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Research article

A new biomarker in the diagnosis and prognosis of pulmonary thromboembolism: Serum profilin-1

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ABSTRACT

Objective: Pulmonary Thromboembolism (PTE) is one of the major cardiovascular diseases with high morbidity and mortality. Early diagnosis and accurate prognosis are essential in clinical management. This study aimed to investigate the efficacy of serum Profilin-1(PFN1) in diagnosing and prognosis PTE.

Materials and methods: This study was conducted on patients older than 18 diagnosed with PTE and healthy volunteers with similar sociodemographic characteristics who applied to the emergency department between March 2022 and March 2023.

Results: In the study, 102 patients diagnosed with PTE were in the patient group, and 64 healthy volunteers were in the control group. The median PFN1 level of the patient group was 2878 (124–5001) pg/mL, while the median PFN1 level of the control group was 579 (125–5001) pg/mL. The PFN1 level of the patient group was significantly higher than the control group ($p < 0.001$). PFN1 levels of 984.46 pg/mL and above had 76.47 % sensitivity and 79.69 % specificity in diagnosing PTE (AUC: 0.817; CI: 0.750–0.873; $p < 0.0001$). The median PFN1 level of patients with mortality was 5001 (1793.3–5001) pg/mL, while the median PFN1 level of patients without mortality was 1858 (124–5001) pg/mL. PFN1 levels of patients who developed mortality were significantly higher than those who did not develop mortality ($p < 0.001$). PFN1 levels of 3292.1 pg/mL and above had 90.91 % sensitivity and 71.25 % specificity in PTE prognosis (AUC: 0.861; CI: 0.778–0.921; $p < 0.0001$).

Conclusion: Serum Profilin-1 levels are helpful as a diagnostic and prognostic indicator in PTE.

1. Introduction

Pulmonary thromboembolism (PTE) stands out among cardiovascular diseases due to its high mortality rate [1]. Hence, early diagnosis is crucial. Computed tomographic pulmonary angiography (CTPA) is the gold standard for diagnosis [2]. However, obtaining

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tomography can sometimes be challenging due to patient-related factors, such as renal failure or hospital-related factors. Moreover, the use of CTPA for PTE diagnosis involves radiation exposure and the intravenous administration of nephrotoxic agents, presenting limitations for certain patients. Although studies have been conducted on many biomarkers, especially D-Dimer, which is thought to be useful in diagnosing the disease and determining its prognosis, satisfactory results have not yet been achieved. The absence of specific signs or symptoms further complicates diagnosis.

Consequently, many biomarkers, including D-dimer, have been attempted to be used in diagnostic algorithms and added to scoring systems for the diagnosis of pulmonary embolism, but studies on this have been inconclusive [3,4]. To date, many article evaluated the role of several biomarkers for predicting the prognosis in patients with PTE [5,6]. Nonetheless, these parameters are influenced by diverse clinical conditions and lack specificity for PTE [7]. Given these challenges, the quest for novel biomarkers persists to enhance disease diagnosis and prognosis prediction.

Profilin-1 (PFN1) is an actin monomer-binding protein [8]. It is involved in cell shape maintenance autophagy-apoptosis and is thought to be related to vascular permeability, angiogenesis, and oxidative stress [9]. In a study, excessive release of PFN1 was shown to cause endothelial dysfunction by increasing blood vessel size, vessel wall thickness, collagen content, and low-density lipoprotein formation [10]. In another study, high levels of PFN1 were observed in hypertensive patients as a result of vessel wall thickening and angiogenesis [11]. In the context of acute myocardial infarction, it was observed that the level of PFN1 increased proportionally with the rise in platelet concentration within thrombi accumulated in the coronary arteries. Furthermore, the same study noted a significant elevation in PFN1 levels when the thrombus maintained prolonged occlusion [11].

A thorough literature analysis identified no studies investigating PFN1 levels in PTE patients. The use of this biochemical marker in the early detection of a condition that can result in severe and potentially fatal outcomes in the emergency department represents an unexplored area. Assessing its significance in determining clinical severity and prognosis remains an avenue for further investigation in medical research.

This study aimed to determine the value of serum PFN1 levels in the diagnosis, clinical severity, and prognosis of PTE.

2. Material and method

This study planned as a single-center, prospective clinical study, was approved by a Samsun University Scientific Research Ethics Committee on March 23, 2022 with protocol number BAEK/2022/4/1. Patients diagnosed with PTE and whose written informed consent was obtained between March 2022 and March 2023 constituted the patient group, and healthy volunteers with similar sociodemographic characteristics and whose written informed consent was obtained constituted the control group. Patients under the age of 18, those using anticoagulant drugs, those with renal failure, those with diabetes mellitus, those with uncontrolled hypertension, those with acute coronary syndrome, those with acute cerebrovascular disease, those with acute aortic syndrome, those with chronic thrombosed aortic aneurysm, those with active malignancy, those with active COVID-19 disease, those with pregnancy, those with PTE diagnosed and treated in another center, and those referred from our hospital to another center were excluded from the study.

Laboratory results (blood gas, biochemistry, haemogram, troponin, D-dimer), imaging results (CTPA), vital signs, presence of comorbidities, demographic characteristics (age, gender), simplified Pulmonary Embolism Severity Index (sPESI) scores were recorded on the data form. The clinical course of the patients was analyzed, and they were grouped as those who were hospitalized in the ward or intensive care unit in terms of follow-up. In addition, patients were grouped as those who developed mortality in the following 30-day period and those who did not develop mortality as the outcome measure. The sociodemographic characteristics and serum PFN1 values of the control group consisting of healthy volunteers at the time of presentation to the emergency department were recorded on the data form.

A 5 ml venous blood sample was obtained within 10 min after admission to the emergency department and centrifuged at 4000 rpm for 10 min. The plasma portion was taken into a separate container and stored at −80 °C until the time of measurement by the Enzyme-Linked ImmunoSorbent Assay (ELISA) method. Human Profilin-1 ELISA Kit (Elabscience Biotechnology Inc., Houston, Texas, USA) was used in this procedure.

The collected data were analyzed using the IBM SPSS package (version 25) and MedCalc (Version 20; MedCalc Software Ltd, Ostend, Belgium). Analyses were performed at a 95 % confidence level. The conformity of the data to normal distribution was determined by the Kolmogrov-Smirnov test. Descriptive statistics were expressed as mean and standard deviation for normally distributed numerical data, median (minimum-maximum) for non-normally distributed data, and number (n) and percentage (%) for nominal data. Student-T test was used for pairwise group comparisons that fit the normal distribution, Mann Whitney *U* test was used for comparisons of non-normally distributed data, and the Chi-square test or Fisher's exact test was used for comparisons of categorical data. Receiver operating characteristics (ROC) analysis was performed to determine the best cut-off value, sensitivity, and specificity of PFN1 levels in diagnosis and prognosis. The correlation between PFN1 levels and disease severity scoring of PTE patients was evaluated using Spearman correlation analysis. Univariate regression analysis was performed to identify possible risk factors affecting prognosis. Additionally, multivariate linear regression analysis was performed to identify independent predictors of prognosis. All statistical tests were two-tailed, and the statistical significance level was accepted as $p < 0.05$ for all analyses.

3. Results

One hundred thirty-eight patients were diagnosed with PTE in our emergency department between the specified dates. 36 patients with incomplete clinical information, referral to an external center, and at least one exclusion criteria were excluded from the study. Therefore, 102 PTE patients were included in our study. A control group was formed with 64 healthy volunteers with

sociodemographic characteristics similar to the patient group. The study flow chart is presented in Fig. 1.

Of 102 patients diagnosed with PTE, 52 (51 %) were female, whereas 30 (46.9 %) of 64 volunteers in the control group were female. The mean age of the patient group was 66.82 ± 17.10 years, while the mean age of the control group was 66.34 ± 14.11 years. The patient and control groups were similar in gender and age characteristics ($p = 0.607$ and $p = 0.851$, respectively). The median PFN1 level of the patient group was 2878 (124–5001) pg/mL, while the median PFN1 level of the control group was 579 (125–5001) pg/mL. The PFN1 level of the patient group was significantly higher than the control group ($p < 0.001$) (Table 1).

Demographic characteristics, symptoms, risk factors for PTE, comorbid diseases, vital signs, and laboratory parameters of the patient group are presented in Table 2. The most common symptom was dyspnea, with a rate of 52 % (n = 53). Among the risk factors was a history of immobilization, with a rate of 34.3 % (n = 35). Hypertension was the most common comorbid disease, with a rate of 42.2 % (n = 43).

The location of the thrombus was in the main pulmonary artery in 11 (10.8 %), the right pulmonary artery in 78 (76.5 %), the left pulmonary artery in 80 (78.4 %), bilateral pulmonary arteries in 59 (57.8 %), segmental branches in 84 (82.4 %), and subsegmental branches in 29 (28.4 %) patients (Table 3).

While 61 (59.8 %) of the patients demonstrated hemodynamic stability, 41 (40.2 %) were classified as unstable. Among the unstable patients, 5 (4.9 %) experienced cardiac arrest either upon arrival at the emergency department or during subsequent monitoring, 28 (27.5 %) presented with obstructive shock, and 11 (10.8 %) exhibited persistent hypotension. Overall, 68 patients (66.7 %) necessitated admission to the intensive care unit (ICU), and 34 patients (33.3 %) were admitted to the ward based on the clinician's decision, all of whom were among the unstable patients. The sPESI score was calculated as an indicator of 30-day mortality. The median sPESI score was 1 (0–4). Based on the sPESI score, 24 patients (23.5 %) were classified as low risk, while 78 patients (76.5 %) were deemed high risk. Within the first 30 days, mortality occurred in 22 patients (21.6 %).

PFN1 levels of the patient group were compared regarding various characteristics (Table 3). No significant difference was found between PFN1 levels of male and female patients ($p = 0.291$). In addition, there was no statistically significant difference between the comorbid diseases of the patient group and PFN1 levels ($p > 0.05$ for each).

The median PFN1 level was 2389 (1277.40–5001) pg/mL in patients with a thrombus detected in the main pulmonary artery by CTPA, whereas the median PFN1 level was 2921.40 (124–5001) pg/mL in patients with a thrombus detected in other locations. In patients with bilateral pulmonary artery involvement, the median PFN1 level was 2389 (124–5001) pg/mL, while in those with a thrombus in other locations, it was 3360.50 (230–5001) pg/mL. There was no significant difference in PFN1 levels based on thrombus localization in both comparisons ($p = 0.965$ and $p = 0.105$, respectively).

The median PFN1 level for the patient group hospitalized in the ward was 989.50 (124–5001) pg/mL, whereas the median PFN1 level for the patient group in the intensive care unit was 3407.70 (230–5001) pg/mL. PFN1 levels in the patient group monitored in the intensive care unit were significantly higher than those in the patient group under ward observation ($p < 0.001$) (Table 3).

Patients were categorized into low-risk and high-risk groups based on the sPESI score, and PFN1 values were compared. PFN1 levels were significantly higher in patients identified as high-risk by the sPESI scoring ($p = 0.011$). In patients who developed mortality, the median PFN1 level was 5001 (1793.30–5001) pg/mL, whereas in patients who did not, the median PFN1 level was 1858 (124–5001) pg/mL. Profilin-1 levels in the group with mortality were significantly higher than those without mortality ($p < 0.001$).

The predictive value of PFN1 levels at presentation for diagnosing PTE was assessed through ROC analysis (Fig. 2). PFN1 levels of

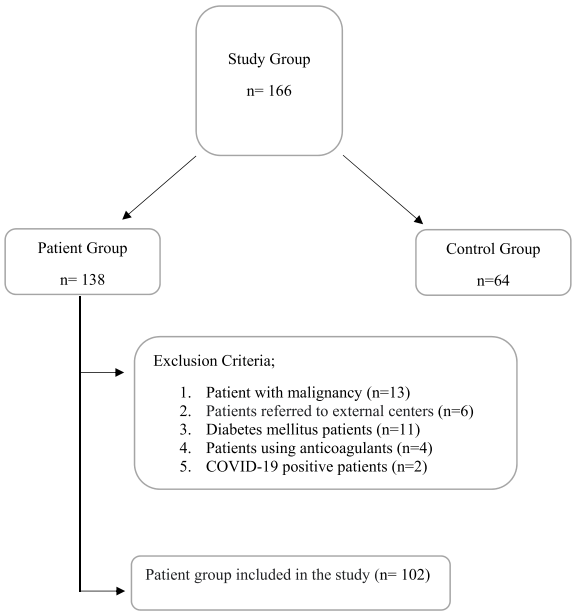

Fig. 1. Study flow chart.

Table 1
Demographic characteristics and Profilin-1 levels of the groups.

		Patient Group	Control Group	p-value
Age (year)[a]		66.82 ± 17.10	66.34 ± 14.11	0.851
Gender[b]	Female	52 (51)	30 (46.9)	0.607
	Male	50 (49)	34 (53.1)	
Profilin-1 (pg/mL)[c]		2878 (124–5001)	579 (125–5001)	**<0.001**

[a] mean ± standard deviation.
[b] n (%).
[c] median (minimum-maximum).

Table 2
Special characteristics and laboratory parameters of the patient group.

Features	Numerical Values
Complaint	n (%)
Shortness of breath	53 (52)
Chest pain	29 (28.4)
Mental status change	25 (24.5)
Leg pain	23 (22.5)
Hemoptysis	7 (6.9)
Risk Factors	**n (%)**
History of immobilization	35 (34.3)
History of DVT/PTE	18 (17.6)
History of surgery/fracture in the last week	3 (2.9)
Additional Diseases	**n (%)**
Hypertension	43 (42.2)
Chronic Lung Disease	17 (16.3)
Heart Failure	16 (15.7)
Alzheimer's/Parkinson's Disease	16 (15.7)
Atrial Fibrilation	6 (5.9)
Vital Signs	**Mean ± standart deviation**
SBP (mm/Hg)	122.35 ± 29.38
DBP (mm/Hg)	73.99 ± 17.50
MAP (mm/Hg)	90.11 ± 20.44
Pulse (beats/minute)	102.08 ± 19.46
Fever (°C)	36.46 ± 0.36
Respiratory rate (breaths/minute	22.14 ± 3.91
Saturation (%)	90.76 ± 8.12
Laboratory parameters	**Median (minimum-maximum)**
pH	7.37 (6.75–7.53)
pO_2 (%)	37.90 (4.80–251)
pCO_2 (%)	44.30 (24.80–69.70)
Lactate (mmol/L)	2.30 (0.70–14.60)
BE (mmol/L)	0.40 (−25.70 – 16)
Platelets (x 10^3)	223 (56–496)
Glucose (mg/dL)	146.20 (72–529)
D-dimer (mg/L)	8.42 (0.43–35.20)

SBP; systolic blood pressure, DBP; diastolic blood pressure, MAP; mean artery pressure, pO2: partial oksijen pressure, pCO2: partial carbon dioxide pressure, BE; base exess.

984.46 pg/mL and above demonstrated a sensitivity of 76.47 % and specificity of 79.69 % in diagnosing PTE (AUC: 0.817; CI: 0.750–0.873; $p < 0.0001$).

The predictive value of serum PFN1 levels in the prognosis of PTE was evaluated using ROC analysis (Fig. 3). PFN1 levels of 3292.1 pg/mL and above indicated a poor prognosis with 90.91 % sensitivity and 71.25 % specificity (AUC: 0.861; CI: 0.778–0.921; $p < 0.0001$).

Table 4 presents the comparison of some variables of the patient group with mortality. Accordingly, it was observed that mortality developed at a higher rate in patients with high s-PESI scores, hemodynamically unstable patients, and patients admitted to intensive care. The univariate and multivariate logistic regression analysis for the risk factors for mortality in PTE are shown in Table 5. The univariate analysis showed significant risk factors: MAP, RR, SpO2, MAP, sPESI score, and PFN1. To assess the independent factors and the ability of PFN1 levels to predict mortality, we subjected the variables to multivariate logistic regression analysis using a stepwise backward method based on the results of the univariate analysis. Multivariate analysis showed that PFN1 levels were associated with mortality in patients with PTE after adjusting for confounders (aOR for PFN1 = 1.001, 95 % CI:1.001–1.002). Additionally, lactate

Table 3
Comparison of Gender, Mortality, Thrombus Localization, Hospitalization Place, Hemodynamic status, Scoring and Profilin-1 Levels of the Patient Group.

Features	n (%)	Profilin-1 (pg/mL)[a]	p-value
Gender			
Female	52 (51)	3133.05 (230–5001)	0.291
Male	50 (49)	2632.50 (124–5001)	
Thrombus Localization			
Main Pulmonary Artery	11 (10.8)	2389 (1277.40–5001)	0.965
Other	91 (89.2)	2921.40 (124–5001)	
Bilateral Pulmonary Artery	59 (57.8)	2389 (124–5001)	0.105
Other	43 (42.2)	3360.50 (230–5001)	
Hospitalization Place			
Service	34 (33.3)	989.50 (124–5001)	**<0.001**
Intensive Care	68 (66.7)	3407.70 (230–5001)	
Hemodynamic stability			
Stable	61 (59.8)	1546.50 (124–5001)	**<0.001**
Un-stable	41 (40.2)	3944.90 (230–5001)	
sPESI results			
Low risk	24 (23.5)	1638 (124–5001)	**0.011**
High risk	78 (76.5)	2968.75 (267.26–5001)	
Mortality			
Mortality (+)	22 (21.6)	5001 (1793.30–5001)	**<0.001**
Mortality (−)	80 (78.4)	1858 (124–5001)	

sPESI; simplified pulmonary embolism severity index.
[a] median (minimum-maximum).

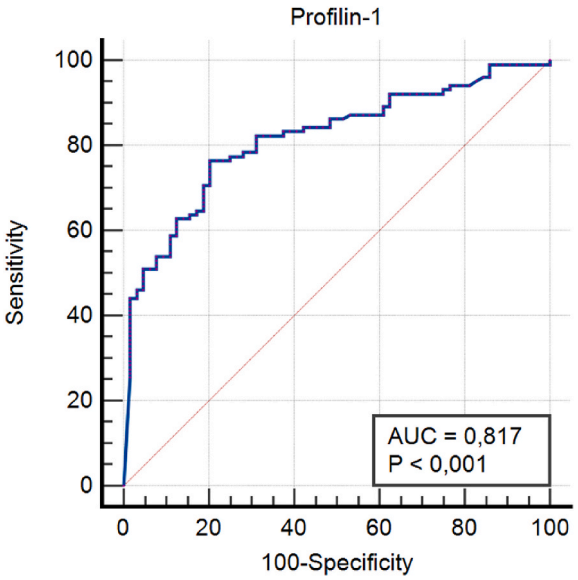

Fig. 2. Roc Curve of serum Profilin-1 levels in the diagnosis of pulmonary thromboembolism.

levels were associated with mortality, while MAP, RR, and SpO2 showed no significant association with mortality. The goodness-of-fit of the model was 0.318 (Hosmer-Lemeshow test).

4. Discussion

In this study, in which we evaluated PFN1 levels in the diagnosis and prognosis prediction of PTE disease, we found that serum PFN1 levels are a helpful parameter in the diagnosis and prognosis determination of the disease. This marker may be helpful in patients with suspected PTE presenting to the emergency department when diagnostic imaging cannot be performed due to patient or hospital-related reasons. After the diagnosis stage, PFN1 levels can be used to determine the disease's clinical severity and predict the prognosis. The clinical process can be managed more efficiently on a patient basis. While D-dimer and Troponin parameters have been previously investigated for similar purposes, no study examining the value of serum PFN1 levels in the diagnostic and prognostic processes of PTE disease has been identified in the literature. Our study holds a unique position in addressing this research gap.

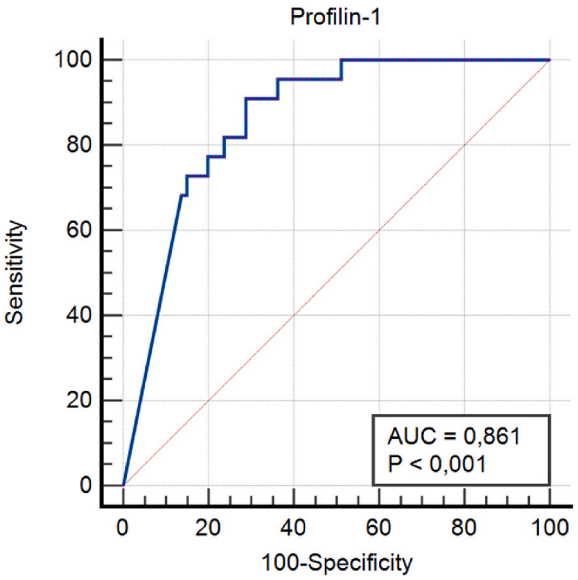

Fig. 3. Roc Curve of serum Profilin-1 Level in the prognosis of patients diagnosed with pulmonary thromboembolism.

Table 4
Comparison of Gender, Thrombus Localization, Hospitalization Place, Hemodynamic status, and Scoring and Mortality of the Patient Group.

Features	n (%)	Mortality -	Mortality +	p-value
Gender				
Female	52 (51)	38 (73.1)	14 (26.9)	0.271
Male	50 (49)	42 (84)	8 (16)	
Thrombus Localization				
Main Pulmonary Artery	11 (10.8)	10 (90.9)	1 (9.1)	0.498
Other	91 (89.2)	70 (76.9)	21 (23.1)	
Bilateral Pulmonary Artery	59 (57.8)	49 (83.1)	10 (16.9)	0.278
Other	43 (42.2)	31 (72.1)	12 (27.9)	
Hospitalization Place				
Service	34 (33.3)	31 (91.2)	3 (8.8)	**0.027**
Intensive Care	68 (66.7)	49 (72.1)	19 (27.9)	
Hemodynamic stability				
Stable	61 (59.8)	55 (90.2)	6 (9.8)	**0.001**
Un-stable	41 (40.2)	25 (61)	16 (39)	
sPESI results				
Low risk	24 (23.5)	23 (95.8)	1 (4.2)	**0.037**
High risk	78 (76.5)	57 (73.1)	21 (26.9)	

sPESI; simplified pulmonary embolism severity index.

Table 5
Univariable and multivariable[a] logistic regression analyses of predictors of mortality.

	Unadjusted OR	%95 CI	p-value	Adjusted OR	%95 CI	p-value
MAP	0.963	0.938–0.988	**0.004**	0.971	0.939–1.005	0.091
RR	1.136	1.011–1.276	**0.032**	0.971	0.800–1.179	0.766
SpO_2	0.934	0.882–0.988	**0.018**	0.977	0.896–1.065	0.596
Lactate	1.426	1.128–1.803	**0.003**	1.498	1.005–2.234	**0.047**
Glucose	1.004	1.000–1.009	0.078	0.993	0.982–1.004	0.222
sPESI (reference: low risk)	8.474	1.076–66.730	**0.042**	2.507	0.233–26.907	0.448
Profilin-1	1.001	1.001–1.002	**<0.001**	1.001	1.001–1.002	**0.001**

CI: confidence interval, OR: odds ratio, MAP: mean arterial pressure, RR: respiratory rate, sPESI: simplified Pulmonary Embolism Severity Index.
[a] Multivariable logistic regression analyses with a stepwise backward method based on the univariable analyses results. The goodness-of-fit of the multivariable logistic model was tested using the Hosmer-Lemeshow test (p = 0.318). Omnibus: <0.001, nagelkerke r2: 0.564.

In a study by Ramaiola et al., in patients with acute myocardial infarction, it was found that the level of PFN1 increased with the increase in platelets in thrombi accumulated in the coronary arteries. In the same study, it was also observed that the level of PFN1 increased in case of persistence of occlusion with thrombus [11]. Our study observed no significant difference in PFN1 levels among patients with various comorbid diseases. In our study, unlike Ramiola et al., patients with acute coronary syndrome were excluded. This difference in study design may have contributed to the observed disparities in the results.

A study conducted by Guo DJ et al. indicated an increased frequency of PTE in the elderly population [12]. In the study by Hsu et al., the mean age was 66 ± 14 years [13]. Similarly, another study by Abul et al. found a mean age of 64.4 ± 14.8 [14]. In our study, the patient's mean age was 66.82 ± 17.10 years. This similarity in age distribution suggests that our study aligns with the demographic characteristics observed in other studies.

In our study, a notable 21.6 % of patients diagnosed with PTE experienced mortality within the first 30 days. A comparison with existing literature reveals a 30-day mortality rate of 20.2 % in the study by Dahhan et al. [15]. In contrast, another study reported a considerably lower 30-day mortality rate at around 1.8 % [16]. While our study aligns with those reporting higher mortality rates, specific distinctive characteristics of our patient group, including advanced age, a history of immobilization, and a prevalent involvement of large vessels, may contribute to the observed elevated mortality rates compared to other investigations. Furthermore, a tertiary emergency department in our facility may have influenced the selection of patients presenting to our emergency department.

When we investigated the correlation between serum PFN1 levels and the localization of the thrombus in the pulmonary artery, we observed that embolism in the main pulmonary artery or bilateral pulmonary artery did not significantly impact PFN1 levels. A separate study noted an elevation in PFN1 levels when the thrombus sustained its occlusion period without dissolution [11]. Consequently, the duration of occlusion is more likely associated with PFN1 levels rather than the specific location of the thrombus. Unfortunately, no significant differences could be identified due to the unavailability of information regarding the duration of thrombus occlusion and challenges in assessing patients' current complaints and the precise time of hospital admission.

When comparing PFN1 levels in patients diagnosed with PTE and hospitalized in either the intensive care unit or the ward during follow-up, we observed higher PFN1 levels in patients admitted to the intensive care unit than those in the ward. Previous studies have indicated hemodynamic instability in patients results from increased thromboses and disruption of pulmonary blood flow within the growing thrombus [17]. As hemodynamically unstable patients are typically managed in intensive care settings, the elevated PFN1 levels in these individuals can be attributed to a thrombus load sufficient to disrupt their hemodynamics.

According to our findings, unsurprisingly, mortality rates were higher in patients with high s-PESI scores, hemodynamically unstable patients, and those admitted to intensive care. This situation actually highlights the importance of clinical follow-up and scoring systems for PTE patients. However, the fact that PFN1 can also predict mortality in a similar way is quite meaningful for us, as it supports the hypothesis of our study. It can be considered that PFN1 is more useful in predicting the outcome of the disease than previously studied biomarkers on this subject [4–6].

We assessed the simplified sPESI scores, indicating clinical severity and 30-day mortality for PTE patients. Our findings revealed that PFN1 levels were higher in patients categorized as high-risk in the sPESI scoring system compared to low-risk patients. Additionally, we identified a positive, albeit low-level, correlation between PFN1 levels and sPESI scores. These results suggest that PFN1 levels indicate diagnosis and mortality and reflect clinical severity. Therefore, PFN1 levels may prove valuable not only in diagnostic algorithms but also in scoring clinical severity.

4.1. Limitations

The primary limitation of our study is its single-center design, which may impact the generalizability of our findings. PFN1 levels in Pulmonary Thromboembolism (PTE) patients were exclusively assessed at admission, restricting our ability to obtain data on pre-admission levels and evaluate changes post-diagnosis. Furthermore, the precise duration between patients' emergency department admissions and the onset of their symptoms could not be accurately determined, impeding our ability to identify the specific timeframe associated with peak PFN1 levels. Another limitation is that the control group was composed entirely of healthy volunteers. This may have prevented the realistic evaluation of PFN1 in evaluating patients with suspected PTE in clinical practice.

5. Conclusion

This study is the first to evaluate PFN1 levels in PTE patients. In this study, serum PFN1 levels are a versatile biomarker capable of diagnosing PTE, evaluating clinical severity, and predicting mortality. Given these promising findings, we advocate for more comprehensive studies involving this biomarker in PTE patients to further solidify its clinical applicability.

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CRediT authorship contribution statement

Elif Erdem: Writing – original draft, Investigation, Data curation. **Metin Yadigaroğlu:** Writing – review & editing, Methodology, Formal analysis. **Murat Güzel:** Writing – review & editing, Methodology, Investigation. **Levent Gülbüz:** Investigation, Data curation. **Metehan Yılman:** Writing – original draft, Methodology. **Metin Ocak:** Writing – review & editing, Data curation. **Esra Arslan Aksu:** Methodology, Investigation, Data curation. **Selim Görgün:** Writing – review & editing, Investigation. **Murat Yücel:** Writing – review & editing, Visualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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