Combination of D-dimer and simplified pulmonary embolism severity index to improve prediction of hospital death in patients with acute pulmonary embolism

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Abstract

Objective: To investigate whether the combination of D-dimer and simplified pulmonary embolism severity index (sPESI) could improve prediction of in-hospital death from pulmonary embolism (PE).

Methods: Patients with PE (n = 272) were divided into a surviving group (n = 249) and an in-hospital death group (n = 23).

Results: Compared with surviving patients, patients who died in hospital had significantly higher rates of hypotension and tachycardia, reduced SaO_2 levels, elevated D-dimer and troponin T levels, higher sPESI scores, and were more likely to be classified as high risk. Elevated D-dimer levels and high sPESI scores were significantly associated with in-hospital death. Using thresholds for D-dimer and sPESI of 3.175 ng/mL and 1.5, respectively, the specificity for prediction of in-hospital death was 0.357 and 0.414, respectively, and the area under the receiver operating characteristic curve (AUC) was 0.665 and 0.668, respectively. When D-dimer and sPESI were considered together, the specificity for prediction of in-hospital death increased to 0.838 and the AUC increased to 0.74.

Conclusions: D-dimer and sPESI were associated with in-hospital death from PE. Considering D-dimer levels together with sPESI can significantly improve the specificity of predicting in-hospital death for patients with PE.

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Introduction

Venous thromboembolism, including deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common severe cardiovascular disease worldwide after myocardial infarction and stroke.[1] In epidemiological studies, PE had annual incidence rates ranging from 39 to 115 cases per 100,000 individuals.[2] Longitudinal studies have revealed an increasing trend in annual PE incidence rates over time.[3] As the clinical signs and symptoms of PE are non-specific, and the condition can even be asymptomatic, it is difficult to evaluate the severity and prognosis of PE based on clinical symptoms. Thus, reliable clinical parameters must be identified to judge severity and evaluate the prognosis of PE patients.

D-dimer, a degradation product of cross-linked fibrin, is elevated during acute thrombosis because of simultaneous activation of coagulation and fibrinolysis. Recent studies have demonstrated that elevated D-dimer is a valuable tool for the diagnosis of acute PE[4] and can also predict PE recurrence after discontinuation of anticoagulant treatment.[5] However, the relevance of D-dimer in predicting PE severity and risk of in-hospital death remains controversial.[6]

The simplified pulmonary embolism severity index (sPESI) has been the most extensively validated tool used to judge severity and prognosis of PE date.[7] sPESI scores predict the 30-day outcomes of PE patients using six clinical criteria. The sPESI was developed using simple clinical data available from review of patient charts to identify patients at low risk of mortality so that they can be discharged with appropriate anticoagulant treatments.[4,8]

Although D-dimer and sPESI both play important roles in predicting the prognosis of PE, D-dimer has limited specificity in predicting prognosis and sPESI has not yet been prospectively used to guide therapeutic management of PE patients. In the present study, we synthesized these two parameters to determine whether they could improve prediction of in-hospital death from PE.

Patients and methods

This retrospective study collected data from patients admitted to the Second Medical Department of the First Hospital of Jilin University between January 2016 and June 2019. The patients were identified by searching the hospital information system database for the diagnostic code of PE (ICD 10: I 26.900 X 001). Clinical data collected from the medical files of all patients included general characteristics, medical history, laboratory tests, ultrasonic imaging examinations, radiological imaging data and in-hospital death.

Qualified data

Twenty-three patients were excluded because of a lack of radiological imaging data and/or important laboratory parameters. Finally, 272 patients (138 women) were enrolled. The patients were divided into a surviving group and patients who died in hospital.

Definitions

The sPESI score is based on six items, with one point given for the presence of each item: age >80 years, history of cancer, history of chronic cardiac or pulmonary disease, pulse >110 beats/minute, systolic blood pressure (BP) <100 mmHg, and SaO_2 <90%.[9] Drinking was defined as alcohol consumption of more than 15 g per day in women and 25 g per today in men. Right ventricular dysfunction (RVD) is defined as right ventricle (RV) dilation, an increased RV-left ventricle (LV) diameter ratio, hypokinesia of the free RV wall, or any combination of the above. High PE risk classification was defined as systolic BP <90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status, in combination with end-organ hypoperfusion or persistent hypotension (systolic BP <90 mmHg or systolic BP drop ≥40 mmHg for >15 minutes) not caused by new-onset arrhythmia, hypovolemia, or sepsis. Intermediate-high risk classification was defined as RVD and elevated cardiac troponin T (TnT) levels with hemodynamic stability. Intermediate-low risk classification was defined as RVD or elevated cardiac TnT levels with hemodynamic stability. Low risk PE classification was defined as the absence of any of the above factors.

Ethics and informed consent

This study was performed according to the principles laid out in the Declaration of Helsinki and its subsequent revisions. Approval was obtained from Ethics Committee of the First Hospital of Jilin University. Because this was a retrospective study and patient data were anonymized, the requirement for informed consent was exempted by the Ethics Committee of the First Hospital of Jilin University.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to assess the normality of continuous variable distribution. Because of the non-normal distributions of continuous variables, the Mann–Whitney U test was used to assess differences between two groups. Continuous variables were presented as medians and interquartile ranges. Categorical variables were expressed as percentages. Differences between two categorical variables were assessed using the Chi-squared test and Fisher's exact test. After performing univariate analyses, variables showing significant results were used in multivariable logistic regression. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from logistic regression analyses. D-dimer and sPESI were analyzed using receiver operating characteristic curve (ROC) analysis, both alone and in combination. The area under the curve (AUC) was calculated to assess prediction of in-hospital death. For all tests, values of $P < 0.05$ were considered statistically significant.

Results

General characteristics of patients

Of 295 potentially eligible patients, 272 were enrolled in the study after excluding those with missing radiological imaging data and/or other laboratory parameters. The patients were divided into the survival group (n = 249) and the in-hospital death group (n = 23). The median age of the patients was 67 years; 50.73% were women, 32.72% were smokers, and 12.50% were drinkers. Hypertension and 3diabetes mellitus affected 37.50% and 15.44% of patients, respectively. Hypotension and tachycardia were evident

in 2.21% and 22.79% of patients, respectively. Chronic lung disease, cancer, and infection were present in 32.35%, 4.78%, and 62.41% of patients, respectively. Levels of D-dimer, N-terminal pro b-type natriuretic peptide and TnT were 4.98 ng/mL, 798.40 pg/mL and 0.022 ng/mL, respectively. $SaO_2 < 90\%$ was observed in 46.69% of patients. Transesophageal echocardiography showed that a left ventricular ejection fraction $< 40\%$ was present in 6.99% of patients while RVD was present in 20.96% of patients. Venous compression ultrasound showed DVT in 70.22% of patients. The median sPESI score was 1. Low-risk, intermediate-high, intermediate-low, and high-risk classifications were assigned in 6.61%, 35.29%, 55.88% and 2.20% of patients, respectively. In-hospital death from PE occurred in 23 (8.46%) patients, including three high risk and one low risk patient (Table 1).

Univariate and multivariable logistic regression analysis of clinical parameters

Compared with surviving patients, patients who died in hospital from PE were significantly more likely to exhibit hypotension (13.04% vs. 2.41%, $P = 0.008$), tachycardia (56.52% vs. 19.68%, $P < 0.01$), $SO_2 < 90\%$ (56.52% vs. 45.78%, $P = 0.021$), elevated D-dimer (9.51 vs. 4.65 ng/mL, $P = 0.003$), elevated TnT (0.05 vs. 0.02 ng/mL, $P = 0.033$), higher sPESI scores (2 vs. 1, $P = 0.002$), and high-risk classifications (13.04% vs. 1.2%, $P < 0.001$) (Table 1).

Variables showing significant results in univariate analyses were used in multivariable logistic regression. The results further showed that D-dimer (OR=1.070, 95% CI 1.003–1.143, $P = 0.046$), sPESI score (OR=3.475, 95% CI 1.239–9.749, $P = 0.018$) and high-risk classification (OR = 7.300, 95% CI 1.243–42.874, $P = 0.028$) were significantly associated with in-hospital death from PE (Table 2).

ROC curve analysis of D-dimer and sPESI for prediction of in hospital death

ROC curve analysis showed that using a threshold for D-dimer of 3.175 ng/mL, the sensitivity and specificity for prediction of in hospital death were 0.913 and 0.357, respectively. The positive and negative predictive values for prediction of in hospital death were 11.61 and 97.80, respectively. The AUC was 0.665 (95% CI 0.561–0.770) (Figure 1, Table 3). ROC curve analysis showed that using a threshold for sPESI score of 1.5, the sensitivity and specificity for prediction of in hospital death were 0.653 and 0.414, respectively. The positive and negative predictive values for prediction of in hospital death were 12.72 and 94.80, respectively. The AUC was 0.668 (95% CI 0.561–0.770) (Figure 1, Table 3). When D-dimer was considered together with sPESI, the specificity for prediction of in-hospital death increased to 0.838 and the AUC increased to 0.74 (Figure 1, Table 3).

Discussion

D-dimer is generated by degradation of fibrin monomers by plasmin. The occurrence of pulmonary artery thrombi leads to activation of the fibrinolytic system because of elevated D-dimer levels. Therefore, elevated D-dimer is widely recognized as an integral part of diagnostic workup, assessment of pulmonary artery thrombus burden and prediction of disease relapse after stopping anticoagulant therapy.[10,11] D-dimer is also used to determine the effectiveness of treatment and is a surrogate marker of PE recurrence.[12] D-dimer is not a specific investigation and can be elevated in other conditions including chronic kidney disease, inflammation, stroke, cancer, and heart failure.[4,13] A study showed that D-dimer was a high sensitivity (95%–97%) but a low specificity

Table 1. Baseline characteristics of patients with pulmonary embolism and univariate analyses comparing surviving and non-surviving patients.

	All patients (n = 272)	Survivors (n = 249; 91.54%)	In-hospital death (n = 23; 8.46%)	P
General characteristics				
Age in years, median (IQR)	67 (59–76)	67 (59–76)	63 (53–80)	0.389
Female, n (%)	138 (50.73)	128 (51.41)	10 (43.49)	0.467
Smoker, n (%)	89 (32.72)	83 (33.33)	6 (26.89)	0.643
Drinking, n (%)	34 (12.50)	31 (12.45)	3 (13.04)	0.934
Hypotension, n (%)	6 (2.21)	3 (2.41)	3 (13.04)	0.008
Heart rate ≥110/minute, n (%)	62 (22.79)	49 (19.68)	13 (56.52)	0.000
Hospital stay in days, median (IQR)	9 (6–14)	9 (6–14)	9 (6–16)	0.299
Medical history				
Hypertension, n (%)	102 (37.50)	92 (36.95)	10 (43.48)	0.653
Diabetes mellitus, n (%)	41 (15.44)	38 (15.26)	3 (13.04)	0.776
Chronic lung disease, n (%)	88 (32.35)	78 (31.33)	10 (43.48)	0.233
Cancer, n (%)	13 (4.78)	12 (4.82)	1 (4.38)	0.919
Infection, n (%)	166 (62.41)	154 (61.85)	12 (52.17)	0.379
Laboratory tests				
SaO$_2$ < 90%, n (%)	127 (46.69)	114 (45.78)	13 (56.52)	0.021
D-dimer in ng/mL, median (IQR)	4.98 (2.64–11.02)	4.65 (2.51–10.59)	9.51 (3.73–20.00)	0.003
NT-pro BNP in pg/mL, median (IQR)	798.40 (182.60–3482.50)	742.30 (178.35–3140.25)	1715 (288.98–5978.50)	0.075
TnT in ng/mL, median (IQR)	0.022 (0.011–0.056)	0.02 (0.01–0.05)	0.05 (0.02–0.11)	0.033
TTE and CUS parameters				
LVEF < 40%, n (%)	19 (6.99)	18 (7.23)	1 (4.35)	0.604
RVD, n (%)	57 (20.96)	49 (19.68)	8 (34.78)	0.089
DVT, n (%)	191 (70.22)	181 (72.69)	10 (43.49)	0.031
sPESI score, median (IQR)	1 (0–2)	1 (0–2)	2 (1–3)	0.002
Risk stratification	0.001			
Low, n (%)	18 (6.61)	17 (6.83)	1 (4.35)	0.661
Intermediate-low, n (%)	96 (35.29)	89 (35.74)	7 (30.43)	0.610
Intermediate-high, n (%)	152 (55.88)	140 (56.22)	12 (52.17)	0.708
High-risk, n (%)	6 (2.20)	3 (1.20)	3 (13.04)	0.000

CUS, lower limb venous compression ultrasonography; DVT, deep venous thrombosis; LVEF, left ventricular ejection fraction; RVD, right ventricular dysfunction; SaO$_2$, arterial oxygen saturation; TTE, transthoracic echocardiogram; TnT, troponin T; sPESI, simplified pulmonary embolism severity index; NT-pro BNP, N-terminal pro b-type natriuretic peptide; IQR, interquartile range.

Table 2. Multivariable logistic regression analysis of factors associated with in-hospital death of PE patients.

	OR	95% CI	P
sPESI	3.475	1.239–9.749	0.018
TnT	0.672	0.008–55.315	0.860
D-dimer	1.070	1.003–1.143	0.046
High-risk classification	7.300	1.243–42.874	0.028

sPESI, simplified pulmonary embolism severity index; TnT, troponin T; OR, odds ratio; CI, confidence interval.
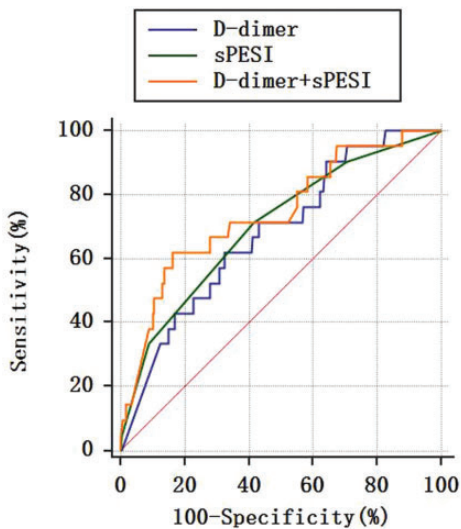
Figure 1. Receiver operating characteristic curve analysis of D-dimer, simplified pulmonary embolism severity index (sPESI) and the combination thereof for predicting in-hospital death of patients with pulmonary embolism.

(39%–43%) for diagnosis and severity prediction of PE.[14] Other studies showed that D-dimer was not a specific prognostic biomarker of PE and did not predict long-term prognosis of patients with PE.[15,16] Thus, the utility of D-dimer in evaluating the severity and prognosis of PE is still controversial. In the present study, both univariate and multivariable logistic regression analysis showed that elevated D-dimer was associated with in-hospital death in PE patients. ROC curve analysis revealed that the specificity of D-dimer for prediction of in-hospital death was only 0.357 with an AUC of 0.665.

sPESI may be a useful tool for identifying patients at low risk who could be discharged early or whose PE could be managed entirely in an outpatient setting. The prognostic performance of the sPESI has been confirmed by observational cohort studies.[8,9] In the present study, univariate analysis showed that D-dimer, sPESI, SaO_2, TnT, hypotension, tachycardia and high-risk classification were significantly more common in the in-hospital death group than in the survival group. Because PE leads to decreased pulmonary artery blood flow, ventilation and blood flow are unbalanced, resulting in a decline of SaO_2.[17] In addition, PE can lead to both decreased LV filling and increased pulmonary artery pressure, resulting in right heart failure and enhanced TnT.[4] A meta-analysis

Table 3. Predictive value of D-dimer, sPESI and the combination thereof for in-hospital death of PE patients.

	D-dimer	sPESI	D-dimer + sPESI
Optimal threshold	3.175 ng/mL	1.500	–
Sensitivity	0.913	0.652	0.619
Specificity	0.357	0.414	0.838
Positive predictive value	11.607	12.72	24.08
Negative predictive value	97.800	94.80	95.41
AUC	0.665	0.668	0.740
95% CI	0.561–0.770	0.548–0.778	0.624–0.855

sPESI, simplified pulmonary embolism severity index; AUC, area under the receiver operator characteristic curve; CI, confidence interval.

showed that elevated TnT was associated with increased risk of mortality.[18] Our results are similar to those of other studies and demonstrate a relationship between these parameters and in-hospital death from PE.[10,15] Multivariable logistic regression analysis further showed that high sPESI scores were significantly associated with in-hospital death from PE. ROC curve analysis showed a low specificity of sPESI in predicting in-hospital death (0.357), similar to D-dimer and consistent with recent research.[12,19,20]

To further improve the prediction of in-hospital death from PE, we investigated whether D-dimer combined with sPESI could improve specificity in predicting in-hospital death. Our results demonstrated that considering D-dimer together with sPESI could significantly improve the prediction of in-hospital death in patients with PE (Figure 1, Table 3).

Limitations of the study

This study had some limitations. First, it had a single-center retrospective design. Second, the small sample size led to wide 95% CIs and low numbers of events, making it difficult to obtain precise estimates for outcomes. Third, only in-hospital death was studied, and the study lacked a 30-day follow-up. Finally, D-dimer levels at admittance may not reflect patient conditions over longer periods. Thus, prospective, multicenter studies with larger cohorts are needed to confirm our findings and draw more definitive conclusions.

Conclusion

The findings of this retrospective study suggest that elevated D-dimer and sPESI are both associated with in-hospital death from PE, but their specificity is limited. Combining D-dimer with sPESI can

significantly improve the specificity of predicting in-hospital death of patients with PE. These results will serve to improve clinician assessments of short-term death in PE patients.

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