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A Novel Diagnostic Marker in Pulmonary Thromboembolism? Platelet-Derived Growth Factor –β

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Abstract

Objective: Pulmonary thromboembolism (PTE) is a condition characterized by severe cardiopulmonary injury. There is a need for a cheap and reliable biochemical marker, which is also easily and rapidly accessible, with high specificity and sensitivity in the diagnosis of PTE. The PDGF ligand receptor system plays a role in the development of pulmonary hypertension and contributes to thickening of the vascular wall and increasing the wall tension. In the present study, we aimed to investigate whether plasma PDGF-B levels increase in patients with PTE and the diagnostic value of PDGF-B in PTE along with its relationship with mortality.

Methods: This prospective clinical study was conducted in the emergency department of a tertiary university hospital between March 1st, 2020 and March 1st, 2021. A total of 44 patients diagnosed as having PTE in the emergency department (patient group) and 34 healthy volunteers without any chronic disease (control group) were included in our study.

Results: The PDGF-β levels of the patients diagnosed as having PTE in the ED were found to be significantly higher than those of patients in the control group (Z=-2.015, p=0.044). There was no significant linear relationship between PDGF-β levels and age, gender, presence of chronic disease, systolic and diastolic blood pressure as well as peak heart rate, respiratory rate, and axillary body temperature values at the time of admission to the emergency department, Geneva, Wells and PESI scores. In our study, no significant linear relationship was found between PDGF-β and D-Dimer levels in patients with PTE and mortality.

Conclusion: The results obtained from this study, which investigated whether PDGF-B was a new prognostic biomarker for PTE, suggest that plasma PDGF-B levels are significantly higher in PTE cases and can aid in the diagnosis of PTE. However, PDGF-B cannot be used as a marker to predict prognosis.

Keywords: Biomarker, mortality, PDGF-B, pulmonary thromboembolism.

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Trombosit Türevli Büyüme Faktörü –β Pulmoner Tromboembolizmde Yeni Bir Tanısal Belirteç midir?

Öz

Amaç: Pulmoner emboli şiddetli kardiyopulmoner hasarla karakterize bir durumdur. Pulmoner emboli tanısında yüksek hasssasiyete sahip, kolay ulaşılabilir, kolay uygulanabilir ve ucu bir biyokimyasal belirtece ihtiyaç duyulmaktadır. PDGF bağlı alıcılar Pulmoner hipertansiyon gelişiminde rol oynamaları yanı sıra , damar duvarı kalınlık artışı ve duvar gerilimi artışında da rol oynamaktadır. Bu çalışmada bizler plazma PDGF-B seviyelerinin Pulmoner tromboembolide artıp artmadığını, bu hastalardaki tanbısal değerini ve mortalite ile ilişkisini tespit etmeyi amaçladık.

Yöntemler: Bu prospektif klinik çalışma, 1 Mart 2020 - 1 Mart 2021 tarihleri arasında üçüncü basamak bir üniversite hastanesinin acil servisinde yapılmıştır. Acil serviste PTE tanısı alan toplam 44 hasta ve herhangi bir kronik hastalığı olmayan 34 sağlıklı gönüllü (kontrol grubu) çalışmamıza dahil edildi.

Sonuçlar: Acil serviste PTE tanısı alan hastaların PDGF-β düzeyleri, kontrol grubuna kıyasla anlamlı derecede yüksek bulundu (Z=-2.015, p=0.044). PDGF-β düzeyleri ile acil servise başvuru anındaki yaş, cinsiyet, kronik hastalık varlığı, sistolik ve diyastolik kan basıncı, tepe kalp hızı, solunum hızı ve aksiller vücut ısısı değerleri arasında anlamlı bir doğrusal ilişki tespit edilmedi. Geneva, Wells ve PESI skorları. Çalışmamızda PTE'li hastalarda PDGF-β ve D-Dimer düzeyleri ile mortalite arasında anlamlı bir doğrusal ilişki tespit edilmedi.

Tartışma: PDGF-B'nın PTE tanısında yeni bir tanısal belirteç olup, olamayacağını araştırdığımız bu klinik çalışmada PTE'li hastalarda PDGF-B nın belirgin derecede yüksek olduğu, ve bunun PTE tanısında yardımcı olabileceği tespit edildi. Ancak PDGF-B nın prognozu belirlemede etkili olmadığı görüldü.

Anahtar kelimeler: Belirteç, mortalite, pulmoner emboli, PDGF-B.

INTRODUCTION

Pulmonary thromboembolism (PTE) is a condition characterized by severe cardiopulmonary injury, such as acute right heart failure, induced by complete or partial occlusion of the pulmonary vascular bed due to an organized thrombus[1-3]. Pulmonary hypertension is the primary cause of acute right heart failure observed in PTE[4,5] and is a serious complication of acute PTE[6,7]. Proximal obstruction and remodeling of adjacent blood vessels occurs due to thrombotic occlusion of the pulmonary vascular bed. This causes a sudden increase in the pressure in the pulmonary vascular bed (pulmonary hypertension), leading to progressive dilatation of the right ventricle and the development of dysfunction[6].

PTE is the third most common acute cardiovascular syndrome following myocardial infarction and stroke. Its exact prevalence is unknown as some of the patients died before they could be diagnosed[8-10]. There are no clinical and physical examination findings specific to this condition. Chest radiography, electrocardiography, biochemical examinations, and arterial blood gases evaluation constitute clinical evaluation. However, these are insufficient for a definitive diagnosis. In addition, although levels of biomarkers, such as BNP, NT-pro BNP, D-Dimer (DD), troponin I and T, and heart-type fatty acid binding protein (H-FABP), that have a prognostic value are evaluated, they are not specific for PTE[2,11-14]. Considering the high mortality and morbidity of this condition, selecting appropriate tests for the diagnosis of this condition is important because the rapid diagnosis and initiation of treatment will reduce mortality. There is a need for a cheap and reliable biochemical marker, which is also easily and rapidly accessible, with high specificity and sensitivity in the diagnosis of PTE[2,15,16].

Platelet-derived growth factor (PDGF) is a mitogenic mediator involved in

pathophysiological vascular hyperplasia or hypertrophy. Experimental models show that the PDGF ligand receptor system plays a role in the development of pulmonary hypertension and contributes to thickening of the vascular wall and increasing the wall tension. These studies have demonstrated increased PDGF ligands and receptors in both pulmonary artery endothelium and smooth muscle cells in response to pulmonary hypertension stimuli[2,17-19].

In the present study, we aimed to investigate whether plasma PDGF-B levels increase in patients with PTE and the diagnostic value of PDGF-B in PTE along with its relationship with mortality. Our study is one of the few studies in the literature investigating the diagnostic value of plasma PDGF-B in PTE cases, and to the best of our knowledge, it is the first study to investigate the relationship between plasma PDGF-B and mortality in PTE cases.

METHODS

This prospective clinical study was conducted in the emergency department of a tertiary university hospital between March 1st, 2020 and March 1st, 2021. The study was conducted according to the World Medical Association Declaration of Helsinki for studies on human subjects and was approved by the Scientific Research Ethics Committee of our university (dated February 17th, 2020; protocol number: TÜTF-BAEK 04/10). A total of 44 patients diagnosed as having PTE in the emergency department (patient group) and 34 healthy volunteers without any chronic disease (control group) were included in our study. Cases under the age of 18 years; pregnant females; and cases with congenital or acquired thrombocytopenia/thrombophilia, those taking estrogen replacements or oral contraceptive medication, those with active cancer in the last five years, and those who did not want to voluntarily participate were excluded from the study.

Plasma PDGF-β Analysis

The plasma PDGF-β levels were determined using SunRed brand Human PDGF-β Elisa kit (catalog number 201-12-2119). Measurements were carried out in the Laboratory of the Department of Medical Biochemistry of our university (BioTek Instruments, μQuant™ 218731).

Statistical Analysis

Data were analyzed using SPSS 23.0 for Windows® statistical program (IBM Inc. Chicago, IL, USA) with license number 10240642 in the Department of Biostatistics and Medical Informatics, Trakya University Faculty of Medicine. The normal distribution characteristics of the data were tested using the Shapiro–Wilk test. Student t or Mann–Whitney U tests were used based on the normal distribution characteristics to compare data between the two groups. Relationships between qualitative variables were investigated using Pearson's chi-square and Fisher's exact tests. The relationship between quantitative variables was examined by Spearman's correlation coefficient. Mean and standard deviation, median and quartiles, and minimum-maximum values were used as descriptive statistics for quantitative variables, whereas frequency and percentages were used for qualitative variables. A significance level of $p<0.05$ was determined.

RESULTS

Descriptive Analysis

Descriptive analyses of patients diagnosed as having PTE in the emergency department revealed that the mean age of patients in the patient group was 68.9±13 years (40–96), whereas 56.8% (n=25) of them were female. In the study, 61.4% (n=27) of the patients diagnosed as having PTE had a history of chronic disease; hypertension (52.3%) and coronary artery disease (34.1%) were the most common chronic diseases, followed by diabetes mellitus (22.7%) and chronic heart failure (15.9%; Table 1).

Table I: Descriptive analyses of patient data from individuals in the patient group

		Med (IR)
Age (years)	68,9±13 (40–96)	68,5 (20,7)
Gender n (%)	**Female** 25 (56.8)	
	Male 19 (43.2)	
Chronic disease history n (%)		
Hypertension	23 (52,3)	
Coronary artery disease	15 (34,1)	
Diabetes mellitus	10 (22,7)	
Chronic heart failure	7 (15,9)	
Chronic pancreatitis	1 (2,3)	
Cerebrovascular event	1 (2,3)	
Vital signs Mean±SD (min–max)		
Systolic Blood Pressure (mmHg)	108,3±24 (70–163)	102 (36,2)
Diastolic Blood Pressure (mmHg)	65±14,2 (37–102)	61,5 (17,5)
Heart beat (/min)	102,5±18,7 (70–150)	97,5 (29,5)
Axillary body temperature (°C)	36,6±0,4 (36–38,1)	36,7 (0,5)
Respiration rate (/min)	20,3±5,2 (12–37)	19 (6)
Laboratory values Mean±SD (min–max)		
WBC (10^3/uL)	12,1±4,8 (2,1–24)	11 (6,4)
RBC	4,5±0,8 (2,8–6,8)	4,5 (0,9)
HGB (g/dl)	12,6±2,4 (8–18)	12,5 (3,6)
PLT (10^3/uL)	248,1±108,8 (66–541)	236 (148,7)
aPTT (sec)	23,6±4,4 (15–37,9)	22,6 (5,3)
PTZ (%)	13,8±2,6 (10,7–24)	13,1 (3,1)
INR	1,2±0,2 (0,92–2)	1,1 (0,3)
D-Dimer (mg/L)	9,7±3,7 (2,8–20,6)	9,7 (6)
CRP (mg/dL)	7,8±7,4 (0,3–31)	5,3 (11,9)
GFR (mL/min)	66,1±29,3 (12,62–116)	63,5 (46,2)
Troponin (ng/L)	159,5±326,7 (1–1700)	35 (101)
pH	7,4±0,1 (7,1–7,55)	7,5 (0,1)
PO2 (mmHg)	80,3±30,8 (41–163)	74 (41,7)
PCO2 (mmHg)	30,4±7,7 (10–57)	30,5 (8,2)
HCO3 (mEq/L)	22,6±4,5 (10,4–31)	23 (5,5)
SO2 (%)	91,9±6,9 (71–99)	93,5 (11)
Lactate (mg/dL)	14,2±15,2 (1,2–92,4)	11,8 (7,4)
Scoring systems Mean±SD (min–max)		
Geneva	8,5±3,7 (1–16)	7,5 (6)
Wells	4,1±1,7 (1–8)	4 (2)
PESI	3,3±1,2 (1–5)	3 (1,7)
Mortality n (%) 12 (27,3)		

SD: Standard deviation; Med: Median; IR: interquartile range

The vital signs and laboratory values of the patients diagnosed as having PTE in the emergency department at the time of admission are shown in Table 1 in detail.

All patients diagnosed as having PTE were evaluated by diagnostic bedside transthoracic echocardiography (ECHO), and the Wells, Genova, and Pulmonary Embolism Severity Index (PESI) scores of these patients were calculated.

The 30-day mortality status of the patient group showed that 27.3% (n=12) of them died (Table 1).

PDGF-β levels of patients in the study groups

The mean PDGF-β levels in the patient group (n=44) was 994.5±541 ng/L, whereas the mean PDGF-β levels in the control group was 748±411.5 ng/L. The PDGF-β levels of the patients diagnosed as having PTE in the emergency department were found to be significantly higher than those of patients in the control group (Z=-2.015, p=0.044) (Table 2; Figure 1).

Table II: PDGF-β levels of patients in the study groups

	PDGF-β levels (ng/L)			
	mean±SD (min–max)	**Med (IR)**	**r**	**p**
Control group	748±411,5 (194,2–1763)	682,6 (509,5)	-2,015	0,044
Patient group	994,5±541 (286–2366,4)	789,7 (925,3)		

SD: Standard deviation; Med: Median; IR: Interquartile range.

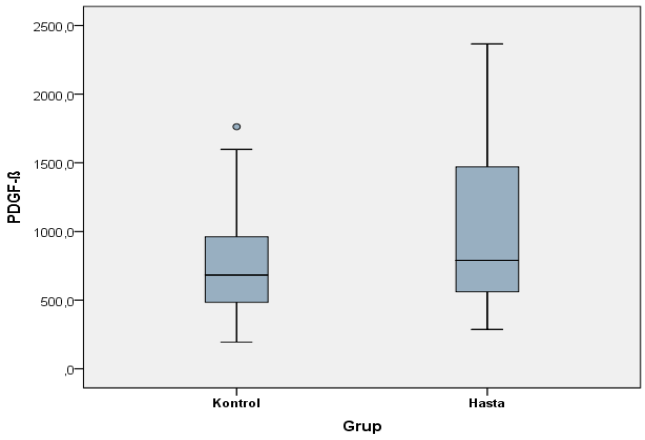

Figure 1. PDGF-β levels by study groups

The PDGF-β levels of 44 patients (patient group) diagnosed as PTE in the emergency department were analyzed.

Relationship between demographic characteristics and PDGF-β level

There was no significant linear relationship between PDGF-β levels and age, gender, and presence of chronic disease (r=-0.006, p=0.967; r=-0.403, p=0.687; and r=-0.928, p=0.353, respectively) (Table 3).

Relationship between vital signs and PDGF-β level

There was no significant linear relationship between PDGF-β levels and systolic and diastolic blood pressure as well as peak heart rate, respiratory rate, and axillary body temperature values at the time of admission to the emergency department (p>0.05) (Table 3).

Table III: The relationship between demographic features, vital signs, and prognostic scoring systems and PDGF-β levels in the patient group

PDGF-β levels (ng/L)					
		mean±SD (min–max)	**Med (IR)**	**r**	**p**
Demographic features					
Gender	Female	946,8±490,8 (302,6–1901,6)	757,9 (907,6)	-0,403	0,687
	Male	1057,2±608,8 (286–2366,4)	809,9 (940,2)		
Age				-0,006	0,967
Chronic disease	-	931±590,6 (286–2366,4)	720,4 (917,7)	-0,928	0,353
	+	1034,4±514,8 (302,6–2315,8)	801,9 (821,3)		
Diabetes Mellitus	-	1026,6±567,1 (286–2366,4)	793,7 (946,9)	0,705	0,710
	+	885,2±449,4 (302,6–1599,5)	779,9 (780,9)		
Chronic Hypertension	-	992,6±577,1 (286–2366,4)	809,9 (1017,4)	-0,153	0,879
	+	996,2±518,9 (302,6–2315,8)	777,4 (873,1)		
Coronary Artery Disease	-	957,2±529,9 (286–2366,4)	801,9 (982,2)	-0,334	0,738
	+	1066,5±573,4 (302,6–2315,8)	777,4 (805,1)		
Chronic heart failure	-	939±492,2 (286–2366,4)	757,9 (851,7)	0,377	0,394
	+	1288±724,2 (302,6–2315,8)	1431,7 (1363,4)		
Vital signs	Systolic Blood Pressure			0,091	0,559
	Diastolic Blood Pressure			-0,180	0,243
	Peak heart rate			-0,109	0,480
	Axillary body temperature			-0,012	0,939
	Respiratory rate			-0,037	0,813
Score	Geneva			0,072	0,640
	Wells			0,126	0,414
	PESI			-0,070	0,652

r: correlation coefficient, SD: Standard deviation; Med: Median; IR: Interquartile range.

Relationship between prognostic scoring systems and PDGF-β level

There was no significant linear relationship between PDGF-β levels and the Geneva, Wells, and PESI scores (r= 0.072, p=0.640; r= 0.126, p=0.414; and r=-0.070, p=0.652, respectively) (Table 3).

Relationship between laboratory values and PDGF-β level

There was no significant linear relationship between PDGF-β levels and laboratory values of various blood parameters in samples collected from the participants at the time of admission to the emergency department (p>0.05) (Table 4).

Table IV: Relationship between laboratory values and PDGF-β levels in the patient group

Laboratory values	r	p
WBC (10^3/uL)	-0,142	0,358
RBC	0,006	0,969
HGB (g/dL)	0,054	0,726
PLT (10^3/uL)	-0,130	0,400
aPTT (sec)	0,169	0,272
PTZ (%)	0,045	0,772
INR	0,008	0,961
CRP (mg/dL)	0,087	0,573
GFR	0,193	0,210
Troponin (ng/L)	0,224	0,143
pH	0,292	0,054
PO2 (mmHg)	0,176	0,254
PCO2 (mmHg)	-0,146	0,345
HCO3 (mEq/L)	0,122	0,431
SO2 (%)	0,203	0,185
Lactate (mg/dL)	-0,179	0,246
D-Dimer (mg/L)	0,124	0,422

r: correlation coefficient

Mortality Analysis

Examination of the factors affecting mortality in our study did not identify a significant linear relationship between age, gender, presence of chronic disease and mortality. (p>0.05; Table 5).

Table V: Association of demographic characteristics with mortality

Mortality					
Demographic features		**Survived** (n=32)	**Death** (n=12)	**t/χ^2**	**p***
Age (years) Mean±SD (Min–Max)		68±13,3 (40–96)	71,3±12,2 (43–86)	-0,755	0,454
Med (IR)		66,5 (21)	71,5 (18,3)		
Gender (n,%)	Female	19 (76)	6 (24)	-0,313	0,576
	Male	13 (68,4)	6 (31,6)		
Chronic disease (n,%)	-	11 (64,7)	6 (35,3)	-	0,489
	+	21 (77,8)	6 (22,2)		
Diabetes Mellitus	-	25 (73,5)	9 (26,5)	-	1,000
	+	7 (70)	3 (30)		
Chronic Hypertension	-	14 (66,7)	7 (33,3)	0,744	0,388
	+	18 (78,3)	5 (21,7)		
Coronary Artery Disease	-	21 (72,4)	8 (27,6)	-	1,000
	+	11 (73,3)	4 (26,7)		
Chronic heart failure	-	26 (70,3)	11 (29,7)	-	0,653
	+	6 (85,7)	1 (14,3)		

**: Fisher's exact test, SD: Standard deviation; Med: Median; IR: Interquartile range.*

As chronic pancreatitis and cerebrovascular events were observed in one person each, statistical analysis could not be performed.

Examination of the relationship between vital signs and mortality in patients with PTE revealed a significant relationship between mortality and all vital signs, except axillary temperature measurements (Table 6).

All prognostic scoring system scores, except for the Geneva score, were found to be significantly associated with mortality. Wells and PESI scores were found to be significantly higher in patients who died (p<0.001; Table 6).

Table VI: Relationship among vital signs and prognostic scoring systems and mortality

Vital signs		Mortality: Survived (n=32)	Mortality: Death (n=12)	t/Z	P
Systolic Blood Pressure	Mean±SD (Min–Max)	114,5±24,7 (70–163)	91,7±11 (75–106)	4,225	<0,001
	Med (IR)	109,5 (33,8)	90,5 (21,8)		
Diastolic Blood Pressure	Mean±SD (Min–Max)	68,7±14,7 (37–102)	55,3±5,9 (48–68)	4,310	<0,001
	Med (IR)	70 (20)	53 (9,8)		
Peak heart rate	Mean±SD (Min–Max)	97,5±15,4 (70–138)	115,8±21 (90–150)	-2,579	0,010
	Med (IR)	94,5 (15,3)	120 (37,3)		
Axillary body temperature	Mean±SD (Min–Max)	36,6±0,3 (36–37)	36,8±0,5 (36–38,1)	-1,333	0,183
	Med (IR)	36,7 (0,4)	36,8 (0,5)		
Respiratory rate	Mean±SD (Min–Max)	18,7±4,1 (12–35)	24,8±5,4 (18–37)	-3,637	<0,001
	Med (IR)	18 (4)	23,5 (7,5)		
Score					
Geneva	Mean±SD (Min–Max)	8,4±3,6 (1–15)	8,8±4,2 (3–16)	-0,294	0,770
	Med (IR)	7,5 (6)	7,5 (6,3)		
Wells	Mean±SD (Min–Max)	3,5±1,5 (1–6)	5,6±1,3 (4–8)	-4,277	<0,001
	Med (IR)	3 (2,1)	5,5 (2,5)		
PESI	Mean±SD (Min–Max)	3±1,1 (1–5)	4,3±0,9 (3–5)	-3,270	0,001
	Med (IR)	3 (2)	4,5 (1,8)		

SD: Standard deviation; Med: Median; IR: Interquartile range.

When the relationship between laboratory values and mortality in patients with PTE was examined, the relationship of mortality with CRP, GFR, and PCO2 values was found to be significant. GFR and PCO2 values were significantly lower, whereas CRP values were significantly higher in deceased patients (p=0.021, 0.011, and 0.004, respectively). In our study, no significant linear relationship was found between PDGF-β and DD levels in patients with PTE and mortality (p=0.687 and 0.173, respectively) (Table 7).

Table VII: Relationship between laboratory values and mortality

		Mortality: Survived (n=32)	Mortality: Death (n=12)	t/Z	P
WBC (10^3/uL)	Mean±sd (Min–Max)	11,9±4,5 (6–24)	12,5±5,9 (2,1–21)	-0,321	0,749
	Med (IR)	11 (6,9)	11,5 (6,6)		
RBC	Mean±sd (Min–Max)	4,4±0,9 (2,8–6,8)	4,6±0,5 (3,8–5,6)	-0,546	0,588
	Med (IR)	4,5 (1,4)	4,6 (0,5)		
HGB (g/dL)	Mean±sd (Min–Max)	12,5±2,7 (8–18)	12,6±1,5 (10,3–16)	-0,106	0,916
	Med (IR)	12,8 (4,6)	12,5 (1,1)		
PLT (10^3/uL)	Mean±sd (Min–Max)	265,6±101,2 (106–541)	201,3±118,8 (66–465)	1,789	0,081
	Med (IR)	253 (118,3)	162 (137,5)		
APTT (sec)	Mean±sd (Min–Max)	23,9±4,3 (18,7–37,9)	22,9±5 (15–33)	-0,752	0,452
	Med (IR)	22,9 (5,3)	21,7 (7,1)		
PTZ (%)	Mean±sd (Min–Max)	13,6±2,6 (10,7–24)	14,4±2,5 (11–18,6)	-1,267	0,205
	Med (IR)	13,1 (2,9)	14,3 (3,7)		
INR	Mean±sd (Min–Max)	1,2±0,2 (0,92–2)	1,2±0,2 (1–1,6)	-1,068	0,285
	Med (IR)	1,1 (0,3)	1,2 (0,4)		
CRP (mg/dL)	Mean±sd (Min–Max)	6,1±7 (0,3–31)	12,5±6,6 (1,6–24)	-2,873	0,004
	Med (IR)	3,2 (5,7)	13,5 (9,3)		
GFR	Mean±sd (Min–Max)	72,2±27 (12,62–116)	49,7±30 (15–102)	2,395	0,021
	Med (IR)	71 (45,3)	45 (43,8)		
Troponin (ng/L)	Mean±sd (Min–Max)	160,8±343,9 (1–1700)	156,2±289,6 (3–966)	-0,053	0,958
	Med (IR)	43 (93,3)	31,5 (100)		
PH	Mean±sd (Min–Max)	7,4±0,1 (7.29–7.55)	7,4±0,1 (7,1–7,53)	-0,026	0,979
	Med (IR)	7,5 (0,1)	7,5 (0,1)		
PO2 (mmHg)	Mean±sd (Min–Max)	76,1±27,1 (41–160)	91,5±38,1 (53–163)	-1,200	0,230
	Med (IR)	70,5 (46)	78,5 (58)		
PCO2 (mmHg)	Mean±sd (Min–Max)	32,1±7,2 (18–57)	25,7±7,1 (10–34)	-2,537	0,011
	Med (IR)	31,5 (5,8)	27 (10,5)		
HCO3 (mEq/L)	Mean±sd (Min–Max)	23,4±3,7 (16–31)	20,6±5,7 (10,4–28)	1,600	0,131
	Med (IR)	23,2 (4,9)	22,1 (9,3)		
SO2 (%)	Mean±sd (Min–Max)	91,2±7,5 (71–99)	93,8±4,9 (85–99)	-0,781	0,435
	Med (IR)	93 (12,8)	96 (8,5)		
Lactate (mg/dL)	Mean±sd (Min–Max)	10,4±4,8 (1,2–20,1)	24,3±26,1 (2–92,4)	-1,793	0,073
	Med (IR)	11,3 (6,2)	14,5 (26,7)		
PDGF-β (ng/L)	Mean±sd (Min–Max)	993,1±533,4 (302,6–2315,8)	998,3±585,1 (286–2366,4)	0,683	0,687
	Med (IR)	742,1 (984,3)	805,9 (765,7)		
D-Dimer (mg/L)	Mean±sd (Min–Max)	9,3±3,5 (2,8–16,1)	11±4,1 (5,4–20,6)	-1,386	0,173
	Med (IR)	9,3 (5,4)	11,4 (5,2)		

SD: Standard deviation; Med: Median; IR: Interquartile range.

DISCUSSION

PTE is a disease having high mortality and morbidity; however, it is often difficult to diagnose due to the lack of specific clinical findings[8-10]. As the rapid diagnosis of this condition and the initiation of treatment will decrease mortality, the use of noninvasive tests to aid in the diagnosis is increasing gradually. Although various biomarkers are used in the diagnosis of PTE today, a marker with high sensitivity and specificity has not yet been identified[15,16]. Hence, there is still a need for endogenous biomarkers with high specificity and sensitivity to shorten the time to diagnosis of PTE. Our study is one of the few studies in the literature investigating the diagnostic value of plasma PDGF-B in PTE cases, and to the best of our knowledge, it is the first study to investigate the relationship between plasma PDGF-B and mortality in PTE cases[1,2].

Pulmonary arterial hypertension, which may occur due to various etiologies, is a condition characterized by increased pulmonary vascular resistance[7,20]. Acute PTE is one of the leading causes of this condition. Mechanical obstruction of the pulmonary arteries by the acute thromboembolic mass is the most important pathophysiological event leading to pulmonary hypertension. Endothelial cells, platelets, and other factors in the coagulation cascade are responsible for the formation of PTE ([4,20,21]). Following the development of these thrombotic lesions, pulmonary arterial hypertension occurs due to persistent vasoconstriction and structural remodeling of the pulmonary artery. According to recent reports, endothelial damage and in situ thrombosis play a prominent role in the pathophysiology of pulmonary hypertension[4,6,21]. Mitogenic mediators, including PDGF, secreted by active platelets during proliferative processes lead to functional and structural changes in the pulmonary vascular bed[22].

PDGF is synthesized by various cell types and consists of two homologous polypeptide chains (A and B). Platelets, macrophages, and endothelial cells can produce both the chains, whereas vascular smooth muscle cells produce only the PDFG-A chain[17]. As observed in acute PTE, the synthesis and release of PDGF-B from the endothelium and platelets increases markedly on exposure to low oxygen pressure and excessive thrombin levels[1,2,18,23]. Therefore, PDGF-B is considered as a key mediator in the development of thrombosis. Studies have reported that a higher PDGF-B concentration than the standard value in healthy or normal controls indicates a risk or presence of thrombosis[2,17]. Accordingly, we aimed to investigate whether plasma PDGF-B levels have a diagnostic value in acute PTE and the relationship of PDGF-B with mortality.

As deep vein thrombosis (DVT) and venous thromboembolism (VTE), including PTE, are the third most common cardiovascular disease worldwide[1], plasma biomarkers having high specificity are needed to estimate the risk of venous thromboembolism. A study by Bruzelius et al.[1] comprehensively analyzed plasma samples from two independent case-control studies and examined a novel VTE-associated plasma protein. This study was based on the Venous thromboEmbolism BIOmarker (VEBIOS) and FARIVE studies (Replication study). In the VEBIOS and FARIVE studies, plasma levels of PDGF-B were reported to be associated with VTE, and the investigators stated that PDGF could be used as a novel VTE-associated plasma protein and emphasized the need for further studies. Based on this study, Alhabibi et al.[2] found, in their study, that PDGF-B is a specific marker in the diagnosis of DVT. In our study, plasma PDGF-β levels were found to be significantly higher in patients diagnosed as having acute PTE compared with those in the control group. This may be associated with increased plasma PDGF-B levels in the presence

of acute thrombosis. As mentioned in the previous sections of the present article, increased plasma PDGF-B levels are intimately associated with an increased risk or the presence of thrombosis.

In our study, there was no significant linear relationship between age, gender distribution, and presence of chronic disease and PDGF-β levels in patients diagnosed as having PTE. Similarly, no significant difference was reported between PDGF-B levels in the FARIVE study that compared PTE cases with or without cardiovascular risk factors[1].

Currently, laboratory and imaging methods are used to diagnose PTE. Complete blood count, arterial blood gas analysis, and biochemical evaluations are insufficient for a definitive diagnosis. Leukocytosis, increased serum LDH and AST levels, and an increase in CRP and sedimentation rate can be detected in PTE cases, but the specificity of these analyses in the diagnosis of acute PTE is quite low. DD measurement is frequently used in our daily practice. However, its reliability is low because it may increase in diseases other than PTE and in elderly patients. The negative predictive property of DD can be exploited. However, a negative DD test in the emergency department can eliminate PTE as a suspected diagnosis in only 30% of patients, even when combined with clinical scoring systems[2,12,13,21,24]. With the discovery of new endogenous biomarkers to aid in the diagnosis of PTE, mortality, morbidity, and healthcare costs are expected to decrease.

A study by Alhabibi et al ([2]) compared PDGF-B and DD levels in the diagnostic evaluation of acute DVT and reported that the specificity of PDGF-B was higher than DD in the diagnosis of acute DVT (95% and 90%, respectively). The investigators suggested that the plasma PDGF-B level can be used as a marker with high specificity in acute DVT cases. In addition, they reported that in cases with high DD levels, such as inflammation, pregnancy, liver disease, and cancer, plasma PDGF-B measurements may be beneficial in the diagnosis of DVT if there is high degree of clinical suspicion. In contrast to the reports in literature, there was no significant correlation between DD levels and plasma PDGF-B levels in acute PTE cases in our study.

Few studies have evaluated the relationship between the DD test used for PTE diagnosis and prognosis. Studies by Lobo et al.[25] and Jeebun et al.[16] found that clot load and DD level were correlated. Our study, however, did not find any significant linear relationship between PDGF-β and DD levels and mortality in patients with PTE.

A study by Nordenholz et al.[26] investigated the diagnostic significance level of 50 different biomarkers in 22 VTE cases and found that the diagnostic accuracy rate of CRP was above 70%, which was not statistically significant to predict mortality. A study by Becattini et al.[27] reported that high troponin I and T levels were significant in determining the short-term mortality of PTE cases. The relationship of mortality with CRP, GFR, and PCO2 values was found to be significant when the relationship between laboratory values other than PDGF-β and DD levels and mortality was examined in our study. GFR and PCO2 values were significantly lower and CRP values were significantly higher in deceased patients. According to our study results, the level of plasma PDGF-B, which is considered as a new biomarker, does not predict mortality in patients with acute PTE, and we conclude that plasma PDGF-B levels cannot be used as a marker to predict prognosis.

CONCLUSION

The results obtained from this study, which investigated whether PDGF-B was a new prognostic biomarker for PTE, suggest that plasma PDGF-B levels are significantly higher in PTE cases and can aid in the diagnosis of PTE. However, PDGF-B cannot be used as a marker to predict prognosis. We believe that

comprehensive studies regarding this in the future will provide precise information and contribute to literature.

Footnote

This study is the speciality thesis in Emergency Medicine of Dağıstan Sakçi.

Ethics Committee Approval: The study was conducted according to the World Medical Association Declaration of Helsinki for studies on human subjects and was approved by the Scientific Research Ethics Committee of our university (dated February 17th, 2020; protocol number: TÜTF-BAEK 04/10).

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