PROGNOSTIC VALUE OF D-DIMER IN YOUNGER PATIENTS WITH PULMONARY EMBOLISM

Ljiljana Jovanović¹, Vesna Subota¹, Milena Rajković¹, Bojana Subotić², Boris Džudović², Nataša Novčić², Jovan Matijašević³, Milica Mirić³, Sonja Šalinger⁴, Nataša Marković Nikolić⁵, Maja Nikolić⁶, Vladimir Miloradović⁶, Ljiljana Kos⁷, Tamara Kovačević-Preradović⁷ and Slobodan Obradović^{2,8}

¹ Institute of Biochemistry, Military Medical Academy, Belgrade, Serbia

² Clinic of Cardiology and Emergency Internal Medicine, Military Medical Academy, Belgrade, Serbia

³ Institute for Pulmonary Diseases of Vojvodina, School of Medicine, University of Novi Sad, Sremska Kamenica, Serbia

⁴ Clinic of Cardiology, Clinical Center Nis, University of Nis, Serbia

⁵ University Clinical Center Zvezdara, School of Medicine, University of Belgrade, Serbia

⁶ Clinic of Cardiology, Clinical Center Kragujevac, School of Medicine, University of Kragujevac, Serbia

⁷ Clinic of Cardiology, Clinical Center Banja Luka, School of Medicine, University of Banja Luka, Bosnia and Herzegovina

⁸ School of Medicine, University of Defense, Belgrade, Serbia

PROGNOŠTIČKA VREDNOST D-DIMERA KOD MLAĐIH PACIJENATA SA PLUČNOM TROMBOEMBOLIJOM

Ljiljana Jovanović¹, Vesna Subota¹, Milena Rajković¹, Bojana Subotić², Boris Džudović², Nataša Novčić², Jovan Matijašević³, Milica Mirić³, Sonja Šalinger⁴, Nataša Marković Nikolić⁵, Maja Nikolić⁶, Vladimir Miloradović⁶, Ljiljana Kos⁷, Tamara Kovačević-Preradović⁷ i Slobodan Obradović^{2,8}

¹ Institut za biohemiju, Vojnomedicinska akademija, Beograd, Srbija

² Klinika za kardiologiju i hitne interne bolesti, Vojnomedicinska akademija, Beograd, Srbija

³ Institut za plućne bolesti Vojvodine, Medicinski fakultet, Univerzitet u Novom Sadu, Sremska Kamenica, Srbija

⁴ Klinika za kardiologiju, Klinički centar Niš, Univerzitet u Nišu, Srbija

⁵ Univerzitetski klinički centar Zvezdara, Medicinski fakultet, Univerzitet u Beogradu, Srbija

⁶ Klinika za kardiologiju, Klinički centar Kragujevac, Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Srbija

⁷ Klinika za kardiologiju, Klinički centar Banja Luka, Medicinski fakultet, Univerzitet u Banja Luci, Bosna i Hercegovina

⁸ Medicinski fakultet, Univerzitet odbrane, Beograd, Srbija

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ABSTRACT

In patients with pulmonary embolism (PE), the D-Dimer assay is commonly utilized as part of the diagnostic workup, but data on D-Dimer for early risk stratification and short-term mortality prediction are limited. The purpose of this study was to determine D-Dimer levels as a predictive biomarker of PE outcomes in younger (<50 years of age) compared to older patients. We conducted retrospective analysis for 930 patients diagnosed with PE between 2015 and 2019 as part of the Serbian University Multicenter Pulmonary Embolism Registry (SUPER). All patients had D-Dimer levels measured within 24 hours of hospital admission. The primary outcome was mortality at 30 days or during hospitalization. Patients were categorized into two groups based on age (≤ 50 and >50 years of age). Younger patients constituted 20.5% of the study cohort. Regarding all-cause mortality, 5.2% (10/191) of patients died in group under the 50 years of age; the short-term all-cause mortality was 12.4% (92/739) in older group. We have found that there was significant difference in plasma D-Dimer level between patients ≤ 50 years of age and older group (>50), $p=0.006$. D-Dimer plasma level had good predictive value for the primary outcome in younger patients (c-statistics 0.710; 95% CI, 0.640-0.773; $p<0.031$). The optimal cutoff level for D-Dimer to predict PE-cause death in patients aged >50 years was found to be 8.8 mg/l FEU (c-statistics 0.580; 95% CI 0.544-0.616; $p=0.049$). In younger PE patients, D-Dimer levels have good prognostic performance for 30-day all-cause mortality and concentrations above 6.3 mg/l FEU are associated with increased risk of death. D-Dimer in patients aged over 50 years does not have predictive ability for all-caused short-term mortality. The relationship between D-Dimer and age in patients with PE may need further evaluation.

Keywords: D-Dimer, pulmonary embolism, younger population, mortality

SAŽETAK

Određivanje D-Dimera je deo dijagnostičkog procesa kod pacijenata obolelih od plućne tromboembolije (PE), međutim ima malo podataka o upotrebi D-Dimera u predviđanju rizika i kratkotrajnog mortaliteta. Cilj ove studije je utvrđivanje uloge D-Dimera kao prediktivnog biomarkera u proceni ishoda plućne tromboembolije kod mlađih (<50 godina) i starijih pacijenata. Retrospektivno je analizirano 930 pacijenata sa dijagnozom plućne tromboembolije u periodu od 2015 do 2019-te godine u okviru srpskog multicentričnog registra za plućnu tromboemboliju. D-Dimer je određivan svim pacijentima u prvih 24 sata od prijema u bolnicu. Praćena je smrtnost tokom hospitalizacije ili u prvih 30-dana od prijema. Pacijenti su na osnovu starosnog doba podeljeni u dve grupe (manje od 50 i više od 50 godina). Mlađi pacijenti sačinjavali su 20.5% studijske kohorte. Kod pacijenata mlađih od pedeset godina umrlo je 5.2% (10/191), dok je kod starijih ukupna smrtnost bila 12.4% (92/739). Pronađena je statistički značajna razlika vrednosti D-Dimera između pacijenata mlađih od 50 godina i starije grupe ispitanika (>50 godina), $p=0.006$. Vrednost D-Dimera u plazmi ima dobru prediktivnu vrednost za smrtnost kod mlađih pacijenata (c-statistika 0.710; 95% CI, 0.640-0.773; $p<0.031$). Utvrđen je odgovarajući cutoff za predviđanje smrtnosti direktno povezane sa PE kod pacijenata koji imaju više od 50 godina i iznosi 8.8 mg/l FEU (c-statistika 0.580; 95% CI 0.544-0.616; $p=0.049$). Kod mlađih pacijenata D-dimer ima dobre prognostičke karakteristike u utvrđivanju 30-to dnevne smrtnosti, tako da su koncentracije D-Dimera iznad 6.3 mg/l FEU povezane sa povećanim mortalitetom. D-Dimer kod pacijenata starijih od 50 godina nema ulogu u predviđanju kratkotrajne smrtnosti. Potrebna su dalja istraživanja kako bi se proučio odnos između vrednosti D-Dimera i starosne dobi kod pacijenata sa plućnom tromboembolijom.

Ključne reči: D-Dimer, plućna tromboembolija, mlađa populacija, smrtnost.

INTRODUCTION

Pulmonary embolism (PE) is a common life-threatening condition which contributes to the global burden of cardiovascular diseases in terms of morbidity and mortality(1-5). The 30-day mortality rate due to PE exceeds 15% (6). Prompt diagnosis, risk assessment and adequate treatment can improve the outcome (7). A reliable risk stratification of PE severity based on the 2019 ESC Guidelines, pulmonary embolism severity index (PESI) or simplified PESI (sPESI) indicates risk of early (in-hospital or 30-day) death(8-11). Adding biomarkers data may help in improving prognosis and categorization of patients with acute PE into risk classes (11-12). The use of elevated D-Dimer levels to evaluate severity of PE remains limited (6). D-Dimer age adapted cutoff level (D-Dimer cut off = age x 10 µg/l FEU, age > 50) defined categories of patients ≤50 and >50 years of age (13,14). Although it is well recognized that PE has been shown to be major cause of mortality in younger population, there are relatively few studies looking particularly at PE in this age group (15). The aim of this study is to determine age-specific role of D-Dimer in both age groups in patients with PE.

MATERIALS AND METHODS

The present report is a retrospective analysis of the Serbian University Multicenter Pulmonary Embolism Registry (SUPER). The PE patients diagnosed by multidetector computed pulmonary angiography (MDCT-PA) in university cardiology or pulmonology clinics (Military Medical Academy Belgrade, Institute for Pulmonary Diseases of Vojvodina Sremska Kamenica, Clinical Center Nis, University Clinic Zvezdara and Clinical Center Kragujevac) from January 2015 to September 2019, were selected. The study end point was defined as thirty-day mortality in patients who died within 30 days of hospital admission. In 930 patients who were aged ≥18 years, D-Dimer tests were performed within 24 hours of hospitalization as a part of diagnostic workup. The D-Dimer levels in citrated plasma were measured via Siemens (Marburg, Germany) BCS analyzer and the immunoturbidimetric assay (Siemens Innovance D-Dimer test kit). Patients were categorized into two groups based on age (≤50, >50 years).

STATISTICAL ANALYSIS

Descriptive statistics are presented as frequency and percentages for categorical data and their distribution was further analyzed with χ^2 test. D-Dimer was given as median and 25th-75th percentile. Comparison in D-Dimer between two independent groups was analyzed with Mann-Whitney test. All tests were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA) and p values of < 0.05 were considered significant. Receiver operating curve (ROC) analysis was utilized to determine area under the curve (AUC) and cutoff level for D-Dimer in both age groups using MedCalc for Windows version 18.11.3 (MedCalc Software, Acaciaaan, Belgium).

RESULTS

The final analysis enrolled 930 patients with PE, mean age 62.96 ± 15.46 and significant difference between deceased patients (69.44 ± 14.74) and survivors (62.16 ± 15.37), $p < 0.001$. There were 102 short-term (within 30 days) all-cause deaths of which 60.78 % caused by PE.

Table 1. shows the baseline characteristics of the studied patients. Among the patients aged > 50 years, BMI higher than 25 ($p = 0.032$), chronic diseases such as diabetes mellitus ($p = 0.043$) and coronary heart failure ($p = 0.015$), history of stroke ($p = 0.001$) and thrombosis ($p = 0.028$), were the major factors that would cause death. Beside kidney failure as the independent predictor of all-cause mortality for all PE patients ($p < 0.001$), malignancy ($p = 0.018$) was the most common risk factor in younger patients (age ≤ 50 years). Younger patients may often have investigation for possible thrombophilia and pregnancy. Of the 36 patients who underwent a thrombophilia screen, 20 of them were positive and 3 patients were pregnant.

There was significant difference in plasma D-Dimer level between patients ≤ 50 years of age and older group (>50), $p = 0.006$. D-Dimer concentration below group specific cutoff were in 1.6% of patients age ≤ 50 years (cut off = 0.5 mg/l FEU) and 2.7% of older population (cut off = age x 0.01 mg/l FEU). D-Dimer values between deceased and survivors was significantly different in patients aged ≤ 50 years ($p = 0.026$). In older group no significant difference was observed with respect to all-cause mortality, but mean D-Dimer level was significantly higher in patients who died of acute PE within 30 days than survivors ($p = 0.005$).

Among patients classified as being at low risk by the sPESI, mortality was 2.7% (9/330). The sPESI classified 600 patients (64.5%) in the high risk group (≥1 point) and mortality of high risk patients was 15.5% (93/600) (Table 2). sPESI and PESI score stratified patients as it was presumed, and 30-day mortality rate were higher in patients with sPESI ≥1 and increased significantly from the first to the fifth PESI risk class in both age groups. The median D-Dimer level in the sPESI ≥1 group was significantly higher than in the sPESI = 0 group, 5.0 mg/l FEU (2.6-9.5 mg/l FEU) versus 4.4 mg/l FEU (2.3-8.0 mg/l FEU), respectively, $p = 0.029$, as shown in Figure 1. According to sPESI criteria in patients ≤ 50 years of age, high-risk patients had significantly higher D-Dimer levels than low-risk group (4.7 mg/l FEU, 3.6 mg/l FEU, $p = 0.005$). On the other hand, PESI classification in patients aged over 50 years showed slightly significant difference between five risk groups ($p = 0.05$).

PE patients were evaluated according to the algorithm proposed by the 2019 ESC guidelines for prediction risk of early mortality. The mortality was 2.2% (7/319) in the low risk class, 5.3% (11/206) in the intermediate-low, 14.8% (41/277) in the intermediate-high and 33.6% (43/128) in the high risk class.

To estimate the predictive capability of the D-Dimer in different age groups (≤ 50 vs > 50), a ROC analysis was conducted (Table 3). D-Dimer concentrations above 6.3 mg/l FEU was good prognostic biomarker for 30-day all-cause mortality in younger patients (c-statistics 0.710; 95% CI, 0.640-0.773; $p=0.031$). In population over 50 years of age, D-Dimer showed modest discriminative power for 30-day PE-cause mortality with 8.8 mg/l FEU cutoff and an c-statistics 0.580; 95% CI 0.544-0.616; $p=0.049$.

DISCUSSION

D-Dimer levels are used in diagnostic workup of suspected PE, and its elevated values are predictive in detecting and recurrence of PE (16-18). There was a relationship between increased D-Dimer concentrations and clot burden, thrombus localization, major bleeding and RV dysfunction (18-20). Studies of D-Dimer in patients with PE have demonstrated various data regarding the severity of PE and early risk stratification (22-23).

In this study, high risk patients stratified according to new revised ESC Guidelines were 18.4% of all PE patients and up to one third of them died within the first 30-days. Since risk of development of PE doubles with each decade after forties (24), 90.7% of deceased in high risk group were older than 50 years. But, D-Dimer levels were not significantly associated with short-term all-cause mortality in older patients. The reason might be as followings: D-Dimer as a fibrin degradation product can be increased in cancer, infections and wide spectrum of inflammatory, vascular and systemic diseases. Also, comorbidities increase with age and may affect the outcome.

Thus comorbidity burden may explain some of limitations of D-Dimer prognostic performance (25-26). Consequently, D-Dimer was slightly significant predictor of PE-cause mortality.

Prognostic ability of D-Dimer to predict short-term mortality in younger population with PE was observed. Our data showed that every fifth patient with PE was under 50 years of age, similar to the other findings (27-28). In this study was found a difference for the AUCs of D-Dimer in patients < 50 and ≥ 50 years of age, showing much better discrimination in the younger group (AUC of 0.710 vs. 0.541, respectively). There were no deaths in patients (< 50 years of age) with sPESI=0 and in higher risk classes of PESI (4th and 5th). It appears that lower mortality, better general health status and lower comorbidity rate in younger patients (27) were reflected by behavior of D-Dimer.

The main limitation of this study is the relatively low number of deaths in younger population and its retrospective nature. Moreover, D-Dimer values below age-adjusted cutoff were present in 2.5% of patients. These results were considered as false negative because of increased age of thrombus, collagenized poorly degradable fibrin and prior treatment with anticoagulation (29).

In conclusion, our findings suggest that high levels of D-Dimer (6.3 mg/l FEU), measured on hospital admission, identify patients under 50 years of age at increased risk of death during the first 30-days of PE diagnosis. The use of D-Dimer in patients aged over 50 years does not have prognostic power for all-cause short-term mortality.

Table 1. Baseline characteristic between PE subgroups

Variables		All patients			≤50 years			>>50 years		
		30-day mortality								
		No N=828	Yes N=102	p value	No N=181	Yes N=10	p value	No N=647	Yes N=92	p value
Gender, N (%)	Male	408 (49.3)	43 (42.2)	0.208	114 (63.0)	7 (70.0)	0.749	294 (45.4)	36 (39.1)	0.265
	Fe- male	420 (50.7)	59 (57.8)		67 (37.0)	3 (30.0)		353 (54.6)	56 (60.9)	
Comorbidities (N, %)										
Smoking		141 (18.2)	11 (12.1)	0.078	60 (34.9)	1 (11.1)	0.215	81 (13.5)	10 (12.2)	0.273
Oral contraceptives		12 (1.5)	0 (0)	0.625	6 (3.4)	0 (0)	1.000	6 (1)	0 (0)	1.000
BMI 25-29.99, Over- weight		247 (35.8)	20 (24.4)	0.032	44 (28.0)	2 (22.2)	0.462	203 (38.2)	18 (24.7)	0.032
BMI ≥30, Obese		165 (23.9)	17 (20.7)		40 (25.5)	1 (11.1)		125 (23.5)	16 (21.9)	
COPD		89 (10.7)	17 (16.7)	0.097	5 (2.8)	0 (0.0)	1.000	84 (13.0)	17 (18.5)	0.148
CHF		102 (12.3)	24 (23.5)	0.003	7 (3.9)	1 (10.0)	0.355	95 (14.7)	23 (25.0)	0.015

CAD	90 (10.9)	19 (19.0)	0.056	1 (0.6)	0 (0.0)	0.948	89 (13.8)	19 (21.1)	0.079
History of DVT/PE	119 (14.5)	5 (5.0)	0.005	30 (16.7)	0 (0.0)	0.368	89 (13.9)	5 (5.5)	0.028
Hypertension	473 (57.3)	62 (60.8)	0.525	29 (16.0)	1 (10.0)	1.000	444 (68.8)	61 (66.3)	0.632
MI+Stroke+ PAD	127 (15.4)	23 (23.0)	0.061	9 (5.0)	0 (0.0)	1.000	118 (18.3)	23 (25.6)	<0.115
DM	147 (17.8)	28 (27.5)	0.022	13 (7.2)	0 (0.0)	1.000	134 (20.7)	28 (30.4)	0.043
History of stroke	49 (5.9)	17 (16.7)	<0.001	5 (2.8)	0 (0.0)	1.000	44 (6.8)	17 (18.5)	0.001
Malignancy	98 (11.8)	21 (20.6)	0.018	10 (5.5)	4 (40.0)	0.003	88 (13.6)	17 (18.5)	0.205
Major surgery	126 (15.2)	15 (14.7)	1.000	23(12.7)	2 (20.0)	0.623	103 (15.9)	13 (14.1)	0.760
Creatinine Clearance <60	223 (27.9)	71 (70.3)	<0.001	8 (4.6)	6 (60.0)	<0.001	215 (34.3)	65 (71.4)	<0.001
Creatinine Clearance <30	45 (5.7)	29 (28.7)	<0,001	1 (0.6)	3 (30.0)	<0.001	44 (7.1)	26 (28.6)	<0.001

Baseline characteristic between PE subgroups.*p value < 0.05 significant; (%) - percentage of PE patients with (Yes) or without (No) adverse events. Abbreviations: M, male; F, female; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CHF, coronary heart failure; DVT, deep vein thrombosis; PE, pulmonary embolism; CAD, coronary artery disease; MI, myocardial infarction; PAD, pulmonary

artery disease; DM, diabetes mellitus; Data were missing for smoking (7.1%), BMI (17.1%), oral contraceptives (3.4%), CAD (0.3%), DVT/PE (0.8%), hypertension (0.2%), MI+Stroke+PAD (0.4%), history of stroke (0.1%), creatinine clearance <60 (3.1%), creatinine clearance <30 (3.8%).

Table 2. Risk assessment in PE subgroups

Variables		All patients			≤ 50 years			>50 years		
		30-day mortality								
		No N=828	Yes N=102	p value	No N=181	Yes N=10	p value	No N=647	Yes N=92	p value
D-dimer (mg/l FEU)		4.6 (2.5-8.7)	5.5 (3.0-10.0)	0.028	4.0 (2.0-7.0)	7.8 (4.1-17.4)	0.026	4.9 (2.7-9.0)	5.2 (3.0-10.0)	0.201
Risk factors (N, %)										
sPESI	0	321 (38.8)	9 (8.8)	<0.001	96 (53.0)	0 (0)	0.002	225 (34.8)	9 (9.8)	<0.001
	≥1	507 (61.2)	93 (91.2)		85 (47.0)	10 (100.0)		422 (65.2)	83 (90.2)	
PESI	0	321 (38.8)	9 (8.8)	<0.001	96 (53.0)	0 (0)	<0.001	225 (34.8)	9 (9.8)	<0.001
	1	266 (32.1)	22 (21.6)		53 (29.3)	3 (3.0)		213 (32.9)	19 (20.7)	
	2	162 (19.6)	27 (26.5)		26 (14.4)	4 (40.0)		136 (21.0)	23 (25.0)	
	3	58 (7.0)	32 (31.4)		4 (2.2)	3 (30.0)		54 (8.3)	29 (31.5)	
	4	19 (2.3)	10 (9.8)		2 (1.1)	0 (0)		17 (2.6)	10 (10.9)	
	5	2 (0.2)	2 (2.0)		0 (0)	0 (0)		2 (0.3)	2 (2.2)	
Mortality risk N (%)	Low	312 (37.7)	7 (6.9)	<0.001	91 (50.3)	1 (10.0)	0.001	221 (34.2)	6 (6.5)	<0.001

	Intermediate-low	195 (23.6)	11 (10.8)		38 (21.0)	0 (0)		157 (24.3)	11 (12.0)	
	Intermediate-high	236 (288.5)	41 (40.2)		32 (17.7)	5 (50.0)		204 (31.5)	36 (39.1)	
	High	85 (10.3)	43 (42.2)		20 (11.0)	4 (40.0)		65 (10.0)	39 (42.4)	

Data for D-Dimer are presented as a median, 25th-75th percentile. Baseline characteristic between PE subgroups.*p value < 0.05 significant; (%) - percentage of PE patients with

(Yes) or without (No) adverse events. Abbreviations: M, male; F, female; PE, pulmonary embolism; sPESI, simplified pulmonary embolism severity index.

Table 3. ROC Analysis for D-Dimer predicting adverse outcomes in PE subgroups

	N	AUC	95% CI	p	Cut-off	Sensitivity	Specificity
All patients	930	0.567	0.534-0.599	0.031	7.6	41.18	70.89
≤50 years	191	0.710	0.640-0.773	0.031	6.3	70.00	72.93
> 50 years	739	0.541	0.504-0.578	0.212	8.8	35.87	74.19

AUC indicates area under the curve.

Figure 1. Median D-Dimer levels (mg/l FEU) in sPESI=0 and sPESI ≥1 (sPESI>0) patients

Data reported as median values, interquartile ranges (boxes), and 2.5th and 97.5th percentiles (whiskers).

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