

Evaluation of factors affecting 90-day mortality in patients hospitalized due to pulmonary thromboembolism

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Cite this article as: Hoşgün D, Aydemir S, Ateş C. Evaluation of factors affecting 90-day mortality in patients hospitalized due to pulmonary thromboembolism. J Health Sci Med 2021; 4(5): 543-551.

ABSTRACT

Aim: Pulmonary thromboembolism (PTE) is a leading cause of death from vascular events. In the pathophysiology of PTE, inflammatory mediators have been shown to be upregulated and to interact with coagulation factors. In this study, we aimed to investigate the role of symptoms, clinical and radiological findings, and the blood parameters measured at presentation within the first 24 h after the onset of the symptoms in predicting 90-day mortality and intensive care unit (ICU) requirement in patients with PTE.

Material and Method: The retrospective study included 264 PTE patients that were followed up at our Chest Diseases clinic and ICU between 2014 and 2019.

Results: The 264 patients comprised 55.3% women and 44.7% men with a mean age of 62.80 ± 15.95 years. Of these, 189 of them were hospitalized in the Chest Diseases clinic and the remaining 75 patients were followed up at ICU. Total mortality occurred in 8 (3%) out of 264 patients. Hospital and ICU mortality were determined at 1.9%, 1.1% respectively. The patients comprised 206 (78.0%) nonmassive PTE, 17 (6.5%) submassive PTE, and 41 (15.5%) massive PTE. Risk factors for 90-day mortality included white blood cell count (WBC), red blood cell distribution width (RDW), mean platelet volume (MPV)/RDW ratio, right ventricular dilatation (RVD), recombinant tissue plasminogen activator (rtPA) therapy, ICU hospitalization, and increased APACHE II (Acute Physiology and Chronic Health Evaluation II) scores ($p < 0.05$).

Conclusion: The results indicated that TTE findings, baseline hemodynamic parameters and symptoms, rtPA therapy, and CBC parameters including WBC, NE, and RDW are significant risk factors for predicting both mortality and ICU requirement.

Keywords: Pulmonary embolism, inflammatory, mortality

INTRODUCTION

In acute PTE, early diagnosis and treatment are of prime importance in the reduction of mortality, and the mortality rates range from 0.3 to 12 per 100 diagnoses (1-3). Right ventricular dilatation (RVD) is partially associated with early mortality and can be evaluated by transthoracic echocardiography (TTE) and spiral thoracic computed tomography pulmonary angiography (CTPA). In the pathophysiology of PTE, inflammatory mediators have been shown to be upregulated and serum levels of inflammatory markers including C-reactive protein (CRP) and interleukin-6 (IL-6) have been shown to be elevated within 48 h after the onset of acute thrombosis (4).

Red blood cell distribution width (RDW), mean platelet volume (MPV), total neutrophil count (NE), and total lymphocyte count (LY) are inexpensive and standard

biomarkers routinely measured in complete blood count (CBC). The percentage of serum RDW typically increases in hemoglobinopathies associated with iron deficiency. Additionally, recent clinical studies indicated that the percentage of serum RDW also increases in patients with increased oxidative stress and inflammation (5). On the other hand, RDW has been shown to be a useful marker in the diagnosis and prediction of prognosis and mortality in PTE patients. MPV, which is also measured in CBC, represents average platelet size and correlates with platelet function and activation. Although the MPV level in bone marrow may decrease or increase depending on the levels of inflammatory cytokines, it remains unknown as to which conditions cause increased or decreased serum MPV levels (6). Additionally, although serum MPV levels have been shown to be higher in patients with deep vein

thrombosis (DVT) compared to control subjects, there is no standardization in the literature regarding serum levels of MPV in PTE patients (7). In the presence of inflammation, NE is increased while LY is decreased as a result of elevated cortisol levels caused by the activation of sympathetic system. Moreover, both the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have been shown to be higher in PTE patients compared to non-PTE individuals (8,9).

The present study was designed to investigate the role of symptoms, clinical and TTE findings, and the blood parameters measured at presentation in predicting 90-day mortality and intensive care unit (ICU) requirement in patients that were diagnosed with PTE in our emergency service and then referred to the Chest Diseases clinic or ICU for treatment within the first 24 h after presentation.

MATERIAL AND METHOD

The retrospective study included 264 PTE patients that were followed up at our Chest Diseases clinic and intensive care unit (ICU) between 2014 and 2019. After obtaining an ethical approval from the Pamukkale University Non-interventional Clinical Research Ethics Committee (Date: 21.05.2019, Decision No: 10). Health Sciences University, Atatürk Chest Diseases and Chest Surgery Education and Research Hospital, Specialization in Medicine Education Board approval (Date: 27.02.2020, Decision No: 664). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patient records, ICU observation charts, and plain radiographic images were retrieved from hospital databases and were reviewed for each patient. All the patients included in the study initially presented to our emergency service and were transferred to the chest diseases clinic or ICU within the first 24 h after presentation, underwent CBC examination at presentation, and were initiated on 90-day mortality follow-up and on appropriate treatments in accordance with international guidelines. Additionally, the findings of both CTPA and 2-point compression ultrasonography of the lower extremity (USG) were evaluated by an experienced radiologist and the diagnosis of PTE was established by an experienced cardiologist based on TTE findings. Due to our retrospective study, USG could not be standardized. At the same time, it could not be repeated in the 3-5-7 days recommended in the guidelines for the diagnosis of DVT (1). The TTE findings were classified in terms of RVD, paradoxical septal motion with left-axis deviation, and pulmonary artery pressure (PAP). Based on hemodynamic monitoring findings, a heart rate of 50-100 beats/min was accepted as normal, >100 beats/min as tachycardia, and <50 beats/min as bradycardia. In noninvasive arterial blood pressure, a systolic blood pressure (SBP) of 90-120 mmHg was accepted

as normotensive, a >20 mmHg increase in SBP compared to baseline values or a SBP of >120 mmHg was accepted as hypertension, and a ≤40 mmHg decrease in SBP within 15 min compared to baseline values or a SBP of <90 mmHg was accepted as hypotension. Oxygen saturation measured by pulse oximetry (SpO₂) >90% was considered as normal. SpO₂<90% was accepted as hypoxemia (1,2). Exclusion criteria were as follow: pregnancy, age below 18 years, signs of active infection, chronic kidney disease, malignancies, connective tissue disease, ongoing anticoagulant therapy, myocardial infarction, hematological malignancies, history of blood transfusion within the last one month, thyroid disease, low iron, vitamin B12, and folic acid levels, and an ongoing treatment. CTPA was performed using a 128-slice CT device (slice thickness, 0.6 mm) (Definition AS, Siemens Medical Solutions, Forchheim, Germany). CBC parameters were measured by the photometric method on a Mindray BC-800 autoanalyzer. Normal ranges of CBC parameters including white blood cell count (WBC), hemoglobin (HB), hematocrit (HCT), platelet count (PLT), RDW, NE, LY, and MPV were accepted as 4.6-10.2 10³/μL, 12-16 g/dL, 40-54%, 142-424 10³/μL, 11.6-17.2%, 2-7 10³/μL, 0.8-4 10³/μL, and 7.8-11 fL, respectively. Based on CBC measurements, NLR, PLR, and the MPV/PLT and MPV/RDW ratios were calculated for each patient.

Statistical Analysis

Data were summarized as mean±standard deviation and median (Range) for continuous variables, frequencies (percentiles) for categorical variables. Student's test or Mann Whitney U test was used for independent group comparisons, depending on the distributional properties of the data. Chi-square test was used for proportions and its counterpart Fisher's Exact test was used when the data were sparse. All analyses were performed IBM SPSS Statistics for Windows, Version 20.0. A p value <0.05 was considered as statistically significant.

RESULTS

The 264 patients comprised 146 (55.3%) women and 118 (44.7%) men with a mean age of 62.80±15.95 years. Of these, 189 (71.6%) of them were hospitalized in the Chest Diseases clinic and the remaining 75 (28.4%) patients were followed up at ICU. In the patients that were hospitalized in ICU, the mean APACHE II (Acute Physiology and Chronic Health Evaluation II) score was 21.40±5.42 (**Table 1**). **Table 2** presents the findings of CTPA and 2-point compression ultrasonography of the lower extremity.

On TTE examination, RVD was detected in 124 (47.0%) and paradoxical septal motion with left-axis deviation was detected in 19 (7.3%) patients, and the mean PAP was 45.90±15.01 mmHg. **Table 3** presents the TTE findings for Chest Disease and ICU clinic.

Table 1. Demographic and clinical characteristics					
Variables		Chest Disease Clinic Mean ± SD	ICU Mean ± SD	Total Mean ± SD	p
Age		62.69 ± 15.85	63.07 ± 16.31	62.80 ± 15.95	0.864
Variables		Chest Diseases Clinic (n, %)	ICU (n, %)	Total (n, %)	p
Gender	Female	105 (71.9)	41 (28.1)	146 (55.3)	0.896
	Male	84 (71.2)	34 (28.8)	118 (44.7)	
Comorbidities	No	93 (75.6)	30 (24.4)	123 (46.6)	0.176
	Yes	96 (68.1)	45 (31.9)	141 (53.4)	
DM	No	170 (72.3)	65 (27.7)	235 (89.0)	0.442
	Yes	19 (65.5)	10 (34.5)	29 (11.0)	
CAD	No	142 (73.6)	51 (26.4)	193 (73.1)	0.239
	Yes	47 (66.2)	24 (33.8)	71 (26.9)	
CHF	No	172 (72.3)	66 (27.7)	238 (90.2)	0.460
	Yes	17 (65.4)	9 (34.6)	26 (9.8)	
AF	No	181 (71.3)	73 (28.7)	254 (93.9)	0.548
	Yes	8 (80.0)	2 (20.0)	10 (6.1)	
COPD	No	145 (69.4)	64 (30.6)	209 (79.2)	0.120
	Yes	44 (23.3)	11 (14.7)	55 (20.8)	
Dyspnea	No	25 (51.0)	24 (49.0)	49 (18.6)	<0.001
	Yes	164 (76.3)	51 (23.7)	215 (81.4)	
Fever	No	156 (72.2)	60 (27.8)	216 (81.8)	0.629
	Yes	33 (68.8)	15 (31.3)	48 (18.2)	
Dry cough	No	156 (75.7)	50 (24.3)	206 (78.0)	0.005
	Yes	33 (68.8)	15 (31.3)	48 (18.2)	
Hemoptysis	No	158 (72.8)	59 (27.2)	217 (82.2)	0.345
	Yes	31 (66.0)	16 (34.0)	47 (17.8)	
Chest pain	No	139 (73.2)	51 (26.8)	190 (82.2)	0.366
	Yes	50 (67.6)	24 (32.4)	74 (28.0)	
Risk factor	No	119 (82.6)	25 (17.4)	144 (54.5)	<0.001
	Yes	70 (58.3)	50 (41.7)	120 (44.5)	
Genetic risk factor	No	186 (71.3)	75 (28.7)	261 (98.9)	0.272
	Yes	3 (100.0)	0 (0.0)	3 (11.0)	
Acquired risk factor	No	119 (83.2)	24 (16.8)	143 (54.2)	<0.001
	Yes	70 (57.9)	51 (42.1)	121 (81.4)	
Variables		n	%		
Mechanical ventilation	No	236	89.4		
	NIV	13	4.92		
	IMV	15	5.68		
Mortality (90 days)	No	256	97.0		
	Yes	8	3.0		
Hospital Mortality	No	261	98.9		
	Yes	3	1.1		
ICU Mortality	No	259	98.1		
	Yes	5	1.9		
Acute PTE	Nonmassive	206	78.0		
	Massive	41	15.5		
	Submassive	17	6.5		
SSBP (mmHg)	Normotensive (SBP 90-120 mmHg)	216	81.8		
	Hypertensive (SBP >120 mmHg or >20 mmHg increase compared to baseline)	4	1.51		
	Hypotensive (SBP <90 mmHg or a ≤40 mmHG decrease in SBP within 15 min compared to baseline)	44	16.7		
Heart rate (beats/min)	Normal (50-100 beats/min)	124	47.0		
	Tachycardic (>100 beats/min)	131	49.6		
	Bradycardic (<50 beats/min)	9	3.4		
SpO ₂ (%)	Normal (>%90)	97	36.7		
	Hypoxemic (<%90)	167	63.3		

DM:Diabetes mellitus, CAD:Coronary artery disease, CHF:Congestive heart failure, AF:Atrial fibrillation, COPD:Chronic obstructive pulmonary disease SBP:Systolic blood pressure, NIV:Noninvasive mechanical ventilation, IMV:Invasive mechanical ventilation, SpO₂: Oxygen saturation measured by pulse oximetry, ICU:Intensive care unit,SD: Standard deviation, PTE: Pulmonary thromboembolism.

Variables		Frequency	Percentage
USG	Left DVT	33	12.5
	Right DVT	14	5.3
	Bilateral DVT	7	2.7
	Right main femoral vein DVT	10	3.8
	Left main femoral vein DVT	7	2.7
	Right iliac+femoral vein DVT	1	0.4
	Right main femoral vein+left DVT	1	0.4
	Bilateral ilioacaval DVT	1	0.4
	Left iliac vein DVT	1	0.4
	No DVT	186	70.5
	Total	264	100.0
CTPA	Main pulmonary artery thrombus	14	5.3
	Bilateral main pulmonary artery thrombus	27	10.2
	Bilateral segmental artery thrombus	7	2.7
	Bilateral subsegmental artery thrombus	94	35.6
	Right main pulmonary artery thrombus	20	7.6
	Right subsegmental artery thrombus	67	25.4
	Left main pulmonary artery thrombus	5	1.9
	Left subsegmental artery thrombus	25	9.5
	Right main pulmonary+left subclavian artery thrombus	1	0.4
	Right main pulmonary+left subsegmental artery thrombus	1	0.4
	Total	261	98.9

USG:2-point compression ultrasonography of the lower extremity, CTPA:Spiral thoracic computed tomography pulmonary angiography, DVT:Deep vein thrombosis

Variables	Chest Diseases Clinic (Mean±SD)	ICU (Mean±SD)	Total (Mean±SD)	p	
PAP	42.50±13.73 mmHg	51.53±15.43 mmHg	45.90±15.01 mmHg	<0.001	
		Mean±SD		p	
PAP	Thrombolytic therapy (rtPA)	53.75±15.41 mmHg		<0.001	
	LMWH	42.53±13.64 mmHg			
	Half-dose thrombolytic therapy (rtPA) (50 mg)	50.63±13.52 mmHg		0.156	
	Full-dose thrombolytic therapy (rtPA) (100 mg)	56.98±17.95 mmHg			
	Chest Diseases Clinic (n, %)	ICU (n, %)	Total (n, %)	p	
RVD	No	125 (72.3)	15 (10.7)	140 (53.0)	<0.001
	Yes	60 (48.4)	64 (51.6)	124 (47.0)	
Paradoxical septal motion with left-axis deviation	No	185 (76.1)	58 (23.9)	243 (92.7)	<0.001
	Yes	4 (21.1)	15 (78.9)	19 (7.3)	
	Half-dose thrombolytic therapy (rtPA) (50 mg) (n, %)	Full-dose thrombolytic therapy (rtPA) (100 mg) (n, %)	Total (n, %)		
RVD	No	4(80.0)	1(20.0)	5(8.8)	0.157
	Yes	21(40.4)	31(59.6)	57(91.2)	

RVD:Right ventricular dilatation, PAP:Pulmonary artery pressure, rtPA:Recombinant tissue plasminogen activator, LMWH:Low-molecular-weight heparin, SD: standard deviation

The patients comprised 206 (78.0%) nonmassive, 17 (6.5%) submassive, and 41(15.5%) massive acute PTE (Table 1).Of the 264 patients, 57 (21.6%) of them received rtPA and 207 (78.4%) of them received LMWH therapy. In the rtPA group, 25 (43.9%) of them received half-dose rtPA therapy (50 mg) and 32 (56.1%) of them received full-dose rtPA therapy (100 mg). Treatment-related complications were observed in 14 (5.4%) of 264 patients, including 7 (3.4%) patients in the LMWH group and 7 (13.0%) patients in the rtPA group.

Table 4 presents complete blood count parameters. Total mortality occurred in 8 (3.0%) out of 264 patients. Hospital and ICU mortality were determined at 1.9% , 1.1% respectively (Table 1).Risk factors for 90-mortality included comorbidities, acquired risk factors, ICU hospitalization, increased APACHE II scores, presence of RVD on TTE, rtPA therapy, invasive and noninvasive mechanical ventilation, and persistent hypotension, tachycardia, and hypoxemia (p=0.008,p=0.025,p=0.001 ,p<0.001, p=0.028, p=0.035, p<0.001, p=0.001, p<0.001,

p=0.028). Of these parameters, WBC, RDW, and MPV/RDW ratio were found to be significant risk factors for 90-day mortality (p=0.032, p=0.041, and p=0.039) (Table 5).

Risk factors for ICU requirement included acquired risk factors, dyspnea, dry cough, syncope, presence of RVD on TTE, paradoxical septal motion with left-axis deviation, PAP, rtPA therapy, invasive and noninvasive mechanical ventilation, use of vasopressors, and persistent hypotension and hypoxemia (p<0.001). Additionally, baseline CBC parameters including WBC, HB, HCT, RDW, and NE were also found to be significant factors for ICU requirement (Table 6).

Table 4. Complete blood count parameters

Variables	Mean±SD	Median (DW)
WBC (10 ³ /μL)	10.07±3.82	21.00 (25.00)
HB (g/dL)	13.27±1.91	13.30 (12.60)
HCT (%)	39.91±5.76	40.00 (38.30)
PLT (μL)	269227.27±95667.25	254000.00 (672000.00)
RDW (%)	15.15±2.12	14.60 (13.80)
NE (10 ³ /μL)	7.30±3.65	6.39 (21.81)
LY (10 ³ /μL)	1.92±1.28	1.71 (12.60)
MPV (fL)	8.31±1.25	8.30 (14.17)
NE/LY ratio	5.83±7.40	3.57 (77.21)
PLT/LY ratio	188234.83±149730.06	155044.93 (175000.00)
MPV/PLT ratio	0.0000349±0.0000138	0.0000327 (0.0000724)
MPV/RDW ratio	0.56±0.11	0.55 (1.03)

WBC:White blood cell count, HB:Hemoglobin, HCT:Hematocrit, PLT:Platelet count, RDW:Red blood cell distribution width, NE:Neutrophil count, LY:Lymphocyte count, MPV:Mean platelet volume, SD: Standard deviation

Table 5. Risk factors for mortality

Variables	No mortality occurred			Mortality occurred			P
	n	Mean±SD	Median(DW)	n	Mean±SD	Median (DW)	
Age	256	62.58±1.59	63.00 (73.00)	8	69.75±14.88	72.00 (44.00)	0.212
APACHE II	256	20.70±5.00	20.00 (24.00)	8	28.71±3.64	28.00 (11.00)	<0.001
PAP	256	46.67±15.15	42.00 (87.00)	8	51.43±10.29	50.00 (30.00)	0.322
Duration of ICU stay (days)	256	3.71±3.27	3.00 (21.00)	8	5.00±8.02	2.00 (22.00)	0.404
Duration of stay at clinic (days)	256	8.62±6.75	7.00 (88.00)	8	4.13±7.36	0.00 (17.00)	0.065
WBC (10 ³ /μL)	256	9.98±3.70	9.30 (23.35)	8	12.93±6.28	11.10 (20.20)	0.032
HB (g/dL)	256	13.29±1.90	13.40 (12.60)	8	12.65±2.27	11.80 (6.90)	0.354
HCT (%)	256	40.01±5.67	40.10 (38.30)	8	36.69±7.89	34.20 (25.00)	0.108
PLT (μL)	256	270664.06±96458.89	255000 (672000)	8	223250.00±49271.12	218000.00(157000.00)	0.168
RDW (%)	256	15.10±2.12	14.60 (13.80)	8	16.66±1.93	16.80 (5.40)	0.041
NE (10 ³ /μL)	256	7.22±3.55	6.32 (19.51)	8	9.71±6.02	7.53 (18.90)	0.058
LY (10 ³ /μL)	256	1.91±1.22	1.74 (12.60)	8	2.23±2.54	1.45 (7.82)	0.490
fL	256	8.32±1.25	8.30 (14.17)	8	7.90±1.14	8.20 (3.10)	0.352
NE/LY ratio	256	5.69±7.05	3.56 (77.21)	8	10.37±14.95	5.75 (45.57)	0.078
PLT/LY ratio	256	188373.40±150855.91	155044 (175000.00)	8	183800.83±115198.63	169500.00(341484.15)	0.932
MPV/PLT ratio	256	0.00±0.00	0.00 (0.00)	8	0.00±0.00	0.00 (0.00)	0.741
MPV/RDW ratio	256	0.56±0.11	0.55 (1.03)	8	0.48±0.08	0.47 (0.25)	0.039

APACHE II:Acute Physiology and Chronic Health Evaluation II, PAP:Pulmonary artery pressure, ICU:Intensive care unit, WBC:White blood cell count, HB:Hemoglobin, HCT:Hematocrit, PLT:Platelet count,RDW:Red blood cell distribution width, NE:Neutrophil count,LY:Lymphocyte count, MPV:Mean platelet volume, SD: Standard deviation

Table 6. Risk factors for ICU requirement

Variables	No ICU required		ICU required		P
	Mean±SD	Median (DW)	Mean±SD	Median (DW)	
Age	62.70±15.90	62.00 (71.00)	63.04±16.21	66.00 (70.00)	0.877
PAP	42.24±13.53	40.00 (87.00)	51.81±15.49	50.00 (60.00)	<0.001
WBC (10 ³ /μL)	9.53±3.52	9.05 (22.90)	11.41±4.21	11.25 (23.05)	<0.001
HB (g/dL)	13.44±1.82	13.50 (12.60)	12.84±2.07	12.85 (9.60)	0.021
HCT (%)	40.37±5.44	40.15 (38.30)	38.76±6.39	38.90 (32.00)	0.039
PLT (μL)	275723.40±97467.55	257000.00 (672000.00)	253157.89±89665.31	227500.00(437000.00)	0.083
RDW (%)	14.97±2.14	14.50 (13.80)	15.59±2.04	15.05 (9.90)	0.032
NE (10 ³ /μL)	6.74±3.32	6.10 (19.40)	8.68±4.07	7.94 (21.81)	<0.001
LY (10 ³ /μL)	1.92±1.27	1.80 (12.50)	1.93±1.30	1.55 (8.13)	0.925
MPV (fL)	8.30±1.16	8.30 (10.45)	8.33±1.45	8.43 (9.17)	0.842
NE/LY ratio	5.28±5.85	3.41 (45.71)	7.19±10.20	4.50 (76.66)	0.059
PLT/LY ratio	186749.15±119104.04	154810.04 (982500.00)	191909.94±207911.52	155061.63(1737310.92)	0.8
MPV/PLT ratio	0.00±0.00	0.00 (0.00)	0.00±0.00	0.00 (0.00)	0.132
MPV/RDW ratio	0.56±0.11	0.55 (0.78)	0.55±0.13	0.55 (0.72)	0.268

PAP:Pulmonary artery pressure, ICU:Intensive care unit, WBC:White blood cell count, HB:Hemoglobin, HCT:Hematocrit, PLT:Platelet count, RDW:Red blood cell distribution width, NE:Neutrophil count, LY:Lymphocyte count, MPV:Mean platelet volume, SD: Standard deviation

DISCUSSION

Risk factors for 90-mortality included WBC, RDW, MPV/RDW ratio, comorbidities, acquired risk factors, ICU hospitalization, increased APACHE II scores, presence of RVD on TTE, rtPA therapy, invasive and noninvasive mechanical ventilation, and persistent hypotension, tachycardia, and hypoxemia.

In Acute PTE, the mechanical obstruction of the pulmonary vascular bed caused by a thrombus localized to the pulmonary arteries leads to hemodynamic alterations, thereby leading to increased ventricular afterload and often resulting in RVD and hypokinesia. TTE is a bedside diagnostic tool commonly used in the detection of RVD and in making systemic thrombolytic treatment decisions (9). A previous study retrospectively evaluated the TTE findings of patients with massive PTE and detected RVD in 90.0%, paradoxical septal motion with left-axis deviation in 65.0%, and PAP >40 mmHg in 60.0% of the patients (10). Similarly, Serra et al. (11) retrospectively evaluated the TTE findings of PTE patients and revealed the baseline PAP as 39 mmHg. In our study, RVD was detected in 53.0% and paradoxical septal motion with left-axis deviation was detected in 7.3% of the patients. The TTE findings of the patients were retrospectively reviewed by an experienced cardiologist and patients with ventricular dysfunction and heart valve disease were excluded from the study. The mean PAP was 45.90 ± 15.01 mmHg, which was higher than most of the values reported in the literature. This difference was attributed to the high prevalence of systemic thrombolytic therapy in our patients who had hemodynamic instability or in those who were hemodynamically stable but had RVD (21.5%). Moreover, the mean PAP in our patients that were hospitalized in the Chest Diseases clinic was remarkably high (42.50 ± 13.73 mmHg), which could be associated with the fact that the TTE findings were examined by different cardiologists and by using different devices and that the TTE findings are not standardized and thus can be affected by hemodynamic alterations such as body weight and tachycardia. As most of the patients hospitalized in ICU were hemodynamically unstable, their TTE findings were statistically significant compared to those of patients who were hospitalized in the Chest Diseases clinic, as consistent with the literature.

Intravenous thrombolytic agents can be used to reduce pulmonary perfusion and PAP and to restore right ventricular function in a prompt manner (12,13). Current international guidelines propose that PTE patients with RVD and hemodynamic instability can be treated with systemic half-dose (rtPA 50 mg) or full-dose (rtPA 100 mg) thrombolytic therapy based on the benefit/loss analysis for each patient (14,15). In some studies, half-dose therapy has been shown to be as effective as full-

dose therapy and has also been reported to promote angiographic revascularization and to provide an improvement in PAP similar to that of full-dose therapy. Streptokinase, urokinase, and rtPA are commonly used thrombolytic agents (16,17). In our study, 57 (21.5%) patients received rtPA as systemic thrombolytic therapy, among whom 25 (43.9%) patients received half-dose rtPA (50 mg) and 32 (56.1%) patients received full-dose rtPA (100 mg). Acute PTE is available in studies that indicate the systemic thrombolytic therapy requirement 4.2% and 18.0% (16,17). In our study, however, the prevalence of systemic thrombolytic therapy was higher than those reported in the literature, which could be associated with several factors including the high rate of ICU hospitalization (28.4%), high APACHE II scores and PAP values, and high prevalence of vasopressor requirement, hemodynamic instability, and RVD in our patients. On the other hand, the prevalence of full-dose rtPA therapy was higher than that of half-dose rtPA therapy (56.1% vs. 43.9%) (11,16,17). However, no significant difference was found between these two groups with regard to PAP and the prevalence of RVD, both of which are significant pathfinders in the decision-making processes regarding thrombolytic therapy and its dosage. This finding could be attributed to the prioritization of hemodynamic findings over TTE findings in the decision-making processes regarding thrombolytic therapy and its dosage.

PTE is a significant cause of mortality and morbidity. In previous studies, 90-day mortality rate has been reported as 58.3% in patients with massive PTE and as 15.1% in patients with submassive PTE (11,18). In our study, massive (15.3%) and submassive (6.5%) PTE ratio has been lower than studies where 90 days of mortality have been evaluated. Hospital stay in patients with acute PTE has been reported to vary between 4 and 10 days (19,20). In our study, 90-day mortality occurred in 8 (3.0%) out of 264 patients. This rate was remarkably lower than those reported in the literature, which could be associated with the administration of systemic thrombolytic therapy in hemodynamically unstable patients and the shorter duration of hospitalization among our ICU patients (3.83 ± 3.87 days). In our study, mean duration of hospital stay was 8.49 ± 6.80 days and the mean duration of ICU stay was 3.83 ± 3.87 days. In our study, the heterogeneous patient groups and the high number of nonmassive acute PTE patients (nonmassive, massive and submassive) caused the number of hospital stay days to be high. No significant difference was found between these two values (hospital and ICU stay days) with regard to 90-day mortality. In our study, it was thought that the data of patients without hemodynamic change may affect our results. Our results are compared to literature information in acute PTE, where 90 days mortality are evaluated. This finding could be associated with the low mortality

rate in our patients. Additionally, the duration of hospitalization in our ICU patients was lower than those of many studies in the literature. On the other hand, the longer hospitalization period in the patients hospitalized in the chest diseases clinic compared to the patients hospitalized in ICU could be ascribed to the fact that most of the patients that were initiated on the LMWH therapy subsequently used oral anticoagulants (warfarin) as maintenance therapy and the patients were discharged after ensuring patient compliance with the anticoagulant warfarin therapy. Risk factors for 90-mortality included comorbidities, acquired risk factors, ICU hospitalization, increased APACHE II scores, presence of RVD on TTE, rtPA therapy, invasive and noninvasive mechanical ventilation, and persistent hypotension, tachycardia, and hypoxemia. In contrast, risk factors for ICU requirement included acquired risk factors, dyspnea, dry cough, syncope, presence of RVD on TTE, paradoxical septal motion with left-axis deviation, PAP, rtPA therapy, invasive and noninvasive mechanical ventilation, use of vasopressors, and persistent hypotension and hypoxemia. Taken together, these findings implicate that hemodynamic parameters were risk factors for both mortality and ICU requirement, as consistent with the literature.

In the pathophysiology of PTE, inflammatory mediators have been shown to be upregulated and to interact with coagulation factors. There is no cellular infiltration in the pulmonary artery during the acute stage while leukocyte infiltration occurs within the subsequent three hours and two days, which decreases on the fourth day and returns to baseline levels on the eighth day (18). Inflammatory markers including WBC, HB, NE, LY, PLT, RDW, and MPV, which are inexpensive and standard biomarkers that are routinely measured in CBC, have recently become a major research area in the evaluation of PTE (21,22). In those studies, serum levels of these markers have been shown to decrease or increase in PTE. Additionally, increased NE counts have been associated with subclinical inflammation and decreased LY counts have been attributed to the elevated glucocorticoid levels induced by sympathetic activation (22). They are used either in isolation or in ratios such as NE/LY and PLT/LY ratios for predicting mortality and risk factors in acute PTE. A previous review suggested that the NE/LY ratio could be used in predicting mortality in PTE patients although there are some studies presenting controversial results regarding the use of NE/LY and PLT/LY ratios in such predictions (23). PLT plays a central role in thromboembolic diseases by secreting prothrombotic and proinflammatory molecules. MPV is a biomarker which represents average platelet size and has been shown to indicate macrothrombocytes when elevated and to play a role in venous thrombosis

(24). RDW reflects the degree of heterogeneity of RBC size and has been shown to be elevated in conditions leading to increased levels of inflammatory markers such as CRP. Additionally, an elevated RDW indicates immature RBC production in the bone marrow and is known to be associated with the changes in blood viscosity and acute inflammation (25,26). In a previous case-control study, Payman et al. (27) evaluated 173 PTE patients and reported that the PLT counts were not elevated in any patient. In contrast, another study evaluated patients with acute DVT and reported that the MPV/PLT ratio and the MPV values were higher in the patients compared to control subjects (28). Kovacs et al. (7) reviewed multiple studies that evaluated DVT patients and revealed that the MPV values were significantly elevated in the patients compared to control subjects and this elevation was found to be statistically significant in patients with acute PTE in subgroup analyses. Some other studies suggested that MPV is an independent risk factor in predicting early mortality in acute PTE (28,29). Similarly, a prospective study evaluated 378 patients with acute PTE and reported that baseline RDW value was an independent risk factor for predicting 17-month mortality (30). Some previous studies proposed low MPV and RDW values for predicting thrombus risk and mortality while some others proposed high values, serial measurements, and different cutoff values for different groups of the same disease. In our study, baseline serum parameters were measured in CBC and the NE/LY, PLT/LY, MPV/PLT, and MPV/RDW ratios were calculated based on these parameters (31). We used these parameters and ratios to investigate their role in predicting 90-day mortality and ICU requirement. The measurements indicated that although the NE and WBC counts were higher than the reference values, no significant decrease was found in the LY counts, unlike in other studies (22). Moreover, WBC, NE, HB, HCT, and RDW were found to be significant risk factors for predicting ICU requirement and WBC, RDW, and the MPV/RDW ratio were significant risk factors for predicting 90-day mortality. Accordingly, RDW was found to be a significant risk factor for predicting both mortality and ICU requirement, which could be attributed to the high prevalence of hemodynamic instability, blood viscosity changes, and acute inflammation in our patients. Additionally, the PLT, NE/LY, PLT/LY, and MPV/PLT ratios were insignificant risk factors and the PLT and LY counts were in normal ranges, which could be ascribed to numerous factors including the retrospective nature of the study, nonstandardization of the methods used in collecting baseline serum samples at hospital presentation (i.e. the absence of a fixed timing schedule for the collection of serum samples), failure to analyze

time-dependent biomarkers such as MPV within one hour after blood collection, and the absence of serial measurements. Accordingly, we consider that serial measurement of inflammatory markers at presentation (baseline) and at 3, 24, and 48 hours after presentation could have revealed an increase in these parameters and their ratios. This assumption is relies on the literature data that indicated that acute inflammation begins to increase three hours after the onset of the symptoms and remains elevated for up to 48 h (18). Accordingly, in our study, the mean WBC and NE values showed an early increase while the MPV, PLT, and LY values showed a normal increase, which could be explained by the fact that MPV, PLT, and LY typically begin to increase at a later period compared to WBC and NE. Based on these findings, we suggest that the levels of these parameters in acute PTE should be standardized by serial measurements. We also consider that RDW can be an early marker of ICU requirement and mortality in acute PTE and further studies involving risk analysis are needed to investigate the role of RDW in acute PTE.

CONCLUSION

The results indicated that TTE findings, baseline hemodynamic parameters and symptoms, rtPA therapy, and CBC parameters including WBC, NE, and RDW are significant risk factors for predicting both mortality and ICU requirement. Further studies are needed to investigate the role of RDW and the MPV/RDW ratio in the risk analysis of PTE and in patients with thrombus or those with a risk of thrombus development.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the Pamukkale University Non-interventional Clinical Research Ethics Committee (Date: 21.05.2019, Decision No: 10). Health Sciences University, Atatürk Chest Diseases and Chest Surgery Education and Research Hospital, Specialization in Medicine Education Board approval (Date: 27.02.2020, Decision No: 664).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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