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What are the mortality markers in elderly patients with acute pulmonary embolism?

G. KARADENIZ[1], E. ÇIL[2]

[1]Department of Pulmonary Disease, University of Health Sciencies, İzmir Faculty of Medicine, Dr Suat Seren Chest Disease and Surgery Training and Research Hospital, İzmir, Turkey
[2]Department of Pulmonary Disease, University of Adıyaman, Training and Research Hospital, Adıyaman, Turkey

Abstract. – OBJECTIVE: This study investigates characteristics and predictors of mortality among elderly patients with acute pulmonary embolism (APE).

PATIENTS AND METHODS: Data on patients with the diagnosis of APE at the first admission to two centers between January 2012 and March 2022 were screened retrospectively. Patients aged 65 years and older were categorized as the elderly group while patients between 18 and 64 years of age constituted the non-elderly group.

RESULTS: Among the 361 enrolled patients, the average age in the non-elderly group was 51.0 (18.0-64.0) years and the average age in the elderly group was 76 (65.0-92) years. While male patients were the majority in the non-elderly group, there was a higher proportion of female patients in the elderly group (p=0.001). In multivariate regression analysis, the independent risk factors of mortality among elderly patients were oxygen saturation [odds ratio (OR): 1.163, 95% confidence interval (CI): 1.613-9.476; p=0.044], C-reactive protein (CRP) (OR: 1.133, 95% CI: 1.041-1.234; p=0.004), simplified Pulmonary Embolism Severity Index (sPESI) score (OR: 3.910, 95% CI: 1.613-9.476; p=0.003), absence of deep vein thrombosis (OR: 12.88, 95% CI: 1.321-125.739; p=0.028), and leukocyte count (OR: 2.591, 95% CI: 1.015-6.617; p=0.047). In ROC analysis, the cut-off values for mortality prediction were ≥7.7 mg/dL for CRP, >0.125 ng/mL for troponin, and ≥2 for the sPESI score.

CONCLUSIONS: If CRP of ≥7.7, troponin of >0.125, and sPESI score of ≥2 are present in elderly patients with APE, extra attention should be paid to the risk of mortality and the utmost care should be taken in planning the monitoring of these patients.

Key Words:
Acute pulmonary thromboembolism, Elderly, Mortality, Markers.

Abbreviations

APE: Acute pulmonary embolism; CT: Computed tomography; CRP: C-reactive protein; BNP: Brain natriuretic peptide; sPESI: Simplified Pulmonary Embolism Severity Index; MPV: Mean platelet volume; PDW: Platelet distribution width; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; pCO2: Partial pressure of carbon dioxide; DVT: Deep vein thrombosis; CI: Confidence interval; ROC: Receiver operating characteristic.

Introduction

Acute pulmonary embolism (APE) is a disorder that occurs as a result of an embolism in the pulmonary arteries and/or their branches with particles breaking off from thrombi that have generally formed in the deep veins of the legs. APE is significant as a recurrent but preventable disorder with high mortality and morbidity rates[1]. It is a medical condition frequently seen in the elderly population with a dramatic increase in incidence after 60 years of age; the incidence of the disease increases with age, rising by 2 or even 3 times with every passing 10 years of age[2]. Although mortality rates vary depending on the underlying medical conditions and the severity of APE, 30-day mortality is between 1% and 2%[3]. With modern guidelines and increased awareness, the mortality rates of APE have decreased, although its incidence has increased. However, mortality still reaches rates of 30-50% in untreated patients[3,4].

The number of elderly patients is increasing as average life expectancy increases worldwide, and comorbidities are seen more frequently in elderly patients[5]. When compared to the non-elderly population, APE is both more frequent and more fatal among the elderly[6,7]. Knowledge of the parameters that predict mortality is significant for better monitoring of these patients and treatment planning. Therefore, in the present study, we

Corresponding Author: Gülistan Karadeniz, MD; e-mail: drglstn35@gmail.com

aimed to investigate the characteristics and predictors of mortality among elderly patients with APE by comparing them to non-elderly patients.

Patients and Methods

Patients and Study Setting

The data of patients with APE, diagnosed by thoracic computed tomography (CT) angiography and/or ventilation/perfusion scintigraphy at first admission to the service and/or intensive care units of the Health Sciences University Dr. Suat Seren Chest Diseases and Surgery Training Hospital and Adıyaman University Training and Research Hospital between January 2012 and March 2022, were examined retrospectively. The recorded patient data included complete blood count, biochemical analyses, D-dimer (normal: <500 µg/L), troponin (normal: <0.14 ng/mL), arterial blood gas, C-reactive protein (CRP; normal: <0.5 mg/dL), pro-brain natriuretic peptide (pro-BNP; normal: <500 pg/mL), and findings from thoracic CT angiography, ventilation/perfusion scintigraphy, and bilateral lower extremity venous Doppler ultrasonography. Patients with a history of acute coronary syndrome, pregnancy, acute renal failure, malignity, infection, or acute trauma were excluded. A total of 361 patients were subdivided into a non-elderly group, which included patients aged 18-64 years, and an elderly group, which included patients aged ≥65 years. The data for the elderly and non-elderly groups were compared statistically. In addition, the elderly group was further subdivided for the comparison of fatal and non-fatal cases.

Simplified Pulmonary Embolism Severity Index (sPESI) scores were calculated as sums of the following criteria: age of >80 years=1 point, cancer history=1 point, history of heart failure and/or chronic lung disease=1 point, pulse of ≥110/min= 1 point, systolic blood pressure of <100 mmHg=1 point, and arterial oxyhemoglobin saturation of <90%=1 point[1].

Spectrophotometry/impedance was used in measuring complete blood counts (Beckman Coulter LH 780 Analyzer, Beckman Coulter Inc., Brea, CA, USA). Pre-treatment hematological parameters were measured by collecting venous blood samples in EDTA tubes. All data for hematological parameters [leukocyte count, neutrophil count/percentage, lymphocyte count/percentage, hemoglobin, hematocrit, platelet count, mean platelet volume (MPV), platelet distribution width (PDW), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR)] were taken at the time of diagnosis. The turbidimetric method was used to measure CRP [cobas c 702 and cobas 8000 ISE, Hitachi High-Technologies Corporation, (Tokyo, Japan)]. Peripheral blood samples were obtained at the time of diagnosis.

Statistical Analysis

Data analysis was performed with IBM SPSS Statistics 22 for Windows (IBM Corp., Armonk, NY, USA). The patients included in the study were divided into two groups as elderly (≥65 years) and non-elderly (<65 years) individuals. Using Kolmogorov-Smirnov and Shapiro-Wilk tests, it was determined whether the quantitative data were normally distributed. Non-normally distributed quantitative data were compared with the Mann-Whitney U test. The data were given as median (min-max). Chi-square and Fisher exact tests were used to compare qualitative data and the results were presented as frequency (%). Parameters with an alpha value of less than 0.1 in univariate regression analysis were evaluated with multivariate regression analysis to determine risk factors for mortality. Values of $p<0.05$ were considered to be statistically significant.

Ethics

This study was approved by the Adıyaman University Ethics Committee (No.: 2022/4-11) and it was designed and performed in accordance with the Declaration of Helsinki and good clinical practices.

Results

While 185 (51.2%) of the 361 enrolled patients were in the elderly group, 176 (48.8%) were in the non-elderly group. The average age in the elderly group was 76 (65.0-92) years, while it was 51.0 (18.0-64.0) years in the non-elderly group. While male patients (58.0%) were in the majority in the non-elderly group, there was a higher proportion of female patients (58.9%) in the elderly group ($p=0.001$). Oxygen saturation was found to be statistically significantly lower in the elderly group ($p=0.002$). sPESI scores were statistically significantly higher in the elderly group ($p<0.001$). There was no difference between the groups regarding recurrence, thrombolytic treatment, presence of deep vein thrombosis (DVT), pH, pCO_2, CRP, D-dimer, or pro-BNP. Thir-

ty-day mortality was 13.5% in the elderly group and 8% in the non-elderly group, and this difference was not statistically significant (p=0.089) (Table I).

When complete blood count values were compared, lymphocyte counts were found to be lower in the elderly group compared to the non-elderly group (p<0.001). MPV and PLR values were higher in the elderly group (p=0.008 and p=0.023, respectively).

When fatal and non-fatal cases in the elderly group were compared, CRP, sPESI scores, troponin, and NLR values were found to be significantly higher among deceased patients than survivors (p=0.002, p<0.001, p=0.005, and p<0.001, respectively). DVT incidence was significantly lower among deceased patients (p=0.003) (Table II).

When mortality risk factors among elderly patients with APE were examined, low oxygen saturation, absence of DVT, and high CRP, sPESI, leukocyte, neutrophil, PLR, and NLR values were found to be independent risk factors in univariate regression analysis. In multivariate regression analysis, on the other hand, oxygen saturation [odds ratio (OR): 1.163, 95% confidence interval (CI): 1.613-9.476; p=0.044], CRP (OR: 1.133, 95% CI: 1.041-1.234; p=0.004), sPESI score (OR: 3.910, 95% CI: 1.613-9.476; p=0.003), absence of DVT (OR: 12.88, 95% CI: 1.321-125.739; p=0.028], and leukocyte count (OR: 2.591, 95% CI: 1.015-6.617; p=0.047) were the independent risk factors (Table III).

In ROC analysis conducted for the parameters predicting mortality in patients with APE, the CRP cut-off was found to be >7.7 (p=0.002, sensitivity: 76.5%, specificity: 68%), the sPESI cut-off was ≥2 (p<0.001, sensitivity: 92%, specificity: 55.6%), the troponin cut-off was >0.125 (p=0.005, sensitivity: 64.3%, specificity: 69.4%), and the leukocyte cut-off was >9.65 (p<0.001, sensitivity: 88%, specificity: 55%) (Table IV).

Discussion

In the present study, low oxygen saturation and higher CRP, sPESI scores, and leukocyte counts were found to be independent risk factors for mortality among elderly patients with APE. For predicting APE mortality among elderly patients, the CRP cut-off was found to be ≥7.7 mg/dL, the troponin cut-off was >0.125 and the sPESI cut-off was ≥2 points. If low oxygen saturation and higher CRP, sPESI scores, and leukocyte counts are present in elderly patients with APE, extra attention should be paid to the risk of mortality and the utmost care should be taken in planning the monitoring of these patients.

In a study conducted by Ösken et al[8], the authors compared the clinical and echocardiographic findings of patients with pulmonary embolisms, and the proportion of female patients, sPESI scores, and basal creatinine levels were found to be statistically significantly higher

Table I. Clinical and demographic characteristics of elderly and non-elderly patients with acute pulmonary embolism.

	Non-elderly (< 65 years) n = 176	Elderly (≥ 65 years) n = 185	p
Age, years	51.0 (18.0-64.0)	76 (65.0-92)	< 0.001
Sex, n (%)			
Male	102 (58.0)	76 (41.1)	0.001
Female	74 (42.0)	109 (58.9)	
Recurrence	15 (8.5)	20 (10.8)	0.463
Thrombolytic therapy	23 (13.1)	13 (7.0)	0.056
Oxygen saturation (%)	95.1 (21.0-99.1)	92.4 (13.6-99.2)	0.002
pH	7.46 (7.22-7.65)	7.45 (7.19-7.65)	0.302
pCO_2	32.0 (11.2-66.0)	30.6 (15.7-55.5)	0.354
CRP	6.95 (0.0-35.30)	5.40 (0.10-42.00)	0.615
D-dimer	4157.0 (301.0-24300.0)	5212.0 (243.0-85600.0)	0.118
sPESI score	1.0 (0.0-4.0)	2.0 (0.0-4.0)	< 0.001
DVT	73 (41.5)	74 (40.2)	0.808
Troponin	0.03 (0.01-1.38)	0.10 (0.01-1.64)	0.221
Pro-BNP	832.0 (18.0-10981.0)	2510.0 (40.0-25000.0)	0.004
Mortality in 30 days, n (%)	14 (8.0)	25 (13.5)	0.089

pCO_2: Partial pressure of carbon dioxide, CRP: C-reactive protein (mg/dL), sPESI: Simplified Pulmonary Embolism Severity Index, pro-BNP: Pro-brain natriuretic peptide.

Table II. Clinical and demographic characteristics of elderly and non-elderly patients with acute pulmonary embolism.

	Elderly survivors n = 160	Elderly non-survivors n = 25	p
Age, years	76.0 (65.0-92.0)	80.0 (65.0-91.0)	0.265
Sex, n (%)			0.450
Male	64 (40.0)	12 (48.0)	
Female	96 (60.0)	13 (52.0)	
Recurrence	19 (11.9)	1 (4.0)	0.320
Thrombolytic therapy	11 (6.9)	2 (8.0)	0.690
Oxygen saturation (%)	93.0 (43.9-99.2)	88.6 (13.6-97.9)	0.067
pH	7.45 (7.31-7.65)	7.44 (7.19-7.61)	0.763
pCO_2	30.6 (15.7-65.5)	28.8 (17.3-57.8)	0.462
CRP	4.45 (0.10-42.00)	14.60 (0.20-33.60)	0.002
D-dimer	5155.5 (243.0-85600.0)	5742.0 (638.0-14900.0)	0.493
sPESI score	1.0 (0.0-4.0)	3.0 (1.0-4.0)	< 0.001
DVT, n (%)	71 (44.4)	3 (12.5)	0.003
Troponin	0.08 (0.01-1.52)	0.18 (0.06-1.64)	0.005
Pro-BNP	2510.0 (40.0-16566.0)	9924.0 (61.0-25000.0)	0.906
PDW	16.3 (1.5-107.0)	14.8 (9.7-19.3)	0.026
PLR	153.3 (24.9-647.5)	187.3 (62.4-540.6)	0.109
NLR	4.1 (0.3-26.5)	6.8 (0.9-35.5)	< 0.001

pCO_2: Partial pressure of carbon dioxide, CRP: C-reactive protein (mg/dL), sPESI: Simplified Pulmonary Embolism Severity Index, DVT: Deep vein thrombosis, pro-BNP: Pro-brain natriuretic peptide, PDW: Platelet distribution width; PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio.

among elderly patients. In addition, atrial fibrillation and mortality rates were also statistically significantly higher among elderly patients with APE. Similarly, in the present study, we found female patients and higher sPESI scores to be significantly more prevalent among the elderly. While 58% of the non-elderly patients were male, 58.9% of the elderly patients were female.

In the study conducted by Tanabe et al[9] on gender-based differences in patients with APE, the average age of female patients was found to be statistically significantly higher, and 30-day embolism-related mortality was statistically significantly higher among female patients.

In a study of unprovoked pulmonary embolisms conducted by Aharoni et al[10], the 30-day mortality rate of elderly patients was found to be 15.7%. Ösken et al[8] reported hospital mortality among elderly patients (≥65 years) to be statistically significantly higher (7.1%) than that of non-elderly patients (<65 years; 2.6%). In our study, although the difference was not statistical-

Table III. Univariate and multivariate analysis for 30-day mortality among elderly patients with acute pulmonary embolism.

Variable	Univariate analysis				Multivariate analysis			
	Beta	OR	95% CI	p	Beta	OR	95% CI	p
Oxygen saturation (%)	-0.033	0.968	0.937-1.000	0.048	0.151	1.163	1.004-1.346	0.044
CRP	0.099	1.104	1.041-1.170	0.001	0.125	1.133	1.041-1.234	0.004
D-dimer	0.000	1.000	1.000-1.000	0.825				
sPESI score	1.009	2.743	1.756-4.285	< 0.001	1.364	3.910	1.613-9.476	0.003
Absence of DVT	1.720	5.584	1.601-19.477	0.007	2.556	12.888	1.321-125.739	0.028
Leukocyte	0.208	1.232	1.109-1.368	< 0.001	0.952	2.591	1.015-6.617	0.047
Neutrophils	0.225	1.252	1.121-1.399	< 0.001	-1.025	0.359	0.119-1.086	0.070
MCV	-0.061	0.940	0.892-0.991	0.022	-0.012	0.988	0.894-1.092	0.820
PLR	0.003	1.003	1.000-1.006	0.087	-0.005	0.995	0.986-1.003	0.237
NLR	0.115	1.122	1.045-1.204	0.001	0.273	1.314	0.939-1.840	0.111

CRP: C-reactive protein (mg/dL), sPESI: Simplified Pulmonary Embolism Severity Index, DVT: Deep vein thrombosis, MPV: Mean platelet volume, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio.

Table IV. ROC analysis for predicted mortality among elderly patients with acute pulmonary embolism.

	AUC	95% CI	p	Cut-off	Sensitivity, %	Specificity, %
CRP	0.731	0.573-0.883	0.002	7.7	76.5	68.0
sPESI score	0.794	0.713-0.874	< 0.001	≥ 2	92.0	55.6
Troponin	0.737	0.614-0.861	0.005	0.1250	64.3	69.4
Leukocyte	0.727	0.632-0.823	< 0.001	9.65	88.0	55.0
Neutrophils	0.751	0.661-0.841	< 0.001	8.25	72.0	70.0
PDW	0.639	0.527-0.750	0.026	16.15	72.0	53.7
PLR	0.600	0.477-0.723	0.106	-	-	-
NLR	0.722	0.611-0.834	< 0.001	5.61	68.0	73.1

ROC: Receiver operating characteristic, CRP: C-reactive protein (mg/dL), sPESI: Simplified Pulmonary Embolism Severity Index, PDW: Platelet distribution width, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio

ly significant, 30-day mortality was 8% in the non-elderly group and 13.5% in the elderly group.

In the study conducted by Büyükşirin et al[11], who compared fatal and non-fatal APE cases over the course of 30 days, CRP levels were found to be significantly higher among deceased patients and CRP could predict early mortality in APE cases. Similarly, in our study, CRP levels were higher among elderly patients and higher CRP was determined to be a significant risk factor for mortality in both univariate and multivariate analyses. The CRP cut-off level of 7.7 can serve as a marker predicting mortality.

The sPESI score has been used as a prognostic marker in cases of APE for many years[12,13]. In a study by Klingenberg et al[14] comparing risk factors in elderly patients diagnosed with APE, sPESI scores showed the highest prognostic accuracy for 6-month mortality compared to troponin, pro-BNP, and CRP levels. Similarly, in our study the odds ratios in regression analyses and the AUC values in ROC analyses were both higher for sPESI scores compared to CRP levels.

In the study conducted by Jimenez et al[12], the 30-day mortality rate was found to be higher for patients with sPESI scores of 1 and above. In our study, the sPESI cut-off value was ≥2 for the prediction of 30-day mortality among elderly patients. Thus, we suggest that sPESI scores of ≥2 can predict mortality in elderly patients.

Data on the relationship between concomitant DVT and mortality in cases of pulmonary embolism are controversial. Lee et al[15] evaluated a total of 1,012 patients with isolated APE (n=322) and APE with concomitant DVT (n=690), and they found that the presence or absence of DVT did not affect the severity or short-term prognosis of pulmonary embolism cases. Morella et al[16] argued that the absence of DVT in elderly patients with pulmonary embolism was associated with more severe cases of pulmonary embolism. Sevestre et al[17], on the contrary, found that 3-month mortality in cases of APE without DVT was 4.6%, while it was 12.9% in cases of APE with DVT. In our study, DVT was significantly less common among non-surviving elderly patients and the absence of DVT was found to correlate with mortality. This finding may be related to lower DVT rates among deceased patients or failure to detect DVT with the use of ultrasonography in more proximal areas such as the pelvic zone. Prospective studies may shed lighter on whether the absence of DVT poses a risk for mortality.

Ay et al[18], in their study titled "The use of biochemical markers and RVD/LVD ratio in acute pulmonary embolism risk stratification in the Emergency Department", recommend using troponin I together with lactate and RVD/LVD (right ventricular diameter / left ventricular diameter) ratio for more accurate differentiation of high, intermediate and low risk patients in acute pulmonary embolism. In our study, we found significant CRP and sPESI scores with troponin to predict mortality in elderly patients with acute pulmonary embolism.

The most important limitation of our study is its retrospective nature. In addition, genetic factors that might play roles in the etiology of APE could not be examined sufficiently.

Conclusions

In elderly patients, if CRP is >7.7 mg/dL, troponin is >0.125 ng/mL, and the sPESI score is ≥2, attention should be paid to the high risk of mortality and maximum care should be taken while planning the follow-up of these patients.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Funding
We have not received any financial support for our study.

Data Availability
The data presented in this study are available upon request from the corresponding author.

Ethics Approval
This study was conducted in accordance with the Declaration of Helsinki and approved by the Adıyaman University Ethics Committee (Protocol Code No: 2022/4-11).

Informed Consent
Since this was a retrospective study, patient consent forms were not considered necessary. However, general informed consent was obtained from all patients during hospitalization.

Authors' Contribution
Conception and design: Gülistan KARADENİZ and Ercan ÇİL. Material preparation and data collection: Gülistan KARADENİZ and Ercan ÇİL. Statistical analyses: Gülistan KARADENİZ. Manuscript preparation and writing: Gülistan KARADENİZ and Ercan ÇİL.

ORCID ID
Gülistan Karadeniz: 0000-0002-1994-6723. Ercan Çil: 0000-0002-8981-4232.

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