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Evaluation of factors associated with mortality after major lower extremity amputation: implications for intensive care

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ABSTRACT

Aims: Amputations performed proximal to the ankle level are defined as major lower extremity amputation (MLEA) and are associated with high postoperative mortality. This study aimed to evaluate the clinical characteristics, laboratory findings, and postoperative complications associated with 30-day and six-month mortality in patients undergoing MLEA for different etiologies.

Methods: The electronic medical records of 419 patients aged 18 years or older who underwent surgery for MLEA between November 2022 and November 2025 were retrospectively analyzed. Patients' demographic data, American Society of Anesthesiologists (ASA) physical status classification, comorbidities, laboratory parameters, length of hospital stay, and 30-day and six-month mortality data were recorded. Patients were divided into two groups according to mortality status. For the 30-day and six-month mortality analyses, patients were separately grouped according to their survival status during the respective follow-up period.

Results: Data from 419 patients were analyzed. Thirty-day mortality occurred in 54 patients (12.9%), and 6-month mortality occurred in 109 patients (26.0%). In the multivariable analysis, postoperative pulmonary complications (adjusted OR, 3.16; 95% CI, 1.77-5.64; $p < 0.001$), older age (adjusted OR, 1.05; 95% CI, 1.03-1.07; $p < 0.001$), higher preoperative creatinine levels (adjusted OR, 1.21; 95% CI, 1.04-1.40; $p = 0.013$), and higher C-reactive protein-to-albumin ratio (CAR) (adjusted OR, 1.08; 95% CI, 1.02-1.14; $p = 0.005$) were independently associated with 6-month mortality. Older age (adjusted OR, 1.030; 95% CI, 1.005-1.056; $p = 0.019$), postoperative pulmonary complications (adjusted OR, 3.993; 95% CI, 2.042-7.806; $p < 0.001$), and higher CAR (adjusted OR, 1.097; 95% CI, 1.030-1.169; $p = 0.004$) were independently associated with 30-day mortality.

Conclusion: Advanced age, elevated preoperative CAR, and postoperative pulmonary complications were independently associated with both early- and intermediate-term mortality after MLEA.

Keywords: Amputation; surgical, lower extremity, mortality

INTRODUCTION

Major lower extremity amputation (MLEA) refers to amputation performed above the level of the ankle.¹ It is often required as a life-preserving procedure in patients with severe limb trauma, peripheral arterial disease, or advanced diabetes-related complications.² Despite improvements in vascular treatment, perioperative care, and risk assessment, mortality and morbidity following MLEA remain substantial.³ A clearer understanding of the factors related to mortality may therefore help improve perioperative assessment and clinical management in this high-risk population.

Outcomes after MLEA are associated with several interacting clinical and perioperative factors. Advanced age, coexisting diseases, impaired renal function, systemic inflammation, poor nutritional status, and postoperative complications have all been linked to adverse outcomes.⁴ The C-reactive protein-to-albumin ratio (CAR) combines two routinely measured laboratory parameters and may provide a practical estimate of inflammatory activity and nutritional reserve.⁵ Pulmonary

complications are also clinically relevant after MLEA, as they may prolong recovery and contribute to poorer survival.⁶

Most previous studies have focused on patients undergoing amputation for a particular indication, particularly diabetes or peripheral arterial disease, or have examined mortality at a single time point.^{3,7,8} Evidence addressing early and six-month mortality within the same cohort, while considering clinical characteristics, laboratory findings, and postoperative complications together, remains limited. The present study therefore investigated the factors associated with 30-day and six-month mortality among patients undergoing MLEA for various indications.

METHODS

Ethics

This study was conducted with the approval of the No. 2 Scientific Researches Evaluation and Ethics Committee of



Ankara Etlik City Hospital (Date: 30.06.2026, Decision No: AESH-BADEK2-2026-531). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The requirement for informed consent was waived by the ethics committee because of the retrospective design of the study. The study population was identified by reviewing the electronic records of adult patients who underwent MLEA at a tertiary referral hospital between November 2022 and November 2025.

Patients were eligible if they were 18 years of age or older and underwent their first MLEA during the study period. Cases with incomplete data for the planned analyses or insufficient information in the medical records were excluded. Repeated entries for the same patient were identified and removed. Demographic and clinical data collected from the records included age, gender, American Society of Anesthesiologists (ASA) physical status, comorbidities, anesthesia technique, use of a peripheral nerve block, level of amputation, and indication for surgery.

Laboratory measurements obtained at the initial hospital admission were used in the analyses. The recorded variables were complete blood count parameters, creatinine, urea, albumin, C-reactive protein (CRP), glucose, calcium, sodium, potassium, international normalized ratio (INR), aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, and red cell distribution width. The CRP-to-albumin ratio (CAR) was calculated by dividing CRP expressed in mg/L by albumin expressed in g/L.

Complications occurring during the postoperative hospital stay were grouped as pulmonary complications, sepsis, or other complications. Pneumonia, atelectasis, and pulmonary thromboembolism were categorized as pulmonary complications. The sepsis category included cases of sepsis secondary to nonpulmonary infections. Cardiac events, bleeding, electrolyte disturbances, and delirium were included under other complications. When a patient experienced more than one complication, each event was entered separately. Intensive care unit admission, duration of intensive care unit stay, and total hospital length of stay were also documented.

Vital status and date of death were determined from hospital records and the national registry system. Survival time was measured from the date of amputation to the date of death. Death from any cause within 30 days of surgery was considered early mortality, and death within 180 days was considered six-month mortality. For the 30-day analysis, patients who died during the first 30 days were compared with those who remained alive at day 30. The same approach was used for the six-month analysis, with patients classified according to their vital status at 180 days. Follow-up data for at least 180 days were available for every patient included in the study.

The primary outcome was all-cause mortality within six months after MLEA. Thirty-day all-cause mortality was evaluated as the secondary outcome. Clinical characteristics, laboratory findings, and postoperative events associated with

each mortality endpoint were subsequently examined using regression analyses.

Statistical Analysis

The distribution of continuous variables was assessed using the Shapiro-Wilk test. Variables with a normal distribution were expressed as mean $\pm$ standard deviation (SD) and compared using the independent samples t-test. Non-normally distributed variables were presented as median (interquartile range [IQR]) and compared using the Mann-Whitney U test. Categorical variables were reported as frequencies and percentages and compared using the Pearson Chi-square test or Fisher's exact test, as appropriate. Factors associated with 30-day and 6-month mortality were examined using univariate and multivariable logistic regression analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. The performance of the final multivariable model for 6-month mortality was assessed by receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was calculated. All statistical analyses were performed using IBM SPSS Statistics for Windows (Version 22.0; IBM Corp., Armonk, NY, USA), and a two-sided p-value <0.05 was considered statistically significant.

RESULTS

A total of 419 patients who met the inclusion criteria during the study period were included in the final analysis. The mean age of the study population was 66.1 $\pm$ 15.7 years, 66.1% were male, and 58.7% were classified as ASA physical status III-IV. At least one comorbidity was present in 87.1% of the patients. The most common comorbidities were diabetes mellitus (74.5%), hypertension (48.2%), and coronary artery disease (32.7%). Below-knee amputation was performed in 82.6% of the patients, whereas 17.4% underwent above-knee amputation. The most common indication for amputation was diabetes mellitus-related disease (n=250, 59.7%), followed by peripheral arterial disease/ischemia (n=104, 24.8%) and trauma (n=53, 12.6%). Postoperative complications occurred in 104 patients (24.8%), with pulmonary complications being the most frequent (n=72, 17.2%). Thirty-day mortality was observed in 54 patients (12.9%), whereas 6-month mortality was observed in 109 patients (26.0%). Detailed demographic, clinical, and laboratory characteristics of the study population are presented in [Table 1](#).

Patients who died within 6 months (non-survivors) were older than survivors and were more likely to have ASA physical status III-IV (both p<0.001). The presence of at least one comorbidity was also more common among non-survivors than survivors (92.7% vs. 85.2%, p=0.044). In the preoperative laboratory evaluation, non-survivors had higher CAR [4.88 (7.38) vs. 3.47 (5.71); p=0.007] and creatinine levels [1.40 (1.64) vs. 1.01 (0.70); p=0.005]. Postoperative complications occurred more frequently in non-survivors than in survivors (37.6% vs. 20.3%, p<0.001), with pulmonary complications being more common among non-survivors (31.2% vs. 12.3%). Overall, 95.4% of non-survivors had been admitted to the intensive care unit, and both ICU and hospital lengths of stay were significantly longer in this group (both p<0.05). In addition, non-survivors had lower calcium, albumin, hemoglobin, platelet, lymphocyte, monocyte, and

Table 1. Demographic and clinical characteristics of the study population

Variable	Overall (n=419)
Age, years	66.1±15.7
Gender, n (%)	
Male/female	277 (66.1)/142 (33.9)
ASA physical status, n (%)	
I-II	173 (41.3)
III-IV	246 (58.7)
Indication for amputation, n (%)	
Diabetic foot infection	250 (59.7)
Peripheral arterial disease/ischemia	104 (24.8)
Trauma	53 (12.6)
Other (pyoderma gangrenosum, burn, vasculitis, malignancy, non-diabetic infection)	12 (2.8)
Amputation level, n (%)	
Below-knee amputation	346 (82.6)
Above-knee amputation	73 (17.4)
Type of anesthesia, n (%)	
Spinal anesthesia	175 (41.8)
General anesthesia	244 (58.2)
Peripheral nerve block, n (%)	69 (16.5)
Comorbidities, n (%)	365 (87.1)
Diabetes mellitus	312 (74.5)
Hypertension	202 (48.2)
Coronary artery disease	137 (32.7)
Peripheral artery disease	93 (22.2)
Chronic kidney disease	72 (17.2)
Cerebrovascular disease	40 (9.5)
Chronic obstructive pulmonary disease	34 (8.1)
Heart failure	29 (6.9)
Hyperlipidemia	25 (6.0)
Arrhythmia	21 (5.0)
Cancer	17 (4.1)
Dementia	12 (2.9)
Thyroid disease	10 (2.4)
Parkinson disease	3 (0.7)
Epilepsy	3 (0.7)
Rheumatoid arthritis	2 (0.5)
Cirrhosis	1 (0.2)
Postoperative complications, n (%)	104 (24.8)
Pulmonary complications	72 (17.2)
Sepsis	21 (5.0)
Other (cardiac complications, hemorrhage, delirium)	11 (2.6)
ICU admission, n (%)	326 (77.8)
Length of hospital stay, days	12 (19)
Length of ICU stay, days	3 (7)
30-day mortality, n (%)	54 (12.9)
6-month mortality, n (%)	109 (26.0)
Calcium, mg/dl	8.44±0.90
Sodium, mmol/L	135.6±5.3
Potassium, mmol/L	4.50±0.76
Albumin, g/L	30.4±6.85
Hemoglobin, g/dl	10.65±2.36
Hematocrit, %	33.61±7.0

(table continues)

Table 1. Demographic and clinical characteristics of the study population (table continues)

Platelet count, ×10 ⁹ /L	349±140
CRP, mg/L	111 (155.4)
Glucose, mg/dl	156 (123)
Serum creatinine, mg/dl	1.05 (0.98)
Urea, mg/dl	49.3 (44.9)
AST, U/L	19 (21)
ALT, U/L	15 (17)
Total bilirubin, mg/dl	0.42 (0.34)
Direct bilirubin, mg/dl	0.19 (0.18)
INR	1.09 (0.17)
WBC, ×10 ⁹ /L	12.9 (9.4)
Neutrophil count, ×10 ⁹ /L	10.1 (9.35)
Lymphocyte count, ×10 ⁹ /L	1.44 (1.0)
Monocyte count, ×10 ⁹ /L	0.83 (0.52)
RDW-CV, %	14.8 (3.0)
CAR	3.80 (1.40-7.37)

Data are presented as mean±standard deviation (SD), median (interquartile range [IQR]), or number (percentage), as appropriate. ASA: American Society of Anesthesiologists, ICU: Intensive care unit, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, INR: International normalized ratio, WBC: White blood cell count, RDW-CV: Red cell distribution width-coefficient of variation, CAR: C-reactive protein-to-albumin ratio, SD: Standard deviation, IQR: Interquartile range

hematocrit levels, whereas INR, RDW, urea, total bilirubin, and direct bilirubin levels were higher (all $p<0.05$) (**Table 2**).

In the univariate logistic regression analysis, older age, female gender, ASA physical status III–IV, lower calcium, albumin, hemoglobin, and platelet levels, higher CAR, RDW-CV, INR, urea, serum creatinine, total bilirubin, and direct bilirubin levels, and the presence of cerebrovascular disease were significantly associated with 6-month mortality (**Table 3**).

Multivariable logistic regression analysis identified pulmonary complications (adjusted OR, 3.16; 95% CI, 1.77–5.64; $p<0.001$), older age (adjusted OR, 1.05; 95% CI, 1.03–1.07; $p<0.001$), higher preoperative creatinine levels (adjusted OR, 1.21; 95% CI, 1.04–1.40; $p=0.013$), and higher CAR (adjusted OR, 1.08; 95% CI, 1.02–1.14; $p=0.005$) were independently associated with 6-month mortality (**Table 4**). The area under the receiver operating characteristic curve (AUC) for the multivariable model was 0.738 (95% CI, 0.684–0.792; $p<0.001$).

To identify factors associated with short-term (30-day) mortality, logistic regression analyses were performed. Older age (adjusted OR, 1.030; 95% CI, 1.005–1.056; $p=0.019$), pulmonary complications (OR, 3.993; 95% CI, 2.042–7.806; $p<0.001$), and higher CAR (OR, 1.097; 95% CI, 1.030–1.169; $p=0.004$) were identified as independent factors in the multivariable analysis. Although ASA physical status III–IV and hematocrit were significantly associated with 30-day mortality in the univariate analysis, they did not retain statistical significance in the multivariable model (**Table 5**).

DISCUSSION

In this retrospective cohort, 30-day and six-month mortality after MLEA were 12.9% and 26.0%, respectively. Multivariable analysis showed that older age, postoperative pulmonary complications, and higher CAR values were independently associated with mortality at both follow-up points. Higher

Table 2. Comparison of demographic and clinical characteristics according to 6-month mortality

Variable	Survivors (n=310)	Non-survivors (n=109)	p ^a
Age, years	64.1±15.7	72.9±13.8	<0.001*
ASA physical status, n (%)			
I-II	144 (46.5)	29 (26.6)	<0.001
III-IV	166 (53.5)	80 (73.4)	
Gender, n (%)			
Male	214 (69)	63 (57.8)	0.035
Female	96 (31)	46 (42.2)	
Peripheral nerve block, n (%)	50 (16.1)	19 (17.4)	0.765
Type of anesthesia, n (%)			
Spinal anesthesia	127 (41)	48 (44)	0.575
General anesthesia	183 (59)	61 (56)	
Comorbidities, n (%)	264 (85.2)	101 (92.7)	0.044
Diabetes mellitus	229 (73.9)	83 (76.1)	0.639
Hypertension	142 (45.8)	60 (55)	0.097
Coronary artery disease	96 (31)	41 (37.6)	0.203
Peripheral artery disease	66 (21.3)	27 (24.8)	0.452
Chronic kidney disease	45 (14.5)	27 (24.8)	0.015
COPD	24 (7.7)	10 (9.2)	0.638
Cerebrovascular disease	23 (7.4)	17 (15.6)	0.012
Heart failure	19 (6.1)	10 (9.2)	0.281
Hyperlipidemia	18 (5.8)	7 (6.4)	0.815
Arrhythmia	12 (3.9)	9 (8.3)	0.071
Cancer	12 (3.9)	5 (4.6)	0.779
Dementia	7 (2.3)	5 (4.6)	0.313
Thyroid disease	3 (1)	7 (6.4)	0.004
Rheumatoid arthritis	2 (0.6)	0	1.000
Parkinson disease	2 (0.6)	1 (0.9)	1.000
Epilepsy	3 (1)	0	0.571
Cirrhosis	0	1 (0.9)	0.260
Amputation level, n (%)			
Below-knee amputation	261 (84.2)	85 (78)	0.094
Above-knee amputation	49 (15.8)	24 (22)	
Indication for amputation, n (%)			
Diabetic foot infection	184 (59.4)	66 (60.6)	0.107
Peripheral arterial disease/ischemia	72 (23.2)	32 (29.4)	
Trauma	46 (14.8)	7 (6.4)	
Other (pyoderma gangrenosum, burn, vasculitis, malignancy, non-diabetic infection)	8 (2.6)	4 (3.7)	
Postoperative complications, n (%)	63 (20.3)	41 (37.6)	<0.001
Pulmonary complications	38 (12.3)	34 (31.2)	
Sepsis	18 (5.8)	3 (2.8)	
Other (cardiac complications, hemorrhage, delirium)	7 (2.3)	4 (3.7)	
ICU admission, n (%)	222 (71.6)	104 (95.4)	<0.001
Calcium, mg/dl	8.52±0.88	8.23±0.90	0.003*
Sodium, mmol/L	135.6±5.0	135.9±6.2	0.644*
Potassium, mmol/L	4.51±0.74	4.44±0.82	0.447*
Albumin, g/L	31.38±6.71	27.62±6.45	<0.001*
Hemoglobin, g/dl	10.87±2.36	10.02±2.23	0.001*
(table continues)			

(table continues)

Table 2. Comparison of demographic and clinical characteristics according to 6-month mortality (table continues)

Hematocrit, %	34.25±6.87	31.81±7.04	0.002*
Platelet count, ×10 ⁹ /L	356.5±137.3	325.8±146.0	0.048*
CRP, mg/L	108.8 (152.74)	126.0 (155.87)	0.069**
CAR	3.47 (5.71)	4.88 (7.38)	0.007**
Glucose, mg/dl	153 (127.5)	160 (101.0)	0.339**
Serum creatinine, mg/dl	1.01 (0.70)	1.40 (1.64)	0.005**
Urea, mg/dl	44.4 (40.70)	60.9 (63.10)	<0.001**
AST, U/L	19.0 (20.25)	20 (23.00)	0.915**
ALT, U/L	15 (16.50)	14 (16.00)	0.134**
Total bilirubin, mg/dl	0.40 (0.33)	0.45 (0.41)	0.031**
Direct bilirubin, mg/dl	0.18 (0.17)	0.21 (0.24)	0.035**
INR	1.08 (0.15)	1.14 (0.23)	<0.001**
WBC, ×10 ⁹ /L	13.19 (8.79)	12.54 (12.57)	0.784**
Neutrophil count, ×10 ⁹ /L	10.04 (8.80)	10.15 (13.09)	0.407**
Lymphocyte count, ×10 ⁹ /L	1.59 (1.08)	1.19 (0.85)	<0.001**
Monocyte count, ×10 ⁹ /L	0.85 (0.56)	0.74 (0.49)	0.008**
RDW-CV, %	14.6 (2.85)	15.3 (3.10)	0.006**
Length of ICU stay, days	2 (5)	6 (14)	<0.001**
Length of hospital stay, days	11 (18)	18 (24)	0.002**

Data are presented as mean±standard deviation (SD), median (interquartile range [IQR]), or number (percentage), as appropriate. ASA: American Society of Anesthesiologists, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit, CRP: C-reactive protein, CAR: C-reactive protein-to-albumin ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio, WBC: white blood cell count, RDW-CV: red cell distribution width-coefficient of variation, SD: Standard deviation, IQR: Interquartile range, a: Chi-square test or Fisher's exact test, as appropriate. *: independent samples t-test; **: Mann-Whitney U test; Statistically significant p-values (p<0.05) are shown in bold.

Table 3. Univariate logistic regression analysis of factors associated with 6-month mortality

Variable	OR (95% CI)	p-value
Age	1.044 (1.026-1.062)	<0.001
Gender (male vs female)	0.614 (0.392-0.963)	0.034
ASA physical status III-IV	2.39 (1.48-3.86)	<0.001
Cerebrovascular disease (no vs. yes)	0.434 (0.222-0.847)	0.014
Calcium	0.685 (0.532-0.883)	0.003
Albumin	0.918 (0.887-0.951)	<0.001
CAR	1.064 (1.015-1.115)	0.009
Hemoglobin	0.849 (0.767-0.939)	0.001
Platelet count (×10 ⁹ /L)	0.998 (0.997-1.000)	0.049
RDW-CV	1.125 (1.040-1.216)	0.003
INR	8.451 (2.696-26.490)	<0.001
Urea	1.009 (1.005-1.014)	<0.001
Serum creatinine	1.240 (1.080-1.424)	0.002
Total bilirubin	1.801 (1.124-2.884)	0.014
Direct bilirubin	1.899 (1.086-3.318)	0.024
Pulmonary complications (yes vs no)	3.245 (1.912-5.508)	<0.001

Statistically significant p-values (p <0.05) are shown in bold. OR: odds ratio, CI: confidence interval, ASA: American Society of Anesthesiologists, CAR: C-reactive protein-to-albumin ratio, RDW-CV: Red cell distribution width-coefficient of variation, INR: International normalized ratio

preoperative creatinine was additionally associated with six-month mortality, whereas no independent association was observed for 30-day mortality.

During the six-month follow-up period, approximately one-quarter of the patients died, and approximately half of these deaths occurred within the first 30 days. This finding indicates

Table 4. Multivariable logistic regression analysis of factors associated with 6-month mortality

Variable	Adjusted OR (95% CI)	p-value
Age	1.05 (1.03-1.07)	<0.001
Pulmonary complications (yes vs no)	3.16 (1.77-5.64)	<0.001
Serum creatinine	1.21 (1.04-1.40)	0.013
CAR	1.08 (1.02-1.14)	0.005

Only variables retained in the final multivariable logistic regression model are presented. OR: Odds ratio, CI: confidence interval, CAR: C-reactive protein-to-albumin ratio

that mortality was concentrated in the early postoperative period, but that deaths continued in the following months. Similarly, Morton et al.⁴ reported a six-month mortality rate of 25% after MLEA, comparable to that observed in our study. The higher rate of 32.4% reported by Reisoğlu et al.⁸ may be explained, at least in part, by the inclusion of patients undergoing amputation exclusively because of diabetes mellitus or peripheral arterial disease. Early mortality rates reported in previous studies range from 4% to 28%.⁹⁻¹¹ Differences in amputation level and indication, patient age, comorbidity profile, study population, geographical setting, and perioperative care may contribute to this wide variation. Therefore, when interpreting mortality rates after MLEA, the region in which the study was conducted and the demographic and clinical characteristics of the patients should be considered together.

In our study, advanced age was independently associated with both 30-day and six-month mortality. For each additional year of age, 30-day mortality increased by approximately 3%, while 6-month mortality increased by approximately 5%. This association may be explained by frailty and the loss of reserve in organ systems that develop with aging. Frailty reflects a diminished ability to re-establish homeostasis after an acute physiological insult. In older patients, the surgical and metabolic burden of MLEA may therefore exceed the capacity of already compromised organ systems, increasing vulnerability to postoperative complications.^{12,13} This vulnerability was particularly relevant in our cohort, in which 87.1% of patients had at least one comorbidity, most commonly diabetes mellitus, hypertension, coronary artery disease, or peripheral arterial disease. These conditions frequently coexist with endothelial dysfunction, chronic inflammation, oxidative stress, and widespread atherosclerosis. Consequently, vascular impairment may extend beyond the affected limb to the coronary, cerebral, and renal circulations, further limiting the ability to tolerate perioperative stress.¹⁴ Age-related deterioration in endothelial function, microcirculation, angiogenesis, immune regulation, and cellular repair may also interfere with stump healing and predispose patients to wound infection, tissue necrosis, and

repeat intervention.¹⁵ Rehabilitation may be further restricted by the greater energy expenditure required after amputation, particularly in older patients with limited cardiopulmonary reserve.¹⁶ These age-related physiological and clinical disadvantages may account for the higher mortality observed in older patients after MLEA.

CAR is considered to reflect systemic inflammation and nutritional status together. CRP is an indicator of systemic inflammation, whereas albumin is one of the indicators of nutritional status and the physiological impact of disease.^{5,17,18} Therefore, a high CAR may indicate the coexistence of increased inflammatory activity and inadequate nutritional status and may be associated with reduced tolerance to surgical stress. Our findings are consistent with previous studies linking higher CAR values to adverse outcomes in patients with peripheral arterial disease and in those undergoing major amputation for diabetic foot disease.^{5,17-19} The presence of this association for both 30-day and six-month mortality suggests that CAR may reflect the impact of inflammatory and nutritional status at admission on short- and intermediate-term prognosis. Among the preoperative laboratory findings, elevated creatinine levels were also associated with mortality; however, unlike CAR, this association was observed only during the six-month period. Aulivola et al.²⁰ similarly reported markedly poorer survival among patients with serum creatinine concentrations above 2 mg/dl, including those without end-stage renal disease. Renal dysfunction commonly accompanies systemic vascular disease and may adversely affect prognosis through anemia-related impairment of tissue oxygen delivery, immune dysfunction, and greater susceptibility to infection.^{21,22} Elevated creatinine may therefore reflect both reduced renal reserve and a broader burden of systemic disease. Its association with six-month mortality supports the inclusion of renal function in preoperative risk assessment and may help identify patients who require closer follow-up after amputation.

Postoperative pulmonary complications were strongly associated with mortality in our cohort. Patients who developed a pulmonary complication had nearly a fourfold increase in 30-day mortality, and almost half died within six months. Brix et al.⁶ likewise identified pneumonia as an important complication contributing to mortality after MLEA. Similar findings have been reported in other surgical populations. Canet et al.²³ found that postoperative pulmonary complications were independently related to prolonged hospitalization and higher mortality, while Piccioni et al.²⁴ demonstrated a significant association between pulmonary complications and death after major abdominal surgery. Several factors may predispose patients undergoing

Table 5. Univariate and multivariable logistic regression analyses of factors associated with 30-day mortality

Variable	Univariate OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	1.025 (1.004-1.046)	0.017	1.030 (1.005-1.056)	0.019
ASA physical status III-IV	2.205 (1.160-4.194)	0.016	1.514 (0.726-3.156)	0.269
Pulmonary complications (yes vs no)	4.392 (2.308-8.357)	<0.001	3.993 (2.042-7.806)	<0.001
CAR	1.096 (1.036-1.159)	0.001	1.097 (1.030-1.169)	0.004
Hematocrit	0.952 (0.911-0.994)	0.024	0.965 (0.921-1.012)	0.144

Statistically significant p-values (p < 0.05) are shown in bold. OR: Odds ratio, CI: Confidence interval, ASA: American Society of Anesthesiologists, CAR: C-reactive protein-to-albumin ratio

MLEA to respiratory complications. Severe postoperative pain, opioid-related respiratory depression, prolonged immobilization, and delayed mobilization can impair deep breathing and coughing, promote secretion retention, and increase the risk of atelectasis.^{25,26} The consequences may be particularly severe in older or frail patients and in those with limited cardiopulmonary reserve. Once a pulmonary complication develops, hypoxemia, increased respiratory workload, infection, and systemic inflammation may further compromise pre-existing cardiac or renal dysfunction.²⁴⁻²⁶ Therefore, the prevention, early recognition, and appropriate treatment of pulmonary complications in patients undergoing MLEA are important for prognosis.

Limitations

This study has several limitations. First, owing to its retrospective design, it was not possible to evaluate all potential confounding variables, and the observed associations could not be interpreted within a causal framework. Some clinical variables that may affect prognosis, such as smoking and alcohol use, body-mass index, frailty level, preoperative mobility, and physical performance, could not be included in the analysis because they were not routinely documented in patient records. Similarly, the limited availability of data on prosthesis use, ambulatory status after amputation, and living conditions prevented a more comprehensive evaluation of long-term outcomes. The inability to determine the exact causes of death limited the detailed investigation of the mechanisms underlying mortality. In addition, although all surgical procedures were performed at a single center, providing a certain degree of standardization in perioperative practices, this may limit the generalizability of the findings to different centers and patient populations.

CONCLUSION

As a result, advanced age, elevated preoperative CAR, and the development of postoperative pulmonary complications were independently associated with early- and intermediate-term mortality after MLEA. The combined evaluation of these variables may assist perioperative risk stratification after MLEA.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the No. 2 Scientific Researches Evaluation and Ethics Committee of Ankara Etlik City Hospital (Date: 30.06.2026, Decision No: AESH-BADEK2-2026-531).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: FA; Design: FA; Control: FÖS; Resources: FA, FÖS; Materials: FA, FÖS; Data Collection and/or Processing: FA, FÖS; Analysis and/or Interpretation: FA, FÖS; Literature Review: FA; Article Writing: FA, FÖS; Critical Review: FÖS.

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Comparison of pulmonary embolism in oncology patients with general population in terms of diagnosis, clinical features and prognosis

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ABSTRACT

Aims: Pulmonary embolism (PE) is a frequent and potentially fatal complication in cancer patients. The diagnosis, treatment, and prognosis of cancer-associated PE (CA-PE) differ from the general population. The primary aim of this study was to compare the clinical presentation and severity of PE between patients with and without malignancy; the secondary aim was to compare short- and long-term mortality.

Methods: Between 2020 and 2023, patients with PE without malignancy (PE group), patients with CA-PE group, and patients with suspected PE in whom PE was excluded by imaging (control group), 80 in each group, were retrospectively analyzed. Symptoms, risk factors, laboratory data, embolism localization, and clinical scores (Wells, modified Geneva, and Khorana for malignancy) were recorded. Prognostic scores (Pulmonary Embolism Severity Index [PESI], Bova, Pompe-C), mortality data (30-day, 3-month, 1-year), and modified Glasgow Prognostic Score were evaluated.

Results: The most common cancers were lung and brain tumors. In the CA-PE group, 67.5% were receiving active chemotherapy, and 50% had metastatic disease. Presenting symptoms were similar between the PE and CA-PE groups (dyspnea, $p=0.10$; chest pain, $p=0.31$), whereas both symptoms differed significantly from the control group ($p<0.001$). Embolism localization did not differ significantly between the groups. Inflammatory markers such as neutrophil/lymphocyte ($p=0.006$), monocyte/lymphocyte ($p=0.01$), and platelet/lymphocyte ratios ($p=0.015$) were higher in CA-PE. PESI score was significantly higher ($p<0.01$), whereas right ventricular dysfunction was not more frequent ($p=0.129$). Troponin-I and B-type natriuretic peptide (BNP) levels were similar. While 3-month and 1-year mortality rates were higher in CA-PE ($p<0.01$), 30-day mortality was similar.

Conclusion: Patients with CA-PE had higher inflammatory indices, but markers of PE severity were not worse than in patients without malignancy. Long-term all-cause mortality was higher in CA-PE, although cause-specific mortality was not assessed. Existing risk models may not be sufficient; malignancy-specific scoring systems are needed.

Keywords: Neoplasms, inflammation, mortality, prognosis, pulmonary embolism

INTRODUCTION

Acute pulmonary embolism (PE) is a common form of venous thromboembolism (VTE), presenting with a wide clinical spectrum, from no symptoms to sudden death. It is the third most common cardiovascular disorder globally, after myocardial infarction and stroke.¹ Due to its nonspecific symptoms, several diagnostic algorithms and risk assessment models have been developed.²

In cancer patients, VTE is a major cause of death, second only to the malignancy itself. Its incidence is 4-7.5 times higher than in the general population.³ Sorensen et al.⁴ reported a one-year survival rate of 12% in cancer patients with VTE, versus 36% in those without. This increased risk arises from multiple factors: patient, tumor, and treatment-related.⁵

Cancer-associated thrombosis involves complex mechanisms; cancer cells activate coagulation via procoagulants,

cytokines, and tissue factor-bearing microparticles.⁶ This prothrombotic state increases both morbidity and mortality. PE symptoms may be masked by cancer-related complaints, complicating diagnosis.⁷

General risk scores like Wells and Modified Geneva are less reliable in cancer patients. The Khorana model targets this group but has limited use due to cancer heterogeneity.⁸ Likewise, the Pulmonary Embolism Severity Index (PESI) overestimates risk by assigning malignancy points regardless of cancer type, stage, or treatment.

Low molecular weight heparins (LMWH) are preferred in initial treatment per current guidelines, with better outcomes than vitamin K antagonists.⁹ Still, the duration of therapy and the role of direct oral anticoagulants (DOAC) remain under investigation.

Most studies compare cancer patients with and without VTE, offering little insight into how malignancy alters PE. Our study directly compares cancer-associated PE (CA-PE) with PE in patients without malignancy. The primary objective was to compare the clinical presentation (presenting symptoms and vital signs) and PE severity (embolism localization, right ventricular dysfunction on echocardiography, cardiac biomarkers and clinical severity scores) between patients with and without malignancy. The secondary objectives were to compare inflammatory indices, treatment approaches and all-cause mortality at 30 days, 3 months and 1 year. A control group of patients with suspected PE in whom PE was excluded was included to provide reference values for clinical and laboratory parameters. These data may support the development of more effective risk and treatment models.

METHODS

Ethics

This study was approved by the Non-interventional Researches Ethics Committee of Bezmialem Vakıf University (Date: 26.07.2023, Decision No: 2023/232). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The requirement for informed consent was waived due to the retrospective nature of the study. This study was conducted and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Study Design and Population

This retrospective study was conducted at the department of pulmonology of a tertiary care university hospital between June 2020 and June 2023. Patients were divided into three groups: patients with PE without malignancy (PE group), patients with CA-PE group and a control group. The control group consisted of adult patients who were evaluated during the same period for suspected acute PE because of a high clinical suspicion (based on presenting symptoms, clinical findings and clinical probability assessment) but in whom PE was excluded by CT pulmonary angiography (CTPA) or V/Q scintigraphy; thus, “negative diagnostic findings” refers to the absence of PE on these imaging studies. The same exclusion criteria applied to the PE groups were applied to the control group. Patients with malignancy were not included in the control group. The control group was included to provide reference values for clinical and laboratory parameters in patients with a similar clinical presentation, rather than in healthy individuals.

From the hospital database, 362 patients with PE diagnosis codes were initially identified and screened according to the predefined criteria described below. To obtain groups of equal size, 80 patients without malignancy and 80 patients with malignancy were randomly selected from the eligible patients. The control group of 80 patients was randomly selected in the same manner from patients with suspected PE and negative imaging during the study period.

Inclusion and Exclusion Criteria

Patients eligible for inclusion were those diagnosed with PE at the study center’s department of pulmonology during

the specified time period. We excluded patients under 18 years of age, pregnant women, and COVID-19 PCR positive patients to prevent confounding factors. Additionally, patients with pneumonia detected on CT were excluded due to potential overlap in clinical presentation. Other exclusion criteria included: patients diagnosed with PE at external centers (n=33), patients who refused treatment or terminated treatment early (n=26), patients with malignancy lacking pathological confirmation (n=21), and patients with insufficient laboratory data (n=4). In the CA-PE group, only patients with histopathologically confirmed malignancy were included. Patients with solid tumors and those with hematological malignancies were both eligible for inclusion in the CA-PE group.

Data Collection and Clinical Assessment

Patient medical records were comprehensively reviewed to collect demographic, clinical, and laboratory data. Demographics included age, gender, body-mass index (BMI), and smoking history quantified in pack-years. Clinical data encompassed presenting symptoms (dyspnea, chest pain, syncope, hemoptysis), symptom duration, vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation), and shock index (heart rate/systolic blood pressure).

Comorbidities and risk factors for VTE were systematically documented, with particular attention to hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, chronic obstructive pulmonary disease, atrial fibrillation, chronic heart failure, immobilization, previous PE history, recent surgery, and blood transfusion. Performance status was evaluated using the Eastern Cooperative Oncology Group (ECOG) score, and comorbidity burden was assessed using the Charlson Comorbidity Index (CCI). Other recorded risk factors included central venous catheter, trauma, rheumatological disease, previous COVID-19, erythropoietin use, superficial vein thrombosis and the postpartum period. Inherited thrombophilia was not screened systematically; a known thrombophilia was recorded when documented in the medical records.

For patients with malignancy, we recorded cancer type, diagnosis date, disease stage (early, locally advanced, or metastatic), metastatic sites, and treatment modalities (chemotherapy, radiotherapy, surgery, hormonal therapy). The time between malignancy diagnosis and PE occurrence, as well as the time between most recent chemotherapy and PE occurrence, were calculated.

Laboratory Investigations

Blood samples were collected at admission for laboratory analysis. Standard laboratory parameters included complete blood count, D-dimer, C-reactive protein (CRP), albumin, creatinine, liver function tests, and cardiac biomarkers (Troponin-I, CK-MB, BNP). Inflammatory indices including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and Systemic Immune-Inflammation Index (SII=platelet count×neutrophil count/lymphocyte count) were calculated from complete blood count data.

Imaging Studies and Diagnostic Procedures

PE was confirmed or excluded primarily by CTPA in

230 patients (95.8%), with ventilation/perfusion (V/Q) lung scintigraphy used in 10 patients (4.2%) who had contraindications to CTPA. The anatomical location of embolism was categorized as pulmonary trunk, main pulmonary artery, lobar, segmental, or subsegmental. The presence of unilateral or bilateral emboli was noted, as was the occurrence of pulmonary infarction.

Echocardiography was performed in 168 patients (70%) to assess right ventricular function, pulmonary artery pressure, and signs of right heart strain. Doppler ultrasonography of the lower extremities was performed in 103 patients (42.9%) to detect deep vein thrombosis, with findings classified as unilateral or bilateral. Echocardiography and lower-extremity Doppler ultrasonography were performed at the discretion of the treating physician and were therefore not available for all patients.

Clinical Risk and Severity Assessment

All patients were evaluated using established risk stratification tools. Clinical probability of PE was assessed using the Wells score and Modified Geneva score. For cancer patients, VTE risk was additionally evaluated using the Khorana score. PE severity was determined using the PESI, with patients classified as low risk (class I-II, score ≤ 85) or high risk (class III-V, score > 85).

Mortality risk was assessed using the Bova score for all PE patients, with additional cancer-specific scores including the Pompe-C score, 30-day mortality score, and Modified Glasgow Prognostic Score (mGPS) for the CA-PE group. Based on clinical and imaging findings, patients were further classified as high-risk (massive), intermediate-risk (submassive), or low-risk (non-massive) PE according to current guidelines.

Treatment and Follow-up

Treatment approaches were recorded, including the use of thrombolytic therapy, low molecular weight heparin (LMWH), vitamin K antagonists (VKA), and DOACs. Hospital length of stay and intensive care unit admission duration were documented. Patients were followed for mortality outcomes at three time points: 30-day, 3-month, and 1-year mortality.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests for each variable within each of the three groups separately. Continuous variables that were normally distributed in all three groups were presented as mean $\pm$ standard deviation; those that deviated from a normal distribution in at least one group were presented as median (interquartile range, IQR). Categorical variables were presented as frequency and percentage.

For comparisons between groups, parametric tests were used for normally distributed variables, including Student's t-test for two-group comparisons and Analysis of Variance (ANOVA) for multiple group comparisons. For non-normally distributed variables, non-parametric alternatives were

employed, specifically the Mann-Whitney U test for two-group comparisons and the Kruskal-Wallis test for multiple group comparisons.

Categorical variables were compared using the Chi-square test; Fisher's exact test was used instead for 2x2 tables when the expected cell count was below 5. For multiple group comparisons that showed statistical significance, post-hoc analyses were conducted with Bonferroni correction to identify specific between-group differences. The significance threshold was set at $p < 0.05$ with a 95% confidence interval for all analyses.

RESULTS

Study Population

A total of 240 patients were included in this study: 80 patients with pulmonary embolism (PE group), 80 patients with cancer-associated pulmonary embolism (CA-PE group), and 80 patients with suspected PE in whom PE was excluded by imaging (control group). The demographic and clinical characteristics of the three groups are presented in **Table 1**.

Malignancy Characteristics

In the CA-PE group, the most frequent malignancies were lung cancer (22.5%) and brain tumors (15%), followed by multiple primary malignancies (11.3%). Prostate cancer (6.25%), breast cancer (5%), ovarian cancer (5%), and non-Hodgkin lymphoma (5%) were also commonly observed.

Of the patients with malignancy, 12 (15%) were in early stage, 28 (35%) in locally advanced stage, and 40 (50%) in metastatic stage. The most common metastatic sites were the liver (20.6%), bone (17.6%), and brain (14.4%). Fifty-four patients (67.5%) were receiving active chemotherapy, with platinum-based regimens being the most common (63% of chemotherapy patients). Radiotherapy had been administered to 43 patients (53.8%), and 36 patients (45%) had undergone cancer-related surgery.

The mean time between malignancy diagnosis and PE occurrence was 501.2 ± 638.1 days. Fifty patients (62.5%) developed PE within the first year after cancer diagnosis. The mean time between the most recent chemotherapy and PE diagnosis was 93.07 ± 272.1 days.

Demographic and Clinical Characteristics

The median age was 71.5 years (IQR 54.8-82.0) in the PE group, 69.0 years (IQR 56.8-76.0) in the CA-PE group, and 62.5 years (IQR 50.0-73.0) in the control group ($p = 0.005$). The gender distribution was similar across groups ($p = 0.432$). BMI was significantly higher in the control group (median 29.4 kg/m², IQR 27.1-33.5) compared to the PE (26.6 kg/m², IQR 24.2-31.0) and CA-PE (25.4 kg/m², IQR 23.4-27.9) groups ($p = 0.006$).

The most frequent presenting symptom in all groups was dyspnea, which was more common in the PE (97.5%) and CA-PE (90%) groups than in the control group (68.8%) ($p < 0.001$). Chest pain was more prevalent in the control group (57.5%) compared to the PE (36.3%) and CA-PE (27.5%) groups ($p < 0.001$). No significant differences were observed in the frequency of syncope ($p = 0.776$) or hemoptysis ($p = 0.707$) among the three groups. The median symptom duration was similar across groups ($p = 0.823$).

Table 1. Comparative demographic and general clinical characteristics of patients

General characteristics	PE (n=80)	CA-PE (n=80)	Control (n=80)	P
Age, years, median (IQR)	71.5 (54.8-82.0)	69.0 (56.8-76.0)	62.5 (50.0-73.0)	0.005***
Gender, n (%)				0.432**
Female	46 (57.5)	43 (53.8)	51 (63.8)	
Male	34 (42.5)	37 (46.2)	29 (36.2)	
BMI, kg/m ² , median (IQR)	26.6 (24.2-31.0)	25.4 (23.4-27.9)	29.4 (27.1-33.5)	0.006***
Symptoms				
Chest pain, n (%)	29 (36.3)	22 (27.5)	46 (57.5)	<0.001**
Syncope, n (%)	5 (6.3)	7 (8.8)	5 (6.3)	0.776**
Dyspnea, n (%)	78 (97.5)	72 (90)	55 (68.8)	<0.001**
Hemoptysis, n (%)	3 (3.8)	4 (5)	2 (2.5)	0.707**
Symptom duration, days, median (IQR)	4.0 (2.0-7.0)	4.0 (2.0-7.0)	3.0 (1.0-10.0)	0.823***
Vital Signs				
Systolic BP, mmHg, mean±SD	132.8±27.5	127.2±22.9	148.3±29.2	<0.001*
Diastolic BP, mmHg, Median (IQR)	70.0 (60.0-81.2)	70.0 (60.0-83.2)	79.0 (67.8-88.2)	0.004***
Shock index, median (IQR)	0.70 (0.60-0.93)	0.80 (0.70-0.93)	0.60 (0.50-0.70)	<0.001***
Shock index >0.9, n (%)	20 (25.0)	20 (25.0)	6 (7.5)	0.005**
Heart rate, /min, median (IQR)	96.0 (81.0-114.2)	105.0 (91.5-118.0)	88.5 (81.8-100.2)	<0.001***
Oxygen saturation, %, median (IQR)	94.0 (87.0-96.0)	89.0 (85.0-95.0)	97.0 (94.0-98.0)	<0.001***
ECOG, median (IQR)	1.0 (0.0-3.0)	2.0 (1.0-3.0)	1.0 (0.0-1.0)	<0.001***
CCI score, median (IQR)	4.5 (2.8-6.0)	9.0 (7.0-10.0)	2.5 (1.0-4.0)	<0.001***

p<0.05 was considered statistically significant. *: Analysis of Variance; **: Chi-square test; ***: Kruskal-Wallis test. Values are presented as mean±SD for variables analyzed with Analysis of Variance (*) and as median (interquartile range) for variables analyzed with the Kruskal-Wallis test (***). PE: Pulmonary embolism, CA-PE: Cancer-associated pulmonary embolism, BMI: Body-mass index, IQR: Interquartile range, BP: Blood pressure, SD: Standard deviation, ECOG: Eastern Cooperative Oncology Group, CCI: Charlson Comorbidity Index

Vital sign measurements showed significant differences between groups. The control group had higher systolic blood pressure (p<0.001) and lower shock index (p<0.001) compared to both PE groups. Oxygen saturation was significantly lower in the CA-PE group (median 89.0%, IQR 85.0-95.0) compared to the PE group (94.0%, IQR 87.0-96.0) and control group (97.0%, IQR 94.0-98.0) (p<0.001).

The CA-PE group demonstrated higher ECOG performance status scores (median 2.0, IQR 1.0-3.0) and CCI scores (median 9.0, IQR 7.0-10.0) compared to both the PE group (1.0, IQR 0.0-3.0 and 4.5, IQR 2.8-6.0, respectively) and control group (1.0, IQR 0.0-1.0 and 2.5, IQR 1.0-4.0, respectively) (p<0.001 for both comparisons).

Comorbidities and Risk Factors

Comorbidities and risk factors for VTE in the study groups are presented in **Table 2**. Hypertension was more prevalent in the PE group (58.8%) compared to the CA-PE group (37.5%) (p=0.007). Similarly, chronic kidney disease was more common in the PE group (18.8%) than in the CA-PE group (7.5%) (p=0.035). The prevalence of the other evaluated comorbidities, including diabetes mellitus, coronary artery disease, COPD, atrial fibrillation and chronic heart failure, did not differ significantly between the PE and CA-PE groups (**Table 2**).

Regarding risk factors for thromboembolism, immobilization was the most common risk factor in both the PE (52.5%) and CA-PE (57.5%) groups, with no significant difference between groups (p=0.525). History of previous PE was noted in 15% of PE patients and 6.3% of CA-PE patients (p=0.073). Recent surgery (within the last month) was equally prevalent in both groups (10%, p=1.0). Blood transfusion was significantly

Table 2. Comorbidities and risk factors for venous thromboembolism

	PE (n=80)	CA-PE (n=80)	Control (n=80)	p (PE vs. CA-PE)
Comorbidities				
Hypertension, n (%)	47 (58.8)	30 (37.5)	41 (51.3)	0.007*
Diabetes mellitus, n (%)	18 (22.5)	14 (17.5)	20 (25.0)	0.429*
Chronic kidney disease, n (%)	15 (18.8)	6 (7.5)	5 (6.3)	0.035*
Coronary artery disease, n (%)	12 (15.0)	9 (11.3)	16 (20.0)	0.482*
COPD, n (%)	8 (10.0)	6 (7.5)	8 (10.0)	0.576*
Asthma, n (%)	10 (12.5)	5 (6.3)	13 (16.3)	0.175*
Atrial fibrillation, n (%)	8 (10.0)	3 (3.8)	4 (5.0)	0.118*
Chronic heart failure, n (%)	7 (8.8)	2 (2.5)	13 (16.3)	0.167**
Previous tuberculosis, n (%)	2 (2.5)	2 (2.5)	2 (2.5)	1.000**
Rheumatological disease, n (%)	3 (3.8)	1 (1.3)	4 (5.0)	0.620**
Risk factors for VTE				
Immobilization, n (%)	42 (52.5)	46 (57.5)	11 (13.8)	0.525*
Previous PE, n (%)	12 (15.0)	5 (6.3)	2 (2.5)	0.073*
Recent surgery (<1 month), n (%)	8 (10.0)	8 (10.0)	0 (0)	1.000*
Blood transfusion, n (%)	0 (0)	22 (27.5)	0 (0)	<0.001*
Central venous catheter, n (%)	1 (1.3)	8 (10.0)	0 (0)	0.034**
Trauma, n (%)	5 (6.3)	1 (1.3)	1 (1.3)	0.210**
Previous COVID-19, n (%)	5 (6.3)	0 (0)	0 (0)	0.059**
Erythropoietin use, n (%)	2 (2.5)	0 (0)	0 (0)	0.497**
Superficial vein thrombosis, n (%)	4 (5.0)	0 (0)	-	0.120**
Postpartum period, n (%)	2 (2.5)	0 (0)	0 (0)	0.497**
Known thrombophilia, n (%)	6 (7.5)	2 (2.5)	0 (0)	0.276**

p<0.05 was considered statistically significant. P values refer to the comparison between the PE and CA-PE groups. *: Chi-square test; **: Fisher's exact test. PE: Pulmonary embolism, CA-PE: Cancer-associated pulmonary embolism, VTE: Venous thromboembolism, COPD: Chronic obstructive pulmonary disease

more common in the CA-PE group (27.5%) compared to the PE group where no patients received transfusions ($p<0.001$).

Laboratory Parameters

Comparison of laboratory parameters between groups revealed significant differences (Table 3). D-dimer levels were significantly higher in both PE groups compared to the control group ($p<0.001$), but did not differ significantly between the PE and CA-PE groups. Leukocyte and neutrophil counts were higher in both PE groups compared to controls ($p<0.001$), while lymphocyte counts were lower in the PE and CA-PE groups compared to controls ($p<0.001$).

Inflammatory indices showed marked differences between groups. The NLR was significantly higher in the CA-PE group (median 5.63, IQR 2.70-10.98) compared to the PE group (3.17, IQR 2.14-5.92) and control group (2.00, IQR 1.55-2.96) ($p<0.001$). Similarly, the monocyte-to-lymphocyte ratio was highest in the CA-PE group (0.47, IQR 0.29-0.78), followed by the PE group (0.36, IQR 0.23-0.52) and control group (0.29, IQR 0.20-0.39) ($p<0.001$). The PLR followed the same pattern, with the highest values in the CA-PE group (166.4, IQR 109.3-286.8) compared to the PE group (127.2, IQR 89.7-165.9) and control group (115.3, IQR 96.5-160.6) ($p=0.004$) (Figure).

The CA-PE group had significantly lower hemoglobin levels (11.3 ± 1.9 g/dl) compared to the PE group (12.3 ± 2.2 g/dl) and control group (12.7 ± 1.6 g/dl) ($p<0.001$). Red cell distribution width (RDW) was highest in the CA-PE group (median 15.0%, IQR 14.0-17.1) compared to the PE group (13.9%, IQR 12.8-15.8) and control group (13.5%, IQR 12.8-14.8) (Kruskal-Wallis $p<0.001$).

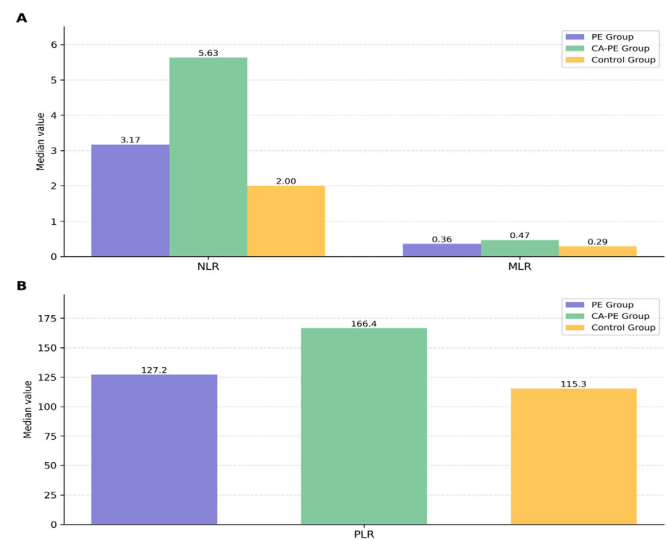


Figure. Comparison of inflammatory indices (NLR, MLR, PLR) between the PE, CA-PE, and control groups. (A) NLR and MLR; (B) PLR. Values are presented as medians. The CA-PE group showed significantly higher values for all three inflammatory indices compared with the PE and control groups ($p<0.05$).

NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PE: Pulmonary embolism, CA-PE: Cancer-associated pulmonary embolism

Lactate dehydrogenase (LDH) levels were significantly elevated in the CA-PE group (median 344.5 U/L, IQR 238.8-490.0) compared to the PE group (258.5 U/L, IQR 212.5-311.2) and control group (202.5 U/L, IQR 173.0-246.8) ($p<0.001$). CRP levels were markedly higher in both the CA-PE (88.77 mg/L, IQR 38.46-119.75) and PE groups (30.53 mg/L, IQR 8.61-98.82) compared to the control group (5.98 mg/L, IQR 0.99-9.41) ($p<0.001$).

Cardiac biomarkers showed that troponin-I levels were elevated in both PE groups compared to controls ($p<0.001$),

Table 3. Evaluation of laboratory values according to diagnostic groups

Laboratory Parameters	PE	CA-PE	Control	p
D-dimer, ng/ml	2298.5 (879.8-10557.8)	1996.5 (899.0-9954.8)	1220.0 (807.5-1647.5)	<0.001***
Leukocyte, $10^3/\mu\text{L}$	9.70 (7.64-12.49)	9.77 (7.23-13.98)	7.68 (6.13-9.54)	<0.001***
Lymphocyte, $10^3/\mu\text{L}$	1.86 (1.46-2.37)	1.40 (0.78-2.01)	2.09 (1.56-2.75)	<0.001***
Neutrophil, $10^3/\mu\text{L}$	6.63 (4.84-8.97)	7.17 (5.25-10.84)	4.50 (3.59-5.96)	<0.001***
Neutrophil/Lymphocyte ratio	3.17 (2.14-5.92)	5.63 (2.70-10.98)	2.00 (1.55-2.96)	<0.001***
SII index value	839.4 (467.2-1571.0)	1214.0 (487.6-2687.7)	507.9 (351.9-827.0)	<0.001***
Monocyte, $10^3/\mu\text{L}$	0.64 (0.51-0.96)	0.64 (0.45-0.93)	0.64 (0.52-0.77)	0.610***
Monocyte/lymphocyte ratio	0.36 (0.23-0.52)	0.47 (0.29-0.78)	0.29 (0.20-0.39)	<0.001***
Hemoglobin, g/dl, mean $\pm$ SD	12.3 $\pm$ 2.2	11.3 $\pm$ 1.9	12.7 $\pm$ 1.6	<0.001*
RDW, %	13.9 (12.8-15.8)	15.0 (14.0-17.1)	13.5 (12.8-14.8)	<0.001***
Platelet, $10^3/\mu\text{L}$	229.5 (178.2-294.8)	229.0 (153.2-313.0)	257.0 (216.8-308.8)	0.069***
Platelet/lymphocyte ratio	127.2 (89.7-165.9)	166.4 (109.3-286.8)	115.3 (96.5-160.6)	0.004***
LDH, U/L	258.5 (212.5-311.2)	344.5 (238.8-490.0)	202.5 (173.0-246.8)	<0.001***
CRP, mg/L	30.53 (8.61-98.82)	88.77 (38.46-119.75)	5.98 (0.99-9.41)	<0.001***
Albumin, g/dl, mean $\pm$ SD	3.6 $\pm$ 0.6	3.4 $\pm$ 0.6	4.1 $\pm$ 0.4	0.013*
Troponin-I, ng/L	10.6 (4.7-57.9)	14.2 (4.0-46.7)	2.5 (2.5-11.4)	<0.001***
CK-MB, $\mu\text{g/L}$	1.00 (0.40-1.77)	0.70 (0.40-1.50)	0.80 (0.30-1.80)	0.791***
BNP, ng/L	62.6 (24.4-200.0)	78.8 (26.2-177.4)	306.1 (56.6-754.6)	0.303***
Serum creatinine, mg/dl	0.93 (0.81-1.08)	0.79 (0.67-0.95)	0.84 (0.71-0.98)	0.001***
GFR, ml/min/1.73m ² , mean $\pm$ SD	73.2 $\pm$ 28.2	82.8 $\pm$ 22.5	81.9 $\pm$ 18.06	0.017*

$p<0.05$ was considered statistically significant. *: Analysis of Variance; **: Chi-square test; ***: Kruskal-Wallis test. Values are presented as mean $\pm$ SD for variables analyzed with Analysis of Variance (*) and as median (interquartile range) for variables analyzed with the Kruskal-Wallis test (***). PE: Pulmonary embolism, CA-PE: Cancer-associated pulmonary embolism, SII: Systemic Immune-Inflammation Index, RDW: Red cell distribution width, LDH: Lactate dehydrogenase, CRP: C-reactive protein, CK-MB: Creatine kinase-MB, BNP: B-type natriuretic peptide, GFR: Glomerular filtration rate, SD: Standard deviation, Min: Minute

but no significant difference was observed between the PE and CA-PE groups. BNP and CK-MB levels did not differ significantly among the three groups.

Risk Stratification and Clinical Scores

Clinical probability, severity and prognostic scores are summarized in **Table 4**. The CA-PE group had significantly higher Wells scores (median 7.0 [IQR 5.5-7.0] vs. 6.0 [IQR 4.5-7.5], $p=0.011$) and Modified Geneva scores (8.0 [7.0-13.0] vs. 6.0 [5.0-10.0], $p<0.001$) compared to the PE group. When categorized by Wells score, a significantly higher proportion of CA-PE patients (56.3%) had high probability scores (>6) compared to PE patients (27.5%) ($p<0.001$).

Table 4. Clinical probability, severity and prognostic scores in the PE and CA-PE groups

	PE (n=80)	CA-PE (n=80)	P
Clinical probability			
Wells score, median (IQR)	6.0 (4.5-7.5)	7.0 (5.5-7.0)	0.011***
Wells score >6 (high probability), n (%)	22 (27.5)	45 (56.3)	$<0.001^*$
Modified Geneva score, median (IQR)	6.0 (5.0-10.0)	8.0 (7.0-13.0)	$<0.001^{***}$
Severity and prognostic scores			
PESI score, median (IQR)	100.0 (72.0-131.5)	135.5 (113.0-158.2)	$<0.001^{***}$
PESI class III-V (>85), n (%)	48 (60.0)	79 (98.8)	$<0.001^*$
Bova score, median (IQR)	1.0 (0.0-2.2)	1.0 (0.0-2.0)	0.952***
Bova score >4 , n (%)	7 (8.8)	5 (6.3)	0.548*
Clinical risk class, n (%)			$<0.001^*$
High risk (massive)	6 (7.5)	6 (7.5)	
Intermediate risk (submassive)	52 (65.0)	73 (91.3)	
Low risk (non-massive)	22 (27.5)	1 (1.3)	
Cancer-specific scores (CA-PE group only)			
Khorana score, mean $\pm$ SD	-	1.4 $\pm$ 1.0	-
Khorana score ≥ 3 (high risk), n (%)	-	12 (15.0)	-
Pompe-C score, %, mean $\pm$ SD	-	31.5 $\pm$ 22.4	-
30-day mortality score, mean $\pm$ SD	-	5.1 $\pm$ 2.0	-
Modified Glasgow Prognostic Score, mean $\pm$ SD	-	1.4 $\pm$ 0.7	-

$p<0.05$ was considered statistically significant. *: Chi-square test; **: Mann-Whitney U test. PE: Pulmonary embolism, CA-PE: Cancer-associated pulmonary embolism, PESI: Pulmonary Embolism Severity Index, IQR: Interquartile range, SD: Standard deviation

Among cancer patients, the mean Khorana score was 1.4 ± 1.0 , with 12 patients (15%) classified as high risk (score ≥ 3). The PESI score was significantly higher in the CA-PE group (median 135.5, IQR 113.0-158.2) compared to the PE group (100.0, IQR 72.0-131.5) ($p<0.001$). Additionally, a significantly higher proportion of CA-PE patients (98.8%) had high-risk PESI scores (>85) compared to PE patients (60%) ($p<0.001$). However, Bova scores were similar between the two groups ($p=0.95$), as was the proportion of patients with high-risk Bova scores (>4) ($p=0.548$). According to the guideline-based clinical classification, the proportion of high-risk PE was

identical in both groups (7.5%), whereas intermediate-risk PE was more frequent (91.3% vs. 65.0%) and low-risk PE less frequent (1.3% vs. 27.5%) in the CA-PE group ($p<0.001$).

In the CA-PE group, the mean Pompe-C score was $31.5\pm 22.4\%$, the mean 30-day mortality score was 5.1 ± 2.01 , and the mean Modified Glasgow Prognostic Score was 1.4 ± 0.7 . Interestingly, PESI scores differed across cancer stages ($p=0.033$), with the lowest values in patients with metastatic disease (130.7 ± 26.6) and the highest in those with locally advanced disease (148.6 ± 31.5).

Echocardiographic and Radiological Findings

Echocardiography was performed in 168 patients (70%): 78 in the PE group, 69 in the CA-PE group and 21 in the control group. Right ventricular dysfunction was detected in 44 of these patients (26.2%). Pulmonary artery pressure (PAP) could be measured in 103 patients (median 35.0 mmHg, IQR 25.0-49.5), 79 of whom (76.7%) had a PAP of ≥ 25 mmHg. Lower-extremity Doppler ultrasonography was performed in 103 patients, all of whom were in the PE groups (59 in the PE group and 44 in the CA-PE group), and deep vein thrombosis was detected in 48 of them (46.6%). Both examinations were performed in 100 patients (58 in the PE group and 42 in the CA-PE group).

Among the 150 patients diagnosed by CTPA, bilateral emboli were found in 97 patients (64.7%) and unilateral in 53 patients (35.3%). Emboli were more frequently detected in the right pulmonary arterial system ($n=133$, 88.7%) than in the left ($n=114$, 76.0%). The pulmonary trunk was numerically more commonly affected in the CA-PE group (10.5%) than in the PE group (2.7%), but the difference was not statistically significant ($p=0.098$). Other locations showed similar distributions between groups (**Table 5**).

Among patients who underwent echocardiography, right ventricular dysfunction was numerically more frequent in the PE group (34.6%) than in the CA-PE group (23.2%), but the difference was not statistically significant ($p=0.129$). Among patients with measured PAP, the proportion with a PAP of ≥ 25 mmHg was similar in the two groups (76.4% vs. 75.0%, $p=0.878$).

Treatment and Outcomes

Treatment characteristics and outcomes are summarized in **Table 6**. Low molecular weight heparin was the most common initial treatment in both the PE (95%) and CA-PE (100%) groups. For long-term anticoagulation, DOAC were more frequently used in the PE group (42.5%) compared to the CA-PE group (23.8%) ($p=0.012$). Similarly, vitamin K antagonists were more commonly prescribed in the PE group (30%) than in the CA-PE group (5%) ($p<0.001$). Thrombolytic therapy was administered to similar proportions of patients in the PE (6.3%) and CA-PE (7.5%) groups ($p=0.755$).

Hospital length of stay did not differ significantly between the PE (median 6.0 days, IQR 4.0-8.2) and CA-PE (7.5 days, IQR 4.0-12.0) groups ($p=0.105$). ICU admission was required in 13 (16.3%) patients in the PE group and 10 (12.5%) in the CA-PE group ($p=0.499$); among these patients, ICU stay was longer in the CA-PE group (median 5.0 days, IQR 4.0-14.2) than in the PE group (3.0 days, IQR 2.0-4.0) ($p=0.011$).

Table 5. Echocardiographic and radiological characteristics of PE patient groups

	PE, n (%)	CA-PE, n (%)	P
DVT†	23 (39.0)	25 (56.8)	0.073*
Unilateral	19 (32.2)	19 (43.2)	0.253*
Bilateral	4 (6.8)	6 (13.6)	0.319**
Echocardiography findings			
Right ventricular dysfunction‡, n (%)	27 (34.6)	16 (23.2)	0.129*
PAP§, mmHg, median (IQR)	40.0 (26.0-53.0)	34.0 (24.5-47.2)	0.258***
PAP ≥25 mmHg§	42 (76.4)	30 (75.0)	0.878*
Embolism Location¶			
Unilateral	23 (31.1)	30 (39.5)	0.282*
Bilateral	51 (68.9)	46 (60.5)	0.282*
Right pulmonary arterial system	65 (87.8)	68 (89.5)	0.752*
Left pulmonary arterial system	60 (81.1)	54 (71.1)	0.150*
Pulmonary trunk	2 (2.7)	8 (10.5)	0.098**
Main pulmonary artery	36 (48.6)	35 (46.1)	0.750*
Lobar artery	21 (28.4)	20 (26.3)	0.777*
Segmental artery	9 (12.2)	6 (7.9)	0.384*
Subsegmental artery	6 (8.1)	7 (9.2)	0.810*
Pulmonary infarction	6 (8.1)	2 (2.6)	0.164**

p<0.05 was considered statistically significant. *: Chi-square test; **: Fisher's exact test; ***: Mann-Whitney U test. Percentages were calculated among patients with the relevant examination: †lower-extremity Doppler ultrasonography (PE, n=59; CA-PE, n=44); ‡echocardiography (n=78; n=69); §measured PAP (n=55; n=40); ¶diagnosis by CTPA (n=74; n=76). PE: Pulmonary embolism, CA-PE: Cancer-associated pulmonary embolism, DVT: Deep vein thrombosis, PAP: Pulmonary artery pressure, CTPA: Computed tomography pulmonary angiography, IQR: Interquartile range, SD: Standard deviation

Table 6. Treatment characteristics and outcomes in the PE and CA-PE groups

	PE (n=80)	CA-PE (n=80)	P
Treatment			
Initial LMWH, n (%)	76 (95.0)	80 (100)	0.120**
Thrombolytic therapy, n (%)	5 (6.3)	6 (7.5)	0.755*
Long-term DOAC, n (%)	34 (42.5)	19 (23.8)	0.012*
Long-term VKA, n (%)	24 (30.0)	4 (5.0)	<0.001*
Hospital course			
Hospital length of stay, days, median (IQR)	6.0 (4.0-8.2)	7.5 (4.0-12.0)	0.105***
ICU admission, n (%)	13 (16.3)	10 (12.5)	0.499*
ICU length of stay, days, median (IQR)†	3.0 (2.0-4.0)	5.0 (4.0-14.2)	0.011***
All-cause mortality			
30-day, n (%)	6 (7.5)	13 (16.3)	0.087*
3-month, n (%)	10 (12.5)	30 (37.5)	<0.001*
1-year, n (%)	13 (16.3)	50 (62.5)	<0.001*

p<0.05 was considered statistically significant. *: Chi-square test; **: Fisher's exact test; ***: Mann-Whitney U test. †Among patients admitted to the ICU (PE, n=13; CA-PE, n=10). PE: Pulmonary embolism, CA-PE: Cancer-associated pulmonary embolism, LMWH: Low-molecular-weight heparin, DOAC: Direct oral anticoagulant, VKA: Vitamin K antagonist, ICU: Intensive care unit, IQR: Interquartile range

Regarding mortality outcomes, 30-day mortality rates were not significantly different between the PE (7.5%) and CA-PE (16.3%) groups ($p=0.087$). However, both 3-month mortality (37.5% vs. 12.5%, $p<0.001$) and 1-year mortality (62.5% vs. 16.3%, $p<0.001$) were significantly higher in the CA-PE group compared to the PE group.

DISCUSSION

This study compared the clinical features, inflammatory markers, severity scores, and outcomes of PE in patients with and without malignancy. Unlike previous studies comparing cancer patients with and without VTE, our direct comparison of CA-PE and PE without malignancy highlights how cancer influences PE presentation, severity and outcomes.

CA-PE patients had higher inflammatory indices and clinical risk scores, whereas clinical presentation and markers of embolism severity were similar. Although 30-day mortality was similar, long-term all-cause mortality was higher in the CA-PE group; because cause-specific mortality was not evaluated, this difference cannot be attributed to a specific cause.

Lung and brain cancers were the most common malignancies in the CA-PE group, in line with studies identifying these as high-risk malignancies.^{1,10} Most CA-PE cases occurred within the first year after cancer diagnosis, consistent with the known timing of peak VTE risk.¹¹

Presenting symptoms were generally similar between the two PE groups, with dyspnea being predominant. Lin et al.¹² reported that cancer patients with PE were less likely to present with chest pain; in our cohort, chest pain was numerically less frequent in the CA-PE group, although the difference did not reach statistical significance. Oxygen saturation was lower in the CA-PE group, which may reflect more pronounced respiratory compromise during the PE event; however, pulmonary involvement by the underlying malignancy may also have contributed.

The higher Wells and Modified Geneva scores in the CA-PE group are likely explained by the fact that both scoring systems assign points for malignancy, highlighting the need for cancer-specific risk assessment tools. The Khorana score classified only 15% of our CA-PE cohort as high-risk, indicating its limited utility. This is consistent with other studies reporting its low sensitivity (40%) but high specificity (88%).⁸

A notable finding of our study was the higher NLR, MLR and PLR values in the CA-PE group compared with the PE group. Several studies have shown that elevated NLR and PLR are associated with increased VTE risk in cancer patients,^{13,14} and Ferroni et al.¹⁵ found that high NLR and PLR values were associated with an approximately twofold increased risk of VTE in ambulatory cancer patients. Nevertheless, these findings should be interpreted with caution. Inflammatory indices derived from the complete blood count are not specific to thrombosis and may be influenced by the malignancy itself, tumor burden, chemotherapy- or radiotherapy-related myelosuppression, corticosteroid use, infections and other concomitant inflammatory conditions; notably, two-thirds of our CA-PE patients were receiving active chemotherapy. In addition, because these indices were measured only at the time of PE diagnosis, our data cannot determine whether elevated inflammatory indices contribute to thrombosis or merely reflect the underlying malignancy. Our findings are therefore consistent with, but do not prove, a role of inflammation in cancer-associated thrombosis.

Despite higher PESI scores in the CA-PE group, right ventricular dysfunction on echocardiography was not more frequent in these patients; it was even numerically less frequent, although this difference was not statistically significant. Similarly, the higher proportion of intermediate-risk PE in the CA-PE group probably reflects the contribution of PESI to guideline-based risk classification rather than a true difference in hemodynamic severity. This discrepancy between risk scores and cardiac findings suggests that the PESI score may overestimate PE severity in cancer patients, as it assigns points for malignancy without considering cancer type, stage or treatment status. Li et al.¹⁶ compared different clinical prognostic scores in patients with PE and active cancer and concluded that existing scoring systems have limited value in predicting outcomes in this population.

Pulmonary trunk embolism was numerically more frequent in the CA-PE group, although the difference was not statistically significant. A higher risk of central PE in cancer patients has also been reported by Karippot et al.¹⁷ Whether this reflects cancer-specific procoagulant mechanisms, such as the expression of tissue factor and cancer procoagulant and the release of procoagulant microparticles,⁶ remains speculative and requires confirmation in larger studies.

The treatment approach differed between the groups. While low molecular weight heparin (LMWH) was the initial treatment in both groups, DOACs and VKAs were more frequently used for long-term treatment in the PE group. This practice aligns with guidelines recommending LMWH for cancer patients.¹⁸ However, recent studies have shown the effectiveness and safety of DOACs in cancer patients, which might influence future practice.¹⁹

The most striking difference between the groups was in long-term outcomes. While 30-day mortality did not differ significantly between the CA-PE and PE groups, both 3-month and 1-year mortality were markedly higher in the CA-PE group. This finding is consistent with previous studies showing that cancer patients with VTE have a poorer overall prognosis; Sorensen et al.⁴ reported a one-year survival rate of only 12% in cancer patients diagnosed with VTE compared with 36% in cancer patients without VTE. However, as cause-specific mortality was not evaluated in our study, we cannot determine whether the excess long-term mortality was due to cancer progression, recurrent VTE, bleeding or other causes. Our results indicate that, while short-term mortality was similar in both groups, long-term all-cause mortality was higher in patients with malignancy.

Interestingly, the PESI score was lowest in metastatic cancer patients compared to those with locally advanced disease. This counterintuitive finding might be related to the age distribution in these subgroups or other factors not captured by the PESI score, further highlighting the limitations of existing risk assessment tools in cancer patients. Au et al.²⁰ similarly reported that cancer stage was not a significant predictor of short-term outcomes in cancer patients with PE.

Limitations

Our study has several limitations. First, its retrospective design may have led to incomplete reporting of symptoms and misclassification of outcomes. Second, the inclusion of

only hospitalized patients might have introduced selection bias, as patients with milder symptoms treated in outpatient settings were not included. Third, to obtain groups of equal size, 80 patients were randomly selected for each group from the eligible population; although random selection limits deliberate selection, the equal group sizes do not reflect the true relative frequency of PE with and without malignancy at our center, and selection bias cannot be completely excluded. Fourth, the heterogeneity of malignancy types and treatments in the CA-PE group might have obscured specific associations between certain cancer types and PE characteristics. Fifth, cause-specific mortality was not evaluated; therefore, the higher long-term mortality in the CA-PE group cannot be attributed to cancer progression or to PE itself. Sixth, inflammatory indices may have been influenced by tumor burden, cancer treatment and concomitant inflammatory conditions, which could not be fully accounted for. Seventh, echocardiography, PAP measurement and lower-extremity Doppler ultrasonography were not performed in all patients, and right ventricular function was assessed qualitatively, which might have varied between observers. Eighth, inherited thrombophilia was not screened systematically, and the contribution of genetic predisposition could not be assessed. Ninth, our dataset did not distinguish between symptomatic and incidentally detected (asymptomatic) PE, which is common in oncology patients undergoing routine staging or surveillance imaging.²¹ Incidentally detected PE has been reported to be associated with less severe echocardiographic findings in some studies, and its inclusion in the CA-PE group may partly explain why right ventricular dysfunction was not more frequent despite higher risk scores in this group; future studies should record and analyze this distinction separately. Finally, our sample size, although comparable to previous studies in this field, may have limited the statistical power to detect smaller differences between groups.

CONCLUSION

In this study, PE in patients with malignancy was associated with higher inflammatory indices and higher malignancy-weighted risk scores, but not with worse echocardiographic indicators of PE severity or higher 30-day mortality compared with PE in patients without malignancy. Long-term all-cause mortality, however, was substantially higher in patients with malignancy. These findings suggest that commonly used risk scores may overestimate PE severity in cancer patients, and they support the development of cancer-specific risk stratification tools and close long-term follow-up of these patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Non-interventional Researches Ethics Committee of Bezmialem Vakıf University (Date: 26.07.2023, Decision No: 2023/232).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved

by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: DK, HO; Design: DK, HAB; Supervision: HAB; Data Collection and/or Processing: DK, HO; Analysis and/or Interpretation: HO, DK; Literature Review: DK; Writing Manuscript: DK, HO; Critical Review: HAB.

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Clinical characteristics and mortality risk factors in COVID-19 patients with pulmonary embolism

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ABSTRACT

Aims: To evaluate the clinical characteristics, radiological findings, and mortality-related factors in patients with COVID-19-associated pulmonary embolism (PE).

Methods: This multicenter retrospective cohort study analyzed data from 13 tertiary centers and included adult patients with molecularly confirmed SARS-CoV-2 infection and radiologically verified PE.

Results: A total of 112 patients were included (mean age: 59.9±14.1 years), of whom 50% had severe pneumonia. PE and COVID-19 were diagnosed simultaneously in 29.5% of cases. The median interval between COVID-19 diagnosis and PE development was 6 days. Despite standard or intermediate-dose thromboprophylaxis, PE occurred in 42.9% of patients. Computed tomography pulmonary angiography demonstrated predominantly peripheral embolic involvement (58.0%). According to early mortality risk stratification, 5.4% of patients were classified as high risk and 19.6% as intermediate-high risk. The in-hospital and 30-day mortality rates were 7.1% and 12.5%, respectively. Mortality was significantly associated with advanced age, comorbidities, severe pneumonia, thrombocytopenia, elevated lactate dehydrogenase and ferritin levels, high/intermediate-high risk classification, intensive care unit admission, and invasive mechanical ventilation. Multivariate logistic regression identified thrombocytopenia as an independent predictor of 30-day mortality (OR 10.11, 95% CI 1.49-68.92; p=0.01).

Conclusion: PE commonly develops during the early phase of COVID-19 and may occur despite thromboprophylaxis. Early recognition and individualized risk-adapted.

Keywords: COVID-19, pulmonary embolism, biomarkers, thrombosis, mortality

INTRODUCTION

The emergence of Coronavirus Disease 2019 (COVID-19) in early 2020 precipitated an unprecedented global health crisis marked by rapid transmissibility and considerable mortality worldwide.¹ Beyond its primary respiratory manifestations, COVID-19 has been increasingly recognized as a multisystem disorder associated with significant thromboinflammatory complications. In particular, critically ill patients demonstrate a markedly increased predisposition

to venous thromboembolism (VTE). Growing clinical evidence has consistently shown that disease severity is strongly associated with an elevated risk of acute thrombotic events, including pulmonary embolism (PE) and deep vein thrombosis.²⁻⁴

The pathophysiological mechanisms underlying VTE in COVID-19 are complex and multifactorial, encompassing

all major components of Virchow's triad: endothelial injury, hypercoagulability, and circulatory stasis. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly infects vascular endothelial cells, leading to diffuse endothelial dysfunction and promoting both localized and systemic thrombotic responses.⁵ The accompanying inflammatory and procoagulant state is characterized by elevated levels of fibrinogen, fibrin degradation products, fibrin, and D-dimer. In addition, direct viral cytopathic injury together with an exaggerated cytokine-mediated inflammatory response is believed to trigger pathological platelet activation, further amplifying the underlying coagulopathic process.^{6,7} Prolonged immobilization, particularly among critically ill and intensive care unit patients, contributes to venous stasis and further increases thrombotic risk, thereby completing the classical prothrombotic framework described by Virchow's triad.

Histopathological examinations and autopsy studies of patients who died from COVID-19 have consistently demonstrated a high prevalence of diffuse pulmonary microthrombi.⁸ These pathological findings have led to the growing recognition that the development of acute respiratory distress syndrome (ARDS), the most severe and life-threatening manifestation of COVID-19, is closely linked to profound pulmonary endothelial injury and dysregulated intravascular coagulation. Accordingly, the pulmonary vascular pathology observed in severe COVID-19 is increasingly considered distinct from classical ARDS and has been described as pulmonary intravascular coagulopathy (PIC) or localized pulmonary thrombosis.^{9,10}

This concept is further supported by clinical evidence demonstrating that the incidence of PE in patients with COVID-19 exceeds that of concomitant deep vein thrombosis (DVT).¹¹ This epidemiological pattern suggests that thrombotic events associated with COVID-19 may differ from the traditional thromboembolic pathway of systemic VTE and instead reflect a process of in situ pulmonary immunothrombosis within the pulmonary vasculature. Collectively, these findings contribute to a better understanding of the distinct pathophysiology underlying COVID-19-associated ARDS and may guide the development of targeted therapeutic strategies aimed at mitigating the localized thromboinflammatory response.

Clinical studies evaluating COVID-19 patients with thromboembolic complications have consistently demonstrated a strong association between PE and increased mortality.¹² These findings suggest that thrombotic events contribute substantially to disease progression and adverse clinical outcomes, highlighting the critical importance of early recognition and appropriate anticoagulation strategies in high-risk patients. Consequently, several national and international guidelines recommend routine pharmacological VTE prophylaxis for hospitalized patients with COVID-19, particularly in those with severe disease or additional thrombotic risk factors.¹³ These recommendations are supported by accumulating evidence indicating that thrombotic risk increases in parallel with the severity of respiratory failure, emphasizing the central role of optimized antithrombotic management in reducing VTE-related morbidity and improving survival.

Nevertheless, despite the widespread adoption of standardized thromboprophylaxis protocols, acute PE remains a frequent, severe, and potentially fatal complication of COVID-19. Although existing studies have associated PE with increased mortality, detailed evidence delineating the specific demographic, biochemical, and clinical profiles that predispose patients to thromboembolic deterioration remains limited. Moreover, there is a relative paucity of data specifically addressing multivariable predictors of mortality within this distinct co-pathological population.

To address this gap, the present study was designed to provide a comprehensive, multidimensional assessment of the clinical characteristics of patients with COVID-19 pneumonia complicated by radiologically confirmed PE. The primary aim was to identify independent determinants of adverse outcomes through systematic evaluation of baseline demographic features, laboratory parameters, and indicators of disease severity. This approach seeks to enhance current understanding of the prognostic significance of PE in COVID-19 and to inform more precise, risk-adapted therapeutic strategies aimed at improving survival.

METHODS

This study was conducted with the approval of the Non-interventional Ethics Committee of Sakarya University (Date: 29.01.2021, Decision No: E-71522473-050.01.04-6095). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This multicenter retrospective cohort study pooled data from 13 tertiary medical centers following approval by the national Ministry of Health and the administrative boards of all participating institutions. The study included adult patients with real-time polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection who developed acute PE either at initial presentation or within 45 days of COVID-19 diagnosis, between April 1, 2020, and February 1, 2021. Pediatric patients (<18 years), pregnant individuals, and those with a prior history of thromboembolic disease were excluded from the analysis. The 45-day interval was selected as a predefined inclusion window to capture PE events occurring during the acute and early post-acute phases of COVID-19. The requirement for written informed consent was waived by the Institutional Review Board due to the retrospective nature of the study. A diagnosis of COVID-19 was established based on positive real-time polymerase chain reaction (RT-PCR) results obtained from oro-nasopharyngeal swab samples, in conjunction with compatible clinical manifestations and characteristic radiological findings consistent with viral pneumonia. The definitive diagnosis of pulmonary thromboembolism (PE) was confirmed exclusively by computed tomography pulmonary angiography (CTPA). This imaging modality was performed in patients presenting with clinical suspicion of thromboembolic disease at hospital admission or in those who developed unexplained acute cardiopulmonary deterioration during hospitalization. This diagnostic approach enabled accurate and comprehensive characterization of both the primary viral infection and secondary thromboembolic complications. Electronic medical records and paper-based files were systematically reviewed to collect data on demographic characteristics,

clinical features, laboratory parameters, radiological findings, therapeutic interventions, and survival outcomes.

In accordance with national COVID-19 management guidelines issued by the Ministry of Health, pharmacological thromboprophylaxis in patients with severe disease consisted of low-molecular-weight heparin (LMWH; enoxaparin 40 mg subcutaneously twice daily) or unfractionated heparin (UFH; 7,500 U subcutaneously twice daily). In patients with non-severe disease, standard prophylaxis was administered as enoxaparin 40 mg subcutaneously once daily.¹³

Risk stratification for PE severity and assessment of early mortality risk (defined as in-hospital or 30-day all-cause mortality) were performed in accordance with the 2019 European Society of Cardiology/European Respiratory Society (ESC/ERS) Guidelines for the diagnosis and management of acute PE. The primary outcome was 30-day all-cause mortality, defined as death from any cause within 30 days of PE diagnosis, with the date of diagnosis serving as the starting point for follow-up. Clinical severity of COVID-19 pneumonia was classified according to national protocols; severe disease was defined as peripheral oxygen saturation (SpO₂) ≤90% on room air, respiratory rate >30 breaths per minute, and radiological evidence of bilateral diffuse pulmonary infiltrates.¹⁴ Secondary macrophage activation syndrome (MAS) was diagnosed after exclusion of bacterial superinfection, based on a characteristic clinical and laboratory constellation including persistent fever, markedly elevated C-reactive protein (CRP), serum ferritin levels exceeding 700 µg/L, increased D-dimer concentrations, absolute lymphopenia, thrombocytopenia, relative neutrophilia, and progressive hepatic dysfunction. Baseline laboratory parameters were obtained from the measurements recorded at the time of PE diagnosis. For baseline laboratory definitions, absolute lymphopenia was defined as a lymphocyte count <800/µL, while thrombocytopenia was defined as a platelet count <150×10⁹/L. Pathological elevations in lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), ferritin, blood urea nitrogen, and creatinine were defined as values exceeding the upper limits of normal according to the reference ranges of the local laboratory.

Statistical Analysis

Data management and statistical analyses were performed using SPSS software (version 20.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the study variables. Categorical variables were expressed as frequencies and percentages, whereas continuous variables were presented as mean±standard deviation (SD) or median, as appropriate. Comparisons of categorical variables between groups were conducted using the Chi-square test. The normality of continuous variables was assessed using the Shapiro-Wilk test. For non-normally distributed variables, between-group comparisons were performed using the Mann-Whitney U test. Variables that demonstrated statistical significance in univariate analyses were subsequently entered into multivariate regression models to identify independent predictors of mortality. Multivariable logistic regression analysis was performed to evaluate factors associated with 30-day all-cause mortality. The model included six variables: age, comorbidity status, lymphopenia, thrombocytopenia, ferritin, and LDH. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Given the limited number of mortality events (n=14) relative to the number of variables included, the regression findings were interpreted cautiously because of the potential risk of overfitting. A two-tailed p-value <0.05 was considered statistically significant. This analytical approach provided a robust framework for evaluating prognostic determinants of survival in the study population.

RESULTS

During the study period, acute PE was radiologically confirmed in 112 patients with COVID-19. Of these, 74 (66%) were male and 38 (34%) were female, with a mean age of 59.9±14 years. A severe pneumonia phenotype was present in 56 patients (50%), while secondary MAS was identified in 18 patients (16.1%). Detailed baseline demographic, clinical, and biochemical characteristics are presented in **Table 1**.

The mean interval between COVID-19 diagnosis and PE detection was 8.8±9.4 days, with a median of 6 days. Synchronous presentation of COVID-19 pneumonia and PE at admission was observed in 33 patients (29.5%). Notably,

Table 1. Clinical features of patients with COVID-19 pneumonia complicated by pulmonary embolism

	Total (n= 112)	No mortality (n=98)	Mortality (n=14)	p
Age (n, years)	59.9 (±14.1)	58.9 (±14.1)	67.3 (±12.0)	0.039*
Male gender (n,%)	74 (66%)	64 (65.3%)	10 (71.4%)	0.769
Occurrence day of embolism (±SD)	8.8 (±9.4)	9.0 (±9.8)	7.14 (±5.9)	0.986
Concurrent embolism diagnosis with COVID-19 (n,%)	33 (29.4%)	31 (31.6%)	2 (14.3%)	0.226
Presence of additional disease (n,%)	68 (60.7%)	56 (57.1%)	12 (85.7%)	0.041*
Presence of severe pneumonia (n,%)	56 (50%)	44 (44.9%)	12 (85.7%)	0.004*
Multiple pneumonia focus at CT (n,%)	94 (83.9%)	81 (82.7%)	13 (92.9%)	0.461
MAS diagnosis (n,%)	18 (16%)	14 (14.3%)	4 (28.6%)	0.236
Steroid use (n,%)	51 (45.5%)	42 (42.9%)	9 (64.3%)	0.132
High and moderate-high risk of early mortality from pulmonary embolism (n,%)	28 (25%)	17 (17.3%)	11 (78.6%)	0.000*
Thrombolytic use (n,%)	7 (6.3%)	3 (3%)	4 (28.6%)	0.004*
Intensive care hospitalization (n,%)	26 (23.2%)	17 (17.3%)	9 (64.3%)	0.01*
Intubation requirement (n,%)	11 (9.8%)	2 (2%)	9 (64.3%)	0.000*

*p<0.05. SD: Standard deviation, CT: Computed Tomography, MAS: Macrophage activation syndrome

PE developed despite standard thromboprophylaxis in 48 patients (42.9%). CTPA revealed predominantly peripheral embolic involvement (segmental or subsegmental, unilateral or bilateral) in 65 patients (58%). According to early mortality risk stratification, 6 patients (5.4%) were classified as high risk, 22 (19.6%) as intermediate-high risk, 24 (21.4%) as intermediate-low risk, and 60 (53.6%) as low risk. Anticoagulation therapy included low-molecular-weight heparin in 88 patients (78.6%), unfractionated heparin in 16 (14.3%), and direct oral anticoagulants in 8 (7.1%). Systemic thrombolysis was administered to 7 patients. Minor bleeding occurred in one patient, while major bleeding was observed in two, including one case following thrombolysis. Intensive care unit admission was required in 26 patients, and 11 patients underwent invasive mechanical ventilation. In-hospital mortality was 7.1% (n=8), while 30-day all-cause mortality was 12.5% (n=14). Exploratory analyses identified advanced age, comorbidities, severe pneumonia, thrombocytopenia, elevated LDH and ferritin levels, higher early mortality risk class, thrombolysis, ICU admission, and mechanical ventilation as significant correlates of 30-day mortality. Although D-dimer levels were higher in non-survivors, the difference was not statistically significant (p=0.33). Similarly, CRP levels, acute renal dysfunction, and hepatic impairment were not significantly associated with mortality (Table 2).

The multivariable logistic regression model included age, comorbidity status, lymphopenia, thrombocytopenia, ferritin, and LDH. Thrombocytopenia was significantly associated with 30-day mortality (OR 10.11, 95% CI 1.485-68.916; p=0.01). In contrast, age (p=0.14), comorbidity status (p=0.99), lymphopenia (p=0.72), ferritin (p=0.82), and LDH (p=0.29) were not significantly associated with mortality in the multivariable model.

DISCUSSION

The present investigation focused on the clinical trajectories of patients with COVID-19 pneumonia who concurrently manifested acute PE, demonstrating an in-hospital mortality rate of 7.1% and an overall 30-day mortality rate of 12.5%. Survival deficits within this cohort were significantly linked to advanced age, preexisting comorbid burdens, severe pneumonia phenotypes, absolute thrombocytopenia, and pathological elevations in serum LDH and ferritin concentrations. Additionally, adverse outcomes closely

correlated with high or intermediate-high early mortality risk classifications, the administration of systemic thrombolysis, intensive care unit escalation, and the requirement for endotracheal intubation.

When contextualized within the regional literature, a large-scale study examining 1,500 hospitalized COVID-19 patients in Türkiye documented a baseline in-hospital mortality rate of 4.5%.¹⁵ In contrast, specific evaluations restricted to COVID-19 pneumonia populations complicated by PE reported a higher in-hospital mortality rate of 8.7%, while a broad meta-analysis estimated pooled mortality figures as high as 45.1% among co-pathological cohorts.^{16,17} The survival data from our study occupies an intermediate position; the recorded mortality was expectedly higher than that traditionally observed in isolated COVID-19 pneumonia lacking embolic complications, yet it remained notably lower than the fatality rates frequently described in historical datasets for COVID-19 patients suffering from concurrent PE.

In exactly 33 instances, acute PE was identified synchronously alongside the initial presentation of COVID-19, underscoring the immediate and aggressive thrombotic drive characterizing this viral syndrome. The temporal analysis showed that the mean interval spanning from the initial molecular detection of COVID-19 to the objective confirmation of PE was 8.8 days, with a median onset occurring at the 6-day mark. Crucially, embolic breakthroughs manifested in 42.9% of our patients despite the active administration of standard-dose or intermediate-dose LMWH prophylaxis, illustrating the profound clinical difficulties encountered when attempting to suppress the hypercoagulable state in this population.

While a consensus across multiple national and international clinical guidelines rigorously dictates the universal implementation of pharmacological thromboprophylaxis for hospitalized COVID-19 pneumonia patients to reduce VTE-driven morbidity,^{13,18-22} thromboembolic failures persist as a major clinical hurdle. This vulnerability is especially pronounced among critically ill individuals, in whom an intense systemic inflammatory response and secondary hypercoagulability frequently override conventional prophylactic measures.²¹ Supporting this observation, a comprehensive meta-analysis focusing on PE epidemiology during the pandemic documented a pooled prevalence of 18.6% among patients managed with standard

Table 2. Laboratory parameters in COVID-19 pneumonia patients with pulmonary embolism

	Total		No mortality		Mortality		p
	n		n		n		
D-dimer level during embolism (µg/L)	101	4408.2(±5443)	89	4027.5(±4950)	12	7231.6(±7967)	0.337
CRP level (n/ mg/L)	109	82.2(±71.3)	95	80.1(±72.9)	14	96.8(±59.2)	0.182
Lymphopenia (n,%)	106	24 (22.6%)	92	20 (21.7%)	14	4 (28.6%)	0.516
Thrombocytopenia (n,%)	112	17 (15.2%)	98	12 (12.2%)	14	5 (35.7%)	0.038*
High ferritin level (n,%)	101	51 (50.5%)	87	40 (46%)	14	11 (78.6%)	0.024*
High LDH level (n,%)	93	66 (71%)	82	57 (69.5%)	11	11 (100%)	0.033*
Liver dysfunction (n,%)	111	29 (26.1%)	93	24 (25.8%)	14	5 (35.7%)	0.521
Kidney dysfunction (n,%)	112	18 (16%)	98	14 (14.3%)	14	4 (28.6%)	0.236

*p<0.05. D-dimer: Fibrin degradation product, CRP: C-reactive protein, Lymphopenia: Decreased lymphocyte count, Thrombocytopenia: Decreased platelet count, Ferritin: Iron-storage protein, LDH: Lactate dehydrogenase

thromboprophylaxis, which altered minimally to 17.3% in cohorts receiving mixed-dose prophylactic strategies.¹²

Although escalating to intermediate-dose antithrombotic regimens succeeds in lowering overall VTE incidence, it concurrently inflates the hazard of hemorrhagic complications. This trade-off was highlighted in another meta-analysis that reported a 3.9% incidence of major bleeding events, noting that both moderate and full-intensity therapeutic dosing schemes were independently tied to escalated bleeding risks.²² Collectively, these dual risks underscore the intricate therapeutic tightrope clinicians must walk when managing COVID-19-associated coagulopathy. Refining preventative antithrombotic frameworks thus demands a highly individualized approach that carefully balances a patient's baseline thrombotic predisposition against their specific hemorrhagic risks, factoring in acute physiological severity and emerging clinical trial data. Consequently, prospective investigations remain vital to establishing optimized prophylactic dosing architectures capable of suppressing embolic breakthroughs without inducing prohibitive bleeding penalties.

The development of severe pneumonia and subsequent hypoxemic respiratory failure are profoundly coupled with escalated mortality rates in the context of COVID-19.²³ Consistent with this pathophysiological link, Jevnikar and colleagues²⁴ identified a heightened frequency of acute PE episodes specifically among individuals presenting with severe hypoxemia. In perfect agreement, our data demonstrates that patients suffering from severe pneumonia experienced significantly higher mortality rates, a clinical decline predominantly driven by profound hypoxemic insult rather than the literal geometric extent of radiological involvement, which failed to demonstrate a significant association with survival outcomes.

Biochemical monitoring within our complete cohort revealed an overall mean D-dimer concentration of 4.408 µg/L, which escalated to a mean of 7.231 µg/L among the deceased subset. For context, historical datasets have reported distinct D-dimer profiles, showcasing means of 3.519 µg/L in patients with confirmed PE compared to 1.371 µg/L in those free of embolic complications.¹⁶ The clinical utility of up-regulated D-dimer magnitudes as a primary predictor of elevated VTE risk during COVID-19 is well-established; notably, Cui et al.³ determined that a biomarker threshold of 1.500 µg/L yielded a sensitivity of 85% and a specificity of 88.5% when forecasting VTE among critically ill individuals in intensive care units. Furthermore, from the inception of the pandemic, marked D-dimer elevations have served as an adverse prognostic signature, with circulating concentrations exceeding 1.0 mg/L independently tied to an 18-fold increase in individual mortality risk.^{1,25} Within our current investigation, although the nonsurvivors exhibited substantially higher absolute D-dimer values than survivors, this mathematical divergence did not cross the threshold for formal statistical significance.

Regarding the anatomical distribution of the vascular occlusions, peripheral emboli were documented in 58% of our study population. A systematic review and meta-analysis of 26 studies involving 4,382 hospitalized patients with COVID-19 reported pooled incidences of peripheral and central pulmonary embolism of 12.3% and 6.8%, respectively.¹²

Prognostic indicators significantly tied to fatal outcomes within our cohort encompassed advanced age, preexisting comorbid conditions, severe pneumonia phenotypes, absolute thrombocytopenia, and pathological elevations in circulating LDH and ferritin. Additionally, markers of acute physiological stress, such as high or intermediate-high early mortality risk classifications, intensive care unit escalation, and the requirement for endotracheal intubation, were powerful correlates of mortality. To date, there remains a distinct void in the literature systematically tracking the multivariable determinants of mortality exclusively within a COVID-19 cohort complicated by acute PE. In our study, thrombocytopenia was significantly associated with 30-day mortality in the original multivariable logistic regression analysis. However, the limited number of mortality events (n=14) raises concerns regarding potential overfitting and the stability of this estimate. Thrombocytopenia may reflect the severity of the underlying COVID-19 infection rather than represent an independent prognostic factor specifically associated with pulmonary embolism. Previous evidence has demonstrated a significant association between thrombocytopenia and severe COVID-19, supporting this interpretation.²⁶ Larger prospective studies are needed to clarify its potential role in mortality risk assessment among patients with COVID-19-associated pulmonary embolism.

Nevertheless, historical data exploring non-selected COVID-19 cohorts has broadly validated advanced age, comorbid burdens, profound hypoxemia, thrombocytopenia, and upregulated D-dimer and LDH concentrations as independent predictors of clinical demise.^{27,28} Parallel to this, classical epidemiological research focusing on PE-related mortality outside the context of SARS-CoV-2 infection has consistently demonstrated a strong survival deficit linked to male gender, advanced age, underlying chronic illnesses, elevated D-dimer levels, acute renal impairment, and high early mortality risk stratifications.²⁹⁻³¹

Collectively, these overlapping clinical architectures highlight the highly complex, multifactorial nature of mortality risks within this specific co-pathological patient population. These insights strongly emphasize the critical necessity for heightened clinical vigilance, intensive biomarkers surveillance, and highly individualized, survival-directed therapeutic strategies designed to optimize patient outcomes.

Limitations

The present study has several limitations that should be acknowledged. Owing to its retrospective cohort design, the analysis is inherently subject to missing or incomplete clinical and laboratory data within electronic medical records, which may limit the granularity and completeness of the findings. In addition, the substantial overlap in clinical manifestations between severe COVID-19 pneumonia and acute PE may have introduced diagnostic challenges, potentially leading to under-recognition of embolic events, particularly in less severely ill patients who did not undergo routine or systematic imaging evaluation. Because our study included only patients with confirmed COVID-19-associated pulmonary embolism, the incidence or prevalence of PE in the overall COVID-19 population could not be determined. Furthermore, the absence of a comparison group without PE precluded assessment of the independent impact of PE on mortality.

To address these limitations, future prospective studies are warranted. Ideally, such investigations should include well-defined, parallel cohorts of COVID-19 patients with and without confirmed thromboembolic disease to more accurately quantify the independent impact of PE on survival. Furthermore, prospective designs would facilitate a more detailed characterization of the underlying pathophysiological mechanisms driving adverse outcomes in this high-risk population.

CONCLUSION

The majority of acute PE events in this cohort occurred during the early, hyperacute phase of COVID-19 symptom onset. This temporal clustering underscores the need for a high index of clinical suspicion and vigilant monitoring for even subtle signs of thromboembolic disease during this critical period. Importantly, the occurrence of PE despite ongoing thromboprophylaxis in a substantial proportion of patients indicates that standard prophylactic regimens may be insufficient to fully counteract the intense prothrombotic milieu associated with SARS-CoV-2 infection. This highlights the limitations of a uniform anticoagulation strategy in this population.

Given the complex interplay between thrombotic risk and bleeding potential in COVID-19 pneumonia, a more individualized, risk-adapted antithrombotic approach appears warranted. Such strategies may include selective escalation to intermediate or therapeutic-intensity anticoagulation in patients with high-risk clinical and laboratory profiles. Ultimately, close clinical surveillance and dynamic adjustment of anticoagulant therapy are essential to optimize survival while minimizing bleeding complications.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Non-interventional Ethics Committee of Sakarya University (Date: 29.01.2021, Decision No: E-71522473-050.01.04-6095).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Sleep-disordered breathing and nocturnal hypoxemia in patients followed for pulmonary hypertension

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ABSTRACT

Aims: To describe sleep-disordered breathing and nocturnal hypoxemia in patients followed for pulmonary hypertension (PH), and explore associations with cardiopulmonary characteristics.

Methods: This retrospective cross-sectional study examined 32 adults who underwent polysomnography (PSG) during PH care between August 2008 and September 2014. Detailed PSG data were available for 29 patients. The Apnea-Hypopnea Index (AHI) quantified respiratory events per hour of sleep. Nocturnal hypoxemia was defined as mean sleep oxygen saturation $\leq 88\%$, retaining the original definition. Mann-Whitney U and Fisher exact tests were used.

Results: Twenty-five patients (78.1%) were women; mean age was 58.3 ± 14.5 years. Among patients with PSG data, 20 (69.0%) had $AHI \geq 5/h$, 10 (34.5%) $AHI \geq 15/h$, and seven (24.1%) $AHI \geq 30/h$. Nocturnal hypoxemia occurred in 12 patients (41.4%) and was associated with a larger right ventricular diameter (median 4.05 vs 3.20 cm; $p=0.002$). Hypoxemia was more frequent in pulmonary arterial hypertension than other PH groups (66.7% vs 23.5%; $p=0.029$). Patients with $AHI \geq 15/h$ had higher body-mass index and lower minimum sleep oxygen saturation ($p=0.005$ and $p=0.029$).

Conclusion: In patients undergoing PSG during PH follow-up, sleep-disordered breathing affected approximately two-thirds and nocturnal hypoxemia two-fifths. Hypoxemia was associated with larger right ventricular diameter. These findings support considering nocturnal oxygenation alongside AHI in clinically selected patients, particularly those with right ventricular enlargement. Prospective studies should clarify whether hypoxemia predicts subsequent right ventricular remodeling.

Keywords: Hypertension, pulmonary, sleep apnea syndromes, hypoxia, polysomnography

INTRODUCTION

Pulmonary hypertension (PH) occurs in association with diverse cardiac, pulmonary, and vascular conditions and affects right heart structure and function. Assessment requires identification of the underlying cause and accompanying conditions that may influence symptoms and functional capacity.¹ Sleep-disordered breathing and impaired nocturnal oxygenation are among the conditions encountered in patients with PH.^{2,3}

The Apnea-Hypopnea Index (AHI), which quantifies respiratory event frequency during sleep, may not capture all aspects of nocturnal oxygenation. Patients with PH may have reduced nocturnal oxygen saturation in association with apneas and hypopneas or without a substantial respiratory event burden. Studies involving pulmonary arterial hypertension (PAH) and other PH groups have reported frequent sleep-related breathing abnormalities, although estimates vary with patient selection and definitions.²⁻⁵ Hypoxia can increase pulmonary vascular tone and right ventricular afterload, providing a physiological basis for examining nocturnal oxygenation in relation to right ventricular size.⁴

Recent studies have linked the duration and severity of nocturnal hypoxemia to pulmonary hemodynamics and right ventricular characteristics, mainly in selected populations with obstructive sleep apnea, PAH, or chronic thromboembolic pulmonary disease.⁶⁻⁸ The relationship between low mean sleep oxygen saturation and recorded right ventricular size in clinically selected patients spanning all PH groups is less well characterized. This study re-evaluated historical records of patients who underwent polysomnography (PSG) during PH follow-up to describe sleep-disordered breathing and nocturnal hypoxemia and explore their cardiopulmonary associations. Daytime oxygenation and six-minute walk distance (6MWD) were examined to place nocturnal findings in the context of baseline gas exchange and functional capacity.

METHODS

Ethics

This study was approved by the Dokuz Eylül University Ethics Committee for Non-interventional Researches (Date: 29.11.2013, Decision No: 2013/43-03). All procedures were



conducted by the ethical standards of the Declaration of Helsinki.

Study Design and Patients

This single-center retrospective cross-sectional study re-evaluated records from a joint pulmonology and cardiology PH clinic at a university hospital. The record period extended from the establishment of the PH clinic in August 2008 through September 2014. PSG had been performed during PH follow-up in patients with clinical suspicion of a sleep-related breathing disorder. Eligibility for the present analysis required adulthood, a documented clinical diagnosis of PH under follow-up, PSG during the specified period, and available clinical records. Records of 32 patients were reviewed; PSG-based analyses included the 29 patients with available detailed PSG parameters. Previously established PH diagnoses and etiological classifications in the follow-up records were retained. Historical diagnoses were not independently revalidated or reclassified using current hemodynamic criteria.

The clinical classification comprised 13 patients with group 1 PAH, nine with group 2 PH, six with group 3 PH, three with group 4 PH, and one with group 5 PH. Right heart catheterization was available in 24 patients, including all 13 patients with PAH. Catheterization had not been performed in the other eight patients because of technical reasons or refusal of consent. Given the small sample, etiological comparisons contrasted group 1 PAH with the remaining PH groups combined.

Clinical and Cardiopulmonary Assessment

Age, gender, height, body weight, and body-mass index (BMI) were recorded. Systolic pulmonary artery pressure (sPAP), right ventricular diameter, and tricuspid annular plane systolic excursion (TAPSE) were extracted from echocardiographic records. Right ventricular diameter was analyzed in centimeters as documented on the original echocardiographic data collection form. The available records did not specify the echocardiographic window, anatomical measurement level, or cardiac phase. Mean pulmonary artery pressure (mPAP) and right atrial pressure were obtained from catheterization records. 6MWD was used as a measure of exercise capacity. The arterial partial pressure of oxygen (PaO₂) measured on room air before PSG was recorded.

Polysomnographic Assessment

PSG recordings included electroencephalography, electrooculography, submental electromyography, electrocardiography, oronasal airflow, thoracoabdominal respiratory movements, and pulse oximetry. Recorded apnea and hypopnea counts, durations of N1, N2, N3, and rapid eye movement sleep, and mean and minimum sleep oxygen saturation (SpO₂) were evaluated. Total sleep time was obtained by summing the durations of the sleep stages. AHI was calculated by dividing the total number of apneas and hypopneas by total sleep time in hours. Respiratory events were taken from the existing scoring records; raw PSG signals were not rescored.

AHI was categorized as <5, 5 to <15, 15 to <30, and ≥30 events/h. AHI ≥5/h was used as the PSG-based threshold for sleep-disordered breathing, and AHI <15/h and ≥15/h

groups were used for clinical comparisons. Obstructive and central event subtypes were not analyzed separately. Nocturnal hypoxemia was defined as mean sleep SpO₂ ≤88% to retain the classification used in the original thesis study. This study-specific definition describes low average nocturnal oxygenation; it does not quantify the duration spent below 88% saturation or the frequency of desaturation events.

Statistical Analysis

The data were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean±standard deviation or median (25th-75th percentile), and categorical variables as counts and percentages. Given the small sample and variable distributions, two-sided Mann-Whitney U tests were used for independent-group comparisons and Fisher exact tests for categorical comparisons. Wilson 95% confidence intervals (CIs) were calculated for the principal proportions.

Missing values were not imputed; each analysis included patients with the relevant available measurements. PSG analyses included 29 patients, 6MWD assessment 28, PaO₂ assessment 31, and descriptive catheterization assessment 24. The numbers of valid observations for each comparison are reported in the tables. Statistical significance was defined as p<0.05. No adjustment for multiple comparisons or multivariable modeling was performed; all group comparisons were interpreted as exploratory.

RESULTS

Patient Characteristics and PSG Findings

Of the 32 patients, 25 (78.1%) were women and seven (21.9%) were men. Mean age was 58.3±14.5 years and mean BMI was 30.6±7.2 kg/m². Median sPAP was 75.0 mmHg, right ventricular diameter 3.35 cm, and TAPSE 19.0 mm. Among the 24 patients with catheterization data, median mPAP was 42.0 mmHg. Clinical and PSG characteristics are summarized in **Table 1**.

Among the 29 patients with detailed PSG data, median total sleep time was 319.9 minutes, AHI 7.5 events/h, mean sleep SpO₂ 91.2%, and minimum sleep SpO₂ 76.0%. AHI ≥5/h was present in 20 patients (69.0%; 95% CI, 50.8%-82.7%), AHI ≥15/h in 10 (34.5%; 95% CI, 19.9%-52.7%), and AHI ≥30/h in seven (24.1%; 95% CI, 12.2%-42.1%). Nocturnal hypoxemia was present in 12 patients (41.4%; 95% CI, 25.5%-59.3%).

Comparisons According to Nocturnal Hypoxemia

The 12 patients with nocturnal hypoxemia had a larger right ventricular diameter than the 17 patients without hypoxemia: 4.05 (3.75-4.50) vs 3.20 (2.80-3.40) cm (p=0.002). Among patients with PSG data, nocturnal hypoxemia was present in eight of 12 patients with PAH (66.7%) and four of 17 patients in the other PH groups (23.5%; p=0.029). Age, BMI, sPAP, TAPSE, mPAP, right atrial pressure, 6MWD, PaO₂, and AHI did not differ significantly between the hypoxemia groups (**Table 2**).

Comparisons According to AHI

The 10 patients with AHI ≥15/h had a higher BMI than the 19 patients with AHI <15/h (median 33.7 vs 25.7 kg/m²; p=0.005). Minimum sleep SpO₂ was lower in the AHI

Table 1. Clinical and polysomnographic characteristics of the patients

Variable	Valid n	Value
Age, years	32	58.3±14.5
Female gender, n (%)	32	25 (78.1)
BMI, kg/m ²	32	30.6±7.2
Group 1 PAH, n (%)	32	13 (40.6)
Group 2 PH, n (%)	32	9 (28.1)
Group 3 PH, n (%)	32	6 (18.8)
Group 4 PH, n (%)	32	3 (9.4)
Group 5 PH, n (%)	32	1 (3.1)
sPAP, mmHg	32	75.0 (60.0-91.2)
RV diameter, cm	32	3.35 (2.90-3.92)
TAPSE, mm	32	19.0 (15.3-22.0)
mPAP, mmHg	24	42.0 (37.2-47.5)
6MWD, m	28	380.0 (322.5-420.0)
PaO ₂ , mmHg	31	70.1 (62.7-79.0)
Total sleep time, min	29	319.9 (284.5-412.0)
AHI, events/h	29	7.5 (3.0-24.8)
Mean sleep SpO ₂ , %	29	91.2 (84.0-93.2)
Minimum sleep SpO ₂ , %	29	76.0 (67.0-83.0)
AHI <5/h, n (%)	29	9 (31.0)
AHI 5 to <15/h, n (%)	29	10 (34.5)
AHI 15 to <30/h, n (%)	29	3 (10.3)
AHI ≥30/h, n (%)	29	7 (24.1)
Nocturnal hypoxemia, n (%)	29	12 (41.4)

Age and BMI are presented as mean±standard deviation; other continuous variables are presented as median (25th-75th percentile). Percentages use the number of valid observations as the denominator. Nocturnal hypoxemia was defined as mean sleep SpO₂ ≤88%. PH: Pulmonary hypertension, PAH: Pulmonary arterial hypertension, BMI: Body-mass index, sPAP: Systolic pulmonary artery pressure, RV: Right ventricular, TAPSE: Tricuspid annular plane systolic excursion, mPAP: Mean pulmonary artery pressure, 6MWD: Six-minute walk distance, PaO₂: Arterial partial pressure of oxygen, AHI: Apnea-Hypopnea Index, SpO₂: Oxygen saturation by pulse oximetry

Table 2. Comparisons according to nocturnal hypoxemia

Variable	n ^a	Hypoxemia (n=12)	No hypoxemia (n=17)	p
Age, years	12/17	59.0 (43.0-64.8)	65.0 (55.0-70.0)	0.278
Female gender, n (%)	12/17	8 (66.7)	14 (82.4)	0.403
BMI, kg/m ²	12/17	33.0 (26.9-35.8)	29.7 (24.4-33.3)	0.232
Group 1 PAH, n (%)	12/17	8 (66.7)	4 (23.5)	0.029
sPAP, mmHg	12/17	82.5 (70.0-100.0)	70.0 (60.0-85.0)	0.131
RV diameter, cm	12/17	4.05 (3.75-4.50)	3.20 (2.80-3.40)	0.002
TAPSE, mm	12/17	16.5 (12.8-21.2)	19.0 (17.0-22.0)	0.213
mPAP, mmHg	10/12	43.0 (39.0-57.8)	41.5 (34.2-44.0)	0.208
RA pressure, mmHg	10/12	10.0 (9.0-11.8)	8.0 (6.8-10.5)	0.207
6MWD, m	12/13	335.0 (322.5-385.0)	400.0 (240.0-420.0)	0.228
PaO ₂ , mmHg	12/16	64.9 (59.5-69.3)	74.0 (66.5-85.1)	0.082
AHI, events/h	12/17	10.4 (6.3-54.6)	6.9 (2.9-16.4)	0.177

Values are median (25th-75th percentile) or n (%). ^aValid observations in the hypoxemia/no hypoxemia groups, respectively. Nocturnal hypoxemia was defined as mean sleep SpO₂ ≤88%. Continuous variables were compared using the Mann-Whitney U test and categorical variables using the Fisher exact test. P-values are unadjusted for multiple comparisons. Percentages in the group 1 PAH row describe the composition of the hypoxemia groups. Conversely, hypoxemia occurred in 8/12 patients with PAH (66.7%) and 4/17 patients in the other PH groups (23.5%). BMI: Body-mass index, PAH: Pulmonary arterial hypertension, PH: Pulmonary hypertension, sPAP: Systolic pulmonary artery pressure, RV: Right ventricular, TAPSE: Tricuspid annular plane systolic excursion, mPAP: Mean pulmonary artery pressure, RA: Right atrial, 6MWD: Six-minute walk distance, PaO₂: Arterial partial pressure of oxygen, AHI: Apnea-Hypopnea Index, SpO₂: Oxygen saturation by pulse oximetry

≥15/h group (median 69.0% vs 81.0%; p=0.029). There were no statistically significant differences in age, sPAP, right

ventricular diameter, TAPSE, mPAP, 6MWD, PaO₂, or mean sleep SpO₂ (Table 3).

Table 3. Comparisons according to Apnea-Hypopnea Index

Variable	n ^a	AHI ≥15/h (n=10)	AHI <15/h (n=19)	p
Age, years	10/19	66.0 (61.0-67.8)	55.0 (42.0-67.5)	0.142
BMI, kg/m ²	10/19	33.7 (32.6-40.5)	25.7 (23.4-32.0)	0.005
sPAP, mmHg	10/19	70.0 (65.5-85.0)	80.0 (60.0-97.5)	0.696
RV diameter, cm	10/19	3.55 (3.35-3.77)	3.20 (2.85-4.10)	0.505
TAPSE, mm	10/19	19.0 (17.2-19.8)	18.0 (14.0-22.0)	0.713
mPAP, mmHg	7/15	43.0 (40.5-50.0)	42.0 (36.5-48.0)	0.697
6MWD, m	7/18	330.0 (270.0-335.0)	390.0 (340.0-420.0)	0.106
PaO ₂ , mmHg	10/18	66.7 (56.8-70.5)	71.3 (62.4-77.5)	0.350
Mean sleep SpO ₂ , %	10/19	88.4 (85.2-91.6)	91.5 (83.2-93.3)	0.614
Minimum sleep SpO ₂ , %	10/19	69.0 (66.2-77.8)	81.0 (73.5-85.5)	0.029

Values are median (25th-75th percentile). ^aValid observations in the AHI ≥15/h and AHI <15/h groups, respectively. Comparisons used the Mann-Whitney U test. P-values are unadjusted for multiple comparisons. AHI: Apnea-Hypopnea Index, BMI: Body-mass index, sPAP: Systolic pulmonary artery pressure, RV: Right ventricular, TAPSE: Tricuspid annular plane systolic excursion, mPAP: Mean pulmonary artery pressure, 6MWD: Six-minute walk distance, PaO₂: Arterial partial pressure of oxygen, SpO₂: Oxygen saturation by pulse oximetry

DISCUSSION

The principal observation was the association of study-defined nocturnal hypoxemia with a larger recorded right ventricular diameter in patients undergoing PSG during PH follow-up. The contribution of this small, etiologically heterogeneous cohort is to place that structural finding alongside respiratory event burden, daytime oxygenation, and exercise capacity. This pattern motivates prospective assessment of nocturnal oxygenation and right ventricular structure across PH etiologies.

The frequency of nocturnal hypoxemia in our PSG sample (41.4%) was lower than in several earlier series. Ulrich et al.² reported nocturnal desaturation in 68% of 38 patients with PAH or chronic thromboembolic PH, while Minic et al.⁴ reported it in 60% of 52 patients with group 1 PAH; both used oxygen saturation <90% for more than 10% of the night or total sleep time. Jilwan et al.³ reported nocturnal hypoxemia in 82.6% of 46 patients with idiopathic PAH or chronic thromboembolic PH. These estimates differ in patient selection, PH composition, and hypoxemia definitions from our mean sleep SpO₂ ≤88% criterion. A low mean saturation and time below a saturation threshold describe different aspects of oxygenation, limiting direct comparison. Yüce et al.⁹ reported obstructive sleep apnea syndrome in 88.2% and nocturnal desaturation in 60.8% of 51 patients with group 1 or group 4 PH. Our AHI-based sleep-disordered breathing frequency (69.0%) also includes events without separation into obstructive and central subtypes.

Huang et al.⁶ studied 205 patients with obstructive sleep apnea undergoing right heart catheterization, 134 of whom had PH. The percentage of time spent with SpO₂ <90% (T90) was associated with mPAP, pulmonary vascular resistance, and right ventricular stroke work index after adjustment for confounders. Lowery et al.⁷ studied 186 patients with group 1 PAH and found that sleep-related hypoxia was more

consistently associated than AHI with right ventricular impairment and adverse outcomes. Our association with right ventricular diameter is directionally consistent with these observations, but concerns a structural measurement rather than demonstrated ventricular dysfunction. In contrast to these larger studies, neither TAPSE nor pulmonary artery pressures differed significantly between our hypoxemia groups. Differences in sample size, PH etiologies, oxygenation measures, and statistical adjustment may help explain the findings.

Han et al.⁸ evaluated 77 patients with chronic thromboembolic pulmonary disease, including 44 with PH and 33 without PH. Both T90 and mean sleep SpO₂ were associated with mPAP and pulmonary vascular resistance after adjustment for AHI and daytime PaO₂, among other covariates. Their assessment of both mean oxygenation and hypoxemia duration provides context for our mean-saturation finding, although our smaller study identified a diameter difference rather than a pressure difference. Çınar et al.⁵ studied 50 patients with chronic thromboembolic PH eligible for pulmonary endarterectomy. Severe nocturnal hypoxemia, defined by SpO₂ <90% for more than 20% of total sleep time, occurred in 62%; age, mPAP, and AHI were independent determinants. Their AHI association differs from our nonsignificant between-group comparison, emphasizing the relevance of PH subtype, hypoxemia definition, sample size, and analytic approach.

AHI did not differ significantly between patients with and without nocturnal hypoxemia ($p=0.177$; [Table 2](#)), and mean sleep SpO₂ did not differ significantly between the AHI <15/h and ≥15/h groups ($p=0.614$; [Table 3](#)). Together, these observations suggest that respiratory event frequency alone may incompletely characterize nocturnal oxygenation in this population. Mean sleep saturation reflects overall oxygenation across the night, whereas AHI counts discrete respiratory events. This distinction is consistent with the complementary information provided by hypoxemia measures in previous studies.⁶⁻⁸ The clinical question is therefore how nocturnal oxygenation adds to AHI when characterizing patients with PH.

Patients with nocturnal hypoxemia also had numerically lower daytime PaO₂ than those without hypoxemia (median 64.9 versus 74.0 mmHg), although the difference was not statistically significant ($p=0.082$; [Table 2](#)). Low mean sleep SpO₂ may therefore partly reflect lower baseline oxygenation, with additional sleep-related changes in ventilation and gas exchange. Jilwan et al.³ identified ventilation-perfusion mismatch, alone or together with obstructive events, as an important contributor to nocturnal hypoxemia. In 163 patients with chronic thromboembolic PH, Taniguchi et al.¹⁰ linked nocturnal desaturation to physiological dead space and ventilation-perfusion mismatch; nocturnal desaturation improved after balloon pulmonary angioplasty but persisted despite substantial hemodynamic improvement. These findings provide plausible context for our observations. Distinguishing baseline impairment from an additional nocturnal component requires paired daytime and overnight measurements with appropriate adjustment.

The higher BMI and lower minimum sleep SpO₂ in patients with AHI ≥15/h indicate that respiratory event burden

remains relevant to individual desaturation episodes. The contrast between minimum and mean sleep SpO₂ may help explain why AHI groups differed in the lowest recorded saturation but not in average nocturnal oxygenation. Pulmonary artery pressures and right ventricular diameter did not differ significantly between the AHI groups, consistent with the absence of differences in most hemodynamic variables by obstructive sleep apnea status in the series by Yüce et al.⁹

Although 6MWD was numerically lower in patients with nocturnal hypoxemia, the difference was not statistically significant; only 25 patients had both measurements available. Murta et al.¹¹ studied 52 patients with precapillary PH and found an association between exercise-induced desaturation and sustained nocturnal hypoxemia in multivariable analysis. Walking distance and exercise desaturation reflect different aspects of functional assessment. Future studies incorporating both could better characterize the relationship between nocturnal gas exchange and exercise performance.

The ESC/ERS guidelines recommend overnight oximetry or PSG when sleep-disordered breathing or hypoventilation is suspected.¹ Within this clinical setting, our findings support attention to nocturnal oxygenation alongside AHI, particularly when right ventricular enlargement or impaired daytime oxygenation raises concern about additional gas-exchange abnormalities. Prospective studies should combine duration-based measures such as T90 with the oxygen desaturation index, which measures desaturation frequency, and standardized right ventricular imaging. Analyses should account for PH etiology, AHI, daytime oxygenation, and treatment. Longitudinal and interventional studies could then determine whether nocturnal hypoxemia precedes adverse right ventricular remodeling and whether its correction modifies that process.

Limitations

This was a single-center record-based analysis of a small sample with heterogeneous PH etiologies. The findings describe patients who underwent PSG during PH follow-up and cannot be directly generalized to the broader PH population. Data from 2008-2014 may not fully represent contemporary patient profiles or treatment approaches. Diagnoses were based on follow-up records and were not independently revalidated. The absence of catheterization in eight patients, unequal distribution of PH groups, and missing measurements limit interpretation.

AHI was calculated from recorded event counts and sleep-stage durations; raw PSG signals were not rescored. Supplemental oxygen use during PSG, treatments, and the intervals between investigations could not be evaluated systematically. The absence of documentation of the echocardiographic window, anatomical level, and cardiac phase for right ventricular diameter limits verification of measurement standardization. The mean saturation threshold retained from the original study is study-specific and is not a universal diagnostic or treatment threshold; it does not quantify hypoxemia duration or desaturation frequency. Neither adjustment for confounders nor correction for multiple comparisons was performed. The greater representation of PAH in the hypoxemia group and possible

differences in baseline oxygenation may have contributed to the right ventricular diameter association. Nonsignificant AHI comparisons do not establish independence from apnea burden, particularly in a small sample. These exploratory cross-sectional findings do not establish causality or justify universal screening. Mortality, hospitalization, and treatment response were not evaluated, precluding conclusions about prognosis or therapeutic benefit.

CONCLUSION

In this clinically selected cohort encompassing all PH groups, PSG identified frequent nocturnal hypoxemia, particularly among patients with PAH, and an association with larger recorded right ventricular diameter. Considering nocturnal oxygenation alongside AHI may provide a fuller description of sleep-related abnormalities in patients undergoing assessment during PH follow-up. Prospective studies using duration-based oximetry measures, adjustment for daytime oxygenation and apnea burden, and standardized right ventricular imaging are needed to clarify the clinical significance and temporal direction of this association.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Dokuz Eylül University Ethics Committee for Non-interventional Researches (Date: 29.11.2013, Decision No: 2013/43-03).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: CS; Design: CS; Control: CS, Oİ; Validation: CS; Resources: ÖK; Materials: Oİ; Data Collection and/or Processing: ÖK; Analysis and/or Interpretation: Oİ; Visualization: ÖK; Literature Review: ARB; Article Writing: ÖK, ARB; Critical Review: All Authors.

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Systemic sclerosis-associated interstitial lung disease complicated by precapillary pulmonary hypertension: a real-world case

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ABSTRACT

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by widespread vasculopathy and progressive fibrosis. Pulmonary involvement, particularly interstitial lung disease (ILD) and pulmonary hypertension (PH), is among the leading causes of morbidity and mortality in these patients. Herein, we present a case of precapillary PH that developed following interstitial lung disease (SSc-ILD) in a patient with SSc. A 60-year-old female diagnosed with SSc in 2019 based on positive antinuclear antibody (ANA) and anti-Scl-70 antibody findings was referred to our outpatient clinic with progressively worsening exertional dyspnea. Initial evaluation revealed a marked reduction in diffusing capacity for carbon monoxide (DLCO, 24% predicted) and a cellular nonspecific interstitial pneumonia (NSIP) pattern on high-resolution computed tomography (HRCT). Over the following years, the NSIP pattern progressed from a cellular to a fibrotic phenotype, accompanied by significant clinical deterioration by 2022. As the disease progressed to the fibrotic stage and the patient was diagnosed with progressive pulmonary fibrosis, nintedanib therapy was initiated. Right heart catheterization revealed a mean pulmonary artery pressure of 39 mmHg, confirming precapillary PH and leading to a diagnosis of group 1 pulmonary arterial hypertension (PAH). Macitentan was initiated for PAH, while nintedanib, administered for ILD, had to be discontinued because of gastrointestinal intolerance. Despite partial improvement in pulmonary artery pressures, pulmonary function continued to deteriorate, with DLCO declining to 13% predicted. The patient died of cardiopulmonary arrest in 2024. The coexistence of SSc-ILD and PH represents a severe clinical phenotype associated with a poor prognosis. A progressive decline in DLCO may serve as a sensitive functional marker of the development of pulmonary vascular disease, while right heart catheterization remains the gold standard for definitive diagnosis. Early recognition and individualized management are crucial for optimizing outcomes in these complex patients.

Keywords: Scleroderma; systemic, lung diseases; interstitial, hypertension; pulmonary, cardiac catheterization, pulmonary diffusing capacity

INTRODUCTION

Systemic sclerosis (SSc) is a rare chronic autoimmune connective tissue disease characterized by immune dysregulation, widespread vasculopathy, and progressive fibrosis. The disease is classified into localized and systemic forms, and in the systemic form, structural and functional abnormalities may develop in various organ systems, including the lungs, gastrointestinal system, heart, and kidneys, in addition to skin involvement. SSc most commonly occurs between 25 and 55 years of age and is approximately four times more frequent in females than in males.¹

Pulmonary involvement is one of the most important causes of morbidity and mortality in SSc. In particular, interstitial lung disease (ILD) and pulmonary hypertension (PH), whether occurring alone or concomitantly, significantly worsen the prognosis of the disease. The pathogenesis of SSc-associated pulmonary disease involves excessive extracellular matrix deposition resulting from endothelial injury, immune activation, chronic inflammation, and fibroblast proliferation. This process leads to progressive parenchymal fibrosis,

impaired diffusion in the interstitial space, and pulmonary vascular remodeling.

SSc-associated interstitial lung disease (SSc-ILD) has been reported with prevalence rates ranging from 26% to 60% in different series. The disease may develop concurrently with the diagnosis of SSc or may emerge several years after the initial diagnosis. Clinically, it most commonly manifests as progressive exertional dyspnea, dry cough, and reduced exercise capacity.

High-resolution computed tomography (HRCT) is the primary imaging modality for the diagnosis of SSc-ILD and assessment of disease extent. The most frequently observed radiological pattern is nonspecific interstitial pneumonia (NSIP), followed by the usual interstitial pneumonia (UIP) pattern. In the early stages, ground-glass opacities and increasing reticular attenuation are predominant, whereas as the disease progresses, traction bronchiectasis, volume loss, subpleural fibrosis, and honeycombing may develop.²



Pulmonary function tests, particularly the diffusing capacity for carbon monoxide (DLCO), are important prognostic indicators in the assessment of the disease. A restrictive ventilatory defect is the most commonly observed functional abnormality in SSc-ILD and is characterized by reductions in FVC and DLCO. In particular, a marked decline in DLCO may be an early indicator not only of interstitial involvement but also of concomitant pulmonary vascular disease and the development of PH. From another perspective, an FVC/DLCO ratio >1.6 may represent a risk factor for PH.³

PH is one of the most severe and potentially fatal complications of SSc and may present as connective tissue disease-associated pulmonary arterial hypertension (group 1 PAH) or PH secondary to interstitial lung disease (group 3 PH-ILD). Differentiating these two phenotypes is of critical importance in terms of both treatment approach and prognosis. The coexistence of SSc-ILD and PH is associated with a marked reduction in exercise capacity, severe impairment in gas exchange, and decreased survival.

In this case report, we present the clinical course, diagnostic evaluation process, and long-term follow-up outcomes of precapillary PH developing in the setting of SSc-associated ILD.

CASE REPORT

A 60-year-old female was evaluated at the rheumatology clinic in 2019 because of Raynaud's phenomenon. Following clinical evaluation and serological investigations, she was diagnosed with SSc. On the autoimmune panel, antinuclear antibody (ANA) was positive, and the anti-Scl-70 level was >200 U/ml, whereas anti-SSA, anti-SSB, anti-Jo-1, anti-CCP, p-ANCA, and c-ANCA were negative. The serum angiotensin-converting enzyme level was within the normal range.

The patient was referred to the pulmonary diseases outpatient clinic because of exertional dyspnea. At the initial evaluation, physical examination revealed digital clubbing, tachypnea following exertion, and fine inspiratory crackles at the left lung base. Pulmonary function tests showed an FEV₁ of 1.54 L (67%), an FEV₁/FVC ratio of 86.6%, and a DLCO of 24%. The DLCO/VA value was 51%. During the six-minute walk test (6MWT), the patient was able to walk 240 meters; oxygen saturation decreased from 92% to 82%, while the Borg dyspnea score increased from 2 to 6 (Figure 1).

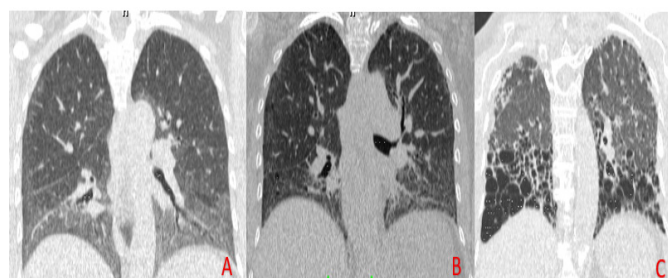


Figure 1. Serial coronal high-resolution computed tomography (HRCT) images showing the progression of systemic sclerosis-associated interstitial lung disease. (A) Early NSIP in 2019. (B) Progressive reticulation and traction bronchiectasis in 2022. (C) Advanced pulmonary fibrosis in 2024

HRCT: High-resolution computed tomography; NSIP: Nonspecific interstitial pneumonia

HRCT revealed a cellular NSIP pattern. Because there were no prominent fibrotic changes radiologically and the patient

did not accept antifibrotic therapy, close clinical follow-up was planned. In addition to oral prednisolone and nifedipine treatments initiated by the rheumatology department, an inhaled corticosteroid/long-acting β_2 -agonist combination was prescribed at the pulmonary diseases outpatient clinic.

The patient was followed at another center until 2022 and presented to our clinic again in the same year. Retrospective review of the patient's medical history and healthcare system records revealed that she had not been using her inhalers regularly, had been prescribed prednisolone frequently, and had been using colchicine. At presentation after a prolonged interval, her resting oxygen saturation was measured at 85%, and fine inspiratory crackles were now detected bilaterally at the bases of both lungs. A marked deterioration was observed in pulmonary function tests; FEV₁ was 1.02 L (49%), DLCO was 17%, and DLCO/VA was 42%. During the six-minute walk test, the distance she was able to walk had decreased to 185 meters, oxygen saturation decreased from 87% to 75%, and the Borg dyspnea score increased from 3 to 9. She was classified as World Health Organization (WHO) Functional Class III.

Because of the clinical and functional deterioration, the patient was hospitalized for further investigation, treatment, and evaluation. Transthoracic echocardiography revealed a systolic pulmonary artery pressure (sPAP) of 52 mmHg. Considering that the underlying connective tissue disease represented a significant risk factor for PH, right heart catheterization was performed. Hemodynamic assessment revealed a mean pulmonary artery pressure of 39 mmHg, a pulmonary capillary wedge pressure of 5 mmHg, a pulmonary vascular resistance of 6 Wood units, and a cardiac output of 4.3 L/min. A vasoreactivity test performed with adenosine, which was available at our hospital, was negative. Based on these findings, the patient was diagnosed with SSc-associated precapillary PAH (group 1 PAH).

Given the current clinical status, the patient was classified as high risk in terms of PAH, and macitentan was initiated for the treatment of PH. In addition, because of clinical, functional, and radiological progression, the patient agreed to antifibrotic therapy, and nintedanib 150 mg twice daily was added to the treatment regimen. Although antifibrotic therapies are currently known to be reimbursed for SSc-ILD patients with a diagnosis of progressive pulmonary fibrosis, our patient did not meet the criteria of FVC $>50\%$ and DLCO $>30\%$, which were among the main application criteria at the time of presentation. An application was therefore submitted for off-label use of antifibrotic therapy, and treatment could be initiated after approval was obtained. In addition, following a rheumatology consultation requested during hospitalization, mycophenolate mofetil was added to the treatment, and continuation of prednisolone and nifedipine was decided.

At the three-month follow-up, the patient was found to have developed significant gastrointestinal adverse effects and dyspeptic symptoms. During the same period, pulmonary function tests continued to deteriorate (FEV₁ 37%, DLCO 16%, DLCO/VA 38%), and antifibrotic therapy was discontinued because the patient did not wish to continue treatment. Nevertheless, partial improvement in the severity of dyspnea was reported, and follow-up echocardiography

showed that the sPAP had decreased to 28 mmHg. On the 6-minute walk test, she walked 200 meters, with oxygen saturation decreasing from 86% at baseline to 77% at the end of the test. The Borg dyspnea score was 4 at baseline and 7 at the end of the test (**Figure 2**).

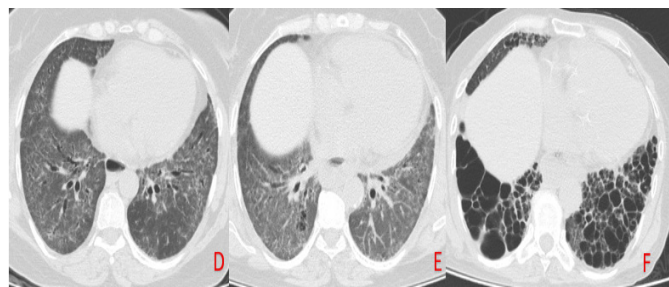


Figure 2. Serial axial HRCT images demonstrating disease progression. (D) Ground-glass opacities in 2019. (E) Increasing reticulation and traction bronchiectasis in 2022. (F) Extensive fibrotic changes and honeycombing in 2024

HRCT: High-resolution computed tomography

During the COVID-19 pandemic, the patient's regular follow-up was disrupted, and she was reassessed approximately two years later, in 2024. At presentation, she was mobilizing with a wheelchair and receiving oxygen support. Oxygen saturation measured on room air was 72%. Physical examination revealed bilateral diffuse inspiratory crackles, decreased breath sounds in the upper lung zones, and a prominent scleroderma facies with marked skin involvement. Pulmonary function tests demonstrated severe restrictive ventilatory impairment and severe diffusion impairment; FEV₁ was 0.57 L (31%), DLCO was 13%, and DLCO/VA was 24%. Follow-up echocardiography revealed an sPAP of 22 mmHg.

The patient was scheduled for another follow-up visit three months later; however, she did not attend the appointment. Subsequently, according to information obtained from an external medical center, it was learned that she had developed cardiopulmonary arrest and died.

DISCUSSION

SSc is a connective tissue disease characterized by widespread vasculopathy and systemic involvement, with a higher prevalence among women. In terms of organ involvement, pulmonary involvement, particularly ILD and PH, constitutes the major causes of morbidity and mortality in this patient population. Despite advances in current treatment options, SSc-ILD remains one of the most important organ manifestations determining survival. The prevalence of SSc-ILD has been reported to range from 26% to 60% in the literature, reflecting the clinical and radiological heterogeneity of the disease.⁴

The present case is noteworthy in demonstrating the progressive nature of SSc-associated ILD over time and the accompanying pulmonary vascular involvement. In our patient, radiological findings initially consistent with a cellular NSIP pattern were observed, while the presence of traction bronchiectasis, one of the important findings indicating progression to the fibrotic stage, also suggested a progressive disease course. During follow-up, both functional and clinical deterioration occurred. The radiological

progression observed in our case supports the transition of the disease from an inflammatory phase to a fibrotic phase.⁵ Indeed, antifibrotic therapy was planned at the time of initial diagnosis based on the pulmonary function tests, DLCO, and radiological findings; however, the patient did not accept the treatment.

The most striking feature of this case was the development of PH accompanied by a marked and progressive decline in diffusion capacity. In patients with SSc, a reduced DLCO may reflect not only interstitial lung involvement but also pulmonary vascular disease. In particular, disproportionately reduced DLCO values relative to the decline in FVC are considered suggestive of concomitant PH. In a study conducted by Sakayori et al.,³ an FVC/DLCO ratio >1.6 was reported to be an early predictive marker for PH. In our patient, an FVC of 66%, a DLCO of 24%, and an FVC/DLCO ratio of 2.75 at the time of diagnosis, together with a low DLCO and a high DLCO/VA, may be considered important markers of PH. The decline in DLCO from 24% at the time of diagnosis to 13% during follow-up demonstrates the progressive nature of pulmonary vascular disease. Indeed, right heart catheterization performed following the echocardiographic findings revealed a mean pulmonary artery pressure of 39 mmHg, a pulmonary capillary wedge pressure of 5 mmHg, and a pulmonary vascular resistance of 6 Wood units; these findings confirmed the diagnosis of SSc-associated precapillary PH.⁶

In SSc, PH may present as connective tissue disease-associated PAH (group 1 PAH) or PH secondary to ILD (group 3 PH-ILD).^{7,8} Differentiation between these two clinical phenotypes is of great prognostic and therapeutic importance. Current guidelines and reviews emphasize that right heart catheterization is the diagnostic gold standard in patients with SSc when PH is suspected.⁶ The hemodynamic findings obtained in our case indicated that the patient could be classified as having a group 1 precapillary PH phenotype.

From a therapeutic perspective, immunomodulatory and antifibrotic therapies constitute the main treatment approaches for SSc-ILD. The Scleroderma Lung Study II reported that mycophenolate mofetil demonstrated similar efficacy to cyclophosphamide but was better tolerated. In addition, the SENSICIS study demonstrated that nintedanib significantly reduced the annual rate of decline in FVC.^{9,10} Although nintedanib therapy was initiated in our patient because of progressive functional loss, treatment could not be maintained due to gastrointestinal adverse effects, treatment non-adherence, and continued progression in pulmonary function tests. Antifibrotic therapy, which had been planned to be initiated in 2019 when early findings of fibrotic NSIP were already present, could only be initiated in 2022 because of patient non-adherence. The advanced degree of fibrosis at the time treatment was initiated, together with the increased loss in pulmonary function and DLCO, constituted the main reasons for the failure of treatment. From this perspective, when criteria for progressive pulmonary fibrosis are present in patients with SSc-ILD, initiating antifibrotic therapy without delay is of vital importance in terms of relatively preventing the progression inherent to the natural course of the disease. Although improvement in echocardiographic parameters

was observed following the initiation of macitentan for the treatment of PH, the overall course of the disease remained progressive.¹¹

This case demonstrates the importance of regular functional monitoring in SSc-associated ILD and, in particular, careful assessment of changes in DLCO. It also emphasizes that echocardiographic evaluation and, when necessary, right heart catheterization should be performed without delay to enable early recognition of PH. Factors such as treatment non-adherence, interruptions in follow-up, and presentation at an advanced stage may also adversely affect the prognosis of the disease.¹²

CONCLUSION

PH accompanying SSc-associated ILD represents a severe clinical phenotype associated with significant functional limitation and increased mortality. This case demonstrates that a progressive decline in DLCO may be an important warning marker for pulmonary vascular disease and that right heart catheterization plays a critical role in the diagnostic process. Early diagnosis, regular functional follow-up, close monitoring for PH, and individualized treatment strategies are of fundamental importance for improving clinical outcomes in this patient population.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the author and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The author declares no conflicts of interest.

Financial Disclosure

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Author Contributions

The author is solely responsible for the entirety of conception, execution, analysis, and writing of the manuscript.

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