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The significance of C-reactive protein for the prediction of net-adverse clinical outcome in patients with acute pulmonary embolism

Značaj C-reaktivnog proteina u predviđanju ukupnog nepovoljnog kliničkog ishoda kod bolesnika sa akutnom plućnom embolijom

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Abstract

Background/Aim. Acute pulmonary embolism (APE) may have different clinical manifestations. Also, its outcome can range from complete recovery to early death. Major bleeding (MB) as a due of the therapy also contributes to the overall adverse outcome. So far, it is unknown what the best predictors are for short-term mortality and MB among the several commonly used biomarkers. The aim of this study was to evaluate the significance of C-reactive protein (CRP) and other biomarkers for the prediction of adverse clinical outcomes. **Methods.** This clinical, observational, retrospective-prospective study included 219 consecutive adult patients treated for APE. **Results.** Among 219 patients, 22 (10%) died within the first month after diagnosis. Twenty seven patients (12.3%) had at least one episode of MB. Composite end-point [net-adverse clinical outcome (NACO)] was estimated in 47 (21.5%) of patients. The average values of all biomarkers were higher in the group of patient who died, and differences were statistically significant. Similar results were obtained for composite end-point. In terms of MB, none of biomarkers did not have significance, but CRP had a slight tendency toward significance. Results from univariate logistic regression model showed that troponin was statistically significant predictor of 30-day mortality. However, after adjusting for other variables, in multivariate logistic regression model troponin failed to be significant independent predictor of 30-day mortality. Unlike troponin, CRP and brain natriuretic peptide (BNP) were significant in all models – uni and multivariate (they were independent predictors of 30-day mortality). **Conclusion.** CRP has a good predictive value for 30-day mortality and NACO, and potential for MB in patients treated for APE.

Key words:
c-reactive protein; mortality; prognosis; pulmonary embolism; treatment outcome.

Apstrakt

Uvod/ Cilj. Akutna plućna embolija (APE) može imati različite kliničke manifestacije. Takođe, njen ishod može varirati od potpunog oporavka do rane smrti. Za sada nije poznato koji su najbolji prediktori kratkoročnog mortaliteta i velikih krvarenja među nekolicinom najčešće upotrebljavanih biomarkera. Cilj ovog istraživanja bio je da se utvrdi značaj C-reaktivnog proteina (CRP) i drugih biomarkera u predviđanju neželjenih kliničkih ishoda. **Metode.** Ova klinička, opservaciona, retrospektivno-prospektivna studija, obuhvatila je 219 uzastopnih odraslih bolesnika sa APE. **Rezultati.** Od 219 bolesnika 22 (10%) je umrlo unutar prvog meseca od postavljanja dijagnoze. Dvadeset sedam bolesnika (12.3%) imalo je najmanje jednu epizodu velikog krvarenja. Kompozitni cilj (ukupni neželjeni klinički ishod) utvrđen je kod 47 (21.5%) bolesnika. Srednje vrednosti svih biomarkera bile su veće u grupi umrlih bolesnika, a razlika je bila statistički značajna. Slični rezultati su utvrđeni za kompozitni cilj. U pogledu velikih krvarenja, nijedan biomarker nije pokazao značajnost, mada je CRP imao trend ka značajnosti. Rezultati univarijantne regresione analize pokazali su da je troponin značajan prediktor 30-dnevnog mortaliteta. Međutim, posle prilagođavanja sa drugim varijablama, multivarijantni logistički regresioni model nije potvrdio da je troponin značajan nezavisani prediktor 30-dnevnog mortaliteta. Za razliku od troponina, CRP i B-tip natriuretskog peptida (BNP) su

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značajni u svim modelima, univarijantnim i multivarijantnim (oni su nezavisni prediktori 30-dnevnog mortaliteta). **Zaključak.** Biomarker CRP ima dobru prediktivnu vrednost za 30-dnevni mortalitet i ukupan neželjeni klinički ishod, kao i potencijalnu prediktivnu vrednost za velika krvarenja kod bolesnika lečenih zbog APE.

Ključne reči:
c-reaktivni protein; mortaltiet; prognoza; pluća, embolija; lečenje, ishod.

Introduction

Acute pulmonary embolism (APE) may have different clinical manifestations, from asymptomatic to severe, life-threatening disease. Also, its outcome can range from complete recovery to early death. Major bleeding (MB) as a due of the therapy also contributes to the overall adverse outcome. In patients with massive pulmonary embolism (PE), the mortality rate is 18–65% (overall); about 20% in treated patients; 25–30% in patient with cardiogenic shock; 65% in patients with resuscitation. In submassive PE, the mortality rate is 5–25%; in PE with mobile thrombi in right-heart chambers – as high as 27% and in small PE up to 1% [1].

On the other hand, Chatterjee et al. [2] in meta-analysis reported that among patients with PE, including those who were hemodynamically stable with right ventricular dysfunction, thrombolytic therapy vs. anticoagulants was associated with lower rates of all-cause mortality (2.17% *vs* 3.89%) and increased risks of MB (9.24 *vs* 3.42%).

So far, it is unknown what the best predictors are for short-term mortality and MB among the several commonly used biomarkers in patients with APE. In the assessment of the early risk of death (in hospital and 30-day) from PE, in the prediction the severity and possible outcome in patients with PE, the most used parameters are D-dimer, cardiac troponin, natriuretic peptides [brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP)] [3–8]. Also, role of an inflammatory biomarker, C-reactive protein (CRP), as a predictor of prognosis in PE, was investigated [9]. Its role as a predictive biomarker of bleeding risk was investigated in other cardiovascular diseases. CRP is independent predictor of MB in elderly patients with myocardial infarction [10].

The aim of this study was to evaluate the significance of CRP and other biomarkers for the prediction of adverse clinical outcomes: 30-day mortality, MB and net-adverse clinical outcome (NACO – mortality plus MB) in patients treated for acute PE.

Methods

For the purpose of our research, we conducted a clinical, observational, retrospective-prospective study. Study was conducted at the Clinic for Emergency Internal Medicine, Military Medical Academy in Belgrade. We treated 243 patients with PE, but 24 patients were excluded because of underlying malignancy, so 219 patients were included in final analysis (116 men and 103 women). In all patients diagnosis was established with multidetector computed tomography with pulmonary angiography (MDCT PA).

Patients were treated according to local guidelines for pulmonary thromboembolism, which are in concordance to European guidelines [11, 12].

Inclusion criteria were as follows: age over 18 years, PE established with MDCT PA, first episode of PE, availability of a patient and his/her findings during the one month follow-up period.

Exclusion criteria were: pregnancy, active malignancy, active infection before PE (subsequent pneumonia due to PE was not exclusion criteria), known innate thrombotic conditions, existence of other conditions that may affect to hemostasis, previous treatment that can affect hemostasis (glycocorticoids, estrogen-progesterone drugs, testosterone, desmopressin), lack of data entering the study. Although the use of inclusion and exclusion criteria reduces the dimension of „real life", they are necessary in order to avoid confounding variables, for example, increasing mortality in case of active malignant diseases.

Variables that were determined: demographic parameters, comorbidities, biomarkers (CRP, BNP, troponin T), outcome – 30-day mortality, MB (according to the International Society of Thrombosis and Hemostasis definition)[13], NACO.

Statistical analysis

Data were analyzed by using IBM® SPSS® Statistics, release 23.0.0.2. Results are presented as count (percent), mean ± standard deviation or median (25th–75th percentile) depending on data type and distribution. Group comparisons were performed using Pearson χ^2 test, Fisher's exact test, *t*-test and Mann-Whitney *U* test. Logistic regression analysis was used to assess significant predictors of 30-day mortality. All *p* values less than 0.05 were considered significant.

Results

During the 10-year period we treated 219 patients with MDCT PA-confirmed PE. The baseline characteristics of enrolled patients are shown in Table 1.

The mean age of patients was 59 ± 17 years, ranging from 17 to 92 years. Distribution by gender was similar, as well as regarding spontaneous/provoked PE. The previous surgery (few months ago) had one fifth of patients. Also, one fifth of patients were active smokers. Arterial hypertension (AH) was the most common comorbidity. About half of the patients had high or intermediate-high risk. Simplified pulmonary embolism severity index (sPESI) score 1 or more was present in slight over half of the patients.

Adverse outcomes

Among 219 patients, 22 (10%) died within the first month after diagnosis. In 15 (68%) of them the cause of death was the APE, intracranial hemorrhage in 2 (9%) patients and other conditions in 5–23%. Twenty seven (12.3%) patient had at least one episode of MB. The most common bleeding site was gastrointestinal tract (11–45.9%); then surgery site (6–25%); urogenital tract (3–12.5%); intracranial (2–8.3%) and other (2–8.3%). Composite end-point (NACO) was estimated in 47 (21.5%) of patients.

Table 1

Baseline characteristics of patients

Parameters	Values
Age (years), mean ± SD	59 ± 17
Male, n (%)	116 (53)
BMI, mean ± SD	27.8 ± 4.8
Provoked APE, n (%)	101 (46.1)
Active smoking, n (%)	46 (21)
Surgery in last few months, n (%)	44 (20.1)
Comorbid conditions, n (%)	
COPD or emphysema	10 (4.6)
CHF	29 (13.2)
AH	93 (42.5)
CAD	18 (8.2)
DM	29 (13.2)
stroke (earlier)	14 (6.4)
Risk, n (%)	
low	71 (32.4)
intermediate-low	35 (16)
intermediate-high	79 (36.1)
high	34 (15.5)
sPESI score, n (%)	
0	89 (40.6)
≥ 1	130 (59.4)

BMI – body mass index; APE – acute pulmonary thromboembolism; COPD – chronic obstructive pulmonary disease; CHF – chronic heart failure; AH – arterial hypertension; CAD – coronary artery disease; DM – diabetes mellitus; sPESI – simplified Pulmonary Embolism Severity Index; SD – standard deviation.

As shown in Table 2, there was no statistically significant difference by gender, in terms 30-day mortality, MB and NACO. Mortality rate and NACO were higher in patients with provoked PTE than with spontaneous one, while the difference in the rate of MB was not statistically significant. Smoking habit had no impact on any adverse outcome in the study population, but it should be noted that the majority of the patients (79%) were nonsmokers. As regards comorbidities, univariate analysis was not indicated statistically significant difference for MB, while 30-day mortality and NACO were significantly higher in patients with concomitant diabetes, AH and stroke. In the other hand, chronic obstructive pulmonary disease and chronic heart failure did not showed influence on the 30-day mortality, while coronary artery disease showed a trend towards significance. Also, the 30-day mortality and NACO were significantly higher in the strata of the patients with high and intermediate-high estimated risk, than in low and intermediate-low strata, while regarding the MB there was not statistically significant difference.

As can be seen from Table 3, age was independent risk factor for the 30-day mortality and NACO. Body mass index did not show significance for any adverse outcome. Also, sPESI score was the independent predictor of mortality and NACO, but not of MB. The average values of all biomarkers were higher in the group of patient who died, and differences were statistically significant. Similar results were obtained for composite end-point. In terms of MB, none of biomarkers did not have significance.

Multivariate analysis was performed to rule out the influence of confounding variables (table 4). Results from univariate logistic regression model showed that troponin was statistically significant predictor of 30-day mortality. However, after adjusting for other variables, in multivariate logistic regression model troponin failed to be significant independent predictor of 30-day mortality. Unlike troponin, CRP and BNP were significant in both, uni and multivariate models. The R square of BNP was the largest in univariate, as in all other models (compared to CRP models).

Table 2

Correlation between the clinicodemographic factors and adverse outcomes

Parameter	Mort, n (%)	*p*-value	MB, n (%)	*p*-value	NACO, n (%)	*p*-value
Gender						
male	8 (6.9)	0.100	14 (13.0)	0.899	22 (19.0)	0.340
female	14 (13.6)		11 (12.4)		25 (24.3)	
APE						
spontaneous	6 (5.1)	0.008	13 (11.6)	0.600	18 (15.3)	0.016
provoked	16 (15.8)		12 (14.1)		29 (28.7)	
Active smoking						
no	21 (12.1)	0.088	17 (11.2)	0.369	39 (22.5)	0.531
yes	1 (2.3)		7 (16.3)		8 (18.2)	
COPD						
no	22 (10.5)	0.405	24 (12.8)	1.000	46 (22.0)	0.366
yes	0		1 (10.0)		1 (10.0)	
CHF						
no	17 (9.2)	0.541	19 (11.4)	0.230	38 (25)	0.223
yes	5 (14.3)		6 (20)		9 (31.0)	

Table 2 – *continued*

Parameter	Mort, n (%)	*p*-value	MB, n (%)	*p*-value	NACO, n (%)	*p*-value
CAD						
no	18 (9.0)	0.091	22 (12.0)	0.394	40 (19.9)	0.073
yes	4 (22.2)		3 (21.4)		7 (38.9)	
DM						
no	14 (7.4)	0.003	21 (11.9)	0.484	34 (17.9)	0.003
yes	8 (27.6)		4 (19.0)		13 (44.8)	
AH						
no	7 (5.6)	0.010	13 (10.9)	0.387	20 (15.9)	0.019
yes	15 (16.1)		12 (15.4)		27 (29.0)	
Stroke						
no	16 (7.8)	< 0.001	24 (12.7)	1.000	39 (19.0)	0.001
yes	6 (42.9)		1 (12.5)		8 (57.1)	
Risk						
low	1 (1.4)	< 0.001	8 (11.4)	0.157	8 (11.3)	< 0.001
intermediate-low	1 (2.9)		2 (5.9)		3 (8.6)	
intermediate-high	8 (10.1)		9 (12.7)		17 (21.5)	
high	12 (35.3)		6 (27.3)		19 (55.9)	

Mort – 30-day mortality; MB – major bleeding; NACO – net-adverse clinical outcome.
For other abbreviations see under Table 1.

Table 3

Clinical parameters and biomarkers related to the adverse outcomes (univariate analysis)

Parameter	30-day mortality		*p*-value	Major bleeding		*p*-value	Net-adverse clinical outcome		*p*-value
	no (n = 197)	yes (n = 22)		no (n = 192)	yes (n = 27)		no (n = 172)	yes (n = 47)	
Age (mean ± SD)	57.9 ± 17.2	68.6 ± 16.2	0.006	57.9 ± 17.4	57.8 ± 17.7	0.995	57.7 ± 17.4	63.55 ± 16.7	0.042
BMI (mean ± SD)	28.0 ± 4.9	26.1 ± 3.3	0.085	28.1 ± 4.7	27.7 ± 6.4	0.756	28.0 ± 4.7	27.2 ± 5.2	0.326
sPESI, Med ($^{25–75}$ perc.)	1 (0–2)	2.5 (1–3)	< 0.001	1 (0–2)	1 (0–2)	0.134	1 (0–2)	2 (1–3)	< 0.001
BNP, Med ($^{25–75}$perc.)	113.0 (42.8–285.5)	498.0 (267.6–988.0)	< 0.001	109.5 (39.7–252.0)	176.0 (74.0–360.0)	0.163	109.5 (39.3–254.6)	331.0 (120.5–506.0)	< 0.001
CRP, Med ($^{25–75}$perc.)	37.2 (18.1–93.0)	95.9 (57–155)	0.002	36.0 (17.95–80.5)	59.4 (21–133)	0.075	36.2 (17.6–80.5)	92.5 (34.4–145.8)	0.001
TnT, Med ($^{25–7p}$Perc.)	0.08 (0–0.46)	0.53 (0.07–1.10)	0.041	0.06 (0–0.45)	0.30 (0.03–0.60)	0.159	0.06 (0–0.44)	0.4 (0.06–0.90)	0.011

SD – standard deviation; Med – median; Perc – percentile; TnT – troponin T.
For other abbreviations see under Table 1.

Table 4

Results from multivariate logistic regression models – 30 day mortality

Parameter	BNP		CRP		Troponin T	
	p-value (R^2)	OR (95% CI)	*p*-value (R^2)	OR (95% CI)	*p*-value (R^2)	OR (95% CI)
No adj	< 0.001 (0.191)	1.002 (1.001–1.003)	0.009 (0.065)	1.007 (1.002–1.012)	0.052 (0.051)	2.192 (0.995–4.830)
Adj age	0.003 (0.240)	1.002 (1.001–1.003)	0.002 (0.204)	1.009 (1.003–1.016)	0.283 (0.231)	1.618 (0.672–3.893)
Adj gender	< 0.001 (0.199)	1.002 (1.001–1.003)	0.005 (0.091)	1.007 (1.002–1.013)	0.092 (0.111)	2.038 (0.891–4.662)
Adj age, DM, AH, stroke	0.005 (0.330)	1.002 (1.001–1.003)	0.003 (0.303)	1.010 (1.003–1.017)	0.279 (0.384)	1.678 (0.658–4.282)
Adj PESI 0/1+	0.004 (0.247)	1.002 (1.001–1.003)	0.020 (0.186)	1.007 (0.001–0.012)	0.297 (0.156)	1.548 (0.681–3.520)

BNP – B-type natriuretic peptide; CRP – C-reactive protein; OR – odds ratio; CI – confidence interval.
For other abbreviations see under Table 1.

CRP and BNP were independent predictors of 30-day mortality. Two models are not shown in Table 4, also showed significance of CRP as predictor of the 30-day mortality – CRP adjusted with risk (p = 0.011; R^2 = 0.239; OR 1.008; 95% CI- 1.002–1.014) and CRP adjusted with risk and age (p = 0.005; R^2 = 0.300 OR 1.010; 95% CI- 1.003–1.016).

Discussion

The aim of this investigation was to find the best biomarker for prediction of adverse outcome in patient treated for APE. While predictive value of troponin and BNP in APE is well known and validated, and they are implemented in guidelines [12], CRP was less investigated as a predictor of mortality in APE, but for the prediction of MB and NACO no relevant data exist in literature.

The role of systemic inflammation in cardiovascular diseases (CVD), including PE, is well known. On the one hand, various systemic inflammatory diseases (e.g. connective tissue diseases) could increase the risk for CVD [14]. Atherosclerosis, as pathological substrate for coronary artery disease, also presents an inflammatory disease. CRP, as surrogate marker of this process, plays role in the activation of the classical pathway of the complement system; increases low-density lipoprotein uptake into macrophages and enhances the ability of macrophages to form foam cells; inhibits endothelial nitric oxide synthase expression in endothelial cells; activates macrophages to secrete tissue factor, a powerful procoagulant; increases plasminogen activator inhibitor (PAI-1) expression and activity [15]. On the other hand, APE may induce local and systemic inflammatory response, by several mechanisms: ischemia, hypoxia, endothelial lesion, etc. These facts have been confirmed both in experimental models [16, 17], and in the study of Stewart et al. [18] where it is shown a partially reversible, systemic acute inflammatory response in APE, established by the significant increase of biomarkers (interleukin 6, CRP, myeloperoxidase and D-dimer) at diagnosis, followed by their decrease in more of 80% of patients over the next 3 months. As previously mentioned, inflammation may be cause or consequence of APE, but in addition, the reperfusion treatment could have the influence on the serum level of CRP [19]. Also, the role of inflammation and inflammatory markers in thrombus resolution and pulmonary vessels wall remodeling is described [20].

In our study, among biomarkers the best predictor of the 30-day mortality was BNP, than CRP, and troponin T. Good predictive value of CRP for the 30-day mortality was shown in both, univariate and multivariate analyses, where CRP was adjusted with some demographic (age, gender) or clinical (comorbidity) factors which were significant in the univariate analysis (CRP and BNP were independent predictors of the 30-day mortality). None of biomarkers did not show predictive value for MB, but CRP had a slight tendency toward significance ($p = 0.075$), so further research on a larger sample is needed to confirm its value. Regarding the composite end-point (NACO), similar results were obtained as for the 30-day mortality.

In respect of clinicodemographic factors, in our study independent predictors of the 30-day mortality and NACO were age, provoked APE, diabetes, AH and stroke. Age is implemented as prognostic factor in both the PESI and sPESI score. Role of comorbidity is also well known, and our results are in concordance with previous investigations. Polo Friz et al. [21] were estimated that in elderly patients with a hemodynamically stable PE, and confirmed the Charlson Comorbidity Index score as an independent predictor of mortality. In our investigation the 30-day mortality was three times higher in patients with provoked pulmonary tromboembolism than with spontaneous one, while NACO was twice higher, and the difference for both variables was highly significant. Gjonbrataj et al. [22] conducted study in Korea and established that the 30-day mortality was 2-fold higher in patients with provoked PE than in those with unprovoked PE, although that difference was not statistically significant.

Also, higher sPESI score, high and intermediate-high estimated risk are confirmed as predictors of the 30-day mortality and NACO, which is consistent with the literature data [23–25].

Conclusion

CRP has a good predictive value for the 30- day mortality and NACO, and potential for prediction of MB in patients treated for APE.

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