Clinica Chimica Acta 492 (2019) 78–83

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Biomarkers for the prediction of early pulmonary embolism related mortality in spontaneous and provoked thrombotic disease

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ARTICLE INFO

Keywords:
Pulmonary embolism
Biomarkers
Brain natriuretic peptide
Mortality

ABSTRACT

Factors associated with provoked PE may influence a biomarker's predictive value for the primary outcome. The aim of this study was to investigate the value of BNP, cTnI, CRP and D-Dimer measurements taken soon after hospital admission for the prediction of 30-day PE-caused death in patients with spontaneous versus provoked PE.Data were extracted from a pool of 726 consecutive PE patients enrolled in the multicenter Serbian PE registry. Blood concentrations of BNP, cTnI, CRP and D-dimer were measured during the first 24 h of hospitalization. BNP blood level had strong predictive value for the primary outcome in spontaneous PE (c-statistics 0.943, 95% CI 0.882–1.000, $p = .001$) and a slightly lower predictive outcome in provoked PE (c-statistics 0.824, 95% CI 0.745–0.902, $p < .001$). NRI and IDI showed that none of the markers, when added to BNP, could improve Cox regression prediction models for 30-day PE-related mortality in either the spontaneous or provoked PE group. Blood levels of BNP measured during the first 24 h of hospital admission had an excellent predictive value for 30-day PE-related mortality in spontaneous PE and slightly lower predictive value in provoked PE, whereas CRP, cTnI and D-Dimer did not contribute significantly to the predictive value of BNP in either group.

1. Introduction

Treatment of a pulmonary embolism (PE) depends on the estimated mortality risk. Patients with high-risk PE who are hypotensive should receive reperfusion therapy, while those with intermediate-risk with normal arterial pressure and right ventricle dysfunction should be monitored and receive anticoagulant therapy. Patients with low-risk should be treated almost immediately with oral anticoagulant drugs with little to no hospitalization at all [1,2]. Biomarkers, such as brain natriuretic peptide (BNP) and cardiac troponin (cTn), serve to further stratify intermediate-risk PE; those who have elevated blood levels of these markers are classified as intermediate-high risk and those who have normal values are intermediate-low risk patients [3–6]. Regarding treatment strategies, patients in the intermediate-high risk group are considered very “close” to high-risk PE and those with intermediate-low risk are closer to low-risk PE patients. However, all existing recommendations are based on studies with an end-point of all-cause mortality. A considerable percent of patients with PE die from other causes. Furthermore, patients with spontaneous PE have relatively clear situations, as the origin of biomarkers accurately represent heart failure (for BNP) and myocardial injury caused by ischemia and stretching of right ventricle (for cardiac troponins) [7–9]. However, in patients with

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https://doi.org/10.1016/j.cca.2019.02.008
Received 24 December 2018; Received in revised form 3 February 2019; Accepted 12 February 2019
Available online 12 February 2019

provoked PE, the provoking factors can have dramatic influences on biomarker levels and thus interfere with their predictive value for PE-related mortality [10,11]. Thus, two problems are raised with risk stratification. The first is that, in order to treat PE appropriately, we must differentiate those factors associated with all-cause death from those associated with PE-caused death. Second, we need to estimate the increase of biomarkers caused by hemodynamic compromise due to PE in order to separate this from the influence of many other provoking factors.

The aim of this study is to investigate the value of BNP, cTnI, C-reactive protein (CRP) and D-Dimer blood concentrations at the time of hospital admission in predicting 30-day PE-caused death in patients with spontaneous versus provoked PE; the study was carried out on consecutive PE patients from the multicenter PE registry.

2. Patients and methods

2.1. Study population

We conducted a retrospective review of 726 patients with a confirmed diagnosis of PE from five university cardiology or pulmonology clinics Military Medical Academy (Belgrade), Institute of Pulmonary Diseases (Sremska Kamenica), Clinical Center (Nis), University Clinic Zvezdara and Clinical Center (Kragujevac) in the period from January 2015 to November 2018. We excluded 29 patients who died within 30 days as a result of death unrelated to PE. The study was approved by each facility's Institutional Review Board.

Two groups of patients were defined based on presumed PE etiology: the ˝spontaneous˝ and the ˝provoked˝ groups. Patients with provoked PE had well-known strong or moderate risk factors for venous thrombosis. The end-point of study was short-term (30-days) mortality defined as death due to acute right ventricle heart failure – that is, a PE-related death.

2.2. Biochemical analysis

Peripheral venous blood specimens from antecubital veins were collected by a member of the clinical team using venipuncture while obtaining routine blood samples for standard clinical assessment in the diagnostic workup. D-Dimer and cTnI were measured upon admission to the clinical ward; BNP and CRP were assessed within 24 h of hospital admission. Samples were immediately centrifuged and analyzed using standard laboratory techniques. Blood samples were collected in tubes with spray-coated silica and polymer gel for serum separation and tubes containing K3-EDTA or sodium citrate for plasma separation (BD Vaccutainer® by Becton, Dickinson and Co., NJ, USA). Samples were then locally separated by centrifugation for 10 min at 3000 ×*g*. Citrated plasma was utilized for hemostatic assays (D-Dimer) and EDTA-plasma was used for BNP measurements. Serum was utilized for cTnI and CRP assays. Serum concentrations of cTnI were quantified using the conventional ADVIA Centaur ultra-cTnI assay (Bulletin 10,629,901-EN Rev.L, 2014–08, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) as a fully automated three-site sandwich immunoassay using direct chemiluminometric technology. D-Dimer was measured by immunoturbidimetric assay using the Innovance D-Dimer assay (BCS, Siemens, Marburg, Germany). BNP was determined via ADVIA Centaur BNP assay (Bulletin 10,629,823-EN Rev.U, 2017–07, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) as a fully automated two-site sandwich chemiluminescent immunoassay for the measurement of BNP in EDTA plasma samples. An ADVIA 1800 analyzer (Siemens Healthcare Diagnostic, Tarrytown, NY, USA) was used to measure CRP levels. The reference values in healthy population were: 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.

2.3. Statistical analysis

Continuous variables were described as the median with a 25th–75th percentile range since the examined variables did not have normal distributions. Mann-Whitney *U* tests were conducted for the comparison of biomarker values in patients who survived versus patients who had died at 30 days in two groups according to established cause of PE. The area under the receiver-operating characteristics (ROC) curve was calculated with 95% confidence intervals. Optimal cut-off values of biomarkers and their sensitivity and specificity for the prediction of 30-day PE-related mortality were calculated in MedCalc for Windows version 18.11.3 (MedCalc Software, Acacialaan, Belgium).Comparisons of nonparametric variables and frequencies of categorical data between survivors and deceased patients were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were both calculated using the “survIDINRI” R package (R-version 3.3.2), through comparing proportional hazards models for the prediction of 30-day PE-related mortality using BNP (adjusted to gender, age and glomerular filtration rate calculated with Cocroft-Gault formula) and models in which CRP, cTnI or D-Dimer were added [12]. A two-tailed p-value < .05 was regarded as statistically significant.

3. Results

During the course of the study, 726 consecutive patients with a diagnosis of PE confirmed by multidetector computed tomography angiography (MDCT-PA) were enrolled in the study. Twenty nine patients were excluded from the study due to subsequent death unrelated to PE. The baseline characteristics of all patients are presented in Table 1. Clinically, 347 patients (49.8%) had spontaneous PE and 350 (50.2%) had provoked PE. Of the 697 total patients, 349 were men (50.1%), 348 (49.9%) were women. The mean age of patients was 62 ± 16 y. All 62 patients who died within 30 days (8.9%) died as result of PE (43.5% vs 56.5%, in spontaneous and provoked PE group, respectively). Patients who died were on average older, more frequently had renal dysfunction and a history of arterial disease, had higher sPESI and a higher risk score (Table 1).

Table 2 compares the mean biomarker levels between the deceased patients and patients who survived 30 days. The mean levels of all biomarkers except D-Dimer were significantly higher in deceased patients in the spontaneous PE group. In patients with provoked PE all examined markers showed marked differences between patients who died and survivors.

ROC curve analyses showed that BNP had the highest c-statistics in both groups. CRP and cTnI demonstrated better predictive values for 30-day PE-related mortality in spontaneous PE patients (Table 3). Only D-Dimer demonstrated a better predictive value for 30-day PE-related death in the provoked PE group compared to the spontaneous group. The optimal cut-off values of biomarkers and their reference sensitivity and specificity values are also presented in Table 3. The cut-off value for early PE-related mortality prediction of BNP was lower in provoked PE than in spontaneous PE (360.0 ng/L vs 416 ng/L). The difference was also striking for CRP, where patients with provoked PE had a much higher cut-off value compared to spontaneous PE patients (154.0 mg/L vs 49.2 mg/L). Sensitivity for the BNP cut-off value for the prediction of 30-day PE-related mortality in spontaneous PE was 100%. It was much lower, but still significant at 80.0% in patients with provoked PE. The CRP cut-off value (76,2%) had solid sensitivity for the prediction of early PE death in the spontaneous PE group, but was poor (44%) in the provoked PE group (76.2% vs 44.0%, respectively). Cut-off values for cTnI had high sensitivity and low specificity for the prediction of 30-day PE-caused mortality in both spontaneous and provoked PE patients.

NRI and IDI showed that none of the markers added to BNP improved Cox regression prediction models for 30-day PE related mortality in either the spontaneous or provoked PE group (Table 4). The

Table 1
Baseline characteristic between PE subgroups.

Variables		All patients			Spontaneous PE			Provoked PE		
		30-day mortality								
		No	Yes	*p* value	No	Yes	p value	No	Yes	p value
		N = 635	*N* = 62		*N* = 320	*N* = 27		*N* = 315	*N* = 35	
Age (Mean, SD)		62 (16)	66 (16)	0.030	62 (15)	68 (15)	0.056	61 (17)	65 (17)	0.198
Gender, N (%)	Male	317 (49.9)	32 (51.6)	0.894	177 (55.3)	14 (51.9)	0.841	140 (44.4)	18 (51.4)	0.476
	Female	318 (50.1)	30 (48.4)		143 (44.7)	13 (48.1)		175 (55.6)	17 (48.6)	
Comorbidities (N, %)										
Smoking		104 (18.2)	5 (9.4)	0.275	51 (18.0)	1 (4.8)	0.247	53 (18.3)	4 (12.5)	0.679
COPD		63 (9.9)	9 (14.5)	0.272	28 (8.8)	5 (18.5)	0.160	35 (11.1)	4 (11.4)	1.000
CHF		80 (12.6)	12 (19.4)	0.166	39 (12.2)	2 (7.4)	0.755	41 (13.0)	10 (28.6)	0.021
CAD		70 (11.0)	12 (19.4)	0.062	33 (10.3)	4 (14.8)	0.511	37 (11.7)	8 (22.9)	0.104
History of DVT/PE		86 (13.7)	7 (11.5)	0.844	62 (19.6)	4 (15.4)	0.797	24 (7.6)	3 (8.6)	0.743
Hypertension		353 (55,8)	33 (53,2)	0.789	183 (57.4)	13 (48.1)	0.420	170 (54.1)	20 (57.1)	0.858
MI + Stroke + PAD		80 (12.6)	16 (25.8)	0.011	43 (13.5)	2 (7.4)	0.553	37 (11.8)	14 (40.0)	< 0.001
DM		107 (16.9)	16 (25.8)	0.083	64 (20.1)	5 (18.5)	1.000	43 (13.7)	11 (31.4)	0.011
History of stroke		39 (6.1)	11 (17.7)	0.003	10 (3.1)	3 (11.1)	0.071	29 (9.2)	8 (22.9)	0.020
Malignancy		68 (10.7)	9 (14.8)	0.390	4 (1.3)	2 (7.4)	0.072	64 (20.3)	7 (20.6)	1.000
Creatinine Clearance < 60		178 (28.6)	44 (72.1)	< 0.001	94 (30.2)	18 (69.2)	< 0.001	84 (27.0)	26 (74.3)	< 0.001
Creatinine Clearance < 30		35 (5.7)	19 (31.1)	< 0,001	17 (5.6)	7 (26.9)	0.001	18 (5.9)	12 (34.3)	< 0.001
Risk factors (N, %)										
PESI	> 0	410 (66.7)	54 (93.1)	< 0.001	195 (62.3)	22 (88.0)	0.009	215 (71.2)	32 (97.0)	0.001
	= 0	205 (33.3)	4 (6.9)		118 (37.7)	3 (12.0)		87 (28.8)	1 (3.0)	
Mortality risk N (%)	Low	192 (30.2)	4 (6.5)	< 0.001	106 (33.1)	3 (11.1)	< 0.001	86 (27.3)	1 (2.9)	< 0.001
	Intermediate-low	162 (25.5)	2 (3.2)		87 (27.2)	2 (7.4)		75 (23.8)	0 (0.0)	
	Intermediate-high	217 (34.2)	21 (33.9)		107 (33.4)	8 (29.6)		110 (34.9)	13 (37.1)	
	High	64 (10.1)	35 (56.5)		20 (6.2)	14 (51.9)		44 (14.0)	21 (60.0)	

Baseline characteristic between PE subgroups.*p value < .05 significant; (%) - percentage of PE patients with (Yes) or without (No) adverse events. Abbreviations: M, male; F, female; 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; PESI, pulmonary embolism severity index; Data were missing for smoking (10.2%), DVT/PE (0.9%), hypertension (0.3%), MI + Stroke+PAD (0.3%), DM (0.1%), malignancy (0.3%), PESI (3.4%), creatinine clearance < 60 (2.0%), creatinine clearance < 30 (3.4%).

Table 2
Association of biomarkers with outcomes. Statistical comparison of study parameters in PE subgroups with (P) vs without (N) adverse outcome.

	All patients			Spontaneous PE			Provoked PE		
CRP (mg/L)	P	N	p value	P	N	p value	P	N	p value
	n = 48	*n* = 615		*n* = 21	*n* = 310		n = 27	*n* = 305	
	80.4 (51.0–179.1)	41.2 (16.0–95.8)	< 0.001	75.0 (45.2–118.5)	25.8 (12.0–63.1)	0.001	104.0	59.0	0.005
							(54.8–202.0)	(24.0–125.5)	
BNP (ng/L)	P	N	p value	P	N	p value	P	N	p value
	n = 20	*n* = 311		*n* = 5	*n* = 155		n = 15	*n* = 156	
	637.8	124.0	< 0.001	988.0	124.5	0.001	470.0	123.5	< 0.001
	(357.8–1097.5)	(44.1–332.4)		(696.0–1734.5)	(42.0–338.7)		(351.0–869.0)	(50.7–321.8)	
Troponin-I (μg/L)	P	N	p value	P	N	p value	P	N	p value
	n = 34	*n* = 396		*n* = 13	*n* = 222		n = 21	*n* = 174	
	0.19 (0.08–1.08)	0.05 (0.01–0.25)	< 0.001	0.13 (0.08–1.30)	0.05 (0.01–0.22)	0.005	0.21 (0.06–0.99)	0.04 (0.01–0.30)	0.003
D-Dimer (mg/L FEU)	P	N	p value	P	N	p value	P	N	p value
	n = 55	*n* = 577		*n* = 23	*n* = 296		n = 32	*n* = 281	
	6.9 (3.4–10.4)	5.0 (2.4–9.8)	0.063	5.2 (3.0–9.0)	4.5 (2.1–9.5)	0.707	9.0 (3.5–16.6)	5.2 (2.9–10.0)	0.031

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

Table 3
ROC Analysis for biomarkers predicting adverse outcomes in PE subgroups.

	N	AUC	95% CI	P	Cut-off	Sens.	Spec.
Spontaneous PE							
CRP (mg/L)	331	0.718	0.666–0.765	< 0.001	49.2	76.2	67.7
BNP (ng/L)	160	0.943	0.895–0.974	< 0.001	416	100.0	81.9
Troponin-I(μg/L)	235	0.732	0.670–0.787	< 0.001	0.06	84.6	58.6
D-Dimer (mg/l FEU)	319	0.524	0.467–0.579	0.639	10.4	0.0	79.1
Provoked PE							
CRP (mg/L)[a]	332	0.664	0.611-0.715	0.003	154.0	44.0	84.3
BNP (ng/L)[a]	171	0.824	0.758-0.878	< 0.001	350.0	80.0	76.9
Troponin-I (μg/L)[a]	195	0.696	0.626-0.759	0.001	0.04	85.7	50.0
D-Dimer (mg/l FEU)[a]	313	0.616	0.560–0.670	0.042	7.2	59.4	64.1

AUC indicates area under the curve.
[a] Patients who had all biomarkers.

model that came closest to that achievement was the model in which CRP was added to BNP in patients with spontaneous PE, where continuous NRI was 0.680 and the *p*-value was 0.106.

4. Discussion

The primary purpose of using biomarkers in PE is to predict risk of mortality and thus guide the treatment of a patient. Two obstacles exist to achieving this goal. First, we must separate PE-related death from non-PE related death (which comprise a considerable percentage of deaths) because the duration of the treatment should be adjusted to the risk of death from PE and bleeding complications. The second obstacle is the influence of factors that provoked PE on biomarker levels. This influence should be minimized to avoid misinterpretation. In the present study, patients who died within 30 days from causes other than PE were excluded, and the predictive value of biomarkers for 30-day mortality was evaluated separately in the spontaneous and provoked PE cohorts.

In this study, BNP values at admission had a very strong predictive value for 30-day PE-related mortality, with c-statistics of 0.943 and 0.824 in spontaneous and provoked PE, respectively. This result was expected because BNP is a well-known marker of heart failure which is the main mechanism of death and circulatory shock in PE [13,14]. The higher BNP predictive value for PE mortality in spontaneous PE might be explained by the influence of provoking factors to PE-related death with mechanisms other than acute heart failure. Serial measurement of BNP or other biomarkers may be advantageous in other chronic diseases, such as chronic heart failure, in which there is typically time to tailor therapies related to the biomarker values before clinical symptoms become evident [15,16]. However, the majority of patients who die from acute PE die during the index hospitalization. Subsequently, other causes and recurrent events (which are rare with appropriate therapy) are causes of death. Thus, prompt risk stratification in acute PE is important to guide the initial escalating therapy, while later measurements of biomarkers will likely be more useful for the prediction of other, non-PE- related causes of death.

On the other hand, CRP and cTnI values at admission only had good predictive value for 30-day mortality in patients with spontaneous PE with c-statistics over 0.7. Their predictive value for 30-day PE-related death was significantly lower in patients with provoked PE. Transient inflammation with elevated markers of this process is part of pathophysiological response in PE [17]. We posit that the main likely reason for the better predictive value for PE- related mortality in spontaneous PE for CRP in our study is that many provoked factors cause strong inflammation and the level of CRP in patients with spontaneous PE is solely a marker of inflammatory reaction to decompensation.

Elevated cardiac troponins are associated with increased risk of all-cause and PE-related mortality in PE [18,19]. However, previous studies did not analyze its predictive values separately in spontaneous and

Table 4
Hazard ratios of biomarkers (per unit) for 30 days PE-related death from the Cox regression models and Integrated discrimination improvement index (IDI) and continuous net reclassification index (NRI) for models with BNP and when CRP or cTnI or D-Dimer added to model, adjusted to gender, age and glomerular filtration rate (GFR).

Cox regression models with biomarkers	HR (95%CI)	p	IDI (95%CI)	p	NRI (95%CI)	p
Spontaneous PE						
BNP	1.002 (1.001–1.004)	0.008	-	-	-	-
BNP + **CRP**[a]	1.014 (1.003–1.025)	0.011	0.094 (−0.056–0.325)	0.239	0.680 (−0.175–0.866)	0.106
BNP + **cTnI**[a]	1.103 (0.636–1.913)	0.727	0.006 (−0.010–0.074)	0.472	0.027 (−0.524–0.539)	0.704
BNP + **D-Dimer**[a]	1.000 (1.000–1.000)	0.324	0.019 (−0.043–0.173)	0.478	0.133 (−0.557–0.470)	0.837
Provoked PE						
BNP	1.002 (1.001–1.003)	0.002	-	-	-	-
BNP + **CRP**[a]	1.000 (0.993–1.006)	0.916	0.001 (−0.005–0.090)	0.339	0.086 (−0.176–0.332)	0.545
BNP + **cTnI**[a]	0.488 (0.089–2.690)	0.410	0.014 (−0.006–0.147)	0.166	0.353 (−0.347–0.632)	0.405
BNP + **D-Dimer**[a]	1.000 (1.000–1.000)	0.410	0.008 (−0.008–0.094)	0.252	0.239 (−0.199–0.510)	0.292

[a] HRs regarding prediction of 30-day PE-related mortality are presented for biomarkers in Cox regression models with BNP.

provoked PE. Our results showed that cTnI was significantly less valuable for prediction of 30-day PE-related deaths in patients with provoked PE. Several provoking factors may contribute to the clinically insignificant troponin I myocardial release resulting in its very low specificity. Increased troponin blood concentration in PE is the consequence of several pathogenic mechanisms. For instance, cardiac troponin can be released as a direct effect of PE because of ischemia during hypotension and hypo-oxygenation or as a cause of extensive stretching of the thin right ventricle wall. However, it may also be a consequence of direct myocardial injury in sepsis, malignancy or autoimmune diseases. Cardiac troponin, and especially high-sensitive troponin, are elevated in the majority of PE patients admitted to intensive care but have low positive predictive value for early death [20,21]. Thus a modest increase of troponin may present a much softer marker of the PE severity than BNP. However, both markers have excellent negative predictive values for early PE-related death.

Furthermore, D-Dimer was not a predictor of PE-related death in spontaneous PE and was only a weak predictor in provoked PE. In the RIETE registry, noncancer PE patients in the highest quartile of D-Dimer had increased risk for fatal PE and all-cause mortality compared with the lowest quartile [22]. In our study, provoked PE patients were analyzed separately from spontaneous PE patients, minimizing the possible influence of provoked factors in the spontaneous group. Unlike BNP and cTnI, D-Dimer does not correlate well with the hemodynamic state in PE (17), and it is associated with intravascular activation of coagulation in many states and diseases that can provoke PE. Thus, D-Dimer is a good marker for prothrombotic state but not for PE severity.

5. Conclusion

The results of our study indicate that various biomarkers have different predictive values for 30-day PE-related death according to the cause of PE. Of tested biomarkers, BNP has the strongest predictive value for both spontaneous and provoked PE; cTnI and CRP have very good predictive value for spontaneous PE but are less valuable in provoked PE; and D-Dimer had no predictive value in spontaneous PE, and only very weak predictive value in provoked PE.

6. Limitations

Classification of PE as either spontaneous or provoked is subjective and relative. Various comorbidities and conditions, known or unknown at hospital admission, could be important. To account for this, we independently evaluated the classifications of spontaneous and provoked PE. When discrepancy was noted, detailed checks of all available data were considered in the final classification.

The purpose of mortality risk stratification in PE patients is to guide therapeutic measures based on the actual risk of PE-related death. In order to avoid introducing the influence of comorbidities on biomarker levels, we excluded patients who died from other causes. However, a clear distinction between a PE-related death and non-PE-related death can be extremely difficult and is made at the discretion of attending doctors. Death that was preceded by signs and symptoms of cardiogenic shock without possible other causes was considered a PE-related death. This definition was accepted by all centers involved in the study.

Both the number of patients in the study and the number of patients who died were too low to enable firm conclusions. This investigation is rather a hypothesis generating study. It is critical to consider the influence of provoked factors on levels of biomarkers and to separate their prognostic value for all-cause and PE-related deaths, as only the former are important for therapeutic decision making.

Declarations of interest

None.

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