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Research Article

Fine-Tuning of Risk Prediction in PE: GFR and sPESi Combined-Powerful Predictor of Survival in Patients with Pulmonary Embolism

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ABSTRACT

Background: The PESI score is an established prognostic score of the severity of the acute-pulmonary embolism (PE). Patients with sPESI class 0 represented a low-risk PE.

Purpose: To investigate whether adding brain natriuretic peptide (BNP) and cardiac troponin (cTn) blood concentrations, echocardiographic parameters or glomerular filtration rate to sPESI can improve the prognostic value of acute PE.

Methods: The study included 1201 consecutive patients with PE which was confirmed using MDCT. All patients underwent echocardiography examination on admission and blood samples were collected for troponin I (TnI), B-type natriuretic peptide (BNP), creatinine and other routine laboratory analyses.

Results: Intra-hospital mortality rate was 11.5%. Using three levels sPESI model: sPESI 0, sPESI 1 and sPESI ≥2, patients were into three groups.

Conclusion: Renal dysfunction on admission, in patients with acute PE, is strongly associated with high intrahospital mortality risk.

Keywords: Pulmonary embolism; sPESI score; Prognosis

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INTRODUCTION

Pulmonary embolism (PE), as the most serious clinical presentation of venous thromboembolism (VTE), with the mortality rate range between 8.7% and 17.4% at 3 months requires immediate prognostic assessment of patients in acute settings [1,2].

Widely used, the Pulmonary Embolism Severity Index is the most extensively validated clinical score to date [3,4]. A recent randomized trial established the identification of low-risk PE (PESI classes I and II), as possible criteria for outpatient treatment of acute PE [5]. Requirements for several clinical variables make this calculation complicated in the acute settings of the emergency department. Simplified PESI (sPESI), that can be calculated using six equally weighted variabales (age, history of cancer, history of chronic lung disease - COPD or chronic heart failure - CHF, heart rate - HR, systolic blood pressure - BP, arterial oxyhaemoglobin saturation <90%) can also provide reliable prognostic information [6,7]. In the already published investigation, the simplified PESI was non-inferior for identification of low risk patients versus imaging and biomarker criteria proposed by the ESC [8]. Unfortunately, sPESI based therapeutic regimen is still questionable.

Another suspicion is the accuracy of sPESI 1 versus sPESI 0 in excluding an adverse outcome in patients with acute PE [9]. On the other hand, biochemical markers have been proposed as an alternative tool for the risk stratification. But, onset and prognostic implication of acute kidney injury, or acute kidney dysfunction on admission or during hospitalization, were underestimated in patients with APE [10]. In acute settings, changes in pulmonary circulation may induce hemodynamic disorder of systemic circulation, causing decreased cardiac output, hypoxemia and elevated central venous pressure leading to reduction of glomerular filtration and appearance of kidney injury. On the other hand, a higher prevalence of PE or venous thromboembolism in chronic kidney disease (CKD) patients has been emphasized in several registries [11,12].

In the present study, we sought to determine the outcome according to sPESI 0, sPESI 1 and sPESI >1 and whether the values of biomarkes such as BNP, TnI, estimated GFR and right ventricular dysfunction at diagnosis improve the sPESI score for risk stratification in patients with APE.

METHODOLOGY

The source of data was the Serbian multicenter PE registry which successively included 8 hospitals (7 university hospitals and one general hospital) during the period from 2014 to 2020. Patients with PE were diagnosed according to ESC algorithm. All had PE confirmed with positive multidetector computed tomography pulmonary angiography. The majority of patients were admitted to intensive care units for the initial evaluation. All patients gave oral informed consent for the participation in registry and the study was conducted according to Helsinki Declaration. Ethics committees of the included university clinics gave their approvals to conduct the study.

Relevant data were recorded from the medical history around the time of hospitalization by the trained doctors who were tasked with the administration of the database. At admission, anamnestic data of comorbidities, oxygen saturation, systolic arterial pressure, and heart rate were recorded for all patients. Echocardiography imaging, cTnI, and BNP or NT-proBNP (depending on the hospital) blood levels were obtained during the first hospitalization day for a considerable fraction of patients. Venous peripheral blood samples for measurement of creatinine were drawn at hospital admission before any treatment. Blood samples were collected in standardized tubes containing dipotassium ethylenedinitrotetraacetic acid (EDTA) and stored at room temperature. All measurements were performed 30 minutes after blood collection. The creatinine value was measured by a rate-blanked method based on the Jaffe reaction [13]. Renal function, or the glomerular filtration rate (GFR), was estimated using the Cockroft Gault formula: {(140 - Age) × wt (kg) × F}/Serum Creatinine (μmol), where F=1.23 if male, and 1.04 if female [14]. According to the presence of severe hypotension and right ventricle dysfunction during the entire hospitalization, patients were stratified into three risk groups according to 2019 ESC PE guidelines as high-, intermediate- and low-risk patients [4].

The sPESI score included the variables of age greater than 80 years, history of cancer, history of chronic cardiopulmonary disease, heart rate of 110 beats/minute or greater, systolic blood pressure less than 100 mmHg, and arterial oxygen saturation less than 90% at the time of diagnosis [14].

Chronic cardiopulmonary disease included heart failure or chronic lung disease. Heart failure was diagnosed if the patient had a history of hospitalization for heart failure, if the patient had symptoms consistent with heart failure (New York Heart Association functional class ≥ 2), or if the left ventricular ejection fraction was less than 40%. Chronic lung disease was defined as persistent lung disorders such as asthma, chronic obstructive pulmonary disease and restrictive lung diseases. Patients with active cancer were defined as those on treatment for cancer such as chemotherapy or radiotherapy, those scheduled to undergo cancer surgery, those with metastases to other organs, and/or those with terminal cancer (expected life expectancy of 6 months or less) at the time of the diagnosis. According to sPESI value, patients were divided into three subgroups I-patients with sPESI=0, II patients with sPESI=1 and III-patients with sPESI ≥ 2.

All-cause mortality was recorded during the period of 30 days starting from the first hospitalization day. All discharged patients had scheduled visits at 30+7 days from the hospitalization.

STATISTICS

Patients' data are presented as frequencies for categorical variables and as mean ± SD or median with the interquartile range depending on the normality of the numerical variables. Differences between two groups based on 30-days all-cause mortality and three groups according sPESI score were tested with Hi square test or with independent samples Kruskal-Wallis test. Unadjusted Cox regression models were tested for the prediction power of BNP, TnI, GFR and RVD regarding the timing for all-cause mortality during the period of 30 days and also for the prediction power or three levels model of sPESI score (sPESI 0, sPESI 1 and sPESI ≥ 2) for all cause 30-days morality rate.

RESULTS

The study included 1201 consecutive patients with PE, 561 males and 640 females. The basic characteristics of patients are presented in Table 1. We summed up three categories of risk and prognostic factors such as: medical history, clinical and laboratory findings at admission and PE severity score according to sPESI score and PE mortality risk. During hospitalization, 138 (11.5%) patients died, and 1063 (88.5%) survived. Comorbidities such as COPD, prior stroke, diabetes, coronary artery disease, history of cancer in the last six months ($p<0.05$), CHF, abnormal liver function and kidney injury ($p<0.001$), were significantly more associated with lethal outcome. According to clinical and laboratory findings, in the statistically significant higher levels of BNP ($p<0.05$), higher heart rate on admission ($p=0.01$), lower oxygen saturation levels ($p=0.001$), lower systolic blood pressure on admission ($p<0.001$), group of patients with the worst outcome, there were and a greater number of patients with systolic blood pressure less than 95 mm Hg ($p<0.001$), higher value of TnI ($p<0.001$) and higher value of right ventricular systolic pressure as a sign of right ventricular dysfunction. In the group of patients with in-hospital death, sPESI ≥ 2 were more prevalent ($p<0.001$), as expected. In this group, there were more patients with clinically high mortality risk and less patients with low mortality risk PE ($p<0.001$). There was also a statistically significant difference between groups in all-cause mortality rate ($p<0.0001$) (Table 1). In the group of patients who survived, sPESI 0, sPESI 1 and sPESI ≥ 2 are almost equally present (Figure 1).

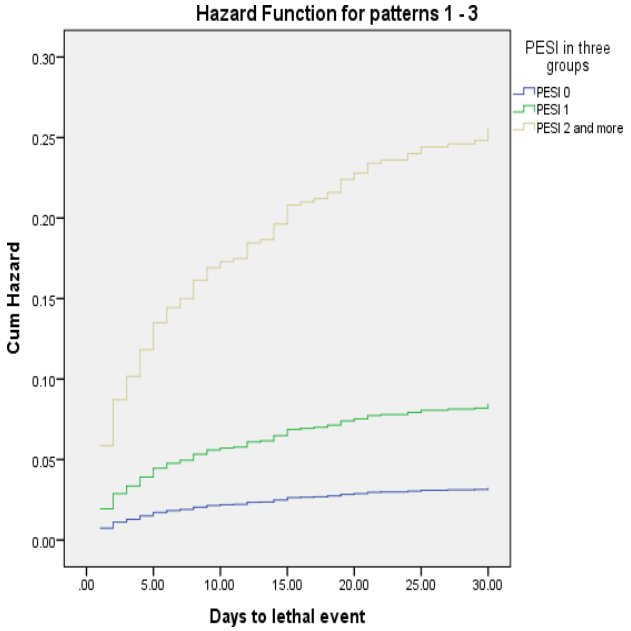

Figure 1: Hazard for intrahospital all-cause death according to sPESI stratified into 3 subgroups sPESI 0, sPESI 1 and sPESI ≥ 2.

Then, we divided the whole group of patients in three subgroups according the sPESI score: sPESI 0 comprised 410 patients, sPESI 1 comprised 370 patients, and sPESI ≥ 2 comprised 421 patients. All-cause mortality and mortality rate due to pulmonary embolism only, were statistically significant different between three groups based on sPESI score ($p<0.0001$). Patients with sPESI ≥ 2 were treated with systemic thrombolytics more frequently than patients with sPESI 1 and sPESI 0, as expected ($p<0.0001$) (Figure 2). Early all-cause mortality rates (1.8% for RV dysfunction and 3.8% for elevated troponin levels) were in the lower range compared to those previously reported for patients with intermediate-risk PE. That was the reason for using the signs of RV dysfunction or elevated cardiac biomarkers for further risk stratification into the intermediate-low-risk category, despite a low PESI or sPESI of 0.

	sPESI=0 N 410	sPESI =1 N 370	sPESI ≥ 2 N 421	p
GFR >60, N=792	322	258	212	<0.001
GFR <60, N=403	85	111	207	<0.001
TnI>0.04, N=467	135	138	194	<0.001
TnI<0.04, N=467	150	91	83	<0.001
BNP>100, N=501	114	161	226	<0.001
BNP<100, N=264	153	72	39	<0.001
RVDF, Y, N=663	173	210	280	<0.001
RVDF, Y, N=413	212	116	85	<0.001
Thromb (%)	73 (17.8)	83 (22.4)	133 (31.6)	<0.0001
Death PTE (%)	7 (1.7)	20 (5.4)	59 (14)	<0.0001
Death N (%)	13 (9.4)	30 (21.7)	95 (68.8)	<0.0001
Major bleeding (%)	32 (7.8)	45 (12.2)	34 (8.1)	ns

Table 1: Biomarkers, estimated glomerular filtration rate, right ventricular dysfunction and 30-day all sauce mortality according three level sPESI model.

Then, we divided the whole group of patients in three subgroups according the sPESI score: sPESI 0 comprised 410 patients, sPESI 1 comprised 370 patients, and sPESI ≥ 2 comprised 421 patients. All-cause mortality and mortality rate due to pulmonary embolism only, were statistically significant different between three groups based on sPESI score ($p<0.0001$). Patients with sPESI ≥ 2 were treated with systemic thrombolytics more frequently than patients with sPESI 1 and sPESI 0, as expected ($p<0.0001$) (Figure 2).

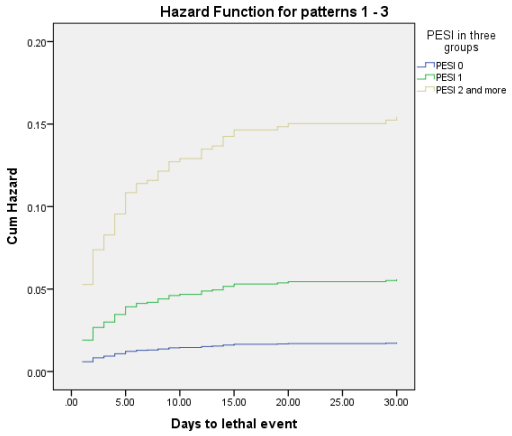

Figure 2: Hazard for pulmonary embolism as a cause death according to sPESI stratified into 3 subgroups sPESI 0, sPESI 1 and sPESI ≥ 2.

DISCUSSION

The PESI score, in original and simplified forms, is one of the widely used scores for prediction of severity of acute PE, due to combining comorbidities and parameters of patient's clinical status. It is well known that a PESI classes 0, I or II are predictors of low-risk PE. In a meta-analysis that included 21 cohort studies with a total of 3295 patients with 'low-risk' PE based on a PESI of I-II or a sPESI of 0, RV dysfunction on echocardiography or CTPA was recorded in 34% (95% CI 30-39%) of cases. Analyzing data on early mortality in seven studies that included 1597 patients revealed an OR of 4.19 (95% CI 1.39-12.58) for all- cause mortality if the RV dysfunction was present as well as elevated cardiac troponin levels. Early all-cause mortality rates (1.8% for RV dysfunction and 3.8% for elevated troponin levels) were in the lower range compared to those previously reported for patients with intermediate-risk PE. That was the reason for using the signs of RV dysfunction or elevated cardiac biomarkers for further risk stratification into the intermediate-low-risk category, despite a low PESI or sPESI of 0.

Our results revealed that three levels sPESI model can be used as better and simpler prognostic tool for risk stratification. Even sPESI 1 differs from sPESI 0, and may indicate high risk patient for 30-days all cause mortality as well as for mortality due to pulmonary embolism only.

On the other side, as mentioned above, clinical, imaging and biochemical parameters can be combined with risk scores in order to improve accuracy of prediction. Troponin, BNP, right ventricular dysfuncton are widely used for risk stratification and for guiding therapy regimen. Another marker that is still underused is estimated GFR. Glomerular filtration rate is not only a sign of renal disease; but can also be associated with hemodynamic alterations. A recently published article clearly showed the importance of GFR and its predictive value for risk stratification in patients with PE, and suggested its incorporation in PE guidelines for diagnosis and treatment. In our study, estimated GFR was, among biomarkes such as TnI, BNp and RVD, the only prognostic marker for 30-days all-cause mortality. Insight into complex multimodal risk estimation guide, offers an opportunity for using eGFR in risk stratification: due to its availability, simplicity and reproducibility. Rise in serum creatinine sometimes may be a sign for worsening of renal function. Nevertheless, eGFR is a precise marker for declining renal function in acute and/or chronic kidney injury and also in cardiovascular diseases. Hemodynamic disturbances in acute PE may be the cause of acute kidney injury.

Our results revealed that taking into account GFR with three level sPESI (0.1>1) can be useful for prediction of 30-day in-hospital lethal event. As previously published, the best cut-off of GFR is 59ml/min. We also proposed that GFR on admission less than 60ml/min with no improvement during next 3 days indicates poor prognosis, with a 30-day mortality rate of approximately 27%.

CONCLUSION

Renal dysfunction, on admission, in patients with acute PE is strongly associated with high intrahospital mortality risk. Established sPESI score may gain additional discriminative power by using simple calculation of GFR in prediction of survival of patients with PE. Three levels model of sPESI score, can be used as more accurate prognostic stratification tool in patients with acute pulmonary embolism. Simple calculation of GFR can be used to to fine tune sPESI score and is useful for prognostic and therapeutic purposes, as well as for possible outpatient treatment. In spite its predictive value, GFR calculation has still not become the clinical routine in PE.

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