic agents. According to available data comparing mepolizumab and omalizumab, most exacerbations in both treatment groups are classi-

fied as eosinophilic. This observation raises the possibility that biologic agents providing more effective control of eosinophilia during treatment may offer additional benefit for this patient population.[88]

Remission in Severe Asthma

Biologic therapies effectively target airway inflammation and may induce short- to mid-term remission; however, their ability to confer sustained, long-term disease modification remains uncertain. Clinical remission is defined by symptom resolution, stable pulmonary function, and the absence of OCS use for at least 12 months, whereas complete remission additionally requires suppression of airway inflammation and, when applicable, normalization of bronchial hyperresponsiveness. Several factors have been investigated as potential predictors of remission in patients receiving biologic therapies for severe asthma, including baseline lung function, eosinophil counts, FeNO levels, disease duration, and comorbidities such as nasal polyposis. In our study examining predictors of remission in severe asthma treated with biologic therapy, baseline FEV_1% predicted emerged as an independent determinant of clinical remission in patients receiving mepolizumab or omalizumab. These findings underscore the importance of baseline lung function and suggest a greater potential for remission when biologic therapy is initiated before irreversible airflow limitation develops.[89]

Beyond its physiological burden, severe asthma can impose substantial emotional distress. Evidence indicates that loneliness tends to be more pronounced among patients with poor asthma control and those requiring long-term systemic corticosteroid therapy. Conversely, lower loneliness scores reported in individuals receiving biologic treatments indicate that these agents may confer psychosocial benefits in addition to their established clinical efficacy.[90] In the context of asthma remission, the psychological burden of disease warrants consideration in future research.

Asthma and Biologic Therapies during the COVID-19 Pandemic

At the onset of the COVID-19 pandemic, patients with chronic respiratory diseases were expected to have higher COVID-19–related morbidity and mortality; however, asthma has not been identified as a major risk factor. These findings suggest that asthma does not increase susceptibility to COVID-19, although key aspects of the underlying pathophysiology remain unclear. Early case reports described a mild disease course in patients with severe asthma receiving biologic therapies, supporting the continuation of these treatments during the pandemic. Subsequent reports, however, have suggested that, contrary to these initial observations, some patients with severe asthma treated with biologic therapies may experience a more severe course of COVID-19 compared with the general population. In this context, our clinical observations in patients with severe asthma receiving omalizumab or mepolizumab demonstrated a higher incidence of COVID-19 compared with previously reported data in the literature. Nevertheless, all patients diagnosed with COVID-19 experienced a mild-to-moderate disease course, achieved complete recovery, and no mortality was observed.[91]

Use of Biologic Therapies for Severe Asthma in Türkiye and Reimbursement Criteria

In Türkiye, as in many other countries, biologic agents are used in the management of severe asthma and are reimbursed by the Social Security Institution (Sosyal Güvenlik Kurumu - SGK) for eligible patients.[92] Currently, three biologics (omalizumab, mepolizumab, and benralizumab) are approved and reimbursed for the treatment of severe asthma.

Omalizumab

Omalizumab (brand name: Xolair®) is indicated for patients who met all of the following criteria:

(a) Patients aged ≥12 years with severe persistent allergic asthma and a body weight between 20 and 150 kg;

(b) Inadequate response to treatment with high-dose corticosteroids in combination with long-acting β_2-agonists and/or leukotriene receptor antagonists;

(c) Sensitization to at least one perennial allergen (e.g., house dust mite, cat or dog dander, cockroach, or mold spores), confirmed by skin testing or specific IgE positivity;

(d) Serum IgE level between 30 and 1500 IU/mL.

Prescription of omalizumab requires a 16-week health committee report approved and signed by at least two specialist physicians in pulmonology, immunology, allergy, or allergy and immunology. If a favorable treatment response is documented at the end of the initial 16-week period, a new health committee report valid for

one year is issued indicating treatment efficacy, and the medication is again prescribed by the same specialists.

Mepolizumab and Benralizumab

Mepolizumab (brand name: Nucala®) and benralizumab (brand name: Fasenra®) are indicated for patients with severe persistent eosinophilic asthma who meet all of the following criteria:

(a) Mepolizumab is indicated for children aged ≥6 years, adolescents, and adults, whereas benralizumab is indicated for adults only.

(b) For mepolizumab, a BEC of ≥300 cells/μL is required, or ≥150 cells/μL in patients receiving long-term maintenance systemic corticosteroid therapy; for benralizumab, a BEC of ≥300 cells/μL is required.

(c) Asthma that has been controlled or uncontrolled while receiving maintenance systemic corticosteroid therapy for at least six months, and/or uncontrolled asthma despite at least one year of treatment with high-dose inhaled corticosteroids (>800 μg/day budesonide or equivalent for patients aged ≥12 years; >400 μg/day budesonide or equivalent for children aged 6–11 years) in combination with a long-acting inhaled β_2-agonist and a third controller medication, with at least two exacerbations per year requiring systemic corticosteroid treatment for a minimum of three days per exacerbation.

Reimbursement is provided when the medication is prescribed by specialists in pulmonology or clinical immunology and allergy, based on a health committee report issued by a tertiary healthcare institution that includes at least one specialist in allergy and immunology.

The initial treatment response must be evaluated at week 16 in a tertiary healthcare institution. If continuation of therapy is deemed appropriate, reimbursement is granted when the medication is prescribed by pulmonology or allergy and immunology specialists, based on a new health committee report that includes at least one specialist in allergy and immunology and documents a favorable treatment response.

Conclusion

Although severe asthma represents only a small proportion of the overall asthma population, it accounts for a disproportionate share of asthma-related morbidity, mortality, and overall healthcare burden. The long-term disease-modifying potential of biologic therapies remains incompletely defined, highlighting ongoing uncertainties regarding optimal treatment duration and appropriate strategies for dose adjustment. Given their substantial cost, the clinical value of these agents is maximized when they are prescribed in accordance with appropriate indications.

Selection of the most appropriate biologic therapy should be guided by an individualized assessment of each patient's clinical characteristics. In this context, biomarkers provide valuable insights into asthma endotypes and support informed treatment selection. Biologic therapy should be continued for at least four months before evaluating treatment response; if the response remains unclear during this period, the assessment period may be extended to 6–12 months. Adherence to maintenance inhaled therapy, smoking status, allergen exposure, and other relevant environmental factors should also be systematically evaluated. Asthma remission is increasingly recognized as an achievable clinical goal; however, failure to attain remission may prompt consideration of transitioning to an alternative biologic therapy.

Finally, it is essential to acknowledge the psychological burden associated with severe asthma. Beyond alleviating physiological disease manifestations, biologic therapies appear to confer meaningful improvements in psychological well-being, thereby extending their benefits beyond traditional clinical outcomes.

Conflicts of Interest

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Impact of chest tube size on patient comfort and outcomes in malignant pleural effusion: A prospective comparative non-randomized study

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Abstract:

BACKGROUND AND AIM: Malignant pleural effusion (MPE) is a common complication of advanced cancer. Both large-bore chest tubes (≥20 Fr) and small-bore catheters (≤14 Fr) are used for drainage and pleurodesis; however, their effects on patient comfort and clinical outcomes remain unclear. This study compared comfort, efficacy, pleurodesis success, and complication rates between these methods.

METHODS: This prospective comparative study enrolled 146 patients with MPE who underwent physician-directed allocation to receive either a large-bore (n=73) or small-bore (n=73) intercostal catheter (ICC) under local anesthesia, followed by talc pleurodesis after lung re-expansion. Outcomes included procedure duration, pain scores, drainage parameters, pleurodesis success, complications, and four-week follow-up.

RESULTS: Baseline characteristics were comparable between groups. Large-bore tubes required a longer insertion time (23.6±2.6 vs. 11.0±1.8 min, p<0.001) and were associated with higher pain scores immediately post-insertion (6.9±1.4 vs. 4.9±1.3, p<0.001), at 6 hours (5.1±1.3 vs. 3.7±1.1, p<0.001), and at 24 hours (3.3±1.2 vs. 2.4±1.0, p<0.001). Drainage volume was higher (1594±340 vs. 1331±415 mL, p<0.001), and time to complete drainage was shorter (34.9±8.8 vs. 39.5±10.5 h, p=0.005) in the large-bore group. Pleurodesis success was comparable (71.2% vs. 68.5%, p=0.686), as was drainage efficacy (80.8% vs. 76.7%, p=0.544). Blockage occurred more frequently in small-bore catheters (5.5% vs. 1.4%, p=0.366), whereas infection (6.8% vs. 1.4%, p=0.209) and dislodgement (5.5% vs. 2.7%, p=0.681) were more common with large-bore tubes.

CONCLUSIONS: Both large- and small-bore chest tubes were effective for pleurodesis in MPE. Large-bore tubes enabled faster and higher-volume drainage but were associated with greater pain and longer procedure times, whereas small-bore tubes provided better patient comfort with comparable efficacy. Small-bore tubes are preferable in most cases, while large-bore tubes may be suitable when rapid, high-volume drainage is required.

Keywords:

Chest tube insertion, large-bore chest tube, malignant pleural effusion, patient comfort, pleurodesis, small-bore catheter

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Introduction

Malignant pleural effusion (MPE) is a common complication in patients with advanced malignancies, particularly lung and breast tumors and lymphomas.[1,2] Although MPE usually signifies advanced disease with a limited prognosis, patients with chemosensitive tumors, such as breast cancer or lymphoma, may experience relatively prolonged survival.[2] In such cases, palliative interventions to relieve symptoms, including dyspnea, orthopnea, cough, and pleuritic pain, are justified to improve quality of life.[1,2] Systemic therapy, either alone or in combination with local measures, may benefit selected patients with chemosensitive tumors. However, systemic therapy alone is often insufficient to control pleural fluid accumulation, necessitating local interventions.[2–4]

Traditional local approaches include repeated thoracentesis and tube thoracotomy; however, both are associated with high recurrence rates, and simple drainage rarely achieves durable control.[1] This limitation has led to the widespread use of chemical pleurodesis employing sclerosing agents such as tetracycline, bleomycin, and talc.[5–8] Over time, talc has become established as the most effective agent, while advancements in catheter design and placement techniques, such as the Seldinger guidewire approach and image-guided insertion, have enhanced both safety and precision.[7–12] These developments have supported the increasing adoption of small-bore intercostal catheters (SB ICCs; ≤14 Fr) as less invasive alternatives to conventional large-bore intercostal tubes (LB ICTs; ≥20 Fr). SB ICCs have been reported to be effective, safe, and well tolerated in the management of pleural effusions, empyema, and pneumothorax.[11,12] Ultrasound-guided placement offers further benefits, including optimal positioning above the diaphragm and the ability to identify insertion sites.[10] Despite these advantages, concerns persist that smaller tubes may result in slower drainage rates or a higher risk of blockage,[4,13,14] even though experimental studies contradict this view. Pass et al.[2] previously observed no significant variation in drainage time with catheters larger than 8 Fr, irrespective of fluid viscosity. Similarly, Laws et al.[3] demonstrated comparable *in vivo* drainage efficiencies of 19 Fr and 28 Fr tubes.

Clinical studies have reported mixed results. Observational studies generally highlight the advantages of SB ICCs; however, comparative trials have been less consistent.[15–17] Vedam and Barnes[13] observed increased complication and recurrence rates with SB ICCs, whereas Parulekar et al.[15] reported no significant differences in pleurodesis success. Furthermore, the Thoracic Interventional Procedures (TIME1) randomized trial demonstrated that 24 Fr tubes achieved higher pleurodesis efficacy than 12 Fr catheters, although at the cost of greater pain.[18] Nevertheless, reviews and guideline statements have consistently highlighted that the ideal tube size remains a subject of ongoing debate.[3,4,19–20]

Thus, the optimal tube size for MPE remains unclear. LB ICCs are still favored in many centers owing to their perceived drainage efficiency, whereas SB ICCs are increasingly preferred because of their superior tolerability and procedural ease. Against this backdrop of uncertainty, the present study was conducted to prospectively compare LB and SB chest tubes in patients with MPE, with a focus on patient comfort, drainage efficacy, pleurodesis success, and complication profiles.

Materials and Methods

Patients

This prospective comparative study was approved by the Ethical Review Board of Government Mozang Teaching Hospital (Approval Number: 5170 /GMTH, Date: 15/03/2024) and conducted between March and December 2024. The study adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained after providing a comprehensive explanation of the study, including its objectives, methodology, potential risks, and benefits. The required sample size was calculated to achieve a power of 80% with a significance level of 5%. Based on the expected difference in drainage efficacy between large- and small-bore tubes (47.3% vs. 23.6%) and allowing for a 20% dropout rate, a total of 146 patients (73 in each group) were required. Convenience sampling was applied. Eligible participants were adults (≥18 years) with a confirmed diagnosis of MPE established by pleural fluid cytology and/or pleural biopsy and who required chest tube insertion. In some patients, malignant pleural effusion was confirmed by cytology and/or pleural biopsy, but the primary tumor site had not yet been identified at the time of enrollment. Exclusion criteria included trapped lung, prior pleurodesis, severe coagulopathy, and refusal to participate. Participants were divided into two groups according to chest tube size:

- Group A (Large-bore): chest tube size ≥20 French,
- Group B (Small-bore): chest tube size ≤14 French.

This study was designed as a prospective comparative study. Formal randomization was not performed; therefore, allocation concealment methods (e.g., computer-generated sequences or sealed envelopes) were not applicable. Tube size selection was based on the treating physician's clinical judgment and the patient's condition.

Procedure, patient assessment, and follow-up

Chest tube insertion was performed under local anesthesia using 2% lignocaine, following strict aseptic precautions. Tubes were inserted at the mid-axillary line in the fifth or sixth intercostal space and connected to an underwater seal drainage system. After radiographic confirmation of complete lung expansion, pleurodesis was performed using sterile talc (4 g). Baseline demographic and clinical data, including age, sex, comorbidities, and underlying malignancies, were recorded. Pain was assessed using a standardized visual analogue scale (VAS; 0=no pain and 10=worst pain imaginable) at three time points: immediately post-insertion, 6 hours, and 24 hours post-procedure. Drainage efficacy was assessed using the total volume of fluid drained within 24–48 hours and the time required for complete drainage. Non-effective drainage was defined as incomplete lung re-expansion and/or significant residual pleural fluid on post-procedural imaging despite an adequate drainage duration. Pleurodesis success was defined as the absence of recurrent effusion on follow-up imaging. Additional outcomes included procedure duration and complications, such as tube dislodgement, blockage, infection, or re-accumulation.

Indications for chest tube insertion included symptomatic dyspnea, recurrent malignant pleural effusion requiring pleurodesis, radiological evidence of significant effusion causing lung compression, and reduced oxygen saturation attributable to pleural fluid. Patients were monitored for four weeks post-discharge to evaluate recurrence, late complications, and pleurodesis outcomes. Follow-up was conducted during outpatient visits and, when required, through telephone interviews.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables (e.g., age, VAS scores, and procedure duration) were expressed as mean±standard deviation (SD) and compared using Student's t-test. Categorical variables (e.g., sex, drainage efficacy, pleurodesis success, and complications) were expressed as frequencies and percentages and analyzed using the chi-squared test. A p-value <0.05 was considered statistically significant.

Table 1: Baseline demographic and clinical characteristics of the study population (n=146)

Variable	Large-bore (n=73)	Small-bore (n=73)	Total (n=146)	p*
Age (years), mean±SD	59.6±9.6	58.0±11.0	58.8±10.3	0.38
Sex, n (%)				
Male	39 (53.4)	44 (60.3)	83 (56.8)	0.41
Female	34 (46.6)	29 (39.7)	63 (43.2)	
Side of effusion, n (%)				
Right	35 (47.9)	45 (61.6)	80 (54.7)	1.00
Left	38 (52.1)	28 (38.5)	66 (45.2)	
Comorbidities, n (%)				
Hypertension	20 (27.4)	18 (24.7)	38 (26.0)	0.97
Diabetes	17 (23.3)	17 (23.3)	34 (23.3)	
COPD	11 (15.1)	11 (15.1)	22 (15.1)	
Diabetes + hypertension	7 (9.6)	8 (11.0)	15 (10.3)	
None	18 (24.7)	19 (26.0)	37 (25.3)	
Underlying malignancy, n (%)				
None	55 (75.3)	61 (83.6)	116 (79.5)	0.42
Breast cancer	3 (4.1)	3 (4.1)	6 (4.1)	
Colon cancer	3 (4.1)	3 (4.1)	6 (4.1)	
Lung cancer	9 (12.3)	5 (6.8)	14 (9.6)	
Prostate cancer	3 (4.1)	1 (1.4)	4 (2.7)	

*: Chi-square test. "None" indicates an unknown primary malignancy despite confirmed malignant pleural effusion. SD: Standard deviation, COPD: Chronic obstructive pulmonary disease.

Results

Baseline and demographic characteristics

A total of 146 patients with MPE were enrolled, with 73 patients in each group. Baseline demographic and clinical characteristics were comparable between the large- and small-bore groups. The mean age was 59.2±9.6 years in the large-bore group and 58.5±11years in the small-bore group. Males comprised 58.9% of the large-bore group and 54.8% of the small-bore group (p=0.41) (Table 1). Although right-sided effusion was slightly more common in the small-bore group (61.6% vs. 47.9%), this difference was not statistically significant. Comorbidities were evenly distributed, with hypertension (27.4% vs. 24.7%), diabetes mellitus (23.3% in both groups), and chronic obstructive pulmonary disease (COPD) (15.1% in both groups) showing no statistically significant differences. The distribution of underlying malignancies was also balanced. Lung cancer was the most frequent primary tumor (12.3% vs. 6.8%), followed by breast cancer

Table 2: Procedural outcomes and patient comfort according to chest tube size

Variable	Large-bore (n=73)	Small-bore (n=73)	Mean difference	95% CI of difference	p
Procedure duration (min)	23.62±2.57	11.03±1.81	12.59	11.86–13.32	<0.001
VAS (immediate)	6.85±1.40	4.88±1.25	1.97	1.54–2.40	<0.001
VAS (6 h)	5.13±1.33	3.70±1.14	1.43	1.02–1.84	<0.001
VAS (24 h)	3.29±1.16	2.37±1.01	0.92	0.56–1.27	<0.001
Drainage volume (mL)	1594.33±340.12	1331.03±414.92	263.30	139.18–387.42	<0.001
Time to complete drainage (h)	34.90±8.82	39.48±10.53	-4.58	-7.75–1.40	0.005

CI: Confidence interval,VAS: Visual analogue scale.

(4.1% vs. 4.1%), colon cancer (4.1% vs. 4.1%), and prostate cancer (4.1% vs. 1.4%). These differences were not statistically significant, indicating that the groups were well matched at baseline (Table 1). Baseline characteristics are presented to demonstrate group comparability.

Procedural outcomes and patient comfort

Statistically significant differences were observed in procedure duration and pain scores. Large-bore tubes required a longer insertion time (23.6±2.6 min vs. 11.0±1.8 min, p<0.001) and were associated with consistently higher pain scores at all measured time points: immediately post-insertion (6.9±1.4 vs. 4.9±1.3, p<0.001), at 6 hours (5.1±1.3 vs. 3.7±1.1, p<0.001), and at 24 hours (3.3±1.2 vs. 2.4±1.0, p<0.001) (Table 2) [Fig. 1].

Drainage efficacy, pleurodesis success, and complications

Drainage efficiency was superior in the large-bore group, with a greater mean volume of fluid removed (1594±340 mL vs. 1331±415 mL, p<0.001) and a shorter time to achieve complete drainage (34.9±8.8 h vs. 39.5±10.5 h, p=0.005) (Table 2). Despite these differences, both groups achieved comparable clinical outcomes. Adequate drainage was achieved in 80.8% of patients in the large-bore group and 76.7% in the small-bore group (p=0.544). Pleurodesis success rates were also similar, at 71.2% in the large-bore group and 68.5% in the small-bore group (p=0.686) (Table 3). The complication profiles differed modestly between groups. Small-bore tubes were more frequently associated with blockage (5.5% vs. 1.4%, p=0.366), whereas large-bore tubes showed higher rates of infection (6.8% vs. 1.4%, p=0.209) and dislodgement (5.5% vs. 2.7%, p=0.681). Re-accumulation of pleural effusion occurred at comparable frequencies in both groups (4.1% vs. 5.5%, p=1.00). Although patients with non-effective drainage were managed according to standard clinical practice, details of subsequent interventions were not systematically recorded in the study dataset. Overall, complication rates were low in both groups, with all individual complications occurring in fewer than 7% of patients [Fig. 2].

Table 3: Clinical outcomes and pleurodesis success by chest tube group

Outcome/ variable	Large-bore (n=73)	Small-bore (n=73)	Total (n=146)	p
Drainage efficacy, n (%)				
Effective	59 (80.8)	56 (76.7)	115 (78.8)	0.544
Non-effective	14 (19.2)	17 (23.3)	31 (21.2)	
Pleurodesis success, n (%)				
Yes	52 (71.2)	50 (68.5)	102 (69.9)	0.686
No	21 (28.8)	23 (31.5)	44 (30.1)	

*Chi-square test.

Discussion

This prospective comparative study demonstrated that chest tube size had a greater impact on patient experience than on clinical outcomes in the management of MPE. Large-bore ICCs achieved faster and higher-volume drainage but were consistently associated with longer procedure duration and greater pain. In contrast, small-bore tubes offered superior comfort and procedural tolerability, with only a modest increase in the risk of blockage. Notably, both tube sizes achieved comparable drainage efficacy and pleurodesis success, suggesting that tube selection should be guided primarily by patient-centered considerations rather than assumptions of superior efficacy with larger drains. These findings align with those of Parulekar et al.,[15] who reported no significant difference in pleurodesis success between small- and large-bore tubes in MPE. Similarly, Hafiza et al.[20] reported better patient comfort and fewer complications with small-bore tubes, although their study included mixed clinical indications. In contrast, the TIME1 randomized trial demonstrated higher pleurodesis efficacy with larger tubes, albeit at the cost of increased pain.[18] Methodological differences, including the standardized use of talc pleurodesis in the present study, which is considered the most effective sclerosing agent, may partly explain

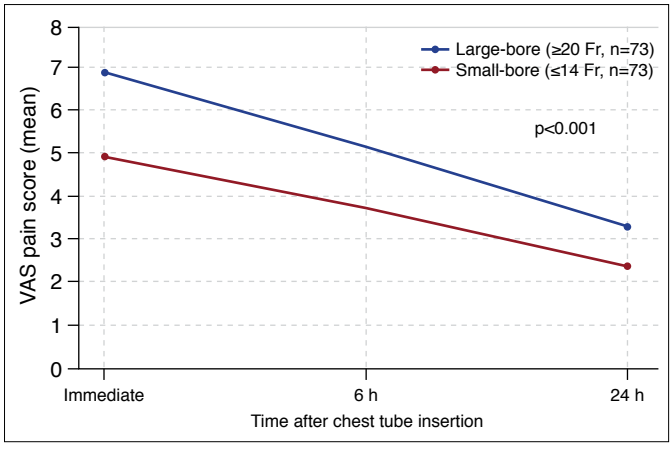

Figure 1: Comparison of mean pain scores assessed using the Visual Analogue Scale (VAS) between large-bore and small-bore chest tube groups immediately after insertion, at 6 hours, and at 24 hours. Pain scores were significantly higher in the large-bore group at all time points (immediate: p<0.001; 6 h: p<0.001; 24 h: p<0.001)

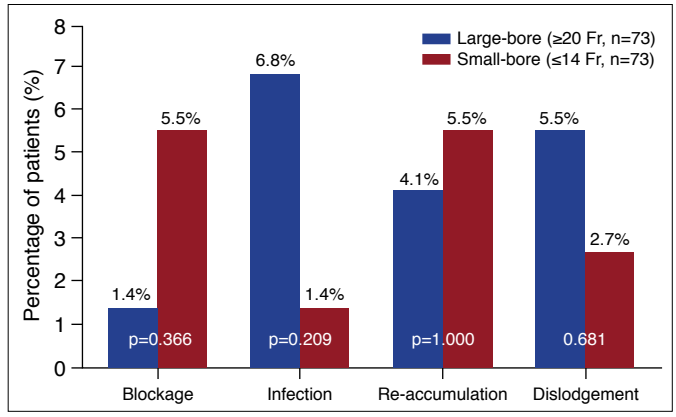

Figure 2: Comparison of complication profiles between large-bore and small-bore chest tubes in patients with malignant pleural effusion (n=146). Percentages are calculated based on group size (n=73 per group). Blockage occurred more frequently in the small-bore group (5.5% vs. 1.4%), whereas infection (6.8% vs. 1.4%) and tube dislodgement (5.5% vs. 2.7%) were more common in the large-bore group. None of these differences were statistically significant (p>0.05 for all comparisons)

these discrepancies.[7,8] In their reviews, McCracken et al.[19] and Light[4] emphasized that the ideal tube size is still a subject of debate and highlighted the importance of prioritizing patient comfort in clinical decision-making. It is also possible that the observed differences in drainage volume and time to complete drainage partly reflect selection bias, as patients with larger or more symptomatic effusions may have been preferentially assigned to large-bore tubes. This should be considered when interpreting drainage-related outcomes.

The complication profile observed in this study was consistent with that reported in the literature. Infections were limited to localized insertion-site infections and were managed conservatively. Horsley et al.[14] and Davies et al.[21] have highlighted the increased risk of blockage associated with small-bore drains, whereas larger drains have been more frequently associated with infection and dislodgement.[14,21–23] These findings are consistent with our observations, highlighting that each tube size has its own complication profile. In recent years, indwelling and tunneled pleural catheters have emerged as effective alternatives for outpatient management, with fewer inpatient days and favorable safety profiles for malignant effusions, including those associated with hematologic malignancies.[24–27]

Overall, these results highlight the importance of prioritizing patient comfort during tube selection. We believe these findings suggest that small-bore catheters may be considered the first choice for most patients with MPE, especially in palliative settings where quality of life is paramount. However, large-bore tubes remain valuable in selected scenarios requiring rapid, high-volume drainage, such as massive effusions or acute respiratory distress. Tailoring tube size to the clinical context allows physicians to balance procedural efficiency with patient-centered care.

Strengths and limitations

This study has several notable strengths, including its prospective design, relatively large cohort, and systematic assessment of both objective outcomes (drainage efficacy and pleurodesis success) and subjective outcomes (pain scores). The standardized use of talc pleurodesis further enhances the consistency and relevance of the findings in contemporary clinical practice. However, subsequent interventions following non-effective drainage were not uniformly documented, which represents a limitation of the study.

This study was conducted at a single center, which may limit the generalizability of the findings. The four-week follow-up period primarily reflects early pleurodesis success and short-term recurrence. Although this duration is commonly used in clinical practice to assess initial outcomes, it may not capture late recurrence or long-term pleurodesis durability. Future studies with longer follow-up periods are needed to confirm sustained efficacy. Detailed radiological stratification of effusion volume, pleural thickening, or septations was not uniformly available for all patients and therefore could not be analyzed. As these features may influence drainage efficiency, their absence represents a limitation of this study.

Conclusion

Overall, this study demonstrated that both large- and small-bore chest tubes/intercostal catheters are effective for drainage and pleurodesis in patients with MPE. Large-bore tubes enabled faster, higher-volume drainage but were associated with greater procedural pain and longer insertion times. Conversely, small-bore tubes offered better patient comfort, with only a slightly increased risk of blockage. Based on these findings, small-bore tubes may be considered a preferred option in most cases, particularly when patient comfort and quality of life are priorities. Nevertheless, large-bore tubes remain useful in situations requiring rapid, high-volume evacuation.

Ethics Committee Approval

The study was approved by the Ethical Review Board of Government Mozang Teaching Hospital (No: 5170/GMTH, Date: 15/03/2024) in collaboration with Ragdah Arif from King Abdulaziz University, Jeddah Saudi Arabia.

Informed Consent

Written informed consent was obtained from the patients.

Conflicts of Interest

The author have no conflicts of interest to declare.

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Peer-review

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Editorial: Size matters—but comfort matters more in malignant pleural effusion

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Malignant pleural effusion (MPE) remains one of the most frequent and challenging problems faced by physicians. While the underlying disease is often incurable, the goal of care is unequivocal: durable symptom control with the least possible burden to the patient. In this context, the study by Raghad Arif[1] provides timely and clinically relevant insight into a deceptively simple but persistently debated question "does chest tube size truly influence outcomes, or does it primarily shape patient experience?"

From a thoracic surgeon's perspective, this question is not trivial. For decades, large-bore chest tubes were considered the default approach, grounded more in surgical tradition than in robust evidence. The assumption was intuitive: larger tubes drain more effectively, more quickly, and more reliably. However, as minimally invasive techniques and patient-centered care have evolved, this paradigm has been increasingly challenged.

This prospective comparative study contributes meaningfully to that shift. The findings are clear and consistent with what many of us observe in daily practice.

- Large-bore tubes deliver faster and higher-volume drainage,
- Small-bore catheters significantly improve patient comfort,
- Most importantly, pleurodesis success and overall efficacy are comparable.

This last point is the most critical. If the ultimate therapeutic goal—successful pleurodesis—is not compromised, then the justification for routinely using larger, more painful tubes becomes difficult to defend.

Pain scores reported in this study are not merely numerical differences; they represent real, measurable impacts on already vulnerable and moribund patients, many of whom are in a palliative phase of their disease. The consistent and significantly higher pain associated with large-bore tubes reinforces what clinicians have long suspected but perhaps have underestimated it in their decision-making.

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In this regard, the study aligns with the growing body of evidence and the current guidelines suggesting that smaller, less invasive interventions can achieve equivalent clinical outcomes with superior tolerability.[2]

Interpreting drainage efficiency: Does faster mean better?

One of the traditional arguments in favor of large-bore tubes is their superior drainage performance. This study confirms that larger tubes result in:

- Greater total drainage volume,
- Shorter time to complete drainage.

However, the key question is whether these differences are clinically meaningful. In most MPE cases, drainage is a means to an end, not the end itself. The objective is to achieve lung re-expansion followed by effective pleurodesis. If small-bore catheters can reliably achieve this—albeit slightly more slowly—the clinical advantage of faster drainage becomes less compelling, particularly when weighed against increased pain and longer procedure times.

That said, the authors appropriately highlight scenarios where large-bore tubes remain valuable:

- Massive effusions,
- Acute respiratory compromise,
- Situations requiring rapid decompression.

Thus, the message is not to abandon large-bore tubes, but to use them selectively rather than routinely.

As thoracic surgeons, we must also critically appraise the methodology. The non-randomized design introduces an inherent risk of selection bias. It is entirely plausible that patients with larger or more symptomatic effusions were preferentially assigned to large-bore tubes, which may partially explain the observed differences in drainage parameters. As the historic TIME2 study has shown patients with malignant pleural effusion and no previous pleurodesis, there was no significant difference between indwelling pleural catheters and talc pleurodesis with large chest tube at relieving patient-reported dyspnea.[3]

Nevertheless, the consistency of patient comfort outcomes, combined with comparable efficacy, strengthens the study's conclusions. Even in the presence of potential bias, the signal favoring small-bore catheters remains robust.

Does this study influence the current practice?

This study reinforces a practical, patient-centered algorithm:

- Small-bore catheters (i.e., ≤14 Fr):
  - First-line in most MPE patients,
  - Particularly appropriate in palliative settings,
  - Preferred when comfort and outpatient feasibility are priorities.
- Large-bore tubes (i.e., ≥20 Fr):
  - Reserved for selected indications,
  - Massive or rapidly accumulating effusions,
  - Situations requiring rapid drainage.

Importantly, this approach aligns with the increasing use of indwelling pleural catheter, which further extend the principle of minimally invasive, patient-friendly care. The study highlights an important reality: despite decades of experience, the "optimal" chest tube size remains unresolved, largely because the definition of "optimal" has evolved. It is no longer solely about fluid dynamics—it is about balancing efficacy, safety, and patients' quality of life.

Future research should aim to incorporate randomized design, include longer follow-up for pleurodesis durability and to compare chest tube strategies with indwelling pleural catheter as well as to integrate patient-reported outcomes as primary endpoints

This study adds to the growing evidence that, in MPE management, larger is not necessarily better. From a thoracic surgeon's standpoint, the findings support a clear and increasingly compelling principle: small-bore catheters are appropriate in the majority of cases. Large-bore tubes still have a role—but no longer the default one.

In the modern era of thoracic oncology, success is not measured solely by what we achieve in the pleural space, but by how we achieve it and how our patients experience it.

Conflicts of Interest

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Survival and mortality risk factors in chronic obstructive pulmonary disease: A three-year cohort analysis

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Abstract:

BACKGROUND AND AIM: Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death and disability worldwide. Precise survival estimates and identification of mortality risk factors are crucial for managing COPD. This prospective study aimed to investigate the survival rate and identify predictors of mortality in patients with COPD.

METHODS: We investigated the association of various factors with three-year survival rates in our COPD cohort. Patients (n=176) underwent baseline assessments including demographics, comorbidities, questionnaires, laboratory findings, and long-term oxygen therapy/bilevel positive airway pressure (LTOT/BPAP) use. The primary endpoint was completion of three-year follow-up, and the secondary endpoint was all-cause mortality. Cox regression analysis was used to explore factors associated with mortality. Survival analysis was performed using the Kaplan-Meier method.

RESULTS: This prospective cohort study of 176 COPD patients (65.4 years old, mostly male) identified a three-year overall survival rate of 86.4%. Age ≥68.5 years ($p<0.001$), Charlson Comorbidity Index (CCI) scores ≥4.5 ($p<0.001$), and eosinophil counts ≤45 cells/μL ($p<0.001$) were independently associated with poorer survival. LTOT use ($p=0.001$) was also associated with reduced survival.

CONCLUSIONS: In this prospective cohort study, age, CCI, LTOT use, and baseline eosinophil count were associated with survival and identified as predictors of mortality. An age cut-off of ≥68.5 years and a CCI cut-off score of ≥4.5 were associated with increased mortality risk, while lower baseline eosinophil counts (cells/μL) predicted poorer survival in this COPD cohort.

Keywords:

Chronic airway diseases, chronic obstructive lung disease, chronic obstructive pulmonary disease, survival

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterized by persistent and progressive airway obstruction resulting from airway (bronchitis/bronchiolitis) or alveolar abnormalities (emphysema) and presenting with chronic respiratory symptoms such as dyspnea, cough, and sputum.[1] COPD is one of the top three causes of mortality and morbidity worldwide.[2]

Accurate survival estimation and identification of prognostic factors are crucial for the optimal management of patients with COPD. In this context, reliable predictors of mortality play a key role in tailoring individualized treatment strategies. Leveraging data on patient characteristics, laboratory parameters, clinical trajectories, and overall health status can empower clinicians to predict individual survival in COPD patients, thereby informing personalized treatment decisions. Frequent COPD exacerbations and hospitalizations due to exacerbations have been shown to be associated with a worse prognosis in COPD patients.[3]

Severe hypoxia is associated with a significant decline in health status, with the degree of impairment directly proportional to the level of oxygen deprivation. General health measures have been explored as predictors of mortality in hypoxic COPD patients.[4,5] Previous studies have shown promising results with disease-specific questionnaires such as the St. George's Respiratory Questionnaire (SGRQ), which demonstrate a correlation between poor health status and an increased risk of death or hospitalization.[6,7] The COPD Assessment Test (CAT) is a validated and simple tool for monitoring health-related quality of life in COPD patients.[8] Its strong correlation with the SGRQ and promising results as a predictor of mortality suggest its potential utility in clinical practice.[8]

The forced expiratory volume in 1 second (FEV_1) has been identified as a predictor of mortality in patients with COPD.[9] Beyond FEV_1, several other clinical parameters have emerged as powerful prognostic indicators, including SGRQ scores reflecting health-related quality of life, body mass index (BMI), age, and peak oxygen uptake (VO_2max).[10,11] These factors offer a more comprehensive assessment of patient health and disease severity, potentially improving the accuracy of mortality prediction.

This prospective study aimed to analyze potential determinants, including demographic, clinical, laboratory, and health status measurements, that could predict mortality and three-year survival rates in this COPD study population.

To our knowledge, the long-term prognostic value of combining baseline clinical, laboratory, and health status data has been scarcely documented. Therefore, this three-year prospective cohort study aimed to rigorously determine the independent predictive capacity of a comprehensive set of baseline markers—notably health status measures such as the Charlson Comorbidity Index (CCI) and SGRQ, as well as demographic, clinical, and laboratory variables—on long-term all-cause mortality in COPD.

Materials and Methods

This prospective study was conducted between January 2019 and June 2023. The study was approved by the University of Health Sciences Izmir Tepecik Health Application and Research Center Non-interventional Ethics Committee (Approval number: 2019/8-20, Date: 08.05.2019), and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. All patients volunteered for the study and received no financial support.

Patients and study design

Patients who presented to our outpatient clinic in a stable condition or with a complication such as an acute exacerbation or pneumonia were enrolled in the study and followed for at least three years. The inclusion criterion was a new or follow-up diagnosis of COPD. Based on the GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2019 guidelines, COPD was defined as a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases.[12] The diagnosis of COPD was established according to the GOLD 2019 guidelines,[12] requiring a post-bronchodilator ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) of less than 0.70. All patients had their diagnosis confirmed by post-bronchodilator spirometry (200 μg of salbutamol) performed in accordance with American Thoracic Society (ATS) and European Respiratory Society (ERS)

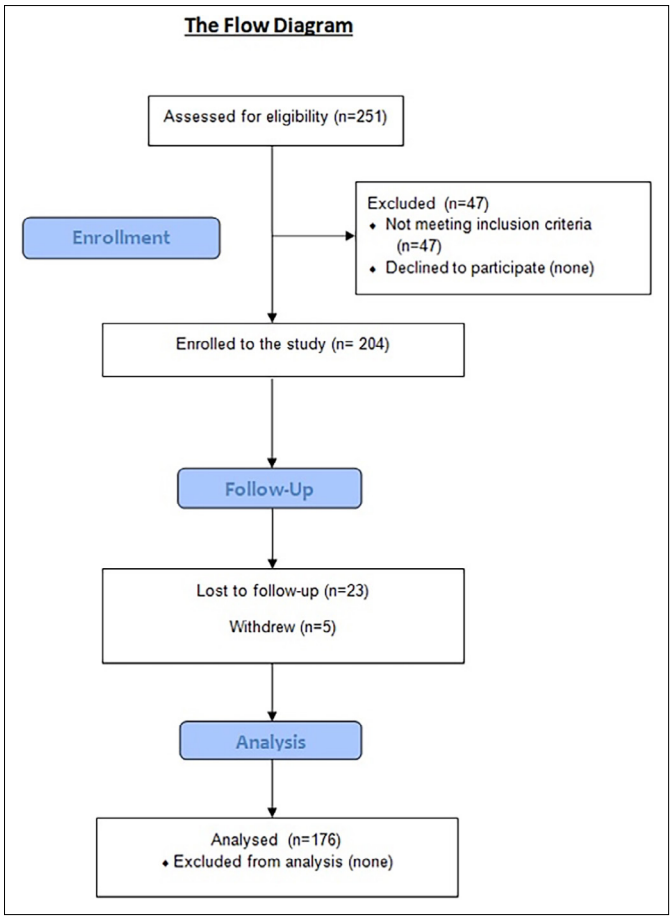

Figure 1: Flow diagram of the study

criteria.[13] Patients with a history of allergic rhinitis, asthma, drug abuse, lung cancer, neuromuscular disorders, sleep apnea, poor motivation, or major psychiatric disorders were excluded from the study.

Among the 204 patients eligible for inclusion, five withdrew from the study and 23 were lost to follow-up. Ultimately, the study included 176 patients with COPD. Figure 1 presents the flow diagram of the study. All measurements and clinical assessments were performed at baseline. All patient data, including changes in health status, baseline medication use, vaccination status, development of comorbidities, and survival outcomes, were prospectively collected from the institutional health record system and the national health database throughout the follow-up period. Long-term oxygen therapy (LTOT) and bilevel positive airway pressure (BPAP) reports were generated for all eligible patients, taking into account the recommendations of the medical review board. Objective criteria for LTOT use were a partial pressure of oxygen (PaO_2) <55mmHg and oxygen saturation (SpO_2) ≤88%, and for BPAP use, a partial pressure of carbon dioxide ($PaCO_2$) ≥55mmHg.

The primary endpoint was all-cause mortality during the follow-up period. The secondary endpoint of the study was completion of at least a three-year follow-up for each surviving patient.

Outcome measures

At baseline, comprehensive data were collected for each patient, including diagnosis and disease status, demographics, comorbidities, influenza and pneumococcal vaccination history, LTOT use, BPAP use, pulmonary function tests (PFT), and scores from disease-specific questionnaires. These questionnaires included the CAT, CCI, Modified Medical Research Council Dyspnea (mMRC) scale, and SGRQ. For deceased patients, the date and cause of death were documented. The number of exacerbations, emergency department visits, and hospitalizations within the preceding year was recorded for each participant using data extracted from the institutional electronic health record system and the national health database. All patient-reported outcome measures were administered by the study team using a structured questionnaire.

Pulmonary function testing (Medical Graphics Co.; Oak Grove Parkway, St. Paul, Minnesota, USA) was performed in accordance with the ATS/ERS criteria.[13] The ratio of FEV_1 to FVC (FEV_1/FVC%) was defined as less than 70% following administration of 200 µg of salbutamol, measured 15 minutes later. The following indices were collected: FEV_1 (ml), FEV_1 (%) predicted, FVC (ml), FVC (%) predicted, FEV_1/FVC (%), and forced expiratory flow between 25% and 75% of vital capacity (FEF25–75) (ml and %).

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) (version 22.0; SPSS Inc., Chicago, IL, USA). Results were presented as mean±standard deviation for normally distributed variables, median±interquartile range for non-normally distributed variables, and frequencies for categorical variables. Unpaired Student's t-tests were used to compare normally distributed continuous variables between groups, while Mann-Whitney U tests were employed for non-normally distributed variables. Cox regression

Table 1: Demographic, clinical, and survival data

Parameter	Mean±SD or number (ratio or range)	Parameter	Mean±SD or number (ratio or range)
Age (years)	65.4±10.3 (39–87)	Pneumococcal vaccination	
Sex		No	101 (57.4%)
Male	170 (96.6%)	Yes	75 (42.6%)
Female	6 (3.4%)	Exacerbations in the previous year	1.77±2.1 (0–11)
BMI (kg/m^2)	25.7±4.8 (15.4–41.5)	CAT score	15±9.2 (5–40)
Smoking status		Charlson comorbidity index score	3.5±1.9 (1–10)
Non-smoker	16 (9.1%)	mMRC scale	2±0.9 (0–4)
Current smoker	33 (18.8%)	SGRQ	
Former smoker	127 (72.2%)	Symptoms	54.9±24 (11–100)
Initial clinical status		Impact	34.8±19.3 (0–86)
Stable	98 (55.7%)	Activity	53.6±22.8 (8–100)
Acute exacerbation/pneumonia	78 (44.3%)	Total	44.5±18.9 (9–87)
Medication use		LTOT use	
None	3 (1.7%)	No	133 (75.6%)
SABA+SAMA	2 (1.1%)	Yes	43 (24.4%)
LABA	8 (4.6%)	BPAP use	
LAMA	30 (17%)	No	153 (86.9%)
LABA+LAMA	16 (9.1%)	Yes	23 (13.1%)
ICS+LABA	81 (46.1%)	Vital status (at the end of follow-up)	
ICS+LABA+LAMA	28 (16%)	Alive	133 (75.6%)
ICS+LABA+LAMA+theophylline	4 (2.2%)	Deceased	43 (24.4%)
ICS+LABA+LAMA+roflumilast	4 (2.2%)	Follow-up duration	40.6±10.3 (9–48)
Influenza vaccination		Three-year overall survival rate	86.4%
No	88 (50%)		
Yes	88 (50%)		

SD: Standard deviation, BMI: Body mass index, CAT: COPD Assessment Test, mMRC: Modified Medical Research Council, SGRQ: St. George's Respiratory Questionnaire, LTOT: Long-term oxygen therapy, BPAP: Bilevel positive airway pressure, SABA: Short-acting beta-agonist, SAMA: Short-acting muscarinic antagonist, LABA: Long-acting beta-agonist, LAMA: Long-acting muscarinic antagonist, ICS: Inhaled corticosteroid

analyses were conducted to determine the prognostic value of variables for the primary and secondary endpoints. Univariable Cox regression analysis was initially performed on 24 baseline covariates (including age, sex, BMI, CCI score, SGRQ score, LTOT use, BPAP use, all PFT indices, and peripheral blood cell counts) to assess their individual prognostic value for all-cause mortality. Variables with a p-value <0.05 were subsequently included in a multivariable Cox regression model using the backward stepwise method, with a removal threshold set at p=0.10. With 24 all-cause mortality events in the cohort, the final four-variable model was tested, resulting in an events-per-variable ratio of 6:1.

Kaplan-Meier plots were used to depict survival probabilities over time, with time calculated from admission to death from any cause. Receiver operating characteristic (ROC) curve analysis was performed to determine cut-off points for parameters found to be significant in Cox regression analysis for survival prediction. Data were expressed as mean (standard deviation; SD), percentage (%), minimum-maximum, or median (interquartile range; IQR), as appropriate. All statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant.

Results

Initially, 204 patients were recruited for this prospective cohort study. However, 28 patients were excluded due to withdrawal from the study or loss to follow-up. Therefore, this study was completed with 176 patients.

Demographics and characteristics

A total of 176 patients with COPD were included in the study (3.4% female and 96.6% male). At cohort entry, the mean age was 65.4±10.3 years (range, 39–87 years), with the majority having received inhaled corticosteroid and long-acting beta-agonist combination therapy. The mean body mass index of all patients was 25.7±4.8.

Table 2: Pulmonary function test and peripheral blood cell count data

Parameter	Mean±SD or ratio (%), (range)
FEV_1 (ml)	1520±610 (490–2920)
FEV_1 (%)	54.2±18.3 (19–92)
FVC (ml)	2440±852 (170–4430)
FVC (%)	70.2±19.2 (28–124)
FEV_1/FVC (%)	60.2±10.9 (30–69)
FEF25–75 (ml)	917.4±684.5 (69–3810)
FEF25–75 (%)	30.4±20 (8–114)
Eosinophil count (cells/μL)	250±360 (10–850)
Lymphocyte count (cells/μL)	2200±1000 (0–6500)
Neutrophil count (cells/μL)	6750±1370 (900–9800)

SD: Standard deviation, FEV_1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, FEF25-75: Forced expiratory flow between 25% and 75% of vital capacity

Thirty-three out of 176 patients (18.8%) were active smokers, 127 (72.2%) were ex-smokers, and 16 (9.1%) were non-smokers. During the study period, 43 of 176 patients (24.4%) died.

At the initial assessment, 98 patients (55.7%) had stable COPD, 28 (15.9%) had an acute exacerbation, and 50 (28.4%) had pneumonia. Participants experienced an average of 1.7 (standard deviation [SD]: 2.1) acute exacerbations in the year prior to inclusion. The mean number of moderate-to-severe acute exacerbations during the follow-up period was 1.6±1.9. Of the 176 patients, 43 (24.4%) were using LTOT and 23 (13.1%) were receiving BPAP therapy. In the year preceding study inclusion, 88 patients (50%) received influenza vaccination, while 75 patients (42.6%) received pneumococcal vaccination.

At baseline clinical assessment, the mean CAT and mMRC scores were 15±9.2 and 2±0.9, respectively. The mean CCI score was 3.2±1.6. The mean SGRQ symptom, impact, activity, and total scores were 54.9±24, 34.8±19.3, 53.6±22.8, and 44.5±18.9, respectively (Table 1). The average values of FEV_1 (ml), FEV_1 (%,) FVC (ml), FVC (%), FEV_1/FVC (%), FEF25-75 (ml), and FEF25-75 (%) were 1520±610, 54.2±18.3, 2440±852, 70.2±19.2, 60.2±10.9, 917±684, and 30.4±20, respectively. The mean peripheral eosinophil, lymphocyte, and neutrophil counts were 250±360 cells/μL, 2200±1000 cells/μL, and 6750±1370 cells/μL, respectively (Table 2).

Survival and regression analyses

The three-year overall survival rate was 86.4% based on Kaplan–Meier estimates. Cox regression analysis using the backward stepwise method revealed the following independent variables as factors affecting survival: age (p<0.001, hazard ratio [HR]: 1.112, confidence interval [CI]: 1.064–1.161), CCI score (p<0.001, HR: 2.056, CI: 1.791–2.360), LTOT use (p=0.001, HR: 2.742, CI: 1.495–5.029), and eosinophil count (p<0.001, HR: 0.489, CI: 0.411–0.583). Baseline evaluations including BMI, medications used, questionnaires (CAT, mMRC scale, SGRQ), BPAP use, spirometry parameters, lymphocyte and neutrophil counts, exacerbation count, emergency department visits and hospitalization count in the year prior to study enrollment, and history of influenza and pneumococcal vaccination did not demonstrate significant associations with mortality (p>0.05). Regression analyses for all parameters are presented in Table 3.

Table 3: Cox regression analysis of baseline covariates

Predictor	p	HR	CI (95%)
Age	<0.001	1.112	1.064–1.161
CCI	<0.001	2.056	1.791–2.360
Eosinophil count	<0.001	0.489	0.411–0.583
LTOT use	0.001	2.742	1.495–5.029
BMI	0.573	0.978	0.906–1.056
CAT	0.647	0.989	0.941–1.038
Medications used	0.356	1.071	0.926–1.239
mMRC	0.558	1.156	0.711–1.880
SGRQ	0.778	1.003	0.983–1.024
FEV_1 (ml)	0.310	0.998	0.994–1.002
FEV_1 (perc)	0.698	1.024	0.907–1.157
FVC (ml)	0.511	1.001	0.999–1.003
FVC (perc)	0.919	1.004	0.921–1.095
FEV_1/FVC	0.796	1.014	0.915–1.123
FEF25–75 (ml)	0.053	1.003	1.000–1.006
FEF25–75 (perc)	0.082	0.920	0.838–1.011
Lymphocyte count	0.292	0.975	0.931–1.022
Neutrophil count	0.734	1.005	0.977–1.034
Influenza vaccination	0.263	1.569	0.713–3.453
Pneumococcal vaccination	0.893	1.047	0.538–2.037
BPAP use	0.085	0.468	0.197–1.111
Exacerbations in the previous year	0.923	0.989	0.789–1.240
Emergency department visits in the previous year	0.058	1.173	0.994–1.384
Hospitalization in the previous year	0.229	0.797	0.551–1.154

HR: Hazard ratio, CI: Confidence interval, CCI: Charlson comorbidity index, LTOT: Long-term oxygen therapy, BMI: Body mass index, CAT: COPD assessment test, mMRC: Modified medical research council, SGRQ: St. George's respiratory questionnaire, BPAP: Bilevel positive airway pressure

ROC curve analysis was performed to identify potential cut-off points for age, CCI, and eosinophil count in relation to mortality. The area under the curve (AUC) values were 0.794, 0.969, and 0.943 for age, CCI, and eosinophil count, respectively [Fig. 2]. A CCI score of 4.5 or higher

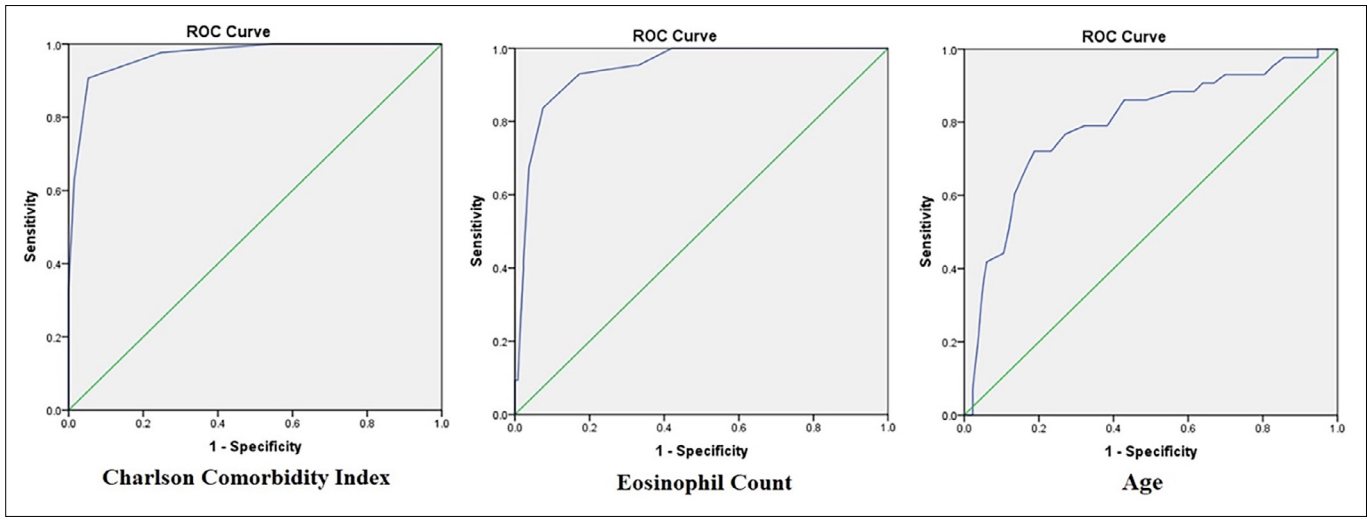

Figure 2: Receiver operating characteristic curves for the Charlson Comorbidity Index and eosinophil count

and an age of 68.5 years or older were significantly associated with increased mortality risk. Conversely, lower eosinophil counts (≤45 cells/μL) were associated with a higher risk of death (Table 4). Increasing age, higher CCI scores, LTOT use, and decreased eosinophil counts were associated with a worse prognosis. Figure 3 shows the Kaplan-Meier survival curves for the significant mortality predictors identified in the study (age, CCI, eosinophil count, and LTOT use).

Discussion

While numerous studies have investigated predictors of mortality in COPD patients with chronic respiratory failure, few have focused on extended follow-up periods exceeding two years. Moreover, prior research has often neglected health status as a potential predictor. This prospective study addresses these gaps by demonstrating that age, LTOT use, blood eosinophil count, and CCI as a disease-specific health status measure independently predict mortality in this population over a three-year period. Notably, other physiological factors, such as exercise performance, did not exhibit significant associations with three-year survival.

In this study, age emerged as a significant predictor of mortality, consistent with findings from studies involving less severe COPD populations.[10,11,14,15] However, the prognostic value of age in patients with respiratory failure has been reported less consistently.[16,17] Additionally, we found that patients aged 68.5 years or older exhibited significantly poorer survival rates compared to younger patients.

Pulmonary function testing remains crucial for COPD management, serving to establish diagnosis, monitor disease progression, and stratify disease severity. However, its utility in mortality prediction and survival assessment remains controversial. Our study did not identify spirometry parameters as independent predictors of mortality. Consistent with our findings, few previous studies have reported weak associations between the FEV_1/FVC ratio and mortality,[16–18] which contrasts with observations in patients with less severe disease.[10,11,19] Notably, the OLIN study (Obstructive Lung Disease in Northern Sweden) with a 20-year follow-up observed slower rates of lung function (FEV_1) decline in long-term survivors, suggesting its potential relevance in different disease stages.[20] Based on our findings, we suggest that the predictive power of FEV_1

Table 4: Cut-off points, statistical significance, sensitivity, and specificity of independent risk factors

Risk factor	AUC (95% CI)	Cut-off value	p	Sensitivity (%)	Specificity (%)
Age (years)	0.794 (0.712–0.876)	68.5	<0.001	76.7%	72.9%
Charlson comorbidity index (score)	0.969 (0.943–0.994)	4.50	<0.001	90.7%	94.7%
Eosinophil count (cells/μL)	0.943 (0.908–0.978)	45	<0.001	83.7%	92.5%

AUC: Area under the curve, CI: Confidence interval

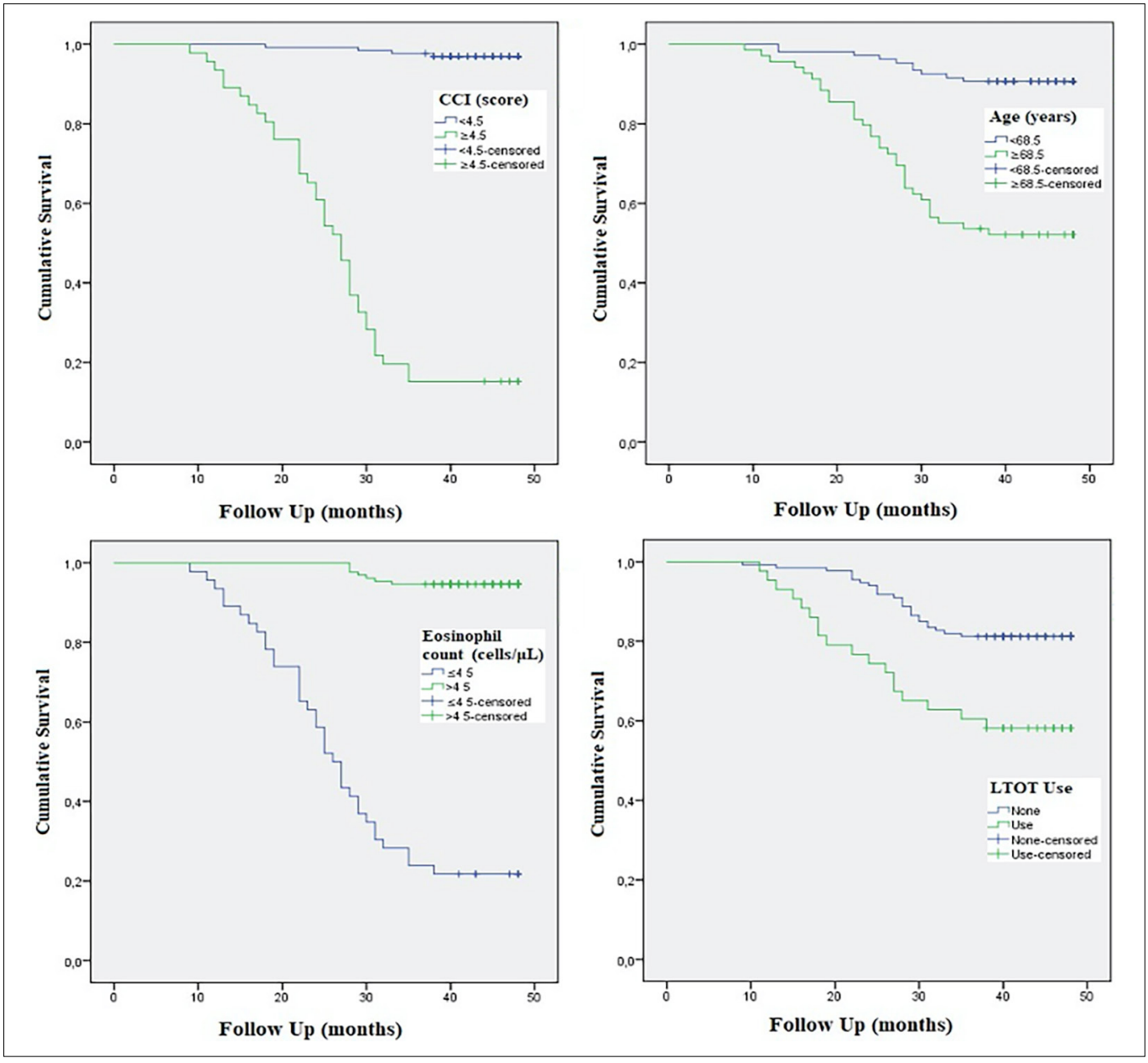

Figure 3: Kaplan-Meier survival curves (cohorts for age, Charlson Comorbidity Index (CCI), and eosinophil count stratified by receiver operating characteristic (ROC)-derived cut-off values)

for mortality likely diminishes in high-risk cohorts with advanced disease, where systemic factors such as comorbidity burden (CCI) and inflammation (eosinophil count) supersede airflow limitation as dominant drivers of long-term mortality, although FEV_1 is a key prognostic factor in COPD.[20]

Traditional lung function tests often fail to capture the full impact of COPD, necessitating the use of disease-specific health status questionnaires. Our study confirmed that poorer baseline health status, particularly when compounded by comorbidities, is associated with increased mortality. This finding aligns with Almagro et al.[21] but contrasts with Soler-Cataluña et al.,[22] who found no such association using the CCI. Questionnaires such as the CAT offer a simple and cost-effective alternative for assessing health-related quality of life, especially when spirometry is impractical; however, Dal Negro et al.[23] cautioned against using the CAT score as a direct substitute for lung function. Our analysis specifically

demonstrated that the CCI emerged as a significant predictor of mortality, while other health assessment tools (CAT, mMRC, SGRQ) were not independently associated with survival. We further identified a CCI score of 4.5 or higher as a potential cut-off point indicating a significantly increased mortality risk. In this aging, highly comorbid cohort (mean CCI 3.5), the pathophysiology of long-term mortality is likely driven more by the cumulative systemic impact of multi-organ disease—objectively captured by the CCI—than by the subjective perception of pulmonary-specific symptoms measured by the CAT, mMRC, or SGRQ, which may explain their lack of independent predictive value in our study.

COPD exacerbations are known to trigger a rise in blood eosinophil counts. Eosinophils are thought to contribute to the inflammatory cascade by promoting the production of other inflammatory cytokines. Despite these established roles, the association between peripheral blood eosinophil levels and mortality in COPD remains an under-investigated area. Casanova et al.[24] reported that persistently elevated eosinophil counts (≥300 cells/μL) were associated with improved survival, although not with an increased risk of exacerbations. This finding highlights the dynamic nature of eosinophil levels, which are influenced by factors such as infection and medication use.[24] Conflicting evidence exists, as the KOLD (Korean Obstructive Lung Disease) cohort study reported that eosinophilic COPD patients lacked distinct characteristics regarding symptoms or exacerbation rates, suggesting that population-specific factors may limit the utility of eosinophil count as a universal biomarker.[25] Conversely, Prudente et al.[26] and our findings suggest that lower eosinophil counts are linked to increased mortality and shorter survival. Specifically, our study identified ≤45 cells/μL as a threshold for poorer survival. Our results therefore support a link between diminished baseline blood eosinophil counts and worse prognosis in COPD. Physiologically, the association between lower eosinophil counts and poorer survival may reflect a state of systemic immune exhaustion or a phenotype dominated by severe, non-Type 2 (neutrophilic) inflammation, suggesting that a low count serves as a biomarker of critical systemic vulnerability, such as increased susceptibility to bacterial infections and pneumonia.[27–29] The recently released GOLD 2026 Report advocates the use of blood eosinophil counts in precision medicine to guide anti-inflammatory therapy, recommending inhaled corticosteroids for patients with counts ≥300 cells/μL to maximize exacerbation prevention and considering biologics for severe Type 2 inflammation.[2]

Long-term oxygen therapy is established for survival prediction in hypoxemic COPD, with some studies reporting an increase in lifespan.[30,31] Carone et al.[14] identified LTOT as an independent predictor of mortality, viewing it as an indirect marker of disease severity. However, controversy exists, as a meta-analysis by Lacasse et al.[32] suggested minimal impact on three-year mortality in moderately hypoxemic patients, raising questions about its routine use. While LTOT initiation often follows persistent hypoxemia after an exacerbation,[33] a survival benefit has been reported following severe acute exacerbations compared to non-hypoxemic patients.[34] The disproportionately high mortality observed in patients after LTOT initiation necessitates closer follow-up and proactive management.[33,34] Rantala et al.[35] also reported shorter survival in COPD patients receiving LTOT. Similarly, the timing of BPAP initiation is critical, with Mosher et al.[36] finding that initiation within the first 8 hours of an acute exacerbation may negatively affect survival. Consistent with this, our findings align with prior research,[31,37,38] suggesting that LTOT use may serve as a predictor of increased mortality in the broader COPD population. However, the association between baseline LTOT use and poorer prognosis should be interpreted with caution; as all patient characteristics were collected at enrollment, this finding is subject to significant indication bias and likely reflects the fact that LTOT is prescribed to patients with more severe underlying disease (e.g., chronic hypoxemia) rather than being a causal factor itself.

Our study of patients with chronic respiratory failure and COPD observed a favorable three-year cumulative survival rate of 86.4%. This rate exceeds the two-year survival rates reported in previous studies.[39–41] Additionally, age, CCI, and peripheral blood eosinophil count emerged as significant predictors of survival, demonstrating high discriminative ability, particularly for CCI and blood eosinophil count. Specifically, the CCI exhibited a sensitivity of 90.7% and a specificity of 94.7%, while the blood eosinophil count showed a sensitivity of 83.7% and a specificity of 92.5%. In contrast, the sensitivity and specificity of age as a predictive factor were relatively lower than those of the other predictors in this study, at 76.7% and 72.9%, respectively.

Several limitations warrant consideration. Our analysis was restricted to a single cohort, potentially limiting generalizability. Overlapping conditions such as asthma were not evaluated. The study population comprised COPD patients from a single referral center with different health status at baseline (stable disease, acute exacerbation, or pneumonia) and substantial comorbidity burden, potentially leading to selection bias and restricting the applicability of our findings to the broader COPD population. The low representation of female patients (3.4% of the cohort) further limits the generalizability of our findings, particularly to the female COPD population. Finally, reliance on single baseline measurements for all clinical and laboratory markers represents a limitation, as longitudinal changes in these predictors over the three-year follow-up period were not assessed. Furthermore, no internal validation was performed, and the findings were not validated in an independent external cohort. The analysis also did not consider the influence of prior therapeutic interventions, as this was not a randomized controlled trial.

Conclusion

This study investigated survival in COPD patients, including those who were stable or presented with an acute exacerbation/pneumonia. We aimed to identify the impact of baseline clinical and laboratory data on mortality prediction. Our analysis identified a CCI score cut-off of 4.5 and an age cut-off of 68.5 years as being associated with increased mortality risk, while lower baseline eosinophil counts (≤45 cells/μL) predicted poorer survival in this COPD cohort. These findings suggest that CCI and eosinophil count may serve as simple and accessible prognostic markers for mortality risk stratification in routine COPD management, warranting validation in larger, multicenter cohorts. Further prospective studies are needed to validate these findings.

Ethics Committee Approval

The study was approved by the University of Health Sciences Izmir Tepecik Health Application and Research Center Non-interventional Ethics Committee (No: 2019/8-20, Date: 08/05/2019).

Informed Consent

All participants provided written informed consent.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

Concept – G.V.Ş., Y.V., G.P.; Design – G.V.Ş., Y.V., G.P., G.K., E.Y.; Supervision – Y.V., E.Y., A.K.Ç.; Resource – E.Y., E.C., Ç.A., A.M.; Materials – G.K., Ç.A., A.M.; Data Collection and/or Processing - G.V.Ş., Ç.A., A.M.; Analysis and/or Interpretation - G.V.Ş., Y.V., G.P., G.K., E.Y., A.K.Ç.; Literature Review – G.V.Ş., Y.V., G.P., Ç.A., A.M.; Writing – G.V.Ş.; Critical Review – Y.V., G.P., G.K., E.Y., E.C.

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Comparative analysis of artificial intelligence–assisted and manual assessment of the Ki-67 proliferation index in pulmonary neuroendocrine tumors

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Abstract:

BACKGROUND AND AIM: The Ki-67 proliferation index is widely used for diagnostic classification and prognostic assessment of pulmonary neuroendocrine tumors. Manual evaluation of Ki-67 immunohistochemistry is subject to interobserver variability, particularly in hot-spot selection and cell counting, which can affect diagnostic reliability. This study aimed to directly compare manual pathologist assessments with an artificial intelligence (AI)–based digital analysis algorithm and to evaluate the reproducibility and reliability of AI-assisted measurements.

METHODS: Fifty-four pulmonary neuroendocrine tumor cases diagnosed between 2020 and 2024 were included: 27 typical carcinoids (TC), 6 atypical carcinoids (AC), and 21 large cell neuroendocrine carcinomas (LCNEC). Ki-67–stained slides were digitized using a high-resolution scanner. Four pathologists independently evaluated hot-spot regions and manually calculated the Ki-67 index (approximately 2,000 tumor cells per hot spot), while the AI algorithm automatically identified hot spots and quantified Ki-67-positive cells (500–2000 tumor cells per case). Interobserver agreement among pathologists was assessed using the intraclass correlation coefficient (ICC), and concordance between manual and AI-based measurements was analyzed using Spearman's correlation coefficient (r).

RESULTS: Very high agreement was observed among pathologists (ICC=0.999, 95% confidence interval: 0.998–1.000). AI-derived Ki-67 indices strongly correlated with the mean pathologist-derived values (Spearman's r=0.972, p<0.001). Consistency was maintained across both carcinoid subtypes and large cell neuroendocrine carcinomas, demonstrating that AI provides reproducible and reliable results comparable to manual assessment.

CONCLUSIONS: AI-assisted digital analysis is a robust, reproducible, and time-efficient alternative to manual Ki-67 counting in pulmonary neuroendocrine tumors. Incorporating AI tools into routine pathology practice can reduce interobserver variability, standardize proliferation marker evaluation, and enhance diagnostic accuracy. This study highlights the potential of AI as a complementary method to manual assessment, rather than a replacement, in clinical pathology.

Keywords:

Artificial intelligence, digital pathology, Ki-67, lung, neuroendocrine tumors

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Introduction

Pulmonary neuroendocrine tumors (NETs) represent a heterogeneous group of neoplasms, including typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC), and small cell lung carcinoma (SCLC).[1] Accurate classification and prognostic assessment of these tumors are essential for guiding clinical management and predicting patient outcomes. The Ki-67 proliferation index, a well-established marker of cell proliferation, is widely used in both diagnostic and prognostic evaluation of pulmonary NETs. Specifically, Ki-67 helps differentiate between tumor subtypes and provides important information regarding tumor aggressiveness and clinical behavior.[2]

Manual evaluation of Ki-67 immunohistochemical staining, however, is prone to interobserver variability, particularly in the selection of "hot spot" regions and in counting positive tumor cells. Such variability may compromise the reproducibility and reliability of proliferation assessments, potentially affecting clinical decision-making.[3]

Recent advances in digital pathology and artificial intelligence (AI)–based image analysis have enabled more standardized, rapid, and reproducible quantification of Ki-67. AI algorithms can objectively identify Ki-67–positive cells in hot spot regions and calculate proliferation indices with minimal observer bias. While AI-assisted Ki-67 analysis has been explored extensively in gastrointestinal and pancreatic NETs, studies focusing on pulmonary NETs remain limited. Notably, prior work has demonstrated that deep learning–based algorithms can achieve high concordance with manual pathologist assessments, improving consistency and potentially supporting clinical workflows.[4,5]

Given the clinical importance of Ki-67 and the potential of AI to enhance its evaluation, this study was designed as a comparative analysis of manual pathologist assessments versus a digital pathology–integrated AI algorithm for Ki-67 quantification in pulmonary NETs. By assessing concordance, reliability, and reproducibility, we aimed to determine whether AI-assisted analysis can serve as a complementary tool to manual assessment in routine diagnostic practice.

Materials and Methods

Ethics statement

This study was conducted in accordance with the ethical standards of the responsible institutional Ethics Committee and the World Medical Association Declaration of Helsinki for studies involving human participants. Ethical approval was obtained from the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (Approval Number: 24237859-630, Date: 24.09.2025). Additionally, permission to use archived pathology materials was granted by the Hospital Directorate. As this was a retrospective study, informed consent was waived; however, all patient data were anonymized, and confidentiality was strictly maintained. No identifiable information, such as names, initials, or hospital numbers, was used in the analysis or illustrative material.

Case selection

This retrospective study included 54 pulmonary neuroendocrine tumor cases diagnosed between 2020 and 2024 in the Department of Medical Pathology, Karadeniz Technical University Faculty of Medicine. The cohort comprised 27 typical carcinoids, 6 atypical carcinoids, and 21 large cell neuroendocrine carcinomas. Only cases with available paraffin-embedded tissue blocks derived from excisional biopsies or surgical resections were eligible for inclusion; consultation cases and small biopsy specimens were excluded. Small cell carcinoma cases were also excluded, as the diagnoses were established exclusively on small needle biopsies without subsequent surgical resection, precluding adequate material for further analysis.

Given the relatively low number of atypical carcinoid cases (n=6), the statistical power for subgroup analyses is limited. Therefore, this study is considered exploratory, aimed at providing preliminary insights into AI-assisted Ki-67 quantification in pulmonary neuroendocrine tumors. A formal power analysis was not feasible due to the rarity of these tumors.

Ki-67 assessment and blinding procedures

Ki-67 immunohistochemical staining had been performed for routine diagnostic purposes. Slides were retrieved from the pathology archive for analysis. Four experienced pathologists independently evaluated the Ki-67 index using the hot-spot method, which identifies regions with the highest density of Ki-67–positive tumor cells. Pathologists were blinded to the AI algorithm re-

sults, to each other's scores, and to clinical information, and prior pathology reports. This blinding approach minimized observer bias and ensured objective evaluation.

For manual Ki-67 assessment, approximately 2,000 tumor cells per hot-spot region were counted, and the percentage of positively stained nuclei was calculated to determine the Ki-67 proliferation index.[6]

Slides were digitized using the VENTANA DP® 200 high-resolution scanner (Roche, Germany). Digital images were analyzed using the uPath Ki-67 image analysis algorithm (version 1.0.0.5; Roche Diagnostics). This commercially validated system employs a convolutional neural network (CNN)–based nuclear detection and segmentation model, trained on a large multicenter dataset that includes Ki-67–stained neuroendocrine and non-neuroendocrine tumor samples.

The algorithm automatically identifies tumor regions, detects hot-spot areas based on the highest density of Ki-67–positive nuclei, and classifies each nucleus as positive or negative using predefined optical density and chromogen intensity thresholds. For each case, the algorithm calculated the Ki-67 labeling index by evaluating a minimum of 500 and a maximum of 2,000 tumor cells, in accordance with international recommendations for neuroendocrine neoplasms.[7]

Potential factors that may influence AI performance—such as image quality, focus, tissue thickness, background staining, and chromogen variability—were examined prior to analysis. All slides were processed in a single laboratory using the same staining protocol and were scanned under identical technical conditions to minimize pre-analytic variability. The final Ki-67 index for each case was automatically computed as the percentage of tumor nuclei classified as Ki-67–positive by the algorithm.[8]

Statistical analysis

All obtained data were entered into the SPSS database (IBM SPSS Statistics, version 27.0; IBM Corp., Armonk, NY, USA). Interobserver agreement among pathologists was assessed using the intraclass correlation coefficient (ICC), and concordance between manual assessments and the AI algorithm was evaluated using Spearman's correlation coefficient (r). To evaluate potential differences in Ki-67 indices across tumor subtypes, a Kruskal-Wallis test was performed. Statistical significance was set at $p<0.05$.

No artificial intelligence-assisted technologies, including large language models (LLMs), chatbots, or image generators, were used in the preparation of this manuscript.

Results

Interobserver agreement among pathologists

The Ki-67 proliferation index was independently assessed by four experienced pathologists using the hot-spot method. Very high agreement was observed among the pathologists, with an intraclass correlation coefficient of 0.999 (95% confidence interval [CI]: 0.998–1.000), indicating excellent reproducibility of manual evaluations.

Descriptive statistics of Ki-67 indices

Ki-67 proliferation indices for each tumor subtype, as assessed by manual pathologist evaluation and AI analysis, are summarized in Table 1. For typical carcinoids (n=27), median Ki-67 values were 2% (range: 0.1–7.7%) for pathologists and 1.9% (range: 0.6–23.3%) for AI. For atypical carcinoids (n=6), median values were 14.8% (range: 13–20.2%) and 23.1% (range: 14.9–27.5%), respectively. For large cell neuroendocrine carcinomas (n=21), median values were 63.7% (range: 35.2–85%) and 60.1% (range: 23.4–82.6%), respectively. These descriptive statistics provide a clear overview of proliferation indices across different tumor subtypes.

Concordance between manual and AI-based assessments

Comparison of the mean Ki-67 indices calculated by the pathologists with the values obtained from the AI algorithm revealed a strong positive correlation (Spearman's $r=0.972$, $p<0.001$), demonstrating that the AI algorithm reliably reproduces manual assessments. Scatter plot analyses [Fig. 1] further illustrate the concordance between AI-derived and pathologist-derived Ki-67 indices, while highlighting minor interobserver variability among pathologists. Regression trendlines indicate that Pathologists 1 (blue) and 2 (green) exhibited the closest agreement with AI, followed by Pathologists 3 (orange) and 4 (purple).

Comparative analysis across tumor subtypes

A comprehensive comparative evaluation of Ki-67 proliferation indices revealed highly significant differences among the three tumor subtypes across both manual pathologist assessments and AI-derived hotspot quantification ($p<0.001$). The proliferation profiles exhibited

Table 1: Ki-67 proliferation index values of pulmonary neuroendocrine tumors determined by four pathologists and an AI algorithm

Case	Pathologist 1	Pathologist 2	Pathologist 3	Pathologist 4	AI Ki-67
1	15	10	14	13	27.5
2	4	4	3	4	4.9
3	3	3	3	3	5
4	8	7	7	9	12.4
5	72	80	75	75	70.3
6	15	15	15	15	15
7	5	5	4	5	4.9
8	21	20	20	20	23.8
9	15	14	15	15	22.5
10	2	2	2	2	3.2
11	2	2	2	2	1.9
12	55	58	55	55	53.6
13	45	50	50	42	57.1
14	60	65	65	60	60.1
15	55	60	60	60	47.3
16	6	5	5	5	8.6
17	52	55	55	55	47.7
18	2	2	2	2	2.1
19	2	2	2	2	23.3
20	2	1	1	2	1.6
21	80	85	85	85	78.4
22	85	85	85	85	77.7
23	75	80	80	80	65.9
24	1	2	1	2	0.9
25	75	75	80	80	68.1
26	2	2	2	2	2.9
27	2	2	2	3	1.6
28	2	2	2	2	1.6
29	45	45	45	50	33.6
30	22	15	20	20	24
31	1	1	1	1	2.4
32	1	1	1	1	1.3
33	1	1	1	1	5.3
34	1	1	1	2	1.4
35	1.5	1.2	1	2	1.7
36	0.1	0.1	0.1	0.1	0.9
37	0.1	0.1	0.1	1	0.6
38	67	70	70	70	67.7
39	4	4	4	5	13
40	35	36	35	35	34.8
41	75	75	75	75	69.8
42	50	50	50	50	47.4
43	2	2	2	2	2.6
44	48	45	45	45	23.4
45	65	60	60	65	37.8
46	85	85	85	85	82.6
47	70	65	65	70	34.4
48	0.1	0.1	0.1	0.1	0.7
49	0.1	0.1	0.1	0.1	1.2
50	0.1	0.1	0.1	0.1	0.8
51	13	13	15	12	14.9
52	65	65	65	60	64.2
53	71	70	70	70	71.4
54	0.1	0.1	0.1	0.1	0.8

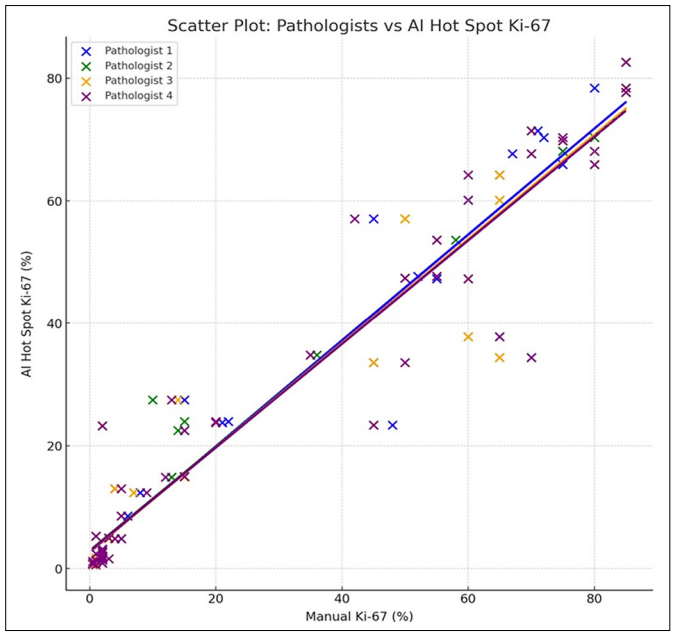

Figure 1: Scatter plot of the Ki-67 labeling index (%) for all 54 cases assessed by four pathologists (Pathologist 1–4; blue, green, orange, and purple) and by the artificial intelligence (AI) hot-spot method. Solid lines represent trendlines for each pathologist, illustrating the degree of concordance and variability between manual and AI-based evaluations

a clear and biologically coherent stratification: typical carcinoids demonstrated minimal proliferative activity, atypical carcinoids displayed intermediate levels, and large cell neuroendocrine carcinomas showed markedly elevated proliferation indices.

This gradient mirrors the known histopathological progression within pulmonary neuroendocrine neoplasms and reinforces the established correlation between tumor grade and proliferative behavior. The consistency of this pattern across manual and AI-based evaluations underscores the robustness of the findings and supports the diagnostic utility of both approaches.

Post hoc pairwise comparisons provided further statistical confirmation of these differences. LCNEC exhibited significantly higher Ki-67 indices than both TC and AC in all analytic frameworks, highlighting its distinct biological aggressiveness and aligning with its well-recognized high-grade clinical course. Conversely, the proliferative distinction between TC and AC, although present, was comparatively modest, consistent with their placement within the low- to intermediate-grade spectrum.

Taken together, these results emphasize that Ki-67 accurately reflects the biological continuum of neuroendocrine tumor behavior and demonstrate the value of integrating AI-assisted quantification into routine analysis to enhance reproducibility. The detailed distribution of these proliferation indices is presented in Figure 2.

Hot spot analysis and AI quantification

AI-based Ki-67 immunohistochemical analysis enabled precise identification and quantification of proliferative

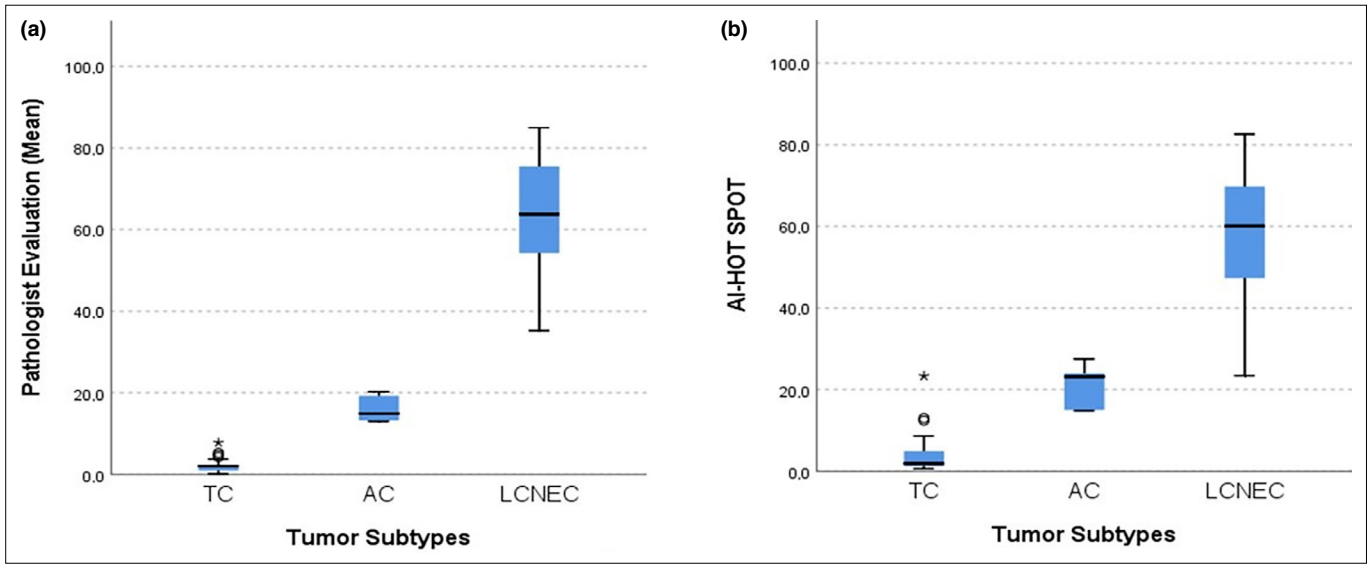

Figure 2: Comparative Ki-67 proliferation indices across pulmonary neuroendocrine tumor subtypes. Box-and-whisker plots depict Ki-67 labeling indices for typical carcinoid (TC), atypical carcinoid (AC), and large cell neuroendocrine carcinoma (LCNEC) as determined by manual pathologist assessment and artificial intelligence (AI)-assisted hot-spot quantification. The data demonstrate a clear gradation in proliferative activity, with TC showing the lowest, AC intermediate, and LCNEC the highest Ki-67 indices. Statistical significance was assessed using post hoc pairwise comparisons ($p<0.001$), highlighting marked differences between LCNEC and the other subtypes, while the distinction between TC and AC was more modest

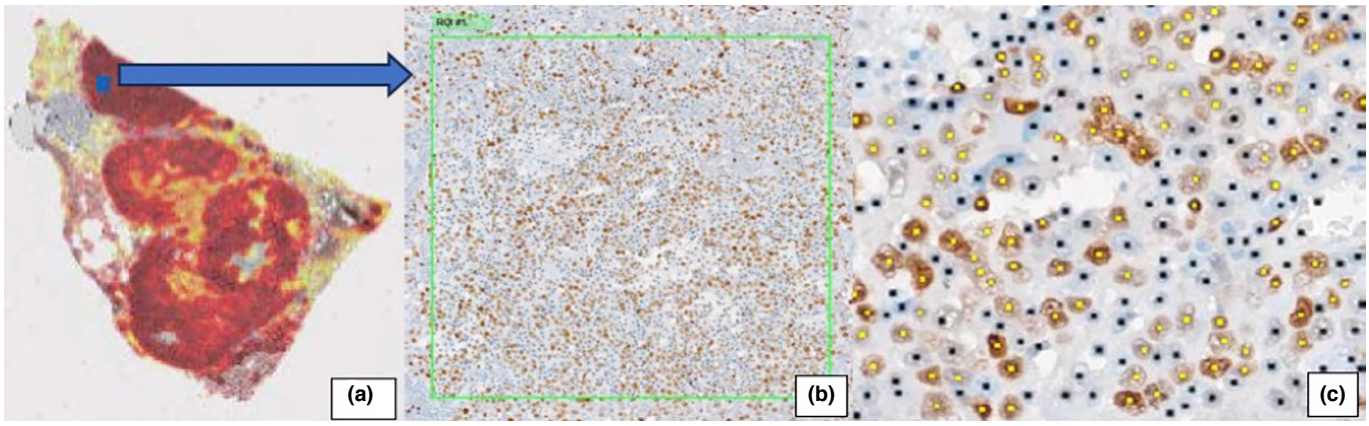

Figure 3: Example of artificial intelligence–based analysis of Ki-67 immunohistochemical staining. (a) A "hot spot" area with high proliferative activity is identified within the tumor tissue. (b) Tumor cell nuclei within the selected square region of interest (ROI) are enlarged and evaluated. (c) At higher magnification, Ki-67–positive nuclei (yellow markings) and Ki-67–negative nuclei (black markings) are automatically distinguished and quantified by the algorithm

tumor regions. Within each tumor, the single area with the highest Ki-67 labeling, referred to as the "top hot spot," was identified [Fig. 3a]. A square region of interest (ROI) was selected from this area, and tumor cell nuclei were segmented and evaluated at higher magnification [Fig. 3b]. The algorithm automatically classified nuclei as Ki-67–positive (yellow) or Ki-67–negative (black), providing accurate measurements of proliferative activity within the selected hot spot [Fig. 3c]. Across all cases, AI-derived indices demonstrated consistent and reproducible results comparable to manual assessment.

Discussion

The Ki-67 proliferation index is a central biomarker for evaluating tumor growth dynamics, offering valuable prognostic and therapeutic insights in neuroendocrine tumors.[1] However, manual evaluation of the Ki-67 index is inherently prone to variability due to differences in hot-spot selection, counting methodology, and interpretation among observers.[3] This study evaluated interobserver agreement among four experienced pathologists and compared manual Ki-67 assessments with AI-assisted measurements in pulmonary neuroendocrine tumors. To our knowledge, this is one of the first studies specifically focusing on AI-assisted Ki-67 quantification in pulmonary neuroendocrine tumors, highlighting the originality and clinical relevance of this work.

Our analysis revealed excellent concordance among pathologists, with an ICC of 0.999 (95% CI: 0.998–1.000), demonstrating highly reproducible manual evaluations under standardized conditions. Similar findings have been reported by Zehra et al.,[4] who observed 98% interobserver agreement. In contrast, Satturwar et al.[9] documented a lower concordance rate (84%) for manual hot-spot evaluation, indicating that reproducibility may vary depending on tumor heterogeneity and methodological consistency. These discrepancies underscore a key limitation of manual Ki-67 assessment—namely, its sensitivity to subjective interpretation, especially in borderline or heterogeneous lesions.

A strong positive correlation was identified between manual Ki-67 indices and AI-generated values, supporting the reliability and reproducibility of AI-assisted quantification. These observations are in agreement with those of Tang et al.,[10] who demonstrated strong concordance between digital image analysis and manual counting (ICC=0.98) and substantial agreement with mean eyeball estimations. The lower intra-observer consistency in manual counts (ICC=0.39±0.26) in our data further illustrates the inherent limitations of manual assessment and highlights the potential utility of AI tools in reducing subjective variability. Together, these results support the growing role of AI-assisted image analysis in enhancing standardization and diagnostic accuracy in pathology.

AI-assisted quantification may complement traditional pathology practice by providing more objective and reproducible metrics, reducing evaluation time, and improving workflow efficiency. In routine laboratory settings, integration of AI requires consideration of cost, software accessibility, personnel training, and compatibility with existing digital pathology infrastructure. Moreover, variability in immunohistochemical staining intensity across institutions—stemming from different fixation protocols, antibody clones, and staining platforms—may

still influence Ki-67 quantification, even when AI is used. Standardizing staining protocols remains essential for maximizing the reliability of AI-based analyses.[11]

This study has several limitations that should be acknowledged to contextualize the findings. First, the dataset was relatively small (n=54), which is expected given the rarity of pulmonary NETs; however, subgroup sizes—particularly for atypical carcinoids—were limited and may constrain statistical power. Second, the study was conducted at a single center, which may limit generalizability to broader patient populations. Third, the research relied on a retrospective design, introducing potential selection bias and limiting control over pre-analytical variables such as fixation and staining protocols. Fourth, only one AI tool was used, and its performance may not represent that of other commercially available or open-source systems. Fifth, the study did not include small cell lung carcinoma cases, restricting the tumor spectrum assessed. Finally, blinding constraints in the evaluation process may have introduced methodological bias. Recognizing these limitations provides transparency and supports appropriate interpretation of the study results.

Conclusion

In summary, our findings demonstrate excellent interobserver agreement among pathologists and strong concordance between manual and AI-assisted Ki-67 assessments in pulmonary neuroendocrine tumors. The results support the potential role of AI as an adjunct tool to enhance the accuracy, reproducibility, and efficiency of Ki-67 evaluation in clinical practice. Moreover, this study contributes original evidence to an emerging field, representing one of the earliest efforts to apply AI-supported Ki-67 quantification specifically to pulmonary NETs.

Future directions

Future research should explore the integration of AI-assisted Ki-67 quantification in multicenter studies and larger cohorts, including diverse pulmonary neuroendocrine tumor subtypes such as small cell lung carcinoma. Further development of AI algorithms, including deep learning and machine learning approaches, may improve detection accuracy, hot-spot selection, and reproducibility. Additionally, prospective studies evaluating the impact of AI-assisted pathology on clinical decision-making, patient outcomes, and workflow efficiency will be essential to fully realize the potential of digital pathology in routine practice.

Ethics Committee Approval

The study was approved by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (No: 24237859-630, Date: 24/09/2025).

Informed Consent

Written informed consent was waived.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Use of AI for Writing Assistance

No use of AI-assisted technologies was declared by the authors.

Author Contributions

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The impact of eosinophilia on treatment duration in patients with newly diagnosed drug-sensitive pulmonary tuberculosis

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Abstract:

BACKGROUND AND AIM: Eosinophilia, defined by an absolute eosinophil count (AEC) ≥500 cells/μl, is a common finding associated with various conditions, including mycobacterial infections, and can rarely be induced by standard anti-tuberculosis (TB) drugs such as isoniazid, ethambutol, and rifampin. While in vitro studies suggest that eosinophil products, such as eosinophil peroxidase, possess mycobactericidal activity, the clinical impact of eosinophilia on TB outcomes is unknown. This study aimed to analyze the association between eosinophilia development during treatment and the duration of therapy in a retrospective cohort of patients newly diagnosed with drug-sensitive pulmonary TB.

METHODS: This was a retrospective cohort study conducted at a tertiary center. A total of 6,045 patients with drug-sensitive pulmonary TB treated between 2017 and 2022 were screened. Patients were excluded if they had conditions that could confound eosinophilia or treatment duration, including allergic diseases, drug-resistant TB, severe comorbidities, and an AEC ≥1500 cells/μL. The final cohort included 121 contemporary non-eosinophilic controls (Group 1) and 119 patients who developed eosinophilia with no identifiable cause (Group 2).

RESULTS: The median age was comparable between Group 1 (43 years, range: 18–82) and Group 2 (45 years, range: 18–84; p=0.485). A statistically significant difference was observed in the duration of anti-TB treatment (p=0.013). The median treatment duration for the control group (Group 1) was 7 months (range: 6–9 months), whereas the median duration for the eosinophilia group (Group 2) was 6 months (range: 6–9 months). Logistic regression analysis confirmed that eosinophilia was significantly associated with treatment duration (odds ratio: 2.06, (95% confidence interval: 1.14–3.71; p=0.017).

CONCLUSIONS: The development of eosinophilia during treatment for drug-sensitive pulmonary TB was associated with a significantly shorter treatment duration. Conversely, the absence of eosinophilia is an independent risk factor for prolonged therapy. These findings suggest that eosinophils may contribute to a more effective host immune response against Mycobacterium tuberculosis, serving as a potential positive prognostic indicator in clinical practice.

Keywords:

Eosinophilia, treatment duration, tuberculosis

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Introduction

Tuberculosis (TB) is a significant global infectious disease caused by the bacterium Mycobacterium tuberculosis (MTB). According to the World Health Organization (WHO), an estimated 10.6 million people developed TB in 2022, continuing an upward trend compared to incidence rates in 2020 and 2021.[1] Despite the development and testing of various therapeutic alternatives, the 6-month regimen remains the standard of care worldwide, comprising isoniazid (H), rifampin (R), ethambutol (E), and pyrazinamide (Z).[2] Numerous studies have identified factors that negatively affect TB treatment success, including, but not limited to male sex, human immunodeficiency virus (HIV) co-infection, poor nutritional status, drug resistance, advanced age, alcohol consumption, smoking, and sputum smear non-conversion at two months.[3,4] However, the potential effect of eosinophil count on TB treatment success has not been explored in the current literature.

Eosinophilia is generally defined by an absolute eosinophil count (AEC) ≥500 cells/μL.[3] Use of the AEC is preferred over the eosinophil percentage (which is typically <5% in healthy individuals) because the latter is influenced by variations in the total white blood cell (WBC) count and the proportions of other leukocytes, such as lymphocytes and neutrophils.[5] Eosinophilia is a frequent clinical finding associated with a broad spectrum of disorders, including allergic, infectious, neoplastic, and idiopathic disease processes.[6] While some mycobacterial infections may induce eosinophilia, and certain standard treatments (e.g., H-E-R) have been rarely associated with it,[7] the precise causes and effects of this condition in the context of TB remain largely unknown. Eosinophils are known to release various mediators, including proteins, growth factors, and interleukins. While the full range of effects of all these released mediators is not fully established, evidence suggests that eosinophil cationic proteins (ECP) possess both mycobactericidal and lytic properties. In vitro studies have further demonstrated that human eosinophil peroxidase (EPO) can induce surface alterations and subsequent lysis of MTB. Furthermore, macrophages containing EPO have exhibited potent antimycobacterial activity.[8,9]

This study was designed to investigate the effect of eosinophilia development on treatment duration in patients newly diagnosed with drug-sensitive pulmonary TB. The potential implications of our findings are significant, as they may inform a more efficient and effective treatment approach for TB management.

Materials and Methods

This was a retrospective cohort study involving patients with TB managed at our center. Our institution, designated as one of four national TB centers, provides comprehensive care for both outpatients and inpatients with TB, including those with drug-resistant disease. A total of 6,045 patients treated for pulmonary TB between 2017 and 2022 were screened for inclusion in this study. All patients diagnosed with TB in our region are managed and followed at our center. Patient follow-up involves monthly chest radiographs and sputum cultures. Treatment termination decisions are made by the center's physicians based on these findings and clinical assessment. In compliance with national regulations, the follow-up process and all patient data are meticulously recorded. The study protocol received approval from Izmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (Approval Number: 2023/38-39, Date: 21.06.2023).

Study design, inclusion, and exclusion criteria

We planned to divide patients who met the inclusion and main exclusion criteria, based on AEC, into the control group (Group 1, no eosinophilia) and the study group (Group 2, eosinophilia). Eosinophilia was defined as an AEC ≥500 cells/μL.[3] We screened a total of 6,045 patients who were treated between 2017 and 2022.

Patients were included in the study if they presented as new cases of TB with simultaneous evidence of TB-compatible lesions on chest imaging (evaluated by both chest X-ray and thoracic computed tomography) and microbiological confirmation of MTB infection, defined by positive acid-fast bacilli (AFB) identification and either polymerase chain reaction (PCR) positivity or culture positivity in sputum or bronchoscopic samples.

We excluded patients with coexisting conditions such as immunologic and hematologic diseases; other pre-existing lung diseases, including asthma or chronic obstructive pulmonary disease (COPD) (based on prior diagnosis in the national database); human immunodeficiency virus (HIV) positivity (routinely checked); thyroid diseases (thyroid-stimulating hormone [TSH] is regularly checked); diagnosed or suspected malignancy; liver or

renal disorders identified at baseline or during follow-up; discontinuation of anti-TB medication(s) for any reason; a smoking history exceeding 10 pack-years (PY); and age under 18 years. These exclusion criteria were applied to the entire study population.

We applied rigorous exclusion criteria to control for confounding factors. A large number of patients were systematically excluded due to confounding factors: 21 cases of HIV; 1,334 with liver dysfunction; 498 with renal dysfunction; 977 with COPD; 136 with asthma; 401 with immunologic/hematologic diseases; 1,241 with a smoking history >10 PY; 391 with malignancy; 127 with thyroid disease; 91 with multi-drug resistance (MDR); 8 with extensive drug-resistance (XDR); 5 with pre-XDR; 186 treatment failures; 96 relapses; 91 treatment withdrawals; 101 deaths; 90 with drug discontinuation for reasons such as gastrointestinal symptoms without elevated liver function tests; and 6 with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Furthermore, a total of 508 cases that were consulted with the Department of Allergy and Immunology were excluded following definitive diagnoses of drug allergy, urticaria, allergic asthma, or idiopathic/immunologic diseases.

To isolate the effect of severe eosinophilia on treatment duration in patients with eosinophilia, the exclusion criteria included an AEC ≥1500 cells/μL, and 5 patients with severe eosinophilia (AEC ≥1500 cells/μL) were excluded from the study group. The AEC was routinely monitored in the blood of all screened patients, both at baseline (before treatment) and during follow-up.

Following these rigorous exclusions, particularly the exclusion of patients with allergic causes of eosinophilia, 240 eligible patients were ultimately included in the final analysis, ensuring a robust sample size. Of these, 121 contemporary patients meeting all inclusion and main exclusion criteria were assigned to the control group (Group 1, no eosinophilia, <500 cells/μL), and 119 patients in whom eosinophilia was present but no underlying cause could be identified after specialized consultation were designated as the study group (Group 2, eosinophilia, ≥500 cells/μL).

Treatment duration was calculated as the total calendar time, in months, from initiation of the anti-TB regimen to the final decision of treatment completion by the center's physician.

Sample size

The study sample size was calculated using a multiple regression approach with G*Power version 3.1.9.7. Accordingly, it was estimated that approximately ten predictors that could affect treatment duration would be included in the model. The minimum number of subjects to be included in the study for the model, which was predicted to have a maximum of 10 independent predictors with Cohen's medium effect (f=0.15), type I error of 0.05, and 0.80 power, was calculated as 118 subjects.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS 28; IBM Corp., Armonk, New York, USA). Nominal variables were presented as frequencies and compared using the chi-square test. Continuous variables were presented as median, minimum, and maximum values, as they were not normally distributed. Comparisons between groups were performed using the Mann-Whitney U test.

For multivariate analysis, the continuous variable "treatment duration" was dichotomized into two categories: standard treatment duration (≤6 months) and prolonged treatment duration (>6 months). Binary logistic regression analysis was then performed to determine the independent effects of comorbidities and eosinophilia on the likelihood of prolonged treatment. Odds ratios (OR) and 95% confidence intervals (95% CI) were reported. The probability of a type I error was set at α=0.05, and all statistical tests were two-sided. A p-value <0.05 was considered statistically significant.

Results

A total of 240 patients were included in the final analysis, divided into two groups: the control group (Group 1, no eosinophilia) with 121 patients and the study group (Group 2, eosinophilia) with 119 patients. A statistically significant difference in gender distribution was observed between the two groups (p=0.001), with Group 1 comprising 85 males (70.2%) and Group 2 comprising 106 males (89.1%). Regarding the clinical setting, significantly more patients in Group 2 were managed as inpatients (26 patients) compared to Group 1 (11 patients), and this difference was statistically significant (p=0.011). Analysis of common comorbidities revealed no statistically significant differences in the prevalence of diabetes mellitus (DM) (23 patients in Group 1 vs. 16 in Group 2;

Table 1: Demographic and laboratory characteristics of the patients

Variables	Group 1 (No Eosinophilia)	Group 2 (Eosinophilia)	p
Age (years)	43 (18–82)	45 (18–84)	0.485
ALT (unit/L)	24 (9–31)	23 (17–32)	0.431
AST (unit/L)	28 (11–40)	28 (12–33)	0.191
Creatinine (mg/dL)	0.9 (0.2–1.2)	0.8 (0.7–1.1)	0.340
Eosinophils (cells/μL) (baseline)	100 (0–400)	200 (0–500)	<0.001
Eosinophils (%) (baseline)	1 (0–5)	2 (0–6)	<0.001
Eosinophils (cells/μL) (1st month)	200 (0–500)	500 (0–1400)	<0.001
Eosinophils (%) (1st month)	2 (0–5)	6 (0–19)	<0.001
Eosinophils (cells/μL) (2nd month)	100 (0–400)	400 (0–1400)	<0.001
Eosinophils (%) (2nd month)	2 (0–6)	4 (0–13)	<0.001
Peak eosinophils (cells/μL)	200 (40–500)	600 (300–1450)	<0.001
Peak eosinophils (%)	3 (0–6)	8 (3–28)	<0.001
Eosinophils (cells/μL) (end of treatment)	100 (0–400)	300 (0–1450)	<0.001
Eosinophils (%) (end of treatment)	2 (0–6)	5 (1–28)	<0.001
Treatment duration (months)	7 (6–9)	6 (6–9)	0.013

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase.

p=0.321) or hypertension (HT) (8 patients in Group 1 vs. 9 in Group 2; p=0.972). Other cardiac comorbidities, such as heart failure (one patient) and coronary artery disease (three patients), were infrequent and observed exclusively in Group 2.

The median age of the control group (Group 1) was 43 years (range: 18–82 years), which was comparable to the study group (Group 2), with a median age of 45 years (range: 18–84 years), indicating no statistically significant difference between the groups (p=0.485). Furthermore, baseline liver and renal function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, and creatinine, showed no significant differences between the groups. Importantly, a statistically significant difference was observed in the duration of anti-tuberculosis treatment between the groups (p=0.013). Specifically, the median treatment duration for Group 1 was 7 months (range: 6–9 months), whereas the median duration for Group 2 was 6 months (range: 6–9 months). The detailed characteristics of the patients are summarized in Table 1.

To determine the independent factors affecting TB treatment duration, logistic regression analysis was performed using the dichotomized outcome of standard (≤6 months) versus prolonged (>6 months) treatment. The model examined the effects of comorbidities, age, gender, and eosinophilia.

In the univariate analysis, no statistically significant associations were observed for age (p=0.438), gender (p=0.699), or hypertension (p=0.414). In contrast, statistically significant associations were found for DM and eosinophilia.

In the multivariate model, variables were entered in a stepwise manner to identify independent predictors. Age was excluded from the final multivariate model because it was evenly distributed between the study groups and showed no significant association with the outcome in univariate analysis. The multivariate model revealed that DM was strongly associated with an increased likelihood of prolonged treatment (OR: 3.20; 95% CI: 1.57–6.52; p=0.001). Regarding eosinophilia, the analysis indicated that the absence of eosinophilia (Group 1) was significantly associated with an increased likelihood of prolonged treatment, with an odds ratio of 2.06 (95% CI: 1.14–3.71; p=0.017). In other words, patients who developed eosinophilia were significantly less likely to require prolonged treatment compared to those who did not. These results are presented in detail in Table 2.

Discussion

Our primary finding demonstrates that TB patients who developed eosinophilia during treatment experienced a significantly shorter treatment duration compared to the non-eosinophilia control group. This primary outcome, observed after rigorously excluding allergic and secondary causes, suggests a potential beneficial role of eosinophilia in the host response to TB. As widely accepted, the AEC is the most reliable metric for defining eosino-

Table 2: Multivariate logistic regression analysis

Step	Variables	B	SE	Wald value	p	OR (CI: Lower-Upper)
Step 1	HT (Present/Absent)	0.14	0.56	0.06	0.797	1.15 (0.38-3.47)
	DM (Present/Absent)	1.11	0.38	8.45	0.004	3.03 (1.43-6.41)
	Sex (Male/Female)	0.36	0.37	0.96	0.328	1.44 (0.69-2.97)
	Group (No eosinophilia/Eosinophilia)	0.72	0.30	5.80	0.016	2.06 (1.14-3.71)
	Constant	-1.52	0.42	13.3	<0.001	0.22
Step 2	DM (Present/Absent)	1.14	0.37	9.65	0.002	3.12 (1.52-6.39)
	Sex (Male/Female)	0.35	0.37	0.91	0.340	1.42 (0.69-2.91)
	Group (No eosinophilia/Eosinophilia)	0.72	0.30	5.77	0.016	2.05 (1.41-3.70)
	Constant	-1.50	0.41	13.4	<0.001	0.22
Step 3	DM (Present/Absent)	1.16	0.36	10.2	0.001	3.20 (1.57-6.52)
	Group (No eosinophilia/Eosinophilia)	0.63	0.28	4.9	0.017	2.06 (1.14-3.71)
	Constant	-1.18	0.23	26.9	<0.001	0.31

SE: Standard error, OR: Odds ratio, CI: Confidence interval, HT: Hypertension, DM: Diabetes mellitus.

philia rather than the percentage threshold, as the latter depends on the total white blood cell count.[3] Consistent with standard definitions, we used an AEC of up to 500 cells/μL as the normal upper limit and applied this cut-off value in peripheral blood for group assignment.

In our multivariate analysis, DM emerged as a strong independent predictor of prolonged treatment duration (OR: 3.20; 95% CI: 1.57–6.52). This finding within our cohort aligns with the well-documented association between DM and susceptibility to MTB infection.[10] Individuals with DM typically experience a state of chronic, subclinical inflammation that impairs overall immune function, often necessitating longer or more complex treatment courses. This negative prognostic impact of DM stands in stark contrast to the protective association observed with eosinophilia in our study. While metabolic comorbidities such as DM appear to hinder rapid clearance, the development of eosinophilia correlates with a shortened treatment duration, suggesting that these two factors may represent opposing immunological influences on TB treatment outcomes.

The shorter treatment duration observed in our eosinophilia group aligns with in vitro evidence suggesting a direct antimycobacterial role for eosinophil products. Specifically, a study by Borelli et al.[8] demonstrated that EPO, released from eosinophils, can strongly disrupt the cell wall of MTB, ultimately leading to the organism lysis. Although no previous human study has investigated the direct link between eosinophilia development during TB treatment and treatment duration, the substantial disruptive effect of EPO on the MTB cell wall may contribute to the observed more rapid clinical recovery. However, contrasting evidence exists, as a separate study conducted in guinea pigs infected with MTB failed to show any direct interaction between eosinophils and mycobacteria within infection lesions.[11]

Previous literature, primarily consisting of case reports, suggests an interaction between TB and eosinophilia, with TB potentially acting as an underlying cause of increased eosinophil counts. For instance, Garg et al.[12] presented a case of a 68-year-old female diagnosed with TB after other causes of marked eosinophilia (total leukocyte count 12×10^9 cells/L with an eosinophil percentage of 32%) were excluded. Similarly, two pediatric case reports described patients with pulmonary and hepatic TB presenting with striking eosinophilia (eosinophil percentages of 72% and 50%, respectively).[13,14] The magnitude of eosinophilia reported in these cases was considerably higher than the levels observed in our study population, given our strict exclusion of patients with an AEC ≥1500 cells/μL. Although a definitive epidemiological association between eosinophilia and TB has not been established, and the impact of eosinophilia on the TB treatment process has not been previously investigated, our robust findings indicate that patients who developed eosinophilia during treatment required a shorter treatment duration. To strengthen the validity of this finding and minimize confounding factors, our study applied strict exclusion criteria, systematically ruling out numerous conditions known to affect both treatment duration and eosinophil count.

The prognostic significance and functional role of eosinophils have also been investigated in other infectious contexts, particularly viral diseases. For instance,

in patients with Coronavirus Disease 2019 (COVID-19), the development of eosinopenia within nine days of onset has been identified as a predictor of poor prognosis, suggesting that eosinophils may provide a protective benefit, possibly by modulating neutrophil-induced inflammation.[15] While the traditional focus has often been on the potentially harmful proinflammatory functions of eosinophils, emerging evidence highlights their specific antiviral capabilities. This is particularly evident in respiratory syncytial virus (RSV) infection, where eosinophils demonstrate antiviral activity through the release of granule proteins such as eosinophil-derived neurotoxin (EDN) and ECP. Furthermore, eosinophils are capable of generating nitric oxide (NO) via the NO synthase pathway, a mechanism that has demonstrated antiviral efficacy against both parainfluenza virus and RSV.[16–18]

Eosinophils are known to express Toll-like receptors (TLRs), specifically TLR-3, TLR-7, and TLR-9, which are typically activated during viral recognition.[19–21] These receptors play a pivotal role in the innate immune response and the subsequent initiation of adaptive immunity against various infectious agents.[22,23] Upon activation, TLRs regulate the transcription of key proinflammatory cytokines (including interleukin-1 beta [IL-1β], tumor necrosis factor-alpha [TNF-α], and IL-6) which are fundamental for the recruitment of immune cells to the site of infection and the effective control of MTB.[24] The importance of this pathway is underscored by murine studies demonstrating that TLR-2 and TLR-4 are essential for recognizing MTB pathogen-associated molecular patterns (PAMPs), and that mice deficient in TLR-2 or TLR-8 genes fail to control the infection and succumb to the disease.[25,26] Furthermore, activation of TLR-2 by bacterial lipoprotein (19-kD) in macrophages has been shown to trigger mycobactericidal activity; however, unlike findings in viral models, some studies indicate that this specific pathway may not involve nitric oxide production.[27,28] Consequently, eosinophils appear to significantly influence the immunopathology of MTB infection; however, their protective effect is likely multifactorial, potentially involving not only TLR activation but also other distinct pathways that remain to be fully established in the literature.

This study is subject to several limitations inherent to its design. First, as a retrospective cohort analysis, despite mandatory and rigorous data registration in our national system, the study is subject to potential selection bias and cannot establish a causal relationship between eosinophilia and shortened treatment duration. Second, the study was conducted at a single tertiary center, which may restrict the generalizability of our findings to other settings. Third, a significant limitation is the absence of data regarding cavitary lesions on baseline chest imaging, a well-established determinant of treatment duration in TB, which was not recorded in our database and may represent a residual confounder. Fourth, we did not specifically analyze the prognostic impact of the timing of eosinophilia onset (e.g., early vs. late development). Fifth, the strict exclusion criteria—necessary to isolate idiopathic eosinophilia—significantly reduced our sample size and resulted in the exclusion of patients with common comorbidities. Additionally, we observed a significant male predominance in the eosinophilia group compared to controls; however, multivariate regression analysis included gender as a covariate and found no significant association between sex and treatment duration, suggesting that this disparity likely did not skew the primary outcome. Finally, we relied on peripheral blood counts and did not quantify specific eosinophil-derived mediators (e.g., ECP or EPO), therefore, the precise biological mechanisms remain speculative.

Conclusion

The immunopathology of TB is intricate and remains a subject of ongoing investigation. The precise function of eosinophils in many disease contexts, including TB infection, is only partially understood. Our study demonstrates that the development of eosinophilia during treatment of drug-susceptible pulmonary tuberculosis is associated with a significantly shorter duration of therapy. Conversely, the absence of eosinophilia emerged as an independent predictor for prolonged treatment duration, highlighting the potential prognostic value of eosinophil kinetics in clinical practice. These findings suggest that eosinophils may play a protective role in the host immune response against MTB, rather than merely representing an allergic drug reaction. While the retrospective nature of this study warrants caution, our results provide a clinical foundation for further prospective investigation into the use of eosinophil counts as a novel, accessible biomarker to guide and potentially personalize TB treatment management.

Ethics Committee Approval

The study was approved by the Izmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (No: 2023/38-39, Date: 21/06/2023).

Informed Consent

Written informed consent was not required due to the retrospective nature of this study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

Concept – S.Y., S.D.; Design – S.D.; Supervision – S.D., O.K.; Resource – S.Y., O.K., G.V.Ş.; Materials – S.Y., O.K., G.V.Ş.; Data Collection and/or Processing - S.Y., O.K., G.V.Ş.; Analysis and/or Interpretation - S.Y., S.D.; Literature Review – S.Y., G.V.Ş.; Writing – S.Y., S.D.; Critical Review – S.D., O.K.

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A nationwide survey of pulmonary rehabilitation practices in Türkiye: A multidimensional perspective

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Abstract:

BACKGROUND AND AIM: Pulmonary rehabilitation (PR) is a cornerstone of chronic respiratory disease management; however, its organization and accessibility vary widely across countries. National data on PR practices in Türkiye are limited. This study aimed to describe the current landscape of PR services in Türkiye and to identify key organizational characteristics and barriers to implementation.

METHODS: A cross-sectional, web-based survey was conducted by the Pulmonary Rehabilitation Working Group of the Turkish Respiratory Society (TÜSAD). The questionnaire was distributed to healthcare professionals involved in PR and explored institutional infrastructure, team composition, program components, assessment practices, target patient populations, and perceived barriers to PR delivery.

RESULTS: Responses were obtained from 40 centers. Fifteen centers (38%) had an active PR unit, while 16 (40%) provided PR through staff-delivered or consultation-based services. Among centers offering PR (n=31), 58% reported reimbursement through the national social security system. Only 35% met the minimum recommended core interdisciplinary team requirements. PR programs were delivered through multiple service delivery models, most commonly in inpatient (71%) and outpatient (52%) settings, and primarily targeted patients with chronic obstructive pulmonary disease (COPD) and other chronic lung diseases. Exercise training and patient education were included in nearly all programs, whereas nutritional counseling (39%) and psychosocial support (23%) were less frequently offered. The mean patient acceptance rate for prescribed PR programs was 60% (standard deviation: 31). Major barriers to PR implementation included transportation difficulties, financial constraints, and lack of patient motivation.

CONCLUSIONS: Pulmonary rehabilitation services in Türkiye have expanded but remain heterogeneous in structure and delivery. Only approximately one-third of centers providing PR meet the recommended minimum core team composition. Our findings highlight the need to strengthen workforce capacity and to standardize PR delivery nationwide.

Keywords:

Pulmonary rehabilitation, policy, healthcare services, access

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Introduction

Chronic respiratory diseases (CRDs), including chronic obstructive pulmonary disease (COPD) and interstitial lung diseases, represent a major and growing global health burden, leading to reduced quality of life, frequent hospitalizations, and increased mortality. Among available non-pharmacological interventions, pulmonary rehabilitation (PR) is recognized as a cornerstone of evidence-based management. PR has been shown to improve exercise capacity, reduce dyspnea, enhance health-related quality of life, and decrease healthcare utilization.[1,2] International statements recommend that PR be integrated into the standard care of individuals with chronic respiratory conditions; however, global practice indicates that this integration is far from complete.[3,4] The persistent gap between strong guideline recommendations and limited real-world implementation continues to hinder the effective translation of evidence into routine clinical practice.

Despite clear evidence supporting its benefits, substantial inequalities exist in PR provision worldwide. Studies have documented wide variation in program structure, staffing, referral pathways, and funding, even among high-income countries.[5,6] In low- and middle-income settings, the availability of PR remains critically low, and patient access is often restricted by inadequate awareness, insufficient numbers of trained personnel, and limited institutional support.[7,8] In recent years, new delivery models such as home-based and tele-rehabilitation programs have emerged, offering promising solutions where resources are scarce or patient mobility is limited; however, their sustainability and integration into national healthcare systems remain inconsistent.[9,10] These ongoing disparities highlight the need for country-specific evaluations of PR organization and accessibility to support systematic improvement and standardization efforts.

In Türkiye, the integration of PR into respiratory care has progressed gradually; however, comprehensive national data on the organization and delivery of these services are still lacking. The diversity of healthcare institutions, variations in workforce capacity, and differences in funding mechanisms further complicate the establishment of unified standards. Understanding these factors is essential for capacity building, policy development, and professional training initiatives. Therefore, this study was conducted by the Pulmonary Rehabilitation Working Group of the Turkish Respiratory Society (TÜSAD) to perform a nationwide survey characterizing the current landscape of PR practice in Türkiye and to identify key facilitators and barriers to its implementation.

Materials and Methods

Study design and participants

A cross-sectional descriptive study was conducted. The target population included all members of the Turkish Respiratory Society, as well as other professionals involved in PR, such as physiotherapists or pulmonologists working in tertiary or secondary care institutions. The survey link was distributed electronically via the society's official mailing list and through professional messaging groups of pulmonary rehabilitation practitioners. Participation was voluntary, and each respondent represented a single healthcare center. Duplicate responses from the same institution were consolidated, resulting in data from 40 distinct centers across the country.

Survey development and content

A structured questionnaire was developed based on previous international surveys and expert consensus. The questionnaire consisted of multiple sections covering:

1) demographic and professional characteristics of respondents;
2) the organization and structure of PR services, including availability of PR units, reimbursement, and referral mechanisms;
3) team composition and components of PR programs;
4) evaluation methods routinely used;
5) targeted patient populations; and
6) barriers to service delivery and patient participation.

Most questions were multiple-choice and allowed selection of more than one option when applicable. Skip logic was applied so that certain questions were displayed only to respondents from institutions providing PR services.

The study was conducted in accordance with the Declaration of Helsinki. Formal ethics committee approval was not required, as the study did not involve patient data and participation was entirely voluntary. All respondents provided electronic informed consent prior to completing the survey.

Data collection and processing

The survey was open between March and December 2024. Responses were collected anonymously using Google Forms. Before completing the questionnaire, participants reviewed an electronic information page describing the study objectives and confirming data confidentiality, which served as informed consent. No personally identifiable information was collected.

Responses were exported for data cleaning and analysis. In cases where multiple respondents represented the same center, data were merged using a "union" approach for multiple-choice items and a majority-rule approach for binary questions. Centers that did not provide PR services were asked additional questions regarding institutional barriers and reasons for not offering such services.

Table 1: Characteristics of participating centers (n=40 centers; 40 respondents)

Respondent characteristics	n
Mean age (years)	43.9±9.7
Female sex	30 (75%)
Professional background, n (%)	
Pulmonologist	18 (45)
Physiotherapist	18 (45)
Thoracic surgeon	2 (5)
Physiatrist	2 (5)
PR service availability, n (%)	
On-site PR unit	15 (38)
No PR unit, staff-delivered PR	8 (20)
No PR unit, PR via consultation	8 (20)
No PR service	9 (22)
PR services reimbursed by SGK	18 (58% of PR-providing centers)

Values are presented as mean±standard deviation (SD) or n (%).
PR: Pulmonary rehabilitation, SGK: Social security institution.

Statistical analysis

All analyses were descriptive. Continuous variables were expressed as mean±standard deviation (SD), and categorical variables were summarized as frequencies and percentages. Data were analyzed at the center level. No inferential statistical tests were performed, given the exploratory and descriptive nature of the study. Statistical analyses were conducted using SPSS software (IBM SPSS Statistics, version 20.0, Chicago, IL, USA).

Results

Responses were obtained from 40 participants representing 40 different centers. The characteristics of respondents and participating centers are presented in Table 1. The mean age of respondents was 43.9±9.7 years, and 75% were female. Of the respondents, 45% were pulmonologists, 45% were physiotherapists, 5% were thoracic surgeons, and 5% were physiatrists.

Of the 40 centers, 15 (38%) had an active PR unit. Eight centers (20%) did not have a PR unit but provided staff-delivered PR, while another eight centers (20%) delivered PR through consultation when needed. Nine centers (22%) neither had a PR unit nor provided any PR services. Among the 31 centers providing PR, 18 (58%) reported that their services were reimbursed through the national social security system (SGK). Among the nine centers that did not provide any PR services, four (44%) reported no intention of establishing a PR unit. Among these four centers, the most commonly cited reasons were lack of belief in cost-effectiveness (50%), lack of qualified personnel (50%), and unwillingness of institutional management (25%). The geographical distribution of all responding centers by city and region is presented in Appendices 1 and 2. İstanbul was the most frequently represented city, accounting for 35.0% of all responding centers, 35.5% of centers providing PR, and 46.7% of centers with an active PR unit (Appendix 1). Similarly, the Marmara Region predominated geographically, representing 50.0% of all responding centers, 48.4% of PR-providing centers, and 60.0% of centers with an active PR unit, exceeding all other regions (Appendix 2).

The organization and content of PR services across the 31 centers providing rehabilitation are summarized in Table 2. Pulmonary rehabilitation programs were most commonly delivered in inpatient (71%) and outpatient (52%) settings, with many centers offering multiple delivery models. Home-based (29%) and tele-rehabilitation (39%) approaches were also reported by several centers. Pulmonologists (71%) and physiotherapists (100%) were the most commonly involved team members, followed by nurses (39%), dietitians (29%), and psychologists (13%).

Exercise training was included in nearly all programs (97%), along with patient education (90%) and physical activity counselling (71%). Nutritional counseling (39%) and psychosocial support (23%) were reported less frequently. Most centers routinely assessed pulmonary function (90%) and exercise capacity using the six-minute walk test (81%); fewer centers included quality-of-life (58%), nutritional (45%), or psychological (58%) assessments.

Table 2: Structure and implementation of pulmonary rehabilitation (PR) services in Türkiye (n=31 centers providing PR)

Service delivery models, n (%)	
Inpatient	22 (71)
Outpatient	16 (52)
Tele-rehabilitation	13 (39)
Home-based (unsupervised)	6 (19)
Healthcare professionals involved, n (%)	
Physiotherapist	31 (100)
Pulmonologist	22 (71)
Nurse	12 (39)
Dietitian	9 (29)
Physiatrist	8 (26)
Psychologist	4 (13)
Program components, n (%)	
Exercise training (aerobic, resistance, or breathing exercises)	30 (97)
Patient education	28 (90)
Physical activity counseling	22 (71)
Nutritional counseling	12 (39)
Psychosocial support	7 (23)
Routine assessments, n (%)	
Pulmonary function testing	28 (90)
Six-minute walk test	25 (81)
Quality-of-life questionnaires	18 (58)
Psychological assessment	18 (58)
Nutritional assessment	14 (45)
Patient groups most frequently included, n (%)	
COPD	31 (100)
Bronchiectasis	23 (74)
Interstitial lung disease	22 (71)
ICU patients	19 (61)
Thoracic surgery patients	18 (58)
Acceptance rate for PR programs (%)	60±31
Most frequently reported barriers to PR, n (%)	
Transportation difficulties	22 (71)
Financial constraints	18 (58)
Lack of patient motivation	15 (48)

Values are presented as n (%) or mean±standard deviation (SD). PR: Pulmonary rehabilitation, SGK: Social security institution, COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit.

All centers providing PR reported offering rehabilitation to patients with COPD (100%). In addition, 74% of centers included patients with bronchiectasis, followed by interstitial lung disease (71%), intensive care–related conditions (61%), and thoracic surgery cases (58%). The mean patient acceptance rate for prescribed PR programs was 60% (SD: 31). The leading barriers to program participation were transportation difficulties (71%), financial constraints (58%), and lack of motivation (48%).

Team composition across 31 centers providing PR is presented in Table 3. Only 35% of centers met the minimum core interdisciplinary team requirement (physician, physiotherapist, and nurse), while 65% did not. When the analysis was restricted to the 15 centers with an active PR unit, 53% met the minimum staffing criteria (Table 4). Compliance of PR-providing centers with core interdisciplinary team requirements is also summarized in Figure 1.

Table 3: Team composition of centers providing pulmonary rehabilitation (n=31)

	n (%)
Centers Meeting Core Interdisciplinary Team Requirements	11 (35)
Physician – Physiotherapist – Nurse – Dietitian – Psychologist	4 (13)
Physician – Physiotherapist – Nurse – Dietitian	3 (9)
Physician – Physiotherapist – Nurse	4 (13)
Centers Not Meeting Core Interdisciplinary Team Requirements	20 (65)
Physician – Physiotherapist – Dietitian	2 (6)
Physician – Physiotherapist	11 (36)
Physiotherapist – Nurse	1 (4)
Physiotherapist	6 (19)

Table 4: Team composition of centers with active pulmonary rehabilitation (PR) unit (n=15)

	n (%)
Centers Meeting Core Interdisciplinary Team Requirements	8 (53)
Physician – Physiotherapist – Nurse – Dietitian – Psychologist	4 (27)
Physician – Physiotherapist – Nurse – Dietitian	2 (13)
Physician – Physiotherapist – Nurse	2 (13)
Centers Not Meeting Core Interdisciplinary Team Requirements	7 (47)
Physician – Physiotherapist – Dietitian	2 (13)
Physician – Physiotherapist	4 (27)
Physiotherapist	1 (7)

Discussion

This multicenter survey provides the first nationwide overview of PR practices in Türkiye, situating the findings within the broader global challenge of translating well-established evidence into routine clinical care. Although PR is firmly endorsed as a cornerstone intervention in the management of chronic respiratory diseases, its real-world delivery remains highly inconsistent across regions and healthcare systems.[2–4] Recent policy and guideline statements emphasize that the primary challenges relate to health system implementation rather than lack of evidence, calling for expanded capacity, workforce training, and stronger integration of PR into chronic care pathways.[2,4,6] Consistent with these global observations, the present study documents similar gaps

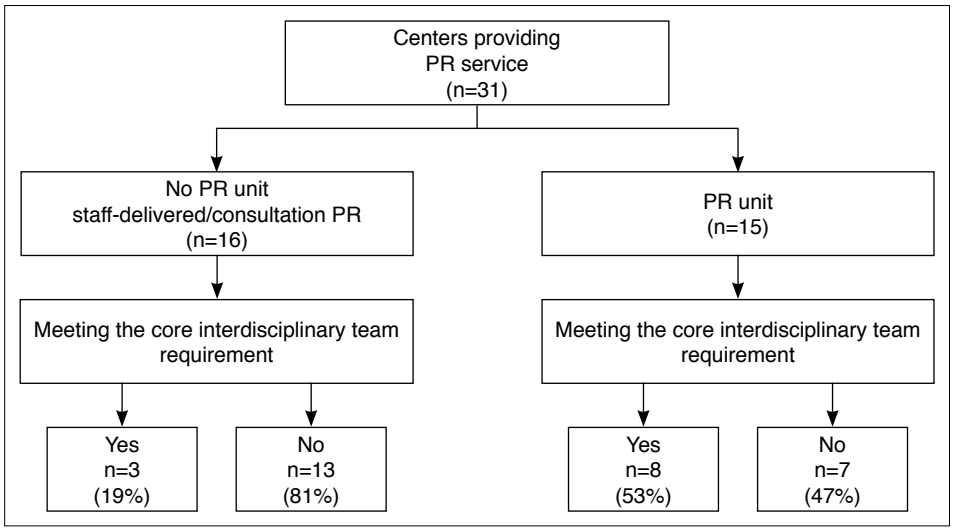

Figure 1: Compliance of centers providing pulmonary rehabilitation (PR) with the core interdisciplinary team requirement (i.e., physician, physiotherapist, and nurse)

in service availability and accessibility in Türkiye, providing essential baseline data to support future national standardization and resource planning efforts.

In this survey, 38% of centers had established PR units, while 40% provided staff-delivered or consultation-based services. European audits have demonstrated wide variation in PR infrastructure,[11] and only 1.2% of individuals with COPD in Canada[5] and 1.5% of Medicare beneficiaries in the United States[12] have access to these programs. Notably, our finding that 23% of centers in Türkiye provide no PR services closely mirrors data from Sweden (24%),[13] suggesting that limited accessibility represents a systemic implementation gap rather than an issue unique to lower-income settings. Recent research has attributed this gap in part to insufficient clinician awareness; some healthcare professionals have even reported that they have never heard of pulmonary rehabilitation, underscoring the need for enhanced education and training.[14] In addition, a study from the United Kingdom identified time constraints, unclear referral pathways, and lack of feedback mechanisms as major barriers, emphasizing the importance of improved communication and structured referral systems to increase PR uptake.[15] Consequently, the heterogeneity observed in the PR landscape in Türkiye highlights the need for unified national strategies to standardize and integrate PR into routine respiratory care. Moreover, the geographical clustering of responding centers—particularly the predominance of İstanbul and the Marmara Region—may reflect broader regional disparities in healthcare infrastructure, workforce availability, and socioeconomic context. Although the present study was not designed to formally assess socioeconomic determinants, the observed regional distribution provides important contextual insight into potential structural influences on PR availability and underscores the importance of region-sensitive planning in future implementation efforts.

According to international standards, PR programs should be delivered by an interdisciplinary team with clearly defined professional roles. The American Thoracic Society (ATS) guidelines recommend a core team consisting of a physician, physiotherapist, and nurse, each contributing expertise in medical oversight, exercise prescription, and symptom management, respectively. Additional professionals, such as dietitians, psychologists, and occupational therapists, are recommended to ensure holistic patient care.[2,3] However, in this survey, only one-third of centers providing PR services met this minimum staffing requirement, indicating a substantial shortfall in the multidisciplinary infrastructure necessary for comprehensive PR delivery. In these centers, physiotherapists and pulmonologists were the most consistently involved professionals, whereas nurses, dietitians, and psychologists participated less frequently. This pattern reflects the global variability in multidisciplinary team composition reported in previous studies.[11,13] In particular, the limited involvement of dietitians and psychologists mirrors international trends and likely reflects workforce constraints or underrecognition of the biopsychosocial dimensions of PR. In addition, the lim-

ited integration of educational and psychosocial counseling components suggests that the holistic model recommended by current guidelines has not yet been fully implemented.[2,3] Strengthening multidisciplinary collaboration and incorporating broader professional expertise may enhance the comprehensiveness and sustainability of PR services within Türkiye's healthcare system.

Most centers routinely assessed pulmonary function (90%) and exercise capacity (81%) using standardized measures such as spirometry and the six-minute walk test, in line with international guideline recommendations.[2] However, the lack of routine cardiopulmonary exercise testing represents a critical gap, as this assessment provides objective and standardized data for individualized exercise prescription and may significantly improve the effectiveness and safety of PR programs. Moreover, fewer centers assessed nutritional status, psychological well-being, or quality-of-life outcomes, reflecting the heterogeneity in outcome assessment previously reported across PR programs worldwide.[3,11] Evidence suggests that program effectiveness is influenced by its design and the inclusion of educational and psychosocial components.[16] In our cohort, PR programs most frequently targeted patients with COPD (100%), followed by bronchiectasis (74%), interstitial lung disease (71%), intensive care-related conditions (61%), and thoracic surgery cases (58%), indicating that PR delivery in Türkiye remains predominantly COPD-focused, similar to global trends.[6,17] While the 60% patient acceptance rate in our survey suggests a general willingness to participate, many patients may never receive a formal referral or offer for PR. Reported barriers to participation included transportation difficulties (71%), financial constraints (58%), and lack of motivation (48%), consistent with findings from other regions.[7,8] In addition to patient-related challenges, systemic barriers such as unclear referral pathways, time constraints, and limited professional feedback further hinder participation.[15,18] To address these accessibility issues, emerging approaches such as web-based or home-based telerehabilitation may help sustain patient engagement.[19]

Overall, the findings of this survey highlight both encouraging progress and persistent disparities in PR delivery across Türkiye. Although the presence of active programs in several institutions reflects growing recognition of pulmonary rehabilitation as an essential component of respiratory care, substantial variability in access, workforce capacity, and program content remains a significant challenge. Recent clinical statements from the British Thoracic Society have emphasized the importance of equitable access, standardized quality frameworks, and the incorporation of home-based and digital models to expand PR availability and sustainability.[20] Similarly, recent reports have underscored that embedding PR within existing healthcare pathways, securing reimbursement mechanisms, and promoting national audit systems are critical for long-term integration.[6] The implementation of post-discharge referral protocols, systematic follow-up, and targeted awareness initiatives has been shown to improve enrollment and participation.[21] Regional experiences indicate that successful large-scale implementation depends on the integration of local leadership, interprofessional collaboration, and supportive health policies.[22] In this context, the similarities observed between Türkiye and other countries regarding implementation barriers also underscore the value of professional engagement and experience sharing. Active participation in scientific platforms and professional societies may facilitate the dissemination of best practices, strengthen interdisciplinary collaboration, and support the development of more consistent and sustainable pulmonary rehabilitation services. Beyond its clinical benefits, pulmonary rehabilitation has also been associated with reduced healthcare utilization, including fewer hospital admissions and shorter lengths of stay, suggesting potential cost savings for healthcare systems. From this perspective, strengthening PR capacity may contribute not only to improved patient outcomes but also to the long-term sustainability of national social security and reimbursement systems facing increasing economic pressure.

This study has several limitations that should be acknowledged. The survey relied on self-reported responses and may therefore reflect subjective interpretation or institutional bias. In addition, there is currently no centralized national registry or official database documenting the number or distribution of pulmonary rehabilitation centers in Türkiye. Consequently, it was not possible to determine the total number of eligible centers nationwide or to calculate a formal response rate. Although the participating centers represented a broad geographic distribution, the absence of national baseline data limits the ability to assess sample representativeness, and the overall sample size was relatively small. The cross-sectional design also precluded causal or temporal analyses, and only descriptive statistics were applied. Future studies

involving larger and more diverse samples, longitudinal follow-up, and direct comparisons between public and private sectors are warranted. Furthermore, incorporating patient perspectives and outcome-based evaluations could provide a more comprehensive understanding of PR implementation and its nationwide impact.

Conclusion

This nationwide survey provides the first comprehensive overview of pulmonary rehabilitation practices across Türkiye. The findings indicate that, although PR is increasingly recognized and implemented, substantial variation persists in service organization, staffing, and program content. While several centers offer PR services, our data show that only approximately one-third meet the recommended minimum core team composition of a physician, physiotherapist, and nurse. Access to PR remains uneven, and both patient-related and systemic barriers continue to limit participation. Addressing these challenges will require coordinated national strategies that promote workforce development, professional awareness, and equitable resource distribution. Strengthening collaboration between clinicians, policymakers, and professional societies will be essential to integrate PR as a standard and sustainable component of respiratory care nationwide.

Informed Consent

All respondents provided electronic informed consent prior to completing the survey.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Use of AI for Writing Assistance

No use of AI-assisted technologies was declared by the authors.

Author Contributions

Concept – G.G.; Design – G.G., M.Z., B.A., N.A., S.T.; Supervision – G.G.; Resource – G.G., M.Z., B.A., N.A., S.T.; Data Collection and/or Processing - G.G., M.Z., B.A., N.A., S.T.; Analysis and/or Interpretation - G.G., M.Z., B.A.; Literature Review –M.Z., B.A.; Writing – M.Z., B.A.; Critical Review – G.G., N.A., S.T.

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Appendix 1: Geographic distribution of responding centers

All responding centers (n=40)		PR-providing centers (n=31)		Centers with active PR units (n=15)	
İstanbul	14 (35.0%)	İstanbul	11 (35.5%)	İstanbul	7 (46.7%)
Ankara	5 (12.5%)	Ankara	5 (16.1%)	Ankara	3 (20.0%)
Bursa	3 (7.5%)	Bursa	3 (9.7%)	Bursa	2 (13.3%)
İzmir	3 (7.5%)	İzmir	3 (9.7%)	İzmir	1 (6.7%)
Aydın	2 (5.0%)	Malatya	2 (6.5%)	Düzce	1 (6.7%)
Malatya	2 (5.0%)	Kocaeli	1 (3.2%)	Malatya	1 (6.7%)
Tekirdağ	1 (2.5%)	Düzce	1 (3.2%)		
Kocaeli	1 (2.5%)	Aydın	1 (3.2%)		
Çanakkale	1 (2.5%)	Denizli	1 (3.2%)		
Eskişehir	1 (2.5%)	Ordu	1 (3.2%)		
Düzce	1 (2.5%)	Tokat	1 (3.2%)		
Denizli	1 (2.5%)	Gaziantep	1 (3.2%)		
Ordu	1 (2.5%)				
Tokat	1 (2.5%)				
Kayseri	1 (2.5%)				
Yozgat	1 (2.5%)				
Gaziantep	1 (2.5%)				

Appendix 2: Geographical regions of responding centers

	All responding centers (n=40)	PR-providing centers (n=31)	Centers with active PR units (n=15)
Marmara Region	20 (50.0%)	15 (48.4%)	9 (60.0%)
Central Anatolia Region	8 (20.0%)	5 (16.1%)	3 (20.0%)
Aegean Region	6 (15.0%)	5 (16.1%)	1 (6.7%)
Black Sea Region	3 (7.5%)	3 (9.7%)	1 (6.7%)
Eastern Anatolia Region	2 (5.0%)	2 (6.5%)	1 (6.7%)
Southeastern Anatolia Region	1 (2.5%)	1 (3.2%)	0 (0.0%)
Mediterranean Region	0 (0.0%)	0 (0.0%)	0 (0.0%)

Case Report

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Removal of a silicone tracheal stent retained for 15 years: A novel technique using an endotracheal tube cuff when rigid bronchoscopy is not feasible

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Abstract:

Long-term silicone airway stents may present challenges during removal, particularly when rigid bronchoscopy cannot be performed. We present the case of a 46-year-old woman with a tracheoesophageal fistula who had a silicone stent placed 15 years earlier following surgical repair after difficult intubation during hysterectomy. Due to the tracheal anatomy, rigid intubation was unsuccessful at that time, necessitating prolonged stent placement. Recently, the patient presented with dyspnea and wheezing, and bronchoscopy revealed distal stenosis near the stent. In our clinic, flexible bronchoscopy and balloon dilation were performed. Initial attempts to remove the stent using foreign-body forceps were unsuccessful due to fragmentation. The stent was ultimately removed using an endotracheal tube cuff, a technique that, to our knowledge, has not been previously described. Following stent removal, cryotherapy was applied to treat granulation tissue, and follow-up bronchoscopy demonstrated significant improvement. This case, representing one of the longest reported follow-ups of a silicone airway stent, highlights an effective alternative technique for stent removal that avoids high-risk surgery and may contribute to airway management strategies.

Keywords:

Bronchoscopy, long term silicone stent, removal technique

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Introduction

The removal of long-term silicone airway stents in the absence of rigid bronchoscopy is technically demanding. In this report, we present a case of successful stent removal in a patient who could not undergo rigid bronchoscopy and had been followed with a stent for many years.

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Case Report

A 46-year-old female patient underwent surgical repair of the esophagus and placement of a silicone tracheal stent due to a tracheoesophageal fistula that developed following difficult intubation during hysterectomy in 2008. Previous attempts to remove the stent at the referring center were unsuccessful due to failed rigid intubation, resulting in the stent remaining in situ for 15 years. Three months before presentation, the patient began experiencing shortness of breath and wheezing. Bronchoscopy performed at the referring center revealed stenosis distal to the stent, and the patient was referred to our clinic for further evaluation and management. The patient was taken to the operating room for rigid bronchoscopy under general anesthesia. However, insertion of a rigid bronchoscope was not possible due to the position of the trachea [Fig. 1a]. Therefore, flexible bronchoscopy was performed through a laryngeal mask airway (LMA). A silicone tracheal stent measuring 16 mm in diameter and 8 cm in length was visualized approximately 2 cm below the cricoid cartilage. A distal stenotic segment causing approximately 80% narrowing of the lumen was observed [Fig. 1b]. The stenotic area was dilated using a balloon. An attempt was then made to remove the stent with flexible foreign-body forceps; however, the stent could not be removed because it fragmented [Fig. 1c]. Due to airway narrowing caused by the stent, a small-diameter (6 mm) endotracheal tube was advanced through the stent under bronchoscopic guidance using a thin bronchoscope. The tube cuff was inflated distal to the stent, and the stent was removed together with the tube under bronchoscopic guidance [Fig. 2]. No airway complications occurred during or after the procedure, and no airway injury was observed. Cryotherapy was applied to the granulation tissue that had formed due to the stent. Control bronchoscopy performed one month later showed significant improvement in the stent-related granulation tissue. The residual stenosis remained at approximately 50% and did not worsen during the two-year follow-up period [Fig. 3].

Discussion

Iatrogenic tracheoesophageal fistula (ITOF) is an uncommon yet potentially serious complication of intubation, reported in 0.03–4% of cases and occurring more frequently in patients requiring mechanical ventilation.[1] Surgical intervention is the primary approach for treating ITOF, aiming to close the fistula and prevent recurrence. When ITOF results from acute trauma during intubation, emergency surgical repair, typically involving either flap or primary repair, is often highly effective and may not require additional airway support.[2] However, if surgical closure is not feasible or if post-surgical tracheal stenosis develops, stent placement may become necessary. In such cases, the stent should be removed once the airway has sufficiently healed.[3]

In our patient's case, it remains unclear why a stent was placed after surgery and why it was not removed earlier. Attempts were made to remove the stent during follow-up; however, these attempts were unsuccessful due to difficulties in intubating the patient with a rigid bronchoscope, likely related to postoperative anatomical changes in the trachea. The ultimate goal of airway stenting is to achieve a stent-free airway. However, complications may arise when silicone stents remain in place for prolonged periods. Common late-stage complications of stenting include granulation tissue formation (76%), stent migration (70%), and mucostasis (17%).[4,5]

To our knowledge, this case represents one of the longest reported durations of silicone stent retention, with

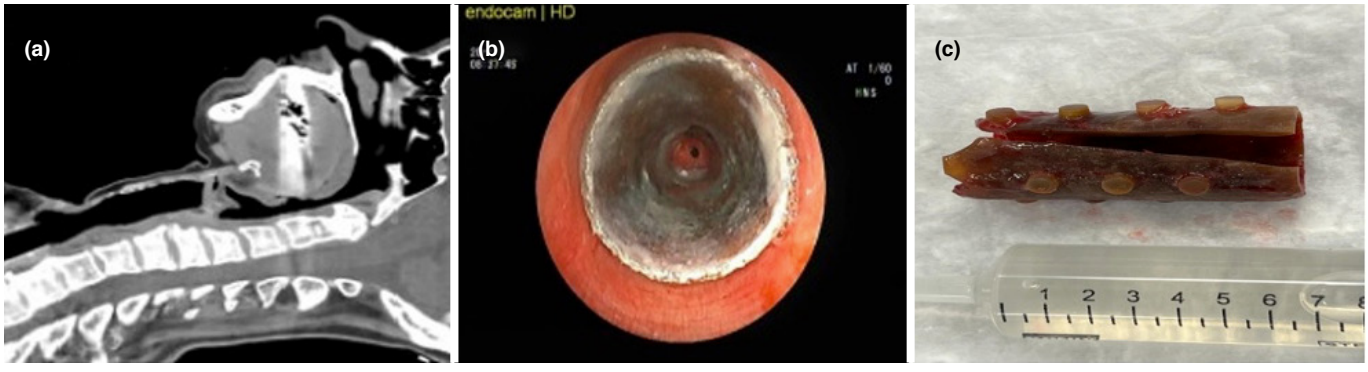

Figure 1: (a) Position of the trachea on a sagittal computed tomography (CT) image. (b) Bronchoscopic view of the stent and the stenosis distal to the stent (c) Image of the removed stent, with debris resulting from attempts to extract it using foreign-body forceps

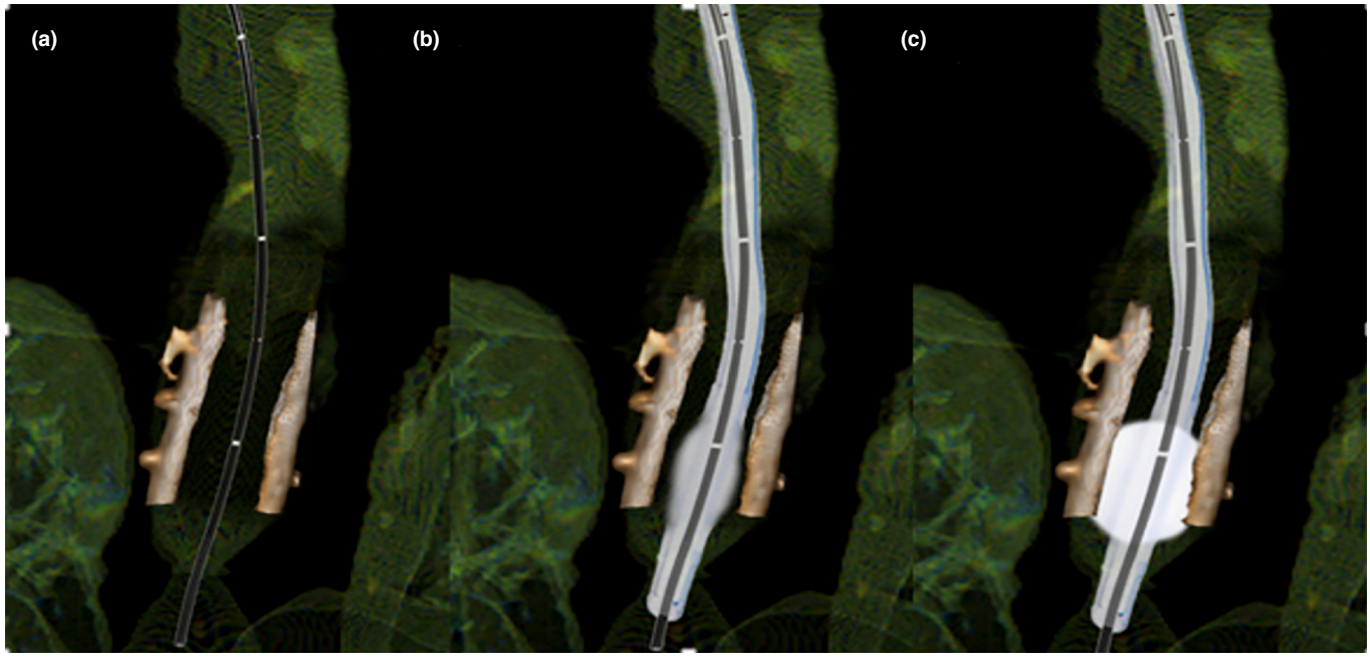

Figure 2: Demonstration of the procedure using the patient's computed tomography images. (a) Evaluation of the airway and the stent using a flexible bronchoscope. (b) Placement of a 6-mm–diameter endotracheal tube into the stent under guidance of a thin bronchoscope. (c) En bloc removal of the stent together with the endotracheal tube after cuff inflation under thin bronchoscope guidance

worsening symptoms attributed to granulation tissue formation distal to the stent. To address this, balloon dilation and cryotherapy were performed, resulting in improved airway patency. Removal of a silicone stent without rigid bronchoscopy can be challenging, and the literature describing alternative removal techniques is sparse. In certain cases, flexible bronchoscopy using forceps (e.g., foreign body or alligator forceps) may facilitate removal; however, long-standing stents present additional difficulties, including tearing, inadequate grasp, and insufficient removal force. Endotracheal tube cuff–assisted extraction may offer a practical alternative when rigid bronchoscopy is not feasible. Nevertheless, potential risks include mucosal trauma, bleeding, distal migration of the stent, hypoxemia, and laryngeal injury. In our case, the procedure was performed under continuous bronchoscopic visualization with close anesthetic monitoring. The cuff was gradually inflated under direct visualization to ensure secure engagement of the stent while minimizing injury to the airway wall. A multidisciplinary team was present, and surgical backup was available in case of airway compromise or procedural failure.

Our case highlights a novel approach in which we successfully removed the stent using an endotracheal tube cuff. This method involves ensuring that the endotracheal cuff securely grasps the stent so that both the stent and the cuff can be carefully removed together. To our knowledge, this technique has not been previously described in the literature. This approach enabled us to avoid a high-risk surgical procedure for the patient.[6] Follow-up revealed no complications, and no further progression of narrowing due to granulation tissue distal to the stent was observed, underscoring the efficacy and safety of this innovative removal method.

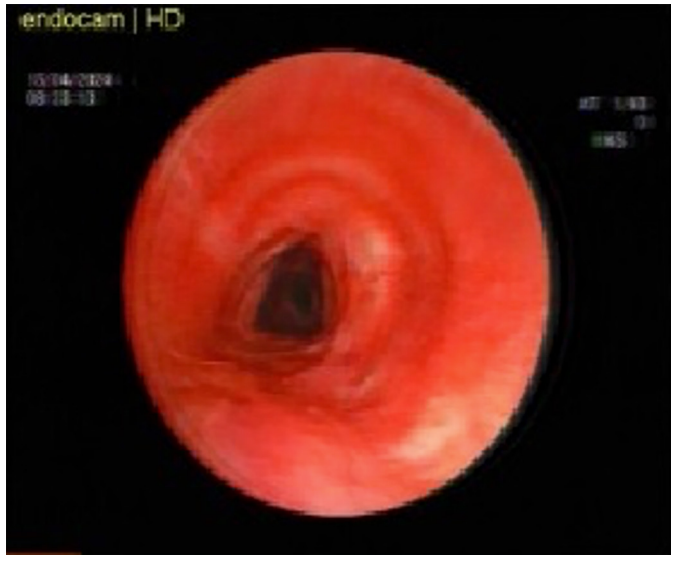

Figure 3: Bronchoscopic appearance of the airway one month after stent removal

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 patient for the procedure and for publication of this case report.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

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

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Letter to the Editor

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Pulmonary rehabilitation in hypersensitivity pneumonitis: A retrospective case series

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Dear Editor,

We read with great interest the case series by Yıldız et al.,[1] which addresses an underrepresented area in hypersensitivity pneumonitis and demonstrates clinically meaningful improvements in functional and upper-extremity exercise capacity following individualized pulmonary rehabilitation.[2]

A key strength of this report is the use of individualized rehabilitation protocols reflecting real-world practice, together with comprehensive outcome measures that enhance the clinical interpretability of the findings.[3]

The use of inspiratory muscle training despite normal baseline values reflects a proactive strategy supported by evidence from the interstitial lung disease population. Emphasis on oxygen supplementation and continuous monitoring highlights important safety considerations in hypersensitivity pneumonitis.[2,4] The disparity between physical gains and psychological outcomes underscores the need for psychosocial support within pulmonary rehabilitation, while the functional improvement observed in a severely deconditioned patient supports its feasibility in advanced hypersensitivity pneumonitis.[5]

Although the retrospective design and limited sample size may restrict broad generalizability, such methodological constraints are unavoidable in the study of rare diseases and do not diminish the hypothesis-generating contribution of this work. Overall, this well-conducted case series provides valuable preliminary evidence supporting the role of structured, individualized pulmonary rehabilitation within the multidisciplinary management of hypersensitivity pneumonitis and offers an important foundation for future prospective and multicenter investigations.

Conflicts of Interest

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Reply to the letter to the editor: Pulmonary rehabilitation in hypersensitivity pneumonitis: A retrospective case series

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We sincerely thank the authors[1] for their thoughtful and encouraging comments regarding our recently published case series.[2] We are grateful for their careful reading of our work and for highlighting key aspects of our study design and clinical approach.

Our individualized pulmonary rehabilitation (PR) protocols were deliberately structured to reflect real-world clinical practice for patients with hypersensitivity pneumonitis (HP) and were supported by comprehensive outcome measures to enhance clinical interpretability. As outlined in our report, the primary aim was to provide a structured, clinically applicable rehabilitation model to inform multidisciplinary management in this underrepresented population.[2]

Inspiratory muscle training was incorporated into our PR protocols, despite normal baseline values of inspiratory muscle strength, to preserve and enhance inspiratory muscle strength, which may decline due to the underlying pathophysiology of interstitial lung disease (ILD). Current evidence indicates that IMT improves inspiratory muscle strength and is associated with reductions in dyspnea, improvements in exercise capacity (e.g., 6-minute walk distance), and enhancements in oxygen consumption in patients with ILD.[3–6] These studies were not restricted to patients with respiratory muscle weakness, suggesting that the benefits of IMT extend beyond a purely deficit-based indication.[7] Because HP is a disease that can progress rapidly and result in early functional limitations, we expected that inspiratory muscle training would yield both physiological and clinical benefits. Given the limited pharmacological treatment options and the early functional deterioration in HP, rehabilitation gains are of particular importance in this pop-

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ulation. In this context, structured PR, including IMT, may influence morbidity and mortality outcomes, and this should be systematically investigated in prospective studies. Continuous monitoring was maintained throughout the exercise sessions, and supplemental oxygen was administered when clinically indicated to ensure patient safety and to allow individualized adjustment of exercise intensity in patients with HP. The divergence between physical and psychological outcomes underscores the multidimensional nature of PR and the need to integrate psychosocial components into structured programs.

Furthermore, the functional improvement observed in a severely deconditioned patient provides preliminary support for the feasibility of individualized rehabilitation in advanced HP. Given the retrospective design, the small number of cases, the rarity of HP, and the limited availability of structured PR data in this population, conducting large prospective studies remains challenging. To our knowledge, this report represents the first case series specifically evaluating structured, individualized PR in HP. Recent evidence published within the last five years consistently supports the role of PR in patients with ILD, particularly in improving exercise capacity and health-related quality of life.[7,8] However, data specific to HP remain limited.[9,10] In this context, our findings provide preliminary evidence and establish a foundation for prospective and multicenter investigations.

This constructive academic exchange underscores a gap in the literature. It emphasizes the clinical importance of structured, individualized PR in HP, while reinforcing the need for continued prospective, multicenter research in this field.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

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Letter to the Editor

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The role of diaphragm thickness and mobility in chronic obstructive pulmonary disease classification and exacerbations

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Dear Editor,

We read with great interest the article by Elmastaş Akkuş et al.[1] titled,' The role of diaphragm thickness and mobility in chronic obstructive pulmonary disease classification and exacerbations', which investigates the role of diaphragm thickness and mobility in the classification of chronic obstructive pulmonary disease (COPD) and the prediction of exacerbations using ultrasonography. The authors are congratulated for addressing diaphragmatic dysfunction, an important yet often underrecognized component of COPD pathophysiology, and for highlighting diaphragmatic excursion as a clinically relevant functional marker.

The demonstrated association between diaphragmatic excursion, GOLD classification, and exacerbation frequency is clinically meaningful and consistent with prior evidence showing that diaphragm mobility influences exercise tolerance, dyspnea, and ventilatory impairment in individuals with COPD.[2] These findings further support the growing role of diaphragm ultrasonography as a practical bedside tool for functional evaluation and clinical stratification, in agreement with established literature on respiratory and peripheral muscle dysfunction in COPD.[3]

In contrast, the lack of a significant relationship between diaphragm thickness and disease severity differs from previous mechanistic studies reporting diaphragm muscle fiber dysfunction and structural remodeling in COPD.[4,5] This discrepancy suggests that functional indices such as diaphragmatic excursion may be more sensitive than static structural measures. It also highlights the importance of standardized ultrasonographic protocols and of including the diaphragm thickening fraction to improve interstudy comparability and clinical interpretation.

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The findings of this study support diaphragmatic excursion as a clinically relevant marker in COPD and indicate the need for future longitudinal validation studies.

Conflicts of Interest

The author have no conflicts of interest to declare.

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Reply to the letter to the editor: The role of diaphragm thickness and mobility in chronic obstructive pulmonary disease classification and exacerbations

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We sincerely thank you for the opportunity to respond to the Letter to the Editor[1] regarding our article, "The Role of Diaphragm Thickness and Mobility in Chronic Obstructive Pulmonary Disease Classification and Exacerbations."[2] We are also grateful to the author(s) for their careful reading of our work and for their thoughtful and constructive comments.

We appreciate the positive remarks concerning the clinical relevance of diaphragmatic excursion and its association with the GOLD classification and the frequency of exacerbations. As emphasized both in the letter and in our study, diaphragmatic dysfunction represents an important yet often underrecognized component of COPD pathophysiology. Our findings demonstrated that deep inspiratory diaphragmatic excursion differed significantly between COPD patients with and without exacerbations in univariate analysis. These results are consistent with previous literature and support the value of diaphragm ultrasonography as a practical tool for functional assessment and clinical stratification in COPD.

Regarding diaphragm thickness, we acknowledge the important point raised that there is no significant relationship with disease severity. The literature indeed contains both concordant and conflicting findings.[3–5] In our study, diaphragm thickness showed a gradual increase from GOLD A to C and then

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decreased in GOLD D, although the differences were not statistically significant. This pattern may suggest early adaptive hypertrophy of inspiratory muscles in response to increased respiratory load, with possible atrophy in advanced stages due to oxidative stress and muscle remodeling. While this observation was not statistically significant, it may reflect the complex structural adaptations occurring across disease stages.

Diaphragm thickening fraction, considered an indirect indicator of muscle fiber contractility, has been proposed as a potentially more sensitive parameter than thickness alone. Experimental data demonstrate alterations in diaphragm fiber structure and contractile proteins in COPD.[6] However, in our cohort, the thickening fraction was not associated with GOLD classification or exacerbation outcomes. Similar findings were reported by Baria et al.,[7] who suggested that diaphragmatic dysfunction in COPD may primarily reflect mechanical limitation related to hyperinflation rather than intrinsic contractile impairment. These findings highlight the complex interplay between structural remodeling and mechanical disadvantage in COPD. Functional parameters such as diaphragmatic excursion may better capture the diaphragm's integrated mechanical performance.

We fully agree that standardization of ultrasonographic techniques and of thickening-fraction calculation methods is important for improving comparability across studies. Further longitudinal investigations incorporating both structural and functional assessments of the diaphragm may help clarify these relationships.

We again thank the author(s) for their valuable comments and for contributing to a constructive scientific discussion.

Sincerely,

On behalf of the authors

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

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