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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  $\geq 68.5$  years ( $p < 0.001$ ), Charlson Comorbidity Index (CCI) scores  $\geq 4.5$  ( $p < 0.001$ ), and eosinophil counts  $\leq 45$  cells/ $\mu\text{L}$  ( $p < 0.001$ ) 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  $\geq 68.5$  years and a CCI cut-off score of  $\geq 4.5$  were associated with increased mortality risk, while lower baseline eosinophil counts (cells/ $\mu\text{L}$ ) 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.<sup>[1]</sup> COPD is one of the top three causes of mortality and morbidity worldwide.<sup>[2]</sup>

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.<sup>[3]</sup>

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.<sup>[4,5]</sup> 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.<sup>[6,7]</sup> The COPD Assessment Test (CAT) is a validated and simple tool for monitoring health-related quality of life in COPD patients.<sup>[8]</sup> Its strong correlation with the SGRQ and promising results as a predictor of mortality suggest its potential utility in clinical practice.<sup>[8]</sup>

The forced expiratory volume in 1 second (FEV<sub>1</sub>) has been identified as a predictor of mortality in patients with COPD.<sup>[9]</sup> Beyond FEV<sub>1</sub>, 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<sub>2</sub>max).<sup>[10,11]</sup> 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.<sup>[12]</sup> The diagnosis of COPD was established according to the GOLD 2019 guidelines,<sup>[12]</sup> requiring a post-bronchodilator ratio of forced expiratory volume in 1 second to forced vital capacity (FEV<sub>1</sub>/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)

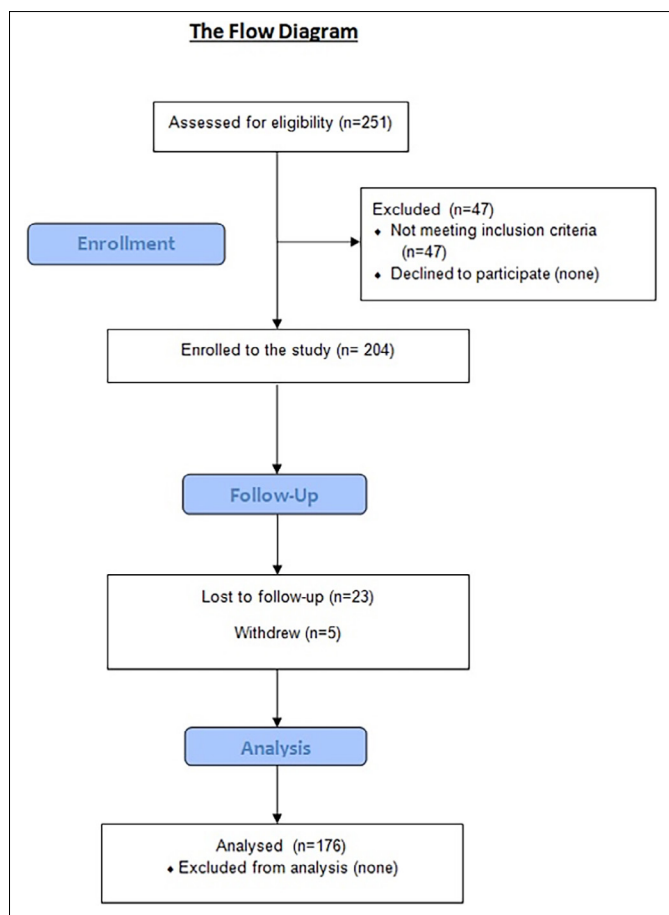


Figure 1: Flow diagram of the study

criteria.<sup>[13]</sup> 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

( $\text{PaO}_2$ )  $<55\text{mmHg}$  and oxygen saturation ( $\text{SpO}_2$ )  $\leq 88\%$ , and for BPAP use, a partial pressure of carbon dioxide ( $\text{PaCO}_2$ )  $\geq 55\text{mmHg}$ .

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.<sup>[13]</sup> The ratio of FEV<sub>1</sub> to FVC (FEV<sub>1</sub>/FVC%) was defined as less than 70% following administration of 200 µg of salbutamol, measured 15 minutes later. The following indices were collected: FEV<sub>1</sub> (ml), FEV<sub>1</sub> (%) predicted, FVC (ml), FVC (%) predicted, FEV<sub>1</sub>/FVC (%), and forced expiratory flow between 25% and 75% of vital capacity (FEF<sub>25–75</sub>) (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 <sup>2</sup> )	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 end-points. 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 <sub>1</sub> (ml)	1520±610 (490–2920)
FEV <sub>1</sub> (%)	54.2±18.3 (19–92)
FVC (ml)	2440±852 (170–4430)
FVC (%)	70.2±19.2 (28–124)
FEV <sub>1</sub> /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<sub>1</sub>: 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<sub>1</sub> (ml), FEV<sub>1</sub> (%), FVC (ml), FVC (%), FEV<sub>1</sub>/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

**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 <sub>1</sub> (ml)	0.310	0.998	0.994–1.002
FEV <sub>1</sub> (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 <sub>1</sub> /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

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.

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

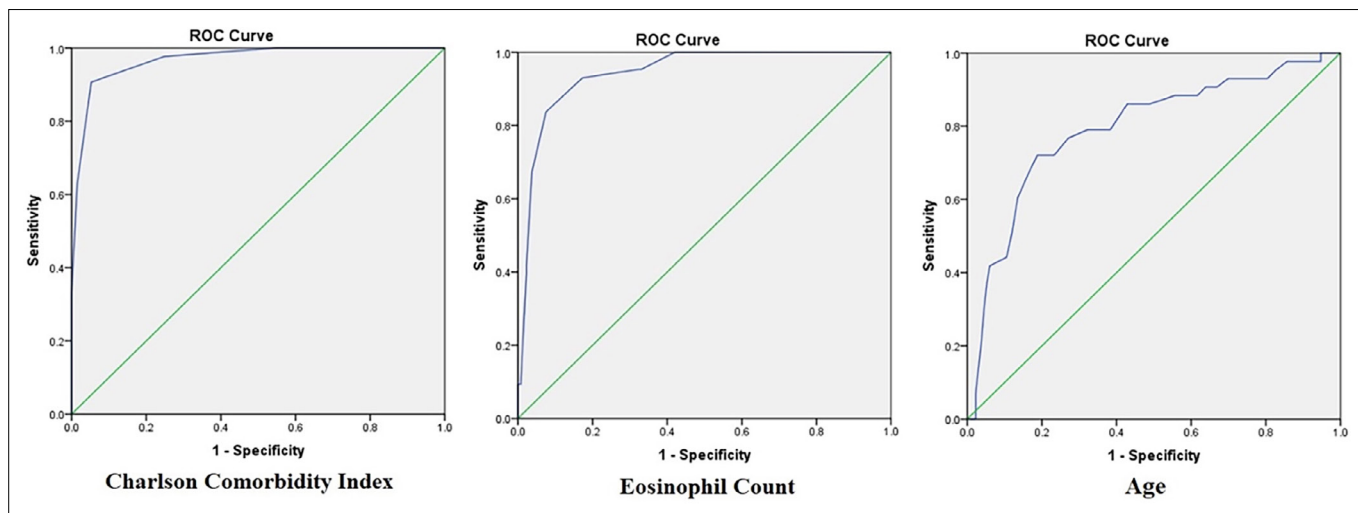


Figure 2: Receiver operating characteristic curves for the Charlson Comorbidity Index and eosinophil count

and an age of 68.5 years or older were significantly associated with increased mortality risk. Conversely, lower eosinophil counts ( $\leq 45$  cells/ $\mu\text{L}$ ) 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.<sup>[10,11,14,15]</sup> However, the prognostic value of age in patients with respiratory failure has been reported less consistently.<sup>[16,17]</sup> 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  $\text{FEV}_1/\text{FVC}$  ratio and mortality,<sup>[16–18]</sup> which contrasts with observations in patients with less severe disease.<sup>[10,11,19]</sup> Notably, the OLIN study (Obstructive Lung Disease in Northern Sweden) with a 20-year follow-up observed slower rates of lung function ( $\text{FEV}_1$ ) decline in long-term survivors, suggesting its potential relevance in different disease stages.<sup>[20]</sup> Based on our findings, we suggest that the predictive power of  $\text{FEV}_1$

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/ $\mu\text{L}$ )	0.943 (0.908–0.978)	45	<0.001	83.7%	92.5%

AUC: Area under the curve, CI: Confidence interval

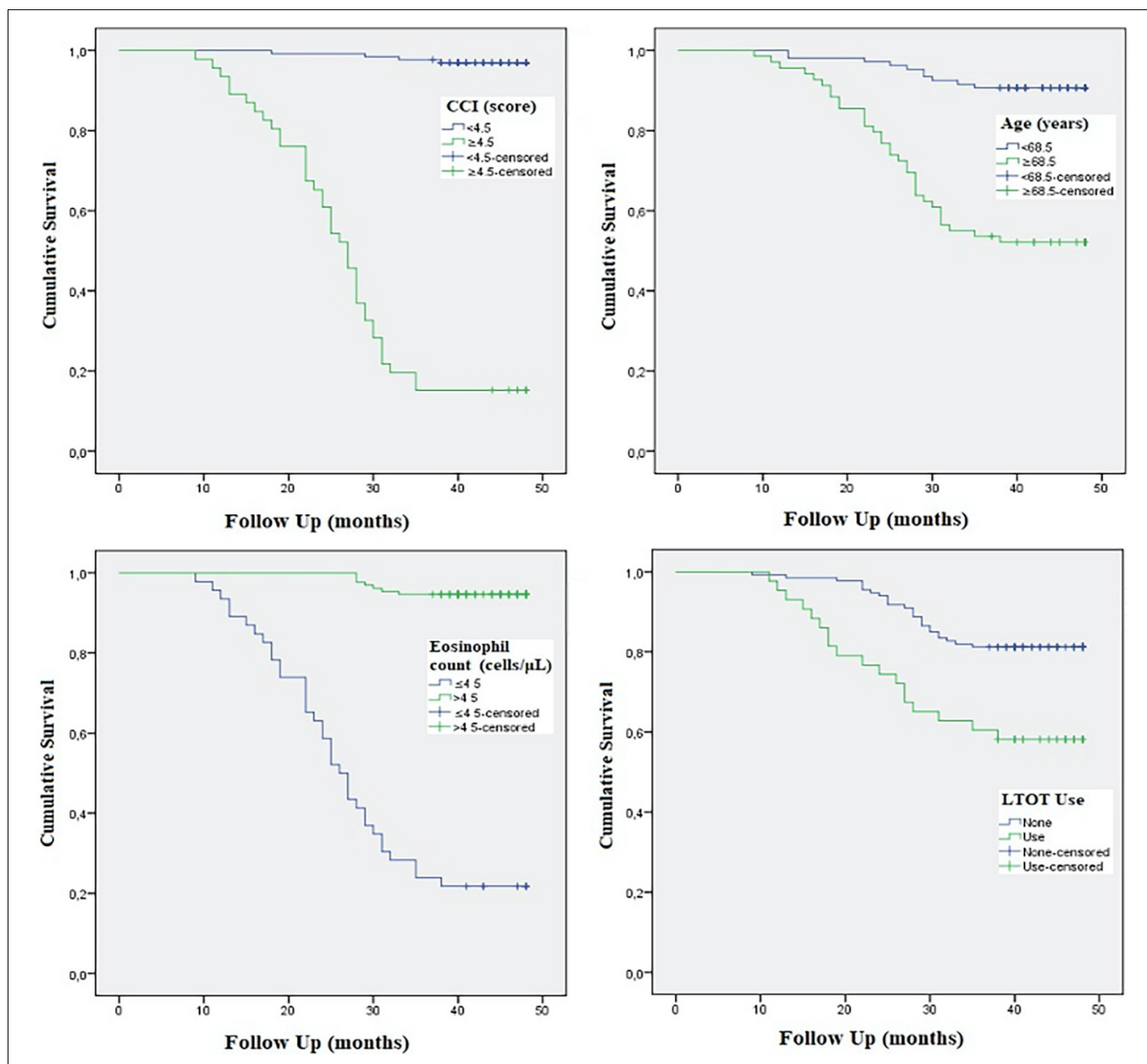


Figure 3: Kaplan-Meier survival curves (cohorts for age, Charlson Comorbidity Index (CCI), and eosinophil count stratified by receiver operating characteristic (ROC)-derived cut-off values)

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<sub>1</sub> is a key prognostic factor in COPD.<sup>[20]</sup>

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.<sup>[21]</sup> but contrasts with Soler-Cataluña et al.,<sup>[22]</sup> 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.<sup>[23]</sup> 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.*<sup>[24]</sup> reported that persistently elevated eosinophil counts ( $\geq 300$  cells/ $\mu\text{L}$ ) 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.<sup>[24]</sup> 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.<sup>[25]</sup> Conversely, Prudente *et al.*<sup>[26]</sup> and our findings suggest that lower eosinophil counts are linked to increased mortality and shorter survival. Specifically, our study identified  $\leq 45$  cells/ $\mu\text{L}$  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.<sup>[27–29]</sup> 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

$\geq 300$  cells/ $\mu\text{L}$  to maximize exacerbation prevention and considering biologics for severe Type 2 inflammation.<sup>[2]</sup>

Long-term oxygen therapy is established for survival prediction in hypoxemic COPD, with some studies reporting an increase in lifespan.<sup>[30,31]</sup> Carone *et al.*<sup>[14]</sup> 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.*<sup>[32]</sup> 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,<sup>[33]</sup> a survival benefit has been reported following severe acute exacerbations compared to non-hypoxemic patients.<sup>[34]</sup> The disproportionately high mortality observed in patients after LTOT initiation necessitates closer follow-up and proactive management.<sup>[33,34]</sup> Rantala *et al.*<sup>[35]</sup> also reported shorter survival in COPD patients receiving LTOT. Similarly, the timing of BPAP initiation is critical, with Mosher *et al.*<sup>[36]</sup> 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,<sup>[31,37,38]</sup> 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.<sup>[39–41]</sup> 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 ( $\leq 45$  cells/ $\mu\text{L}$ ) 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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## Use of AI for Writing Assistance

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

## 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.

## Peer-review

Externally peer-reviewed.

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