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Different predictive value for short-term all-cause mortality with commonly used biomarkers regarding the cause of pulmonary embolism

Različite prediktivne vrednosti rutinskih biomarkera u proceni smrtnosti obolelih od plućne embolije u odnosu na njen uzrok

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Abstract

Background/Aim. The evaluation of blood levels of cardiac troponin I (cTnI), D-dimer, B-type natriuretic peptide (BNP), and C-reactive protein (CRP) on admission and during the treatment of pulmonary embolism (PE) are the part of routine diagnostic process and estimation of mortality risk. The aim of this study was to evaluate the predictive value of these biomarkers on admission for all-cause 30-day mortality in consecutive PE patients regarding whether they classified as spontaneous, transiently provoked, or permanently provoked PE. **Methods.** This retrospective analysis was gained from the data of 590 PE patients from the Serbian University Multicenter Pulmonary Embolism Registry (SUPER). Patients had at least one of these biomarkers (BNP, CRP, cTnI, and D-dimer) measured during the first 24 hours upon admission. **Results.** Receiver operating characteristic (ROC) curve analyses demonstrated that BNP had the highest prognostic accuracy for 30-day mortality in patients (n = 219) who had data for all examined biomarkers. BNP provided an AUC of 0.785 ($p < 0.001$). Separately, BNP had the highest c-statistic for all three groups of patients. CRP had a modest predictive value for the 30-day all-cause mortality in the group with transient provoked PE. Troponin I had a very modest predictive value for the 30-day all-cause mortality only in patients with spontaneous PE, and D-dimer was a very weak predictor of this end-point only in patients with persistent provoked PE. **Conclusion.** Patients with spontaneous, transient provoked, and persistent provoked PE have a significantly different profile of blood biomarkers level with different prognostic significance for early all-cause mortality.

Key words:
pulmonary embolism; biological factors; mortality; risk assessment; natriuretic peptides; troponin I; c-reactive protein.

Apstrakt

Uvod/Cilj. Rutinski dijagnostički proces i procena rizika od smrtnosti tokom prijema i lečenja plućne embolije (PE) obuhvata i analizu nivoa kardijalnog troponina I (cTnI), D-dimera, natriuretičnog peptida B-tipa (BNP) i C-reaktivnog proteina (CRP). Cilj ove studije bio je utvrđivanje prediktivne moći ovih biomarkera kako bi se odredio rizik od 30-to dnevne smrtnosti kod bolesnika obolelih od PE i to u odnosu na različite uzroke bolesti koji mogu biti spontani ili kratkotrajno i dugotrajno provocirani. **Metode.** Ova retrospektivna studija obuhvatila je 590 bolesnika obolelih od PE, iz multicentričnog Registra za plućnu emboliju. Tokom prvih 24 časa od prijema, bolesnicima je vršeno merenje bar

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jednog od analiziranih biomarkera (BNP, CRP, cTnI i D-dimer). **Rezultati.** *Receiver operating characteristic* (ROC) analiza je pokazala da BNP ima najvišu prognostičku vrednost u proceni 30-dnevne smrtnosti kod bolesnika (n = 219) kod kojih su bile poznate vrednosti svih analiziranih biomarkera. BNP je imao AUC od 0,785 ($p < 0,001$). Pojedinačno posmatrano, BNP je imao najvišu c-statistiku (*concordance*) za sve tri grupe bolesnika. CRP je pokazao skromnu prediktivnu moć za 30-dnevnu smrtnost u grupi bolesnika kod kojih je PE bila izazvana prolaznim faktorom. Troponin I je imao malu prediktivnu vrednost za 30-dnevnu smrtnost samo kod bolesnika sa spontanom PE, dok je D-dimer bio veoma slab prediktor i to kod bolesnika kod kojih je PE bila rezultat stalnih provocirajućih faktora. **Zaključak.** U odnosu na spontane, prolazne ili stalne provocirajuće uzroke nastanka PE, biohemijski profil ovih grupa bolesnika značajno je različit, kao i prognostički značaj biomarkera u proceni rane smrtnosti.

Ključne reči:
plućna embolija; biološki faktori; mortalitet; rizik, procena; natriuretski peptid; troponin I; c-reaktivni protein.

Introduction

Pulmonary embolism (PE) is a huge global health problem and life-threatening condition associated with significant morbidity and all-cause mortality [1–5]. PE is considered to be provoked in the presence of permanent or temporary risk factors or unprovoked in the absence thereof [6, 7]. Different states and diseases, sometimes quite clearly and sometimes completely hidden, often underlie PE. Their presence is often crucial for the management and prognosis of patients with PE. The determination of some blood biomarkers on admission and during the treatment of PE is a part of the routine diagnostic process and estimation of mortality risk [8–10]. The blood levels of different biomarkers used in PE patients for different purposes, such as brain natriuretic peptides (BNP), cardiac troponins (cTn), D-dimer, and C-reactive protein (CRP), depend on different but somehow connected pathophysiological mechanisms, and many of the underlying PE diseases and states can have a strong influence on their levels. Since that, we speculate that patients with spontaneous PE, transient provoked PE, and persistent provoked PE must have a significantly different profile of blood biomarkers level with different prognostic significance regarding the main grouping causes of PE.

The aim of this study was to evaluate the association of blood levels of commonly used biomarkers in PE patients: cardiac troponin I (cTnI), D-dimer, BNP, and CRP early in the course of admission with all-cause 30-day mortality in consecutive PE patients admitted to intensive care unit for at least one day, regarding the main causality grouping method to spontaneous, transiently provoked, and permanently provoked PE. This retrospective analysis was gained from the data of the Serbian University Multicenter Pulmonary Embolism Registry (SUPER), founded in 2015.

Methods

This retrospective study was performed after the approval of the local Ethics Committee. Patients over 18 years old of both genders, with confirmed acute PE diagnosis by multidetector computed tomography pulmonary angiography (MDCT-PA), were included in this study. During the study period from January 2015 to June 2018, 607 cases were enrolled from five university cardiology or pulmonology clinics (Military Medical Academy in Belgrade, Institute for Pulmonary Diseases of Vojvodina in Sremska Kamenica, Clinical Center in Niš, University Clinic Zvezdara in Belgrade, and Clinical Center in Kragujevac).

Participants were divided into three groups. Patients with idiopathic or unprovoked PE were included in the first group. Provoked PE groups were identified according to different risk factors associated with PE. In the second group, PE is considered a consequence of the setting-related reversible factors, such as surgical procedure, trauma, immobilization, oral contraceptive use, pregnancy, and infections. PE patients with underlying serious chronic medical illness (malignancies, chronic inflammatory disorders, such as systemic connective tissue diseases or inflammatory bowel disease, prolonged immobilization due to irreversible neurologic deficit) were taken in the third group. The endpoint of the study was the all-cause short-term (30-day) mortality defined as death due to any cause after the diagnosis of PE.

Biochemical analysis

Peripheral venous blood specimens from the antecubital vein were collected, centrifuged, and immediately analyzed using standard laboratory techniques. cTnI and D-dimer were measured upon admission, BNP and CRP were analyzed within 24 hours of the hospital admission (which minimizes the influence of administrated therapy). Serum was utilized for cTnI and CRP assays. Citrated plasma was utilized for D-dimer assay and EDTA-plasma for BNP measurements. cTnI was determined *via* the fully-automated electrochemiluminescent assay using the conventional ADVIA Centaur ultra-cTnI assay (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). D-dimer was measured by an immunoturbidimetric assay using the Innovance D-dimer assay (BCS, Siemens, Marburg, Germany). BNP was studied in Siemens ADVIA Centaur System (ADVIA Centaur BNP assay, Bulletin 10629823-EN Rev.U, 2017-07, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). CRP measurements were performed with an ADVIA 1800 analyzer (Siemens Healthcare Diagnostic, Tarrytown, NY, USA). The reference values in the healthy population were as follows: 0.01–0.04 μg/L for cTnI, 0–0.5 mg/L FEU for D-dimer, 0–4 mg/L for CRP, and BNP upper reference level was 100 ng/L.

Statistical analysis

The continuous variables were expressed as the median with a 25th–75th percentile range since all investigated variables did not have a normal distribution. Mann-Whitney U-tests were performed for the comparison of biomarker blood concentrations in patients who survived versus patients who died within 30 days in all groups and according to the presumed cause of PE across the three groups. *P*-values being < 0.05 denoted statistical significance. The area under the receiver operating characteristics (ROC) curve was used to determine the diagnostic and prognostic value of biomarkers and select optimal cutoffs. SPSS 21.0 (SPSS Inc., Chicago, IL, USA) was used for data processing and statistical analysis.

Results

The aim of the study was to investigate the effectiveness of the panel of biomarkers to predict adverse events in different PE subgroups. The baseline clinical characteristics of the study patients are presented in Table 1. Out of 607 patients, 301 (49.6%) were men, 306 (13.7%)

Table 1

Baseline characteristic pulmonary embolism (PE) subgroups

Variables	30-day mortality										
	all patients			unprovoked PE			transient provoked PE			persistent provoked PE		
	no n = 524	yes n = 83	*p*	no n = 271	yes n = 32	*p*	no n = 144	yes n = 18	*p*	no n = 109	yes n = 33	*p*
Age (years), mean (SD)	61 (16)	68 (16)	< 0.001	62 (15)	69 (17)	0.03	57 (18)	73 (10)	< 0.001	65 (14)	65 (16)	0.956
Gender, n (%)												
male	267 (51.0)	34 (41.0)	0.099	153 (56.5)	15 (46.9)	0.349	58 (40.3)	5 (27.8)	0.443	56 (51.4)	14 (42.4)	0.429
female	257 (49.0)	49 (59.0)		118 (43.5)	17 (53.1)		86 (59.7)	13 (72.2)		53 (48.6)	19 (57.6)	
Comorbidities, n (%)												
COPD	51 (9.7)	14 (16.9)	0.057	24 (8.9)	5 (15.6)	0.210	11 (7.6)	0 (0)	0.613	16 (14.7)	9 (27.3)	0.118
CHD	66 (12.6)	18 (21.7)	0.038	33 (12.2)	5 (15.6)	0.573	12 (8.3)	4 (22.2)	0.083	21 (19.3)	9 (27.3)	0.337
CAD	50 (9.8)	15 (19.5)	0.018	22 (8.3)	2 (7.4)	1.000	15 (11.0)	6 (35.3)	0.252	13 (12.0)	7 (21.2)	0.015
history of DVT/PE	67 (12.9)	6 (7.2)	0.203	54 (20.3)	4 (12.5)	0.353	6 (4.2)	0 (0)	1.000	7 (6.4)	2 (6.1)	1.000
hypertension	277 (53)	50 (60.2)	0.237	149 (55.2)	17 (53.1)	0.853	66 (45.8)	14 (77.8)	0.012	62 (56.9)	19 (57.6)	1.000
MI+stroke+ PAD	61 (11.7)	20 (24.1)	0.005	33 (12.2)	3 (9.4)	0.780	15 (10.5)	9 (50)	<0.001	13 (11.9)	8 (24.2)	0.096
DM	83 (15.9)	19 (22.9)	0.116	51 (18.9)	5 (15.6)	0.812	16 (11.1)	5 (27.8)	0.062	16 (14.7)	9 (27.3)	0.118
history of stroke	31 (5.9)	13 (15.7)	0.005	12 (4.4)	4 (12.5)	0.075	11 (7.6)	4 (22.2)	0.067	8 (7.3)	5 (15.2)	0.180
malignancy	59 (11.3)	15 (18.3)	0.100	4 (1.5)	4 (12.5)	0.005	9 (6.2)	2 (11.8)	0.327	46 (42.2)	9 (27.3)	0.155
creatinine clearance < 30 mL/min	28 (5.8)	20 (27.4)	< 0.001	17 (6.7)	7 (28.0)	0.003	0 (0.0)	3 (20.0)	0.001	11 (10.7)	10 (30.3)	0.011
Risk factors, n (%)												
PESI												
> 0	339 (67.3)	73 (94.8)	< 0.001	171 (65.0)	26 (92.9)	0.002	85 (63.4)	15 (93.8)	0.022	83 (77.6)	32 (97.0)	0.009
= 0	165 (32.7)	4 (5.2)		92 (35.0)	2 (7.1)		49 (36.6)	1 (6.2)		24 (22.4)	1 (3.0)	
Risk of PE, n (%)												
low	147 (28.4)	6 (7.3)	< 0.001	77 (28.8)	4 (12.9)	< 0.001	48 (33.6)	1 (5.6)	0.016	22 (20.4)	1 (3.0)	< 0.001
intermediate-low	137 (26.4)	8 (9.8)		72 (27.0)	1 (3.2)		27 (18.9)	2 (11.1)		38 (35.2)	5 (15.2)	
intermediate-high	184 (35.5)	32 (39.0)		99 (37.1)	13 (41.9)		50 (35.0)	9 (50.0)		35 (32.4)	10 (30.3)	
high	50 (9.7)	36 (43.9)		19 (7.1)	13 (41.9)		18 (12.6)	6 (33.3)		13 (12.0)	17 (51.5)	

COPD – chronic obstructive pulmonary disease; CHD – coronary heart disease; DVT – deep vein thrombosis; CAD – coronary artery disease; MI – myocardial infarction; PAD – pulmonary artery disease; DM – diabetes mellitus; PESI – pulmonary embolism severity index; SD – standard deviation.

Data were missing for CAD (3.5%), DVT/PE (1.0%), hypertension (0.2%), MI+stroke+PAD (0.3%), DM (0.2%), malignancy (0.2%), PESI (4.3%) and risk of PE (1.2%).

were women, with a mean age of 62 ± 16. Among all patients, 83 died within 30 days; of those, 50 patients died as a result of PE, which is 60.2% of all-cause deaths (50.4% vs. 27.5% vs. 22%, in spontaneous, transient, and persistent provoked PE group, respectively). Venous thromboembolism (VTE) is the second leading cause of death in cancer patients [11]. Therefore, in the persistent provoked group, a significant number of patients with malignancy died (27.3%), unlike 12.5% vs. 11.8% in the spontaneous and transient provoked PE group, respectively.

If we analyze the differences between the characteristics of patients across these three groups, we can see that in patients with spontaneous PE and PE caused by the transient provoked factor, patients who died at 30 days were older and there was no difference in age in comparison with the rate of death and survival in the group with persistent provoked factor (Table 1). The distribution of gender was similar regarding the 30-day mortality across these three groups (Table 1). History of arterial symptomatic disease was more prevalent in patients who died from spontaneous PE (Table 1). Both simplified Pulmonary Embolism Severity Index (sPESI) score and mortality score stratified patients as it was expected, and 30-day mortality rate were much higher in patients with sPESI > 0 comparing to sPESI 0, and increased significantly from the low, intermediate-low, intermediate-high to high-risk PE patients in all three groups (Table 1).

BNP and cTnI represent a part of risk stratification algorithm for intermediate-high risk or intermediate-low risk patients and indicate treatment strategies. Comparison of blood levels of biomarker between the deceased from any cause and patients who survived the 30-day period showed that CRP and BNP levels were significantly higher in deceased patients in all three groups and cTnI level only in spontaneous PE patients (Table 2). D-dimer levels were not different between the deceased and survivors in neither group (Table 2).

ROC curve analyses demonstrated that BNP had the highest prognostic accuracy for 30-day mortality in patients (n = 219) who had all examined biomarkers. BNP provided an AUC of 0.785 ($p < 0.001$). Besides BNP, D-Dimer had modest predictive power with an AUC=0.703 and *p*-value of 0.002. CRP showed an AUC of 0.672 ($p = 0.008$). The AUC for cTnI was 0.631, but it was not statistically significant ($p = 0.063$) (Figure 1).

In general, BNP separately as a continuous variable had the highest c-statistic for all three groups of patients, but with a modest predictive value for 30-day all-cause mortality in patients with persistent provoked PE with an AUC of 0.699 ($p = 0.025$). C-reactive protein had solid predictive value for the 30-day all-cause mortality in the group with transient provoked PE, and it was less appreciated in spontaneous and persistent provoked PE. cTnI had a very modest predictive value for the 30-day all-cause mortality only in patients with spontaneous PE, and D-dimer was a very weak predictor of this endpoint only in patients with persistent provoked PE.

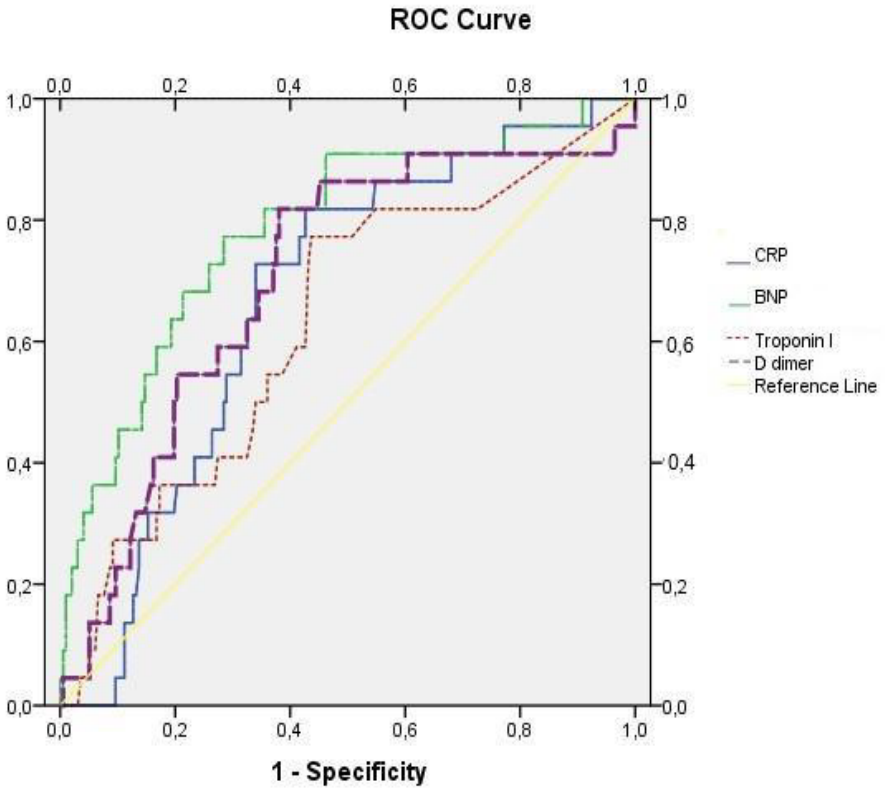

Fig. 1 – Receiver operating characteristic (ROC) curve analysis for assessing the capacity of biomarkers to predict 30-day mortality.
CRP – C-reactive protein; BNP – B-type natriuretic peptide.

Table 2

Association of biomarkers with outcomes. Statistical comparison of study parameters in pulmonary embolism (PE) subgroups with (P) vs without (N) adverse outcome

Parameters	All patients			Unprovoked PE			Transient provoked PE			Persistent provoked PE		
	yes	no	*p*	yes	no	*p*	yes	no	*p*	yes	no	*p*
CRP (mg/L)	n = 67 93.9 (57.0–164.3)	n = 506 43.5 (15.8–100.0)	< 0.001	n = 27 78.1 (50.5–145.8)	n = 261 28.0 (12.2-76.8)	0.001	n = 15 111.0 (77.0-240.0)	n = 138 60.6 (24.7-133.8)	0.004	n = 25 99.0 (37.5-175.6)	n = 107 52.0 (20.1-100.0)	0.009
BNP (ng/L)	n = 31 422.0 (161.6–970.0)	n = 284 117.0 (44.0–315.0)	< 0.001	n = 10 696,0 (129.4-1424.5)	n = 157 130,0 (45.6-323.5)	0.011	n = 7 413.6 (267.6-512.0)	n = 80 108.8 (40.5-303.5)	0.008	n = 14 426.5 (147.2-935.2)	n = 47 107.0 (49.2-351.0)	0.025
cTnI (µg/L)	n = 49 0.13 (0.04–0.88)	n = 323 0.05 (0.01–0.29)	0.001	n = 22 0.15 (0.08–0.72)	n = 195 0.05 (0.01–0.30)	0.021	n = 12 0.09 (0.02-0.81)	n = 78 0.04 (0.00-0.28)	0.168	n = 15 0.18 (0.04-1.10)	n = 50 0.05 (0.00-0.16)	0.092
D-dimer (mg/lFEU)	n = 73 6.9 (3.5–16.1)	n = 473 5.2 (2.5–10.0)	0.032	n = 29 5.4 (3.5-9.7)	n = 248 4.5 (2.3-9.5)	0.298	n = 16 7.4 (2.4-19.0)	n = 124 5.9 (3.3-10.6)	0.500	n = 28 8.8 (3.5-22.3)	n = 101 5.1 (2.2-9.9)	0.050

Note: Data are presented as a median, 25th – 75th percentile.

CRP – C-reactive protein; BNP – B-type natriuretic peptide; cTnI – cardiac troponin1.

Table 3

Receiver operating characteristic (ROC) Analysis for biomarkers predicting adverse outcomes in pulmonary embolism (PE) subgroups

Parameters	Unprovoked PE				Transient provoked PE				Persistent provoked PE			
	n	AUC	95% CI	*p*	n	AUC	95% CI	*p*	n	AUC	95% CI	*p*
CRP (mg/L)	288	0.695	0.589–0.801	0.001	153	0.728	0.620–0.835	0.004	132	0.669	0.552–0.785	0.009
BNP (ng/L)	167	0.741	0.553–0.929	0.011	87	0.804	0.696–0.911	0.008	61	0.699	0.544–0.854	0.025
Troponin-I (µg/L)	217	0.650	0.533–0.768	0.021	90	0.623	0.450–0.795	0.172	65	0.643	0.487–0.800	0.094
D- dimer (mg/L FEU)	277	0.559	0.458–0.660	0.298	140	0.552	0.381–0.723	0.500	129	0.621	0.493–0.749	0.050
CRP (mg/L)*	122	0.750	0.564–0.936	0.018	61	0.584	0.424–0.745	0.535	35	0.564	0.337–0.791	0.571
BNP (ng/L)*		0.701	0.477–0.924	0.058		0.835	0.734–0.936	0.014		0.799	0.622–0.977	0.008
Troponin-I (µg/L)*		0.578	0.354–0.803	0.460		0.635	0.386–0.884	0.320		0.705	0.513–0.897	0.070
D-dimer (mg/L FEU)*		0.672	0.480–0.865	0.104		0.626	0.325–0.927	0.352		0.761	0.593–0.928	0.021

***Patients who had all biomarkers.**

AUC – area under the curve; CI – confidence interval.

For other abbreviations see under Table 2.

Since not all patients had measured values of all markers, we performed a c-statistic analysis marker by marker (Table 3) and a combination of each marker with BNP (Table 4).

In the c-statistic analysis with a combination of markers and BNP, the CRP had a comparable, high c-statistic as BNP in spontaneous and transient provoked PE. However, both markers were not doing well for the prediction of 30-day all-cause mortality in patients with persistent provoked PE with C-indices below 0.700. On the other hand, cTnI in combination with BNP was significantly weaker from BNP for the prediction of 30-day all-cause mortality in patients with spontaneous and transient provoked PE, but much better, yet significantly less respectable as BNP for persistent provoked PE with an AUC of 0.712. D-dimer in combination with BNP also had a very low predictive value for 30-day all-cause mortality, but slightly better but not comparable with BNP in patients with transient and provoked PE.

In the previous study [12], it was demonstrated that none of these markers (CRP, cTnI, D-Dimer) added to BNP (adjusted to gender, age, and glomerular filtration rate calculated with Cockcroft-Gault formula) improved Cox regression prediction models for 30-day PE-related mortality.

BNP had a high predictive value for 30-day all-cause mortality in all three groups of patients, which means that heart failure with its surrogate BNP was an important predictive factor for death regardless of the cause of PE. There are a lot of studies that showed that BNP is a good predictor for short-term mortality in patients with PE regardless of the presence of left ventricle performance. However, our study showed that BNP is a good predictor for short-term mortality, especially in patients with spontaneous PE and PE with transient provoked factor, but less good in patients with provoked PE who had a persistent factor. The possible reason for that is that the cause of death in this group was more often the consequence of other reasons and not PE itself.

Table 4

Comparison of B-type natriuretic peptide (BNP) and its combination with other biomarkers

Parameters	Unprovoked PE				Transient provoked PE				Persistent provoked PE			
	n	AUC	95% CI	*p*	n	AUC	95% CI	*p*	n	AUC	95% CI	*p*
BNP												
BNP (ng/L)	167	0.741	0.553–0.929	0.011	87	0.804	0.696–0.911	0.008	61	0.699	0.544–0.854	0.025
30-day mortality (n, %)			10 (6.0)				7 (8.0)				14 (23.0)	
BNP + CRP												
BNP (ng/L)	162	0.744	0.558–0.930	0.010	86	0.801	0.693–0.910	0.009	60	0.693	0.535–0.850	0.030
CRP (mg/L)		0.772	0.621–0.923	0.004		0.728	0.573–0.883	0.047		0.596	0.435–0.758	0.297
30-day mortality (n, %)			10 (6.2)				7 (8.1)				14 (23.3)	
BNP + cTnI												
BNP (ng/L)	128	0.692	0.464–0.919	0.070	63	0.834	0.732–0.937	0.014	36	0.790	0.612–0.968	0.010
Troponin-I (μg/L)		0.578	0.352–0.804	0.463		0.631	0.380–0.882	0.334		0.712	0.522–0.902	0.060
30-day mortality (n, %)			8 (6.3)				5 (7.9)				9 (25.0)	
BNP + D-dimer												
BNP (ng/L)	164	0.743	0.555–0.930	0.010	83	0.805	0.700–0.909	0.008	57	0.722	0.560–0.884	0.016
D-dimer (mg/L FEU)		0.595	0.401–0.789	0.316		0.706	0.468–0.943	0.073		0.688	0.524–0.852	0.041
30-day mortality (n, %)			10 (6.1)				7 (8.4)				13 (22.8)	

For abbreviations see under Tables 2 and 3.

Discussion

Since PE includes various diseases and conditions behind heterogeneous pathophysiology, it is logically that different biochemical markers have different prognostic values for mortality depending on that. Besides that, the cause of PE-related mortality can be divided into at least three major groups, mortality caused by PE itself, mortality due to comorbidities, and hemorrhage complications. This study showed that several biomarkers had very different values for the prediction of 30-day all-cause death regarding the main cause of PE. In general, BNP had a solid predictive value for 30-day all-cause mortality regardless of the cause of PE. The serum concentration of CRP had a good predictive value for 30-day all-cause mortality in patients with spontaneous and transient provoked PE. Cardiac troponin I and D-dimer levels had only modest but significantly lower predictive value for 30-day all-cause mortality compared to BNP in both provoked groups of PE. Thus, the value of biomarkers for the prediction of 30-day all-cause mortality very much depends on whether the patient had spontaneous, provoked PE with transient or persistent factors.

CRP level also had a good predictive value for early all-cause mortality, especially in patients with spontaneous PE. Several inflammatory markers are elevated in patients with acute PE even when febrile state or pulmonary consolidation on computed tomography (CT) is not present. CRP, as a well-known marker of inflammation, has a good predictive value for mortality and bleeding complications which can also contribute to death. Since causes of death, other than PE, were presented more often in patients with provoked PE, CRP was not such a good predictor for early mortality in those patients.

According to previous reports, D-dimer was not a good indicator of PE prognosis and severity [13, 14], although the results of D-dimer have had general application in excluding PE due to its high negative predictive value [15]. In the present study, plasma D-dimer levels were increased in all subgroups of patients regardless of the causality. However, a significant difference was observed only between survivors and 30-day mortality for all cohorts of PE patients. In our study, D-dimer had a good predictive value for 30-day all-cause mortality only in the subgroup of patients with persistent provoked PE.

This result might be partly explained as active malignant disease, autoimmune diseases, and other severe comorbidities predominate in this subgroup of patients. Moreover, it is well-known that in these cohorts of patients, D-dimer *per* se is the predictive factor for mortality [16–18].

There are a lot of assays for cardiac troponins with various sensitivity and likelihood ratios making usefulness for cardiac troponins in the prediction of outcome complicated for clinical practice [19]. In our study, the cTnI assay had a relatively weak prognostic value for 30-day all-cause mortality only in the subgroup of patients with spontaneous PE when it was used as a solo marker. As we mentioned before, in this group of patients, PE-related death was the most prominent cause of death, and the myocardial necrosis during the stretching of the right ventricle (RV) was the mechanism of raised troponin in this subgroup. Groups with provoked PE had predominantly other pathological mechanisms of death with a lower role of RV failure and a smaller amount of release of cardiac troponin.

The main limitation of this study was that a considerable number of patients did not have all tested biomarkers. However, according to the European Society of Cardiology (ESC) guidelines, patients with low and intermediate-low risk of PE do not require results of all these biomarkers.

Conclusion

Overall, this study showed that the cause of PE very much influences the predictive power of biomarkers for early PE-related mortality. Brain natriuretic peptide is the probable biomarker that is the most resistant to different influences because heart failure, surreally presented through BNP blood level, is the final process firmly associated with death outcome. C-reactive protein and cardiac troponin I blood concentrations were better markers for the prediction of early death in patients with spontaneous PE than in provoked PE. Although D-dimer had predictive value for early mortality in the whole group of PE patients, it had poor predictive value in patients with spontaneous PE and PE provoked with transient factor. However, it also had a modest predictive value for PE patients with persistent provoked PE.

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