

Comparison of Different Clinical Prognostic Scores in Patients with Pulmonary Embolism and Active Cancer

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Abstract

Objective This article aimed to validate and compare the prognostic performance of generic scores (Pulmonary Embolism Severity Index [PESI] and Hestia) and cancer-specific pulmonary embolism (PE)/venous thromboembolism (VTE) scales (Registro Informatizado de la Enfermedad TromboEmbólica [RIETE], POMPE-C, and modified Ottawa) in PE patients with active cancer.

Methods A retrospective study was conducted among 460 patients with PE and active cancer. The primary outcome was 30-day overall mortality. Secondary outcomes were 30-day PE-related death and overall adverse outcomes. The prognostic accuracy of clinical scores was determined using receiver operating characteristic (ROC) curve analysis.

Results Within 30 days, 18.0% of patients died, 2.0% suffered major bleeding, and 0.2% presented recurrence of VTE. All scales showed a high area under the ROC curve (AUC) for predicting 30-day overall mortality except modified Ottawa (0.74 [0.70–0.78] for PESI, Hestia, and RIETE; 0.78 (0.74–0.81) for POMPE-C; 0.64 (0.59–0.68) for modified Ottawa]. PESI divided the least patients (9.1%) into low risk, followed by modified Ottawa (17.0%). Hestia stratified the most patients (65.4%) as low risk. But overall mortality of low-risk patients based on these three scales is high (>5%). RIETE and POMPE-C both classified 30.9% of patients as low risk, and low-risk patients stratified by these two scales presented a low overall mortality (1.4 and 3.5%). Similar predictive performance was found for 30-day PE-related death and overall adverse outcomes in these scores.

Conclusion Cancer-specific PE prognostic scores (RIETE and POMPE-C) performed better than generic scales (PESI and Hestia) and a cancer-specific VTE prognostic scale (modified Ottawa) in identifying low-risk PE patients with active cancer who may be suitable for outpatient treatment.

Keywords

- ▶ pulmonary embolism
- ▶ active cancer
- ▶ clinical prognostic scores

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Introduction

Venous thromboembolism (VTE) is a common complication and constitutes the second leading cause of death after tumor progression in oncologic patients. Cancer patients are four to seven times more likely to develop VTE than those without cancer.^{1–3} Pulmonary embolism (PE) is the most serious clinical presentation of VTE, and its clinical spectrum ranges from potentially fatal events to incidental findings on computed tomography (CT) scans.⁴ The prognosis of PE patients combined with cancer is usually worse than those without cancer, and PE is associated with increased morbidity and mortality in these patients.^{5–8} In addition, cancer patients with PE are at a higher risk of VTE recurrence and bleeding during anticoagulant therapy.^{9,10}

Previous studies¹¹ suggest that the risk of adverse outcomes, especially short-term mortality, in PE patients can be stratified by clinical prognostic scores. It can aid physicians in identifying patients at different risk of adverse events, and helps facilitate proper disposition decisions. In addition, current practice guidelines^{12,13} also recommend that appropriately selected low-risk PE patients may be considered for early hospital discharge or home treatment. This strategy could reduce the waste of medical resources and improve the quality of life in these patients. Therefore, low-risk patient selection becomes the most critical issue in this setting.

Several prognostic models have been derived and validated for risk stratification in PE patients,^{14–18} but current literature lacks a consensus tool to quantify the short-term prognosis among cancer patients. In the general population, the Pulmonary Embolism Severity Index (PESI) and the simplified PESI (sPESI) are usually used to estimate 30-day mortality after PE. However, PESI has not been tested specifically in cancer patients. In addition, PESI includes a history of cancer as a highly relevant predictor, in spite of the heterogeneity of these patients.¹⁴ Furthermore, sPESI classifies all patients with cancer as high risk, limiting its discriminatory power.¹⁹ Hestia criteria is another widely used tool to stratify PE patients.¹⁵ It contains 11 criteria and has been proven useful in decision-making. The British Thoracic Society also suggests that the Hestia criteria may be used to select candidates for outpatient management of PE in cancer patients (Grade D),²⁰ but rigorous evidence for this recommendation is lacking.

Because the clinical courses of patients with cancer-associated PE differ vastly from those without cancer, and malignancy itself contributes to a substantial proportion of the high-risk scores in generic prognostic scales, cancer-specific prognostic scores such as Registro Informatizado de la Enfermedad TromboEmbólica (RIETE), POMPE-C, and modified Ottawa were developed.^{16–18} RIETE is a six-item score derived from an independent multinational cohort of patients with acute symptomatic PE and active cancer enrolled in the RIETE and assigns patients into three risk categories of 30-day mortality.¹⁶ Low-risk patients based on this score have a low 30-day mortality of 2.1 and 4.4% in the derivation and internal validation sample, respectively.¹⁶ In addition, its external validation showed that none of the low-risk patients stratified by RIETE died within 30 days.¹⁶

POMPE-C is a logistic regression model developed from a preplanned secondary analysis of the multicenter EMPEROR (Emergency Medicine Pulmonary Embolism in the Real World) Registry dataset to predict the 30-day mortality in patients with acute PE and active cancer.¹⁷ The POMPE-C tool demonstrated good overall prognostic accuracy in both the derivation dataset and the validation sample with an area under the receiver operating characteristic (AUC) curve over 0.8 (0.84 [95% confidence interval, CI: 0.82–0.87] in the derivation set and 0.86 [95% CI: 0.78–0.93] in the validation sample).¹⁷ Moreover, the external validation showed an excellent sensitivity of 100% for 30-day death.¹⁷ Modified Ottawa is a well-validated prognosis assessment score for cancer-associated VTE population, covering both PE and DVT, which was mainly used to predict the risk of 6-month VTE recurrence in these patients.¹⁸ Studies also indicated this scale has a good predictive value for 30-day mortality after VTE and low-risk patients based on this scale present a low 30-day overall mortality less than 5%.^{21,22} While these models showed a high accuracy for predicting 30-day mortality after PE in cancer patients, with high sensitivities and negative predictive values, there have been few independent external validations and performance comparisons between these scales.^{16,17,21,23}

In summary, although a variety of prognostic tools have been developed, the ability to predict short-time adverse outcomes is still limited in cancer patients with PE, and the identification of low-risk PE patients remains a challenge. In this study, we aimed to evaluate and compare the prognostic performances of different clinical prognostic scores (including two cancer-specific PE scores, one cancer-specific VTE score, and two generic scores) in predicting 30-day post-PE adverse outcomes among patients with PE and active cancer.

Methods

Study Design and Patients

This study is a retrospective analysis of a prospectively collected VTE database from the VTE Registration Center of the West China Hospital which was founded in 2009. This database consecutively enrolled all VTE patients admitted to our hospital using the ICD (International Classification of Diseases)-10 codes (I26, I80, I82) and followed them up for 2 years after discharge by phone or outpatient visit when it is necessary (the follow-up time points were 1, 3, 6, 12, 18, and 24 months after discharged). In the present study, patients with objectively diagnosed, acute symptomatic PE, and active cancer from August 2014 to December 2019 were included from the VTE database. Exclusion criteria included younger than 18 years, 30-day clinical outcomes unavailable, and data missed. For patient inclusion, we screened the database for patients with PE and cancer first, and then the patient records were reviewed to determine whether they are eligible for inclusion. PE was confirmed by a positive CT pulmonary angiography ($n=457$) or high probability ventilation/perfusion scintigraphy ($n=3$). The symptoms of PE were defined as new onset or worsening acute dyspnea, chest pain, hemoptysis, and syncope.²⁴ Additionally, new

onset or worsening abnormalities in vital signs such as a decrease in arterial oxygen saturation and hypotension, which cannot be explained by other causes, were also regarded as symptoms of PE. Active cancer was defined as solid or hematological cancer requiring chemotherapy, radiation therapy, surgery, or palliative care during the last 3 months. All patients were treated according to clinical practice standards in our institution. This study was approved by the institutional review board of the West China Hospital of Sichuan University. As all data were anonymized and the study posed no significant risks, the requirement for written informed consent was waived.

Data Collection

Clinical data including the baseline demographics, medical history, comorbidities, length of hospital stay, and therapy data were extracted from the database, and the variables comprising the clinical prognostic scores were also extracted to retrospectively calculate the PESI, Hestia, RIETE, POMPE-C, and modified Ottawa scores for all patients. Furthermore, medical records were also reviewed to supplement information not collected in the database. In this study, immobilization (from RIETE scale) was defined as an activity subscore of 1 or 2 in the Braden scale, which is commonly used for predicting the risk of pressure ulcer.²⁵ Medical reasons for hospital treatment (from Hestia scale) were defined as the presence of other comorbidities or complications that require hospitalization (such as infection, cardiac dysfunction, pleural effusion, and cancer treatment). Because of the retrospective design and the absence of documentation on social issues in the medical records, it is unable for us to determine whether the patient had social reasons for hospitalization (such as elderly people in poor general conditions living alone without family care and patients living in remote areas with poor medical resources). But in fact, according to our experience, there are few patients hospitalized for social reasons in our hospital, and most patients with social reasons for hospitalization often also have medical reasons that require hospitalization (serious/complex comorbidities or complications). So we assumed that no patients were admitted to the hospital for social reasons in this study. Early discharge is defined as the length of hospital stay ≤ 72 hours. The decision on whether a patient could be discharged early was made by their treating physicians based on clinical experience. For outcome collection, the 1-month outpatient or telephone follow-up records were reviewed for patients who had been discharged before 30 days. And the clinical outcome was determined by inpatient medical records from the database for those who were still hospitalized at 30 days after diagnosis or died during hospitalization. In this study, 32.0 and 50.2% of the patient outcomes were confirmed by 1-month outpatient or telephone follow-up records, and 17.8% were determined by inpatient medical records.

Clinical Prognostic Scores

Prognostic variables comprising the clinical scores were determined to retrospectively calculate the total scores of PESI, Hestia, RIETE, POMPE-C, and modified Ottawa for all

patients. Based on commonly accepted definitions, patients with a PESI score ≤ 85 (risk classes I and II), Hestia < 1 , RIETE < 2 (risk classes I), POMPE-C $\leq 5\%$ (risk classes I), and modified Ottawa ≤ -1 were considered at low risk of 30-day post-PE adverse outcomes.^{14–18} All other patients were considered at higher risk of adverse outcomes (**► Supplementary Table S1**, available in the online version).

Study Outcomes

The primary outcome was overall mortality at 30-day after PE diagnosis. The secondary outcomes were PE-related death and overall adverse outcomes defined as all-cause death, recurrence of VTE, or major bleeding occurred within 30 days after the diagnosis of PE. Death was judged related to PE if it was confirmed by autopsy or if death followed an objectively diagnosed PE in the absence of another more likely cause of death.²⁶ Recurrent VTE was defined as PE and/or DVT with symptoms accompanied by confirmation of new thrombus or exacerbation of the thrombus by objective imaging examinations or autopsy.²⁷ Major bleeding was defined as bleeding at a critical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome) or overt bleeding with a reduction in hemoglobin levels of ≥ 20 g/L, or resulting in transfusion of at least two units of packed red blood cells.²⁸ All clinical outcomes were adjudicated by the independent clinical event committee composed of three experienced physicians.

Statistical Analysis

Categorical variables are presented as number and percentage, and continuous variables are median and interquartile range (IQR). As for patient characteristics, categorical variables were compared using the chi-squared test or Fisher's exact test, and continuous variables were compared using the Wilcoxon's rank-sum test. Pairwise comparisons of the proportion of patients classified as low risk by the four scores were performed by the McNemar's test. We estimated the discriminative power of each score in predicting the 30-day overall mortality, 30-day PE-related death, and overall adverse outcomes by calculating the area under the ROC curve (AUC). Other predictive reliability indices including sensitivity, specificity, positive predictive values, and negative predictive values were also measured. Furthermore, multiple imputations were conducted to impute missing clinical outcomes by using the Mice package in R. And analysis was also performed in datasets which have included patients with imputed clinical outcomes or excluded those from surgical wards/with recent surgery. All statistical analyses were conducted using SPSS version 22.0 (IBM, Armonk, New York, United States), MedCalc version 19.3.1, or R version 4.0.3. All statistical analyses were two tailed and p -values < 0.05 were considered statistically significant.

Results

Clinical Scores and Patient Characteristics at Baseline

Overall, 617 patients with acute PE and cancer were initially screened for inclusion in this study, of which 157 patients

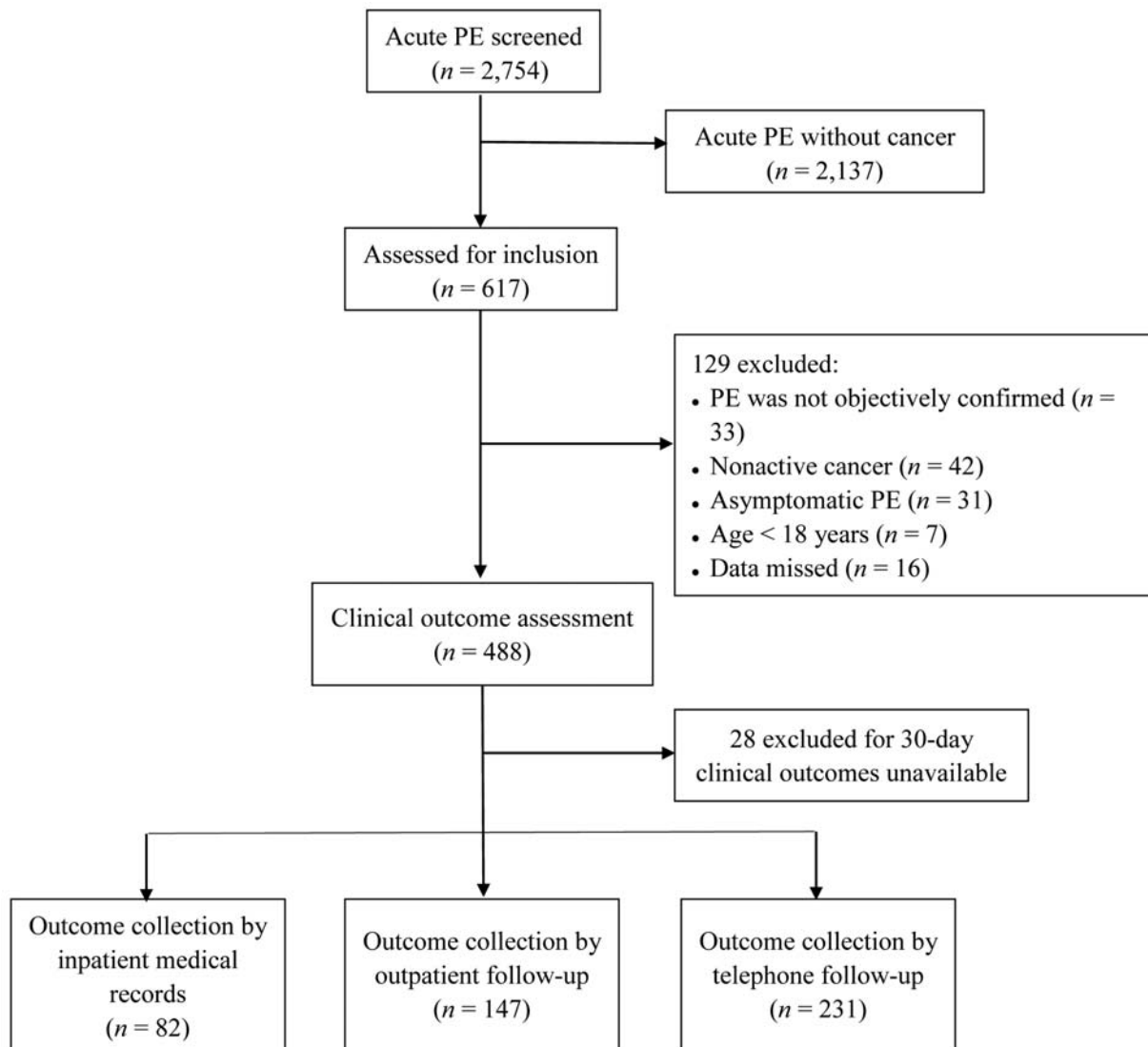


Fig. 1 Patient inclusion flowchart. PE, pulmonary embolism.

were excluded because of the following reasons: (1) PE was not objectively confirmed ($n=33$), (2) nonactive cancer ($n=42$), (3) asymptomatic PE ($n=31$), (4) younger than 18 years ($n=7$), (5) data missed ($n=16$), and (6) 30-day clinical outcomes unavailable ($n=28$). Ultimately, 460 patients were enrolled (**Fig. 1**), and there was no significant difference in baseline characteristics between the included patients and patients with data missing or clinical outcomes unavailable (**Supplementary Table S2**, available in the online version).

Patient characteristics at baseline are shown in **Table 1**. The average patient age was 63 years, and 57.2% of the patients were male, 19 (4.1%) patients were treated in the intensive care unit, and 29 (6.3%) were discharge early (≤ 72 hours). Concomitant DVT was found in 61.3% of the patients. Lung cancer was the most common type of cancer ($n=220$; 47.8%). More than half (54.6%) of the population had metastatic cancer, and 85.4% patients had received therapy for their cancers in the previous month. Predictor variables of each clinical prognostic scale among the includ-

ed patients are shown in **Supplementary Table S3** (available in the online version). In this study, 70.9% of the patients were admitted to hospital mainly because of VTE. Details on the ward of hospitalization are shown in **Supplementary Table S4** (available in the online version).

Compared with patients who survived, those died within 30 days have a higher proportion of metastatic cancer and Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2 , more patients were admitted to the intensive care unit, and no patients were discharged early (≤ 72 hours). There was no significant difference in age, sex, body mass index, type of cancer, cancer treatment, the percentage of DVT, history of VTE, and chronic heart failure between the two groups. The average scores and proportions of patients classified as higher risk for all clinical scales were significantly higher in patients with 30-day death than those who survived with the exception of PESI. The PESI score almost classified all patients (418/460, 90.9%) into higher risk, and there was no difference in the proportion of higher-risk patient (PESI ≥ 86) between the two groups.

Table 1 Patient characteristics at baseline

Characteristics	All, n (%) or median (IQR)	With overall mortality, n (%) or median (IQR)	Without overall mortality, % (n) or median (IQR)	p-Value
Total, n	460	83	377	
Age, y	63 (52–71)	64 (54–73)	62 (52–70)	0.164
Age >65 y	193 (42.0)	36 (43.4)	157 (41.6)	0.773
Male gender	263 (57.2)	47 (56.6)	216 (57.3)	0.911
BMI	22.7 (20.7–24.9)	22.3 (20.8–25.2)	22.9 (20.7–24.8)	0.897
Smoking (current or past)	184 (40.0)	41 (49.4)	143 (37.9)	0.054
The type of cancer				0.952
Lung	220 (47.8)	37 (44.6)	183 (48.5)	
Esophagus gastric	38 (8.3)	8 (9.6)	30 (8.0)	
Colorectal	33 (7.2)	7 (8.4)	26 (6.9)	
Hepatobiliary	38 (8.3)	7 (8.4)	31 (8.2)	
Other	131 (28.5)	24 (28.9)	107 (28.4)	
Metastatic cancer	251 (54.6)	63 (75.9)	188 (49.9)	<0.001
ECOG PS ≥ 2	181 (39.3)	53 (63.9)	128 (34.0)	<0.001
Therapy of cancer in the previous month				0.056
Surgery	63 (13.7)	13 (15.7)	50 (13.3)	
Chemotherapy or/and radiotherapy	269 (58.5)	56 (67.5)	213 (56.5)	
Targeted therapy	61 (13.3)	4 (4.8)	57 (15.1)	
Untreated or palliative care	67 (14.6)	10 (12.0)	57 (15.1)	
Concomitant DVT	282 (61.3)	55 (66.3)	227 (60.2)	0.305
History of VTE	9 (2.0)	2 (2.4)	7 (1.9)	0.668
Chronic pulmonary disease	36 (7.8)	11 (13.3)	25 (6.6)	0.042
Chronic heart failure	20 (4.3)	7 (8.4)	13 (3.4)	0.067
Location of treatment				<0.001
Intensive care unit	19 (4.1)	15 (18.1)	4 (1.1)	
Medical wards	421 (91.5)	66 (79.5)	355 (94.2)	
Surgical wards	20 (4.3)	2 (2.4)	18 (4.8)	
Early discharge (≤ 72 h)	29 (6.3)	0 (0.0)	29 (7.7)	0.005
VTE anticoagulant treatment				0.124
VKA (warfarin)	26 (5.7)	3 (3.6)	23 (6.1)	
DOAC (rivaroxaban)	21 (4.6)	3 (3.6)	18 (4.8)	
LMWH (enoxaparin or nadroparin)	410 (89.1)	75 (90.4)	335 (88.9)	
Did not receive anticoagulant therapy	3 (0.7)	2 (2.4)	1 (0.3)	
PESI	105 (93–118)	125 (106–145)	103 (92–113)	<0.001
PESI ≥ 86 points	418 (90.9)	80 (96.4)	338 (89.7)	0.054
Hestia	0 (0–1)	1 (0–1)	0 (0–1)	<0.001
Hestia ≥ 1 point	159 (34.6)	61 (73.5)	98 (26.0)	<0.001
RIETE	4 (1–5)	5 (4–6)	4 (1–5)	<0.001
RIETE ≥ 2 points	318 (69.1)	81 (97.6)	237 (62.9)	<0.001
POMPE-C	6.1 (4.5–12.1)	21.8 (6.3–41.2)	5.7 (4.3–9.5)	<0.001
POMPE-C $> 5\%$	318 (69.1)	78 (94.0)	240 (63.7)	<0.001
Modified Ottawa	0 (0–1)	1 (0–1)	0 (0–1)	<0.001
Modified Ottawa ≥ 0 points	382 (83.0)	79 (95.2)	303 (80.4)	0.001

Abbreviations: BMI, body mass index; DOAC, direct oral anticoagulant; DVT, deep venous thrombosis; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Similar differences were observed when categorizing patients according to whether or not suffered 30-day PE-related death or overall adverse outcomes, but there was no significant difference in the proportion of modified Ottawa ≥ 0 between patients with 30-day PE-related death and those without (**Supplementary Table S5**, available in the online version).

Comparison of Outcomes

Overall, 20.2% (93/460) of the patients experienced one of the clinical outcomes during the 30-day follow-up period (**Table 2**). 18.0% (83/460) of the patients died within 30 days. Of these, 50.6% (42/83) died from PE, and 34.9% (29/83), 10.8% (9/83), 2.4% (2/83), and 1.2% (1/83) died from cancer, infection, heart failure, or stroke, respectively. 2.0% of the patients (9/460) suffered major bleeding and 0.2% (1/460) presented recurrence of VTE.

The incidences of overall death, PE-related death, and overall adverse outcomes in the higher-risk group were significantly higher than that in the low-risk group for Hestia, RIETE, and POMPE-C ($p < 0.001$ for all outcomes in Hestia, RIETE, and POMPE-C) with the exception of PESI ($p = 0.054$ for overall mortality, $p = 0.158$ for PE-related death, and $p = 0.070$ for overall adverse outcomes) and modified Ottawa ($p = 0.001$ for overall mortality, $p = 0.078$ for PE-related death, and $p = 0.002$ for overall adverse outcomes).

RIETE and POMPE-C both classified 30.9% (142/460) of patients as low risk. Modified Ottawa divided 17.0% (78/460)

of patients into low risk. PESI stratified a significantly smaller proportion of patients as low risk (9.1% [42/460]) than the other four scales and Hestia divided the most patients into low risk (65.4% [301/460]). The low-risk patients classified by RIETE or POMPE-C showed a low 30-day overall mortality of 1.4% (95% CI: 0.4–5.0%) and 3.5% (95% CI: 1.5–8.0%), respectively. However, the 30-day overall mortality was relatively high in the low-risk population stratified by modified Ottawa and generic scores, with 5.1% (95% CI: 2.0–12.5%) for modified Ottawa, 7.1% (95% CI: 2.5–19.0%) for PESI, and 7.3% (95% CI: 4.9–10.8%) for Hestia.

Low-risk patients classified by each clinical score all had a low 30-day PE-related mortality less than 4%, and the mortality in low-risk patients identified by RIETE and POMPE-C were only 0.7% (95% CI: 0.1–3.5%) and 0.0% (95% CI: 0.0–2.6%), respectively. In addition, the 30-day overall adverse outcomes among low-risk patients stratified by RIETE and POMPE-C were also low (2.1% [95% CI: 0.7–6.0%] for RIETE and 3.5% [95% CI: 1.5–8.0%] for POMPE-C). But low-risk patients classified by modified Ottawa and generic scales presented a high incidence of 30-day overall adverse outcomes with 7.7% (95% CI: 3.6–15.8%) for modified Ottawa, 9.5% (95% CI: 3.8–22.1%) for PESI, and 9.0% (95% CI: 6.2–12.7%) for Hestia.

Similar results were obtained in datasets which exclude patients from surgical wards/with recent surgery or include patients with imputed clinical outcomes. But in the dataset excluding patients from surgical wards/with recent surgery, low-risk patients stratified by modified Ottawa also had a low

Table 2 Outcomes in low- versus higher-risk patients

Outcome	Low risk		Higher risk		All patients	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
30-d overall mortality						
PESI	3/42	7.1 (2.5–19.0)	80/418	19.1 (15.7–23.2)	83/460	18.0 (14.6–21.9)
Hestia	22/301	7.3 (4.9–10.8)	61/159	38.4 (31.2–46.1)		
RIETE	2/142	1.4 (0.4–5.0)	81/318	25.5 (21.0–30.5)		
POMPE-C	5/142	3.5 (1.5–8.0)	78/318	24.5 (20.1–29.5)		
Modified Ottawa	4/78	5.1 (2.0–12.5)	79/382	20.7 (16.9–25.0)		
30-d PE-related death						
PESI	1/42	2.4 (0.4–12.3)	41/418	9.8 (7.3–13.0)	42/460	9.1 (6.7–12.1)
Hestia	11/301	3.7 (2.0–6.4)	31/159	19.5 (14.1–26.4)		
RIETE	1/142	0.7 (0.1–3.5)	41/318	12.9 (9.7–17.0)		
POMPE-C	0/142	0.0 (0.0–2.6)	42/318	13.2 (9.9–17.4)		
Modified Ottawa	3/78	3.9 (1.3–10.7)	39/382	10.2 (7.6–13.8)		
30-d overall adverse outcomes						
PESI	4/42	9.5 (3.8–22.1)	89/418	21.3 (17.6–25.5)	93/460	20.2 (16.6–24.2)
Hestia	27/301	9.0 (6.2–12.7)	66/159	41.5 (34.1–49.3)		
RIETE	3/142	2.1 (0.7–6.0)	90/318	28.3 (23.6–33.5)		
POMPE-C	5/142	3.5 (1.5–8.0)	88/318	27.7 (23.0–32.8)		
Modified Ottawa	6/78	7.7 (3.6–15.8)	87/382	22.8 (18.9–27.2)		

Abbreviations: CI, confidence interval; PE, pulmonary embolism.

Table 3 Association between 30-day post-PE adverse outcomes and risk stratification according to different clinical prognostic scores

Scale	n, %	30-day overall mortality	30-day PE-related death	30-day overall adverse outcomes
PESI				
Class I (≤ 65 points)	5 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Class II (66–85 points)	37 (8.0)	3 (8.1)	1 (2.7)	4 (10.8)
Class III (86–105 points)	197 (42.8)	17 (8.6)	7 (3.6)	17 (8.6)
Class IV (106–125 points)	133 (28.9)	24 (18.0)	11 (8.3)	30 (22.6)
Class V (> 125 points)	88 (19.1)	39 (44.3)	23 (26.1)	42 (47.7)
Hestia				
No criteria present	301 (65.4)	22 (7.3)	11 (3.7)	27 (9.0)
At least one criteria present	159 (34.6)	61 (38.4)	31 (19.5)	66 (41.5)
RIETE				
Class I (< 2 points)	142 (30.9)	2 (1.4)	1 (0.7)	3 (2.1)
Class II (2–4 points)	171 (37.2)	31 (18.1)	15 (8.8)	35 (20.5)
Class III (5–7 points)	142 (30.9)	47 (33.1)	25 (17.6)	52 (36.6)
Class IV (> 7 points)	5 (1.1)	3 (60.0)	1 (20.0)	3 (60.0)
POMPE-C				
Class I ($\leq 5\%$)	142 (30.9)	5 (3.5)	0 (0.0)	5 (3.5)
Class II (6–10%)	173 (37.6)	23 (13.3)	9 (5.2)	27 (15.6)
Class III (11–25%)	90 (19.6)	17 (18.9)	7 (7.8)	21 (23.3)
Class IV (26–50%)	47 (10.2)	31 (66.0)	22 (46.8)	33 (70.2)
Class V (51–75%)	7 (1.5)	6 (85.7)	3 (42.9)	6 (85.7)
Class VI (76–100%)	1 (0.2)	1 (100.0)	1 (100.0)	1 (100.0)
Modified Ottawa				
Low (≤ -1 point)	78 (17.0)	4 (5.1)	3 (3.8)	6 (7.7)
Intermediate (0 points)	157 (34.1)	25 (15.9)	10 (6.4)	26 (16.6)
High (≥ 1 point)	225 (48.9)	54 (24.0)	29 (12.9)	61 (27.1)

Abbreviations: PE, pulmonary embolism.

incidence of 30-day post-PE adverse events (**►Supplementary Tables S6 and S7**, available in the online version).

Comparison of Predictive Accuracy and Discriminative Power

As shown in **►Table 3**, the incidence of 30-day adverse events increased with the upgrade of risk stratification among all clinical scores. The cancer-specific PE prognostic scales (RIETE and POMPE-C) and generic scales (PESI and Hestia) all showed an acceptable accuracy in predicting 30-day adverse events (AUC: 0.74–0.78, 0.73–0.83, and 0.73–0.78 for 30-day overall mortality, PE-related death, and overall adverse outcomes, respectively; **►Table 4** and **►Fig. 2**). However, the overall discrimination powers for 30-day adverse events of the cancer-specific VTE prognostic modified Ottawa score were all poor (AUC: 0.64, 0.63, and 0.64 for 30-day overall mortality, PE-related death, and overall adverse outcomes, respectively; **►Table 4** and **►Fig. 2**).

Except for the Hestia scale, the other four clinical scores all presented a high sensitivity ($\geq 94\%$) for 30-day overall mortality, whereas the sensitivity of Hestia was only 73.5%. All scales showed an excellent negative predictive value ($> 92\%$) among 30-day overall mortality, especially for RIETE and POMPE-C (98.6 and 96.5%). However, their specificity (10.3–74.0%) and positive predictive values (19.1–38.4%) were low. Similar predictive performance was found for 30-day PE-related death and overall adverse outcomes in these clinical scores.

The aforementioned results of ROC analysis did not change markedly after excluding patients from surgical wards/with recent surgery or including those with imputed clinical outcomes, as shown in **►Supplementary Tables S8 and S9** (available in the online version).

Discussion

Our study indicates that cancer-specific PE prognostic scores (RIETE and POMPE-C) performed better than generic scales

Table 4 Measures of performance to predict 30-day post-PE adverse outcomes

	AUC (95% CI) p-value	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
30-day overall mortality					
PESI Cut-off 86 points	0.74 (0.70–0.78) <0.001	96.4 (89.8–99.2)	10.3 (7.5–13.9)	19.1 (15.5–23.2)	92.9 (80.5–98.5)
Hestia Cut-off 1 point	0.74 (0.70–0.78) <0.001	73.5 (62.7–82.6)	74.0 (69.3–78.4)	38.4 (30.8–46.4)	92.7 (89.1–95.4)
RIETE Cut-off 2 points	0.74 (0.70–0.78) <0.001	97.6 (91.6–99.7)	37.1 (32.2–42.2)	25.5 (20.8–30.6)	98.6 (95.0–99.8)
POMPE-C Cut-off 5%	0.78 (0.74–0.81) <0.001	94.0 (86.5–98.0)	36.1 (31.2–41.1)	24.5 (19.8–29.5)	96.5 (91.9–98.8)
Modified Ottawa Cut-off 0 points	0.64 (0.59–0.68) <0.001	95.2 (88.1–98.7)	19.6 (15.7–24.0)	20.7 (16.7–25.1)	94.9 (87.4–98.6)
30-day PE-related death					
PESI Cut-off 86 points	0.76 (0.72–0.80) <0.001	97.6 (87.4–99.9)	9.8 (7.1–13.1)	9.8 (7.1–13.1)	97.6 (87.4–99.9)
Hestia Cut-off 1 point	0.73 (0.69–0.77) <0.001	73.8 (58.0–86.1)	73.8 (58.0–86.1)	19.5 (13.6–26.5)	96.3 (93.5–98.2)
RIETE Cut-off 2 points	0.73 (0.69–0.77) <0.001	97.6 (87.4–99.9)	33.7 (29.2–38.5)	12.9 (9.4–17.1)	99.3 (96.1–100.0)
POMPE-C Cut-off 5%	0.83 (0.79–0.86) <0.001	100.0 (91.6–100.0)	33.7 (29.2–38.5)	13.2 (9.7–17.4)	100.0 (97.4–100.0)
Modified Ottawa Cut-off 0 points	0.63 (0.59–0.68) 0.001	92.9 (80.5–98.5)	17.9 (14.4–22.0)	10.2 (7.4–13.7)	96.2 (89.1–99.2)
30-day overall adverse outcomes					
PESI Cut-off 86 points	0.75 (0.71–0.79) <0.001	95.7 (89.4–98.8)	10.4 (7.4–13.9)	21.3 (17.5–25.5)	90.5 (77.4–97.3)
Hestia Cut-off 1 point	0.73 (0.69–0.77) <0.001	71.0 (60.6–79.9)	74.7 (69.9–79.0)	41.5 (33.7–49.6)	91.0 (87.2–94.0)
RIETE Cut-off 2 points	0.74 (0.70–0.78) <0.001	96.8 (90.9–99.3)	37.9 (32.9–43.1)	28.3 (23.4–33.6)	97.9 (93.9–99.6)
POMPE-C Cut-off 5%	0.78 (0.74–0.82) <0.001	94.6 (87.9–98.2)	37.1 (32.1–42.2)	27.6 (22.8–32.8)	96.5 (91.9–98.8)
Modified Ottawa Cut-off 0 points	0.64 (0.59–0.68) <0.001	93.6 (86.5–97.6)	19.6 (15.7–24.1)	22.8 (18.7–27.3)	92.3 (84.0–97.1)

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; PE, pulmonary embolism.

(PESI and Hestia) and a cancer-specific VTE prognostic score (modified Ottawa) in identifying patients with PE and active cancer who are at low risk of 30-day adverse outcomes. And cancer-specific PE prognostic scores (RIETE and POMPE-C) may be considered to select candidates for early hospital discharge or outpatient treatment among PE patients with active cancer.

In this study, both cancer-specific PE prognostic scales (RIETE and POMPE-C) and generic scales (PESI and Hestia) showed a good performance in predicting 30-day adverse events (AUC \geq 0.73 for all 30-day adverse events). However, the overall prognostic accuracy for 30-day adverse outcomes of the cancer-specific VTE prognostic modified Ottawa score were poor (AUC: \leq 0.64 for all 30-day adverse events) which is worse than that in its derivation and a

recent external validation study.^{18,21} The following reasons may responsible for this result. First, modified Ottawa scale was generated and previously validated in cancer-associated VTE population which includes patients with only DVT.^{18,21} In addition, the modified Ottawa score was mainly designed to predict the 6-month VTE recurrence,¹⁸ and factors used to evaluate the severity of PE were not included in this scale which would lead to its poor predictive ability for PE-related death, an important component of the 30-day adverse outcomes. As shown in this study, there is no difference in PE-related mortality between higher-risk and low-risk patients based on modified Ottawa score. Therefore, the modified Ottawa scale may be of limited value for the short-term prognosis of specific PE populations.

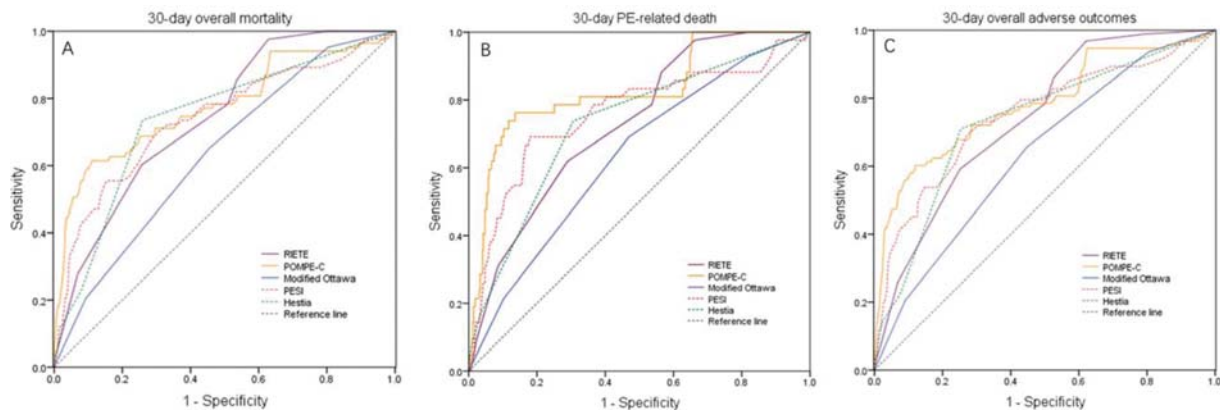


Fig. 2 (A) Receiver operating characteristic (ROC) curves for 30-day overall mortality. (B) ROC curves for 30-day pulmonary embolism (PE)-related death. (C) ROC curves for 30-day overall adverse outcomes.

Cancer-specific PE prognostic scores and PESI scale both showed good sensitivities (>92%) for predicting the 30-day adverse events in this study, whereas the sensitivity of Hestia was only approximately 70%. Notably, although PESI displayed a high sensitivity, it stratified more than 90% of the patients as higher risk, and there was no difference in the incidence of 30-day adverse events between the low- and high-risk populations based on PESI. This may be due to the inclusion of cancer itself as an important component of risk assessment in PESI,¹⁴ which compromised its discriminate power and limited its usage in these patients. The Hestia scale showed the lowest sensitivity in this study and was also lower than that reported by previous studies in general patients.²⁹ The reason could be that Hestia was derived from the general population and did not include risk predictors specifically for the cancer population. In addition, because of the unavailability of social reasons related to hospitalization, we assumed that no patients were admitted because of social reasons in this study, which may also underestimate this scale's sensitivity to identify higher-risk patients. All scales had excellent negative predictive values ($\geq 91\%$), but their specificities and positive predictive values were low. Generally, an ideal clinical prognostic scale should have an excellent sensitivity and specificity at the same time, but actually there is an inherent trade-off between these two parameters. For PE patients, considering the catastrophic consequences³⁰ if a patient is falsely judged to be at low risk of early adverse events and prescribed home treatment or discharged too early, high sensitivity and negative predictive value may be preferable to high specificity in this setting.

PE patients were traditionally treated with hospitalization because of the high incidence of early adverse events and PE patients with active cancer usually have a worse prognosis than general PE patients.^{6,9} However, for cancer patients, especially end-stage cancer patients, the quality of life may be more important to them and they always prefer home management. Studies in patients with advanced oncological disease showed significant decline in quality of life during

hospitalization, especially with longer duration of hospitalization.^{31,32} So it is meaningful for clinicians to fully consider these patients' treatment willingness and weigh the pros and cons to determine their treatment location. In addition, allowing proper low-risk patients to receive outpatient treatment or discharge them early could also ease their financial burden of hospitalization and reduce the unnecessary waste of medical resources. Therefore, patient selection becomes the most critical part of this strategy. In this study, PESI divided the least patients (9.1%) as low risk and Hestia classified the most patients (65.4%) into low risk. Modified Ottawa stratified 17.0% of patients as low risk. But the 30-day overall mortality and overall adverse outcomes of the low-risk patients based on these three scales are high (>5% for all). RIETE and POMPE-C both classified 30.9% of patients as low risk, and low-risk patients stratified by these two scales presented a low overall mortality (1.4 and 3.5%) and overall adverse outcomes (2.1 and 3.5%). This result indicates that approximately 30% of the patients with PE and active cancer actually have a low incidence of adverse events and hospitalization may not benefit them much. So considering the cost-effectiveness, patient's quality of life, and the risk of management outside the hospital, home treatment may be a good option for these patients. And cancer-specific PE prognostic scales (RIETE and POMPE-C) could be useful for screening these low-risk patients.

Lung cancer is the most common solid tumor prone to PE.³³ In our study, lung cancer also accounts for the largest proportion of all tumor types (47.8%), but the proportion is higher than that in other similar studies.^{16,21} This may be because our hospital has a specialized clinic lung cancer center and more patients with lung cancer were admitted to our institution. And the higher proportion of lung cancer patients may account for the high PE-related mortality (9.1%) in our study for a large part of the patients enrolled have basic impaired lung function, and PE may be fatal for them. In our study, the percentage of low-risk patients classified by RIETE and POMPE-C was slightly greater than that in their derivation or original validation samples (31 vs. 22–27%), but

the incidence of adverse events in low-risk patients remains at a low level ($\leq 3.5\%$).

To sum up, cancer-specific PE prognostic scores (RIETE and POMPE-C) performed better than the generic scales (PESI and Hestia) and a cancer-associated VTE risk stratification model (modified Ottawa score) in predicting 30-day post-PE adverse events in our study. A good prognostic tool should be easily and effectively used by physicians at the same time. POMPE-C consists of an equation not easily computed without the use of calculator.¹⁷ RIETE contains only six dichotomizing variables¹⁶ and also more timesaving and much easier to perform than POMPE-C scale; so, it is more useful to use the RIETE score in the clinical practice.

Our study had potential limitations. First, our study was performed in a single center and the percentage of patients with lung cancer is higher than other hospitals due to the differences in the proportion of cancer types of patients admitted; so, its generalizability might be limited. Second, our study is a retrospective analysis of a consecutively collected VTE database which enrolled all VTE patients admitted to our hospital using the ICD codes, but it may still result in some incorrectly coded and uncoded cases being missed. And because of the retrospective design and the absence of documentation on social issues in the medical records, it is unable for us to determine whether the patient had social reasons for hospitalization, and we assumed that no patients were admitted to the hospital for social reasons in this study which may underestimate the patients' risk score of Hestia and also this scale's sensitivity to identify higher-risk patients. Third, a total of 28 patients were excluded due to outcome unavailable in this study which may bias the results, but we have performed multiple imputations to impute these missing outcomes and the analyses showed similar results after including patients with imputed clinical outcomes as that conducted in patients with complete data. Lastly, we enrolled only symptomatic PE patients because all the prognostic models except modified Ottawa included in our study¹⁴⁻¹⁷ were derived from this subtype population. Therefore, the study results cannot be extrapolated to the whole spectrum of cancer-associated PE. Future studies should pay more attention to incidentally discovered PE among oncological patients, and multicenter prospective studies should be conducted to further validate the prognostic performance of existing risk stratification tools in patients with PE and active cancer.

Conclusion

Cancer-specific PE prognostic scores (RIETE and POMPE-C) performed better than generic scales (PESI and Hestia) and a cancer-specific VTE prognostic scale (modified Ottawa) in identifying low-risk PE patients with active cancer who may be suitable for outpatient treatment. However, multicenter, prospective studies are still needed to further validate the predictive ability of existing risk stratification tools in this population.

What is known about this topic?

- Several prognostic models have been derived and validated for risk stratification in pulmonary embolism (PE) patients, but current literature lacks a consensus tool to quantify the short-term prognosis among PE patients with active cancer.
- Appropriately selected low-risk PE patients may be considered for early hospital discharge or home treatment, but the safety and efficacy of existing clinical prognostic scales in identifying low-risk patients among PE patients with active cancer is unclear.

What does this paper add?

- Cancer-specific PE prognostic scores (RIETE and POMPE-C) performed better than generic scales (PESI and Hestia) and a cancer-specific venous thromboembolism (VTE) prognostic score (modified Ottawa) in predicting 30-day post-PE adverse events.
- Low-risk patients classified by cancer-specific PE scales presented low 30-day post-PE mortality.
- Cancer-specific PE prognostic scales (RIETE and POMPE-C) may be used to select candidates for early discharge and outpatient management in PE patients with active cancer.

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Conflict of Interest

X.L. reports grants from the National Key Research Program of China and the Sichuan Science and Technology Program, during the conduct of the study.

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