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Original article

Refining Risk Stratification in Pulmonary Embolism: Integrating Glomerular Filtration Rate and Simplified Pulmonary Embolism Severity Index as a Potent Predictor of Patient Survival

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SUMMARY

Background/Aim. Patients classified as belonging to simplified pulmonary embolism severity index (sPESI) class 0 are considered to have low-risk pulmonary embolism (PE). Yet, certain laboratory and echocardiographic parameters not accounted for in the sPESI score might suggest a likelihood of worse outcomes in PE cases. This study seeks to determine if the prognostic value of the sPESI score in acute PE can be improved, refined, and optimised by incorporating brain natriuretic peptide (BNP) and troponin I (TnI) levels, echocardiographic parameters, or glomerular filtration rate.

Methods. The study encompassed 1,201 consecutive patients diagnosed with PE, confirmed by - multidetector computed tomography (MDCT). Upon admission, each patient underwent an echocardiography exam, and blood samples were taken to measure B-type natriuretic peptide (BNP), troponin I (TnI), creatinine, and other routine laboratory markers.

Results. The in-hospital mortality rate was 11.5%. The patients were categorized into three groups using the three-level sPESI model: sPESI 0, sPESI 1, and sPESI ≥ 2. Statistically significant differences were found among these groups regarding mortality rates, TnI values, BNP levels, estimated glomerular filtration rate (eGFR), and the presence of right ventricular dysfunction (RVD). Cox regression analysis identified eGFR as the most reliable predictor of 30-day all-cause mortality [HR 2.24 (CI 1.264-3.969); p = 0.006] across all sPESI categories. However, incorporating TnI, BNP, or RVD did not improve risk prediction beyond the three-level sPESI model.

Conclusion. Renal dysfunction at the time of admission is closely related to an elevated risk of in-hospital mortality in patients with acute PE. The three-level sPESI score offers a more accurate method for prognostic stratification in these patients.

Keywords: **pulmonary embolism, sPESI score, prognosis**

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INTRODUCTION

Pulmonary embolism (PE), being the most severe manifestation of venous thromboembolism (VTE), has a three-month mortality rate ranging from 8.7% to 17.4%, and, as such, it necessitates the prompt evaluation of the patient in an acute care setting (1, 2). The pulmonary embolism severity index (PESI) is one of the most commonly used and thoroughly validated clinical scoring systems available (3, 4). A recent randomized trial identified low-risk pulmonary embolism (PE) classes (PESI classes I and II) as a potential criterion for outpatient treatment of acute PE (5).

This calculation is complex in the emergency department setting due to the need for multiple clinical variables in the acute management of pulmonary thromboembolism (PTE). The simplified PESI (sPESI) score, which is determined using six equally weighted variables—age, chronic lung disease (such as COPD), cancer history, chronic heart failure (CHF), heart rate (HR), systolic blood pressure (BP), and arterial oxyhaemoglobin saturation below 90%—provides dependable prognostic insights (6, 7). A recent study indicated that the sPESI is as reliable as the imaging and biomarker criteria recommended by the European Society of Cardiology (ESC) for identifying low-risk patients (8). However, the therapeutic approach based on sPESI is still a subject of debate. Additionally, several registries have highlighted an increased occurrence of pulmonary embolism (PE) or venous thromboembolism in individuals with chronic kidney disease (CKD) (11, 12).

It is important to question the reliability of distinguishing between sPESI scores of 1 and 0 when excluding the possibility of adverse outcomes in patients with acute PE (9). Biochemical markers have been suggested to be used as an alternative method employed for risk stratification. Yet, the occurrence and prognostic significance of acute kidney injury or dysfunction, whether present upon admission or developing during hospitalization, have been neglected and underestimated in patients with acute PTE (10). In acute situations, alternations and disruptions in pulmonary circulation can cause systemic hemodynamic instability, leading to decreased cardiac output and increased central venous pressure and hypoxemia. These factors can diminish and reduce glomerular filtration, potentially leading to kidney injury. Furthermore, several registries have highlighted a higher incidence of pulmonary embolism (PE) or venous thromboembolism (VTE) in patients with chronic kidney disease (CKD) (11, 12).

The present study aims to determine and evaluate the outcomes in patients with sPESI scores of 0, 1, and greater than 1, and to assess whether biomarkers such as BNP, TnI, and estimated glomerular filtration rate (GFR), along with right ventricular dysfunction on admission, enhance the predictive power of the sPESI score for risk stratification in acute pulmonary embolism (APE) patients.

METHODOLOGY

The data for this study were obtained from the Serbian multicentre PE registry, which consecutively included eight hospitals (seven university hospitals and one general hospital) from 2014 to 2020. Patients with pulmonary embolism (PE) were identified using and following the European Society of Cardiology (ESC) algorithm, with all diagnoses confirmed through positive findings on multidetector computed tomographic pulmonary (MDCT) angiography. Most patients were initially admitted to intensive care units for check-ups and evaluation. All participants provided oral informed consent for inclusion in the registry, and the study was carried out in accordance with the guidelines and principles of the Helsinki Declaration. The ethics committees of the participating university clinics approved the study.

Trained doctors responsible for managing the database recorded relevant data from the patients' medical history around the time of hospitalization. Upon admission, they documented the patients' history of comorbidities, heart rate, oxygen saturation, as well as systolic arterial pressure.

Echocardiographic imaging was performed, and blood levels of cTnI, as well as BNP or NT-pro BNP (depending on the hospital), were measured on the first day of hospital admission. Before any treatment was initiated, peripheral venous blood samples were taken for creatinine testing upon hospitalisation. The samples were placed in standardized tubes with dipotassium ethylene dinitro tetra acetic acid (EDTA) and kept at room temperature. Measurements were carried out 30 minutes after the blood was collected. The measurement of creatinine levels was conducted using a method based on the rate-blanked Jaffe reaction technique (13). Renal function, or glomerular filtration rate (GFR), was calculated by means of the Cockcroft-Gault formula:

(140–Age) x weight (kg) x F/Serum Creatinine (mmol/L), where F equals 1.23 for males and 1.04 for females. Based on the presence of severe hypotension and right ventricular dysfunction throughout their hospitalization, patients were categorized into three risk groups—high, intermediate, and low, following the 2019 ESC PE guidelines (4).

The sPESI score, used for evaluating risk in pulmonary embolism patients, accounts for various factors such as history of cancer, age over 80, chronic cardiopulmonary disease, heart rate of 110 beats per minute or more, systolic blood pressure less than 100 mmHg, and arterial oxygen saturation under 90% at diagnosis (14). Chronic cardiopulmonary disease encompasses conditions like chronic lung disease or heart failure. A diagnosis of heart failure is established based on the presence of the following factors: history of hospitalization for the condition, symptoms indicative of heart failure (New York Heart Association functional class above 2), or a left ventricular ejection fraction below 40%.

Chronic lung disease is characterized by persistent respiratory conditions, including restrictive lung diseases, asthma, and chronic obstructive pulmonary disease (COPD).

Patients are considered to have active cancer if they are currently undergoing chemotherapy or radiotherapy, are scheduled for cancer-related surgery, have metastases, or are diagnosed with terminal cancer with an estimated life expectancy of six months or less at the time of diagnosis.

Based on their sPESI scores, patients were categorized into three groups: group I consisted of patients with an sPESI score of 0; group II included those with an sPESI score of 1; group III comprised patients with an sPESI score greater than ≥ 2. All-cause mortality was tracked from the very first day of hospitalisation through the entire hospital stay.

Statistics

The patient data were expressed as frequencies for categorical variables and as the mean ± SD or the median with an interquartile range for numerical variables, depending on the data distribution. Differences between the two groups, based on in-hospital all-cause mortality, and among the three groups, categorized by sPESI score, were analysed using the Chi-square test or the Kruskal-Wallis test for independent samples. Unadjusted Cox regression models were employed to evaluate the predictive power of right ventricular dysfunction (RVD), BNP, TnI, and GFR, concerning the timing of all-cause mortality during hospitalization. Additionally, the predictive power of the sPESI score, categorized into three levels, was assessed.

RESULTS

The study examined 1,201 patients hospitalized for pulmonary embolism (PE), including 561 men and 640 women. The main patient characteristics are outlined in Table 1. Risk and prognostic factors were categorized into three main groups: medical history, clinical and laboratory findings upon admission, and PE severity according to the sPESI score, which also indicated mortality risk. During the hospital stay, 138 patients (11.5%) passed away, while 1,063 patients (88.5%) survived. The average duration of hospitalization was 11.5 ± 6.9 days, with a statistically significant difference between the lengths of stay for survivors and those who passed away (11.9 ± 6.5 days vs. 8.1 ± 8.7 days, $p < 0.0001$).

Higher mortality rates were significantly more associated with comorbidities like abnormal liver function and kidney injury ($p < 0.001$), as well as a history of cancer within the last six months ($p < 0.05$), coronary artery disease, diabetes, prior stroke, CHF, and COPD.

In the group of patients with the poorest outcomes, the clinical and laboratory findings indicated significantly higher BNP levels ($p < 0.05$), elevated heart rates on admission ($p < 0.01$), reduced oxygen saturation ($p = 0.001$), and lower systolic blood pressure on admission ($p < 0.001$). Additionally, a larger number of these patients had systolic blood pressure below 95 mmHg ($p < 0.001$), elevated TnI levels ($p < 0.001$), and increased right ventricular systolic pressure, indicative of right ventricular dysfunction.

Among the patients who passed away during their hospitalization, a higher sPESI score (> 1) was more commonly observed ($p < 0.001$), as anticipated. This group also had a greater proportion of patients classified as being at high risk of mortality ($p < 0.001$). There was also a statistically significant difference in all-cause mortality rates between the groups ($p < 0.0001$) (Table 1). In contrast, among the patients who survived, the distribution of sPESI scores (0, 1, and ≥ 2) was relatively even.

Table 1. *Baseline patients' characteristics according to 30-day all-cause mortality*

	Hospital death		*p* value
	NO N = 1063 (88.5%)	**YES N = 138 (11.5%)**	
Female gender	559 (52.6)	81 (58.7)	0.2
Age in years	62.6±15.4	69.4 ± 14.5	0.07
MEDICAL HISTORY			
COPD	112 (10.5)	22 (15.9)	0.044
CHF	149 (14)	34 (24.6)	< 0.001
Coronary artery disease	118 (11.1)	116 (16.3)	0.006
Arterial hypertension	635 (59.7)	81 (58.7)	0.442
Prior stroke	64 (6.0)	20 (14.5)	0.001
Diabetes mellitus	187 (17.6)	37 (26.8)	0.008
Renal failure			
GFR < 60 ml/min	297 (27.9)	89 (64.5)	< 0.001
GFR < 30 ml/min	56 (5.3)	35 (25.4)	< 0.001
Abnormal liver function	38 (3.6)	19 (13.8)	< 0.001
Surgery within 6 months	159 (15)	20 (14.5)	**0.455**
History of cancer in last 6 months	133 (12.5)	27 (19.6)	0.017
Unprovoked PE	584 (54.9)	52 (37.7)	0.141
CLINICAL AND LABORATORY FINDINGS AT ADMISSION			
SaO_2 < 90%	938 (22.2)	122 (29.7)	0.001
SAP in mmHg	125±23	105 ± 30	< 0.001
SAP ≤ 95 mmHg	126 (11.9)	53 (38.4)	< 0.001
Heart rate in bpm	100±24	107 ± 27.8	0.01
RVSP[1] in mmHg	44.2±17.9	55.7 ± 16.0	< 0.001
BNP[2] in pg/ml	*127 (44-350)*	450 (44-350)	< 0.031
Troponin I[3] in μg/L	*0.05 (0.01-0.3)*	0.17 (0.05-0.9)	< 0.001
PE SEVERITY			
sPESI = 0	397 (37.3)	13 (9.4)	< 0.001
sPESI = 1	340 (32.0)	30 (21.7)	< 0.001
sPESI ≥ 2	326 (30.7)	95 (68.8)	< 0.001
PE mortality risk[4]			
Low risk	407 (38.3)	13 (9.4)	< 0.001
Intermediate risk	465 (43.7)	57 (41.3)	0.4
High risk	104 (9.8)	53 (38.4)	< 0.001
Hospital stay duration	11,9959 ± 6,56002	8,1207 ± 8,74758	< 0.0001

Abbreviations: IQR – interquartile range; COPD – chronic obstructive pulmonary disease; CHF – congestive heart failure; PE – pulmonary embolism; SaO_2 – oxygen saturation; SBP – systolic blood pressure; BPM– beats per minute; RVSP – right ventricular systolic pressure, GFR – glomerular filtration rate, 1RVSP was measured on admission in 1019 patients; BNP-brain natriuretic peptide, 2BNP was measured in 484; cardiac troponin I was measured in 690 patients; sPESI – simplified Pulmonary Embolism Severity Index. 4PE mortality risk was estimate for the time of entire hospitalization.

Table 2. *Biomarkers, estimated glomerular filtration rate, right ventricular dysfunction and 30-day all sauce mortality according to three-level sPESI model*

	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
L-Tx (%)	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

Abbreviations: BNP - brain natriuretic peptide; TnI - cardiac troponin I; GFR - glomerular filtration rate; RVD - right ventricular dysfunction; L-Tx – thrombolytic therapy; death PTE – pulmonary embolism as cause of death; death – all cause mortality

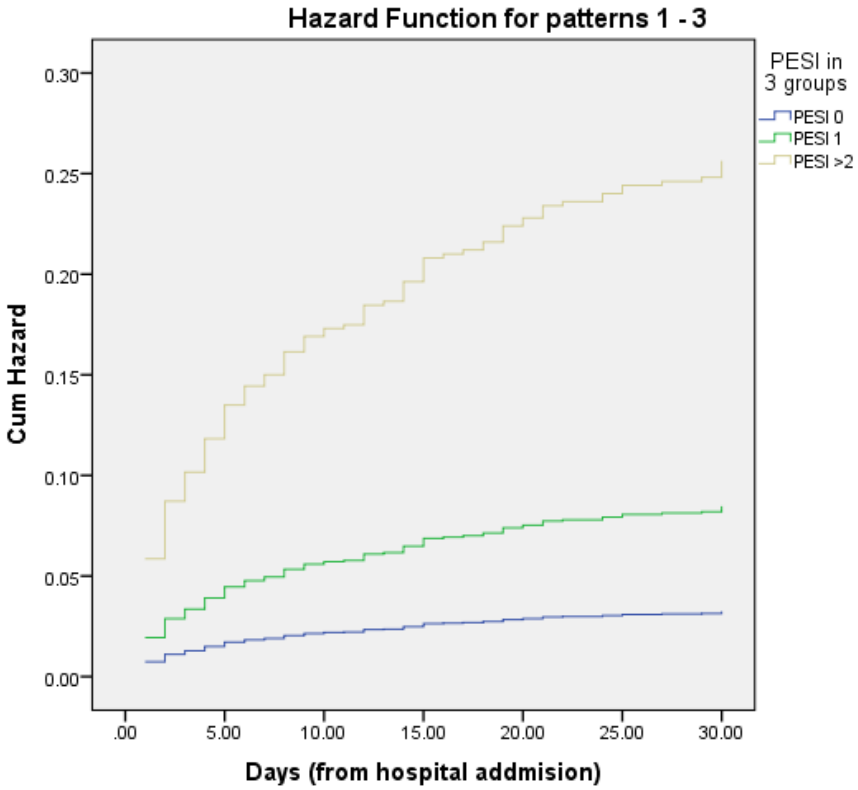

Figure 1. *Hazard for intrahospital all-cause death according to sPESI stratified into three subgroups sPESI 0, sPESI 1 and sPESI ≥ 2*

Patients were categorized into three subgroups based on their sPESI scores:

1. The sPESI 0 group included 410 patients.
2. The sPESI 1 group consisted of 370 patients.
3. The sPESI ≥ 2 group involved 421 patients.

The all-cause mortality rate and the mortality rate specifically due to pulmonary embolism differed significantly across the three groups categorized by sPESI scores ($p < 0.0001$) (Table 2). As anticipated, patients with sPESI scores greater than 1 were more often treated using systemic thrombolytics compared to those with sPESI scores of 1 or 0 ($p < 0.0001$).

An analysis of routine laboratory markers, including BNP, TnI, estimated GFR, and right ventricular dysfunction, showed significant variations across the groups with different sPESI scores (sPESI 0, sPESI 1, and sPESI ≥ 2) ($p < 0.001$). There were also notable differences in all-cause mortality rates among these groups, with hazard ratios indicating significant disparities [HR 0.127 (CI 0.071-0.226); $p < 0.0001$; HR 0.330 (CI 0.219-0.498); $p < 0.0001$]. Mortality rates specifically due to pulmonary embolism also varied significantly among all the groups [HR 0.113 (CI 0.052-0.247); $p < 0.0001$; HR 0.362 (CI 0.218-0.601); $p < 0.0001$] (Figure 1).

To identify additional parameters that could enhance the sPESI score, the Cox regression analysis was performed, including BNP, GFR, TnI, and right ventricular dysfunction across all three sPESI score groups (Table 3). The analysis revealed that GFR was the most effective predictor of all-cause in-hospital mortality [HR 2.24 (CI 1.264-3.969); $p = 0.006$] (Table 3) and mortality specifically due to pulmonary embolism (Figure 2). Right ventricular dysfunction [HR 1.608 (CI 0.977-4.203); $p = 0.262$], BNP levels [HR 0.733 (CI 0.288-1.866); $p = 0.514$], and TnI levels were not identified as significant predictors of in-hospital mortality independent of the sPESI score.

Table 3. *Hazard ratios for glomerular filtration rate, BNP, TnI, and RV dysfunction according to three-level sPESI score and 30-day all-cause mortality*

	HR	CI	p
GFR	2.24	1.264-3.969	0.006
BNP	0.733	0.288-1.866	ns
TnI	0.608	0.296-1.251	ns
RVD	1.687	0.677-4.203	ns

Abbreviations: BNP - brain natriuretic peptide; TnI - cardiac troponin I; GFR - glomerular filtration rate; RVD - right ventricular dysfunction

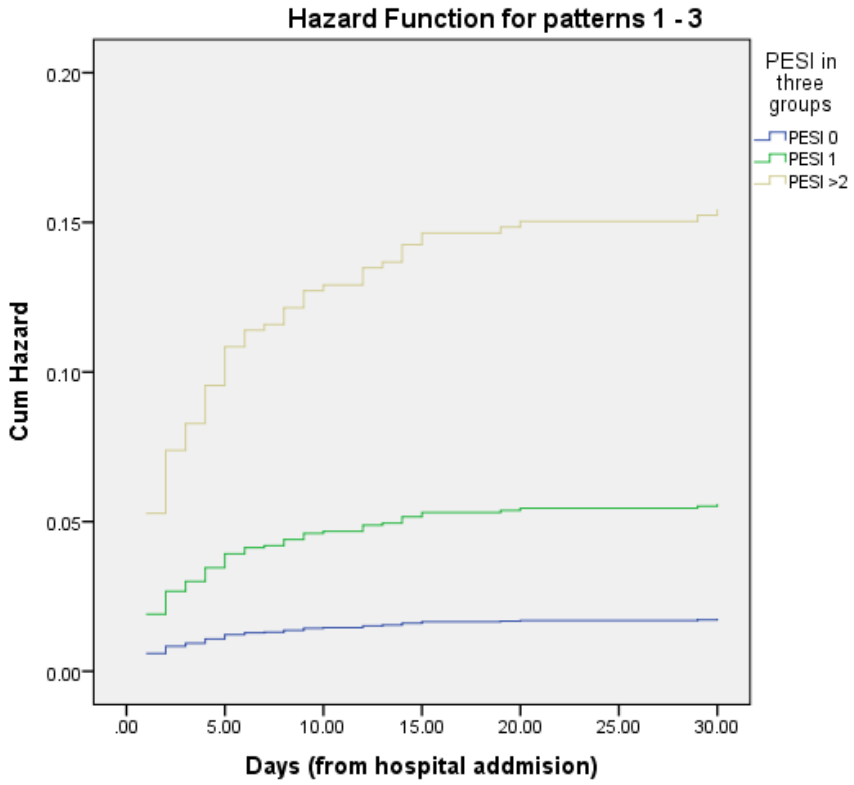

Figure 2. *Survival curve for pulmonary embolism as a cause of death according to sPESI stratified into three subgroups sPESI 0, sPESI 1 and sPESI ≥ 2*

DISCUSSION

The PESI score, whether in its original or simplified version, is frequently employed to assess the severity of acute pulmonary embolism (PE) because it integrates both comorbidities and clinical status parameters. PESI classes 0, I, and II are recognized as markers for low-risk PE. A meta-analysis encompassing 21 cohort studies with 3,295 patients diagnosed with "low-risk" PE based on PESI classes I-II or sPESI of 0 found that right ventricular (RV) dysfunction, detected via echocardiography or CTPA, was present in 34% (95% CI 30-39%) of cases. An analysis of early mortality data from seven studies, which encompassed 1,597 patients, indicated an odds ratio (OR) of 4.19 (95% CI 1.39-12.58) for all-cause mortality when RV dysfunction and elevated cardiac troponin levels were present (15). Early all-cause mortality rates were relatively low compared to previous reports for intermediate-risk PE patients, with rates of 1.8% for RV dysfunction and 3.8% for elevated troponin levels (16). As a result, we incorporated RV dysfunction signs and elevated cardiac biomarkers to refine risk assessment within the intermediate-low-risk category, even among patients with a low PESI or sPESI of 0.

Our findings indicate that the three-tier sPESI model serves as an improved and more straightforward prognostic tool for risk assessment. Although sPESI 1 differs from sPESI 0, it may identify patients at higher risk for both in-hospital all-cause mortality and mortality specifically due to pulmonary embolism. Exclusively utilizing the sPESI score and GFR provides a rapid method for the prognostic stratification of acute PE patients, even at the time of hospital admission. Additionally, as previously noted, integrating clinical, biochemical, and imaging parameters with risk scores can enhance predictive accuracy. Troponin I, BNP, and right ventricular dysfunction are commonly employed for risk assessment and to guide treatment decisions. However, estimated GFR remains underutilized. While the glomerular filtration rate is often indicative of renal function, it can also reflect hemodynamic changes and alternations (17). Altinsoy B et al. published a study highlighting the significant role of GFR in pre-

dicting risk and its value for stratification in PE patients. They advocated for its inclusion in PE diagnostic and treatment guidelines (18).

Our study showed that estimated GFR was a strong prognostic marker for in-hospital all-cause mortality besides biomarkers such as TnI, BNP and RVD. Utilizing a multifaceted approach to risk estimation allows for the inclusion of eGFR in risk stratification, given its ease of use, availability, and reliability. Elevated serum creatinine levels may occasionally signal a decline in renal function. Despite this, eGFR remains a reliable marker for detecting deteriorating renal function in both acute and chronic kidney injuries, as well as in cardiovascular conditions. In cases of acute pulmonary embolism, hemodynamic disturbances may contribute to the onset of acute kidney injury (19).

Our findings suggest that incorporating GFR with the three-tier sPESI (0, 1, ≥ 2) enhances the prediction of in-hospital mortality. Previous studies have identified a GFR cutoff of 59 ml/min as optimal. Kostrubiec et al. also noted that a GFR below 60 ml/min on admission, with no subsequent improvement within three days, is indicative of a poor prognosis, with a 30-day mortality rate approximating 27% (20).

Limitations

While the three-tier sPESI model offers a straightforward method for risk stratification and prognosis, further internal and external validation is required. Additionally, a larger patient cohort that includes a diverse range of comorbidities and treatment strategies would be beneficial for increasing the accuracy of the model and supporting its broader acceptance.

CONCLUSION

The three-tier sPESI model (sPESI 0, sPESI I, and sPESI ≥ 2) represents a simple, efficient and straightforward prognostic tool for stratifying patients with acute pulmonary embolism. It effectively predicts both all-cause mortality and mortality specifically due to pulmonary embolism. The integration of GFR into the sPESI framework can further enhance its prognostic and therapeutic accuracy, potentially minimizing the need for additional biomarkers such as TnI, BNP, or indicators of right ventricular dysfunction in the risk assessment process and allowing for outpatient treatment.

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Unapređenje stratifikacije rizika kod plućne embolije: Integracija brzine glomerularne filtracije i pojednostavljenog indeksa težine plućne embolije kao snažnog prediktora preživljavanja bolesnika

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SAŽETAK

Uvod/Cilj. Bolesnici sa plućnom embolijom (PE) i pojednostavljenim indeksom ozbiljnosti plućne embolije (engl. *simplified pulmonary emolism severity index* – sPESI) 0 imaju nizak rizik od letalnog ishoda. Laboratorijski i ehokardiografski parametri, koji nisu uključeni u sPESI skor, mogu predstavljati prediktore nepovoljnog ishoda. Istraživanje je sprovedeno radi ispitivanja mogućeg poboljšanja prediktivne vrednosti sPESI skora uz pomoć vrednosti moždanog natriuretskog peptide (engl. *brain natriuretic peptide* – BNP), troponina (engl. *tropanin I* – TnI), ehokadriografskih parametara ili vrednosti glomeluralne filtracije (engl. *gromenular filtration rate* – GFR).

Metode. Ispitivanjem je obuhvaćen 1201 konsekutivni bolesnik sa potvrđenim PE-om. Na prijemu su svim bolesnicima urađeni ehokardiografski pregled, rutinske laboratorijske analize, TnI, BNP, kreatinin i GFR.

Resultati. Intrahospitalni mortalitet bio je 11,5%. Bolesnici su podeljeni u tri grupe korišćenjem trostepenog sPESI modela: sPESI 0, sPESI 1 i sPESI ≥ 2. Postojale su statistički signifikantne razlike mortatiliteta između tri grupe bolesnika, kao i vrednosti BNP-a, TnI-a, procenjene vrednosti glomenuralne filtracije (engl. *estimated gromenular filtration rate* – eGFR) i znakova disfunkcije desne komore (engl. *right venticular systolic dysfunction* – RVD). Prema Coxovoj regresionoj analizi, najbolji prediktor tridesetodnevnog ukupnog mortliteta bio je eGFR [HR 2,24 (CI 1,264–3,969); p = 0,006] u sve tri grupe. Korišćenjem trostepenog sPESI modela, zaključili smo da TnI, BNP ili RVD nisu doprineli poboljšanju stratifikacije rizika.

Zaključak. Renalna disfunkcija na prijemu bolesnika sa PE-om udružena je sa visokim rizikom od intrahospitalnog mortaliteta. Trostepeni sPESI model može se koristiti sa ciljem prognostičke stratifikacije bolesnika sa akutnom plućnom embolijom

Ključne reči: **pulmonalna, embolija, skor pojednostavljenog indeksa ozbiljnosti plućne embolije, prognoza**