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Validation of risk assessment scores in predicting venous thromboembolism in patients with lung cancer receiving immune checkpoint inhibitors

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Abstract

Introduction Several risk scores have been proposed to predict venous thromboembolism (VTE) in hospitalized patients. However, their predictive performances in lung cancer patients receiving immune checkpoint inhibitors (ICIs) is unclear. We aimed to validate and compare their performances of the Caprini, Padua and Khorana risk scores in lung cancer patients receiving ICIs.

Methods This was a retrospective cohort study of patients with lung cancer treated with ICIs at West China Hospital between January 2018 and March 2022. The primary outcome was VTE during 12 months of follow-up from the first day of treatment with ICIs. The predictive performances of risk scores was determined using receiver operating characteristic (ROC) curve analysis.

Results Among the 1115 eligible patients with lung cancer who received ICIs, 105 patients (9.4%) experienced VTE during the 12-month follow-up period. There was a statistically significant difference in the cumulative incidence of VTE between the different risk levels as determined by Caprini and Padua scores (all $P < 0.001$). However, no significant difference was observed for the Khorana score ($P = 0.488$). The Caprini and Padua scores demonstrated good discriminative performances (AUC 0.743, 95% CI 0.688-0.799 for Caprini score; AUC 0.745, 95% CI 0.687-0.803 for Padua score), which were significantly better than that of the Khorana score (AUC 0.553, 95% CI, 0.493-0.613) ($P < 0.05$).

Conclusion In our study, the Caprini and Padua risk scores had better discriminative ability than the Khorana score to identify lung cancer patients treated with ICIs who were at high risk of VTE.

Keywords Lung cancer, Immune checkpoint inhibitors, Venous thromboembolism, Risk assessment scores

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Introduction

Lung cancer is one of the most prevalent malignancies and is the primary cause of cancer death worldwide [1]. In recent years, immune checkpoint inhibitors (ICIs), a new milestone for cancer treatment, mainly target the protein programmed cell death 1 (PD-1) receptor and its ligand (PD-L1), which have made important and impactful contributions to cancer medicine [2–5]. A subset of lung cancer patients receiving ICIs, either used alone or in combination with chemotherapy, have a realistic chance of achieving better overall survival and response rates [5]. Venous thromboembolism (VTE) is a frequent complication of lung cancer, with reported 12-month incidence rates as high as 6.5-13.1% [6–8]. In addition, the reported incidence of VTE varies from 4.5 to 17.8% in hospitalized patients with lung cancer receiving ICIs [9–11]. The development of VTE strongly correlates with a poor prognosis, leading to more severe health conditions and worse overall survival [12].

VTE, consisting of deep venous thrombosis (DVT) and pulmonary embolism (PE), is preventable, with common prophylaxes including mechanical methods and pharmacological agents [13]. The American College of Chest Physicians (ACCP) and the National Comprehensive Cancer Network (NCCN) guidelines both recommend thromboprophylaxis for lung cancer patients who are at high risk of VTE [14, 15]. However, the VTE thromboprophylaxis for lung cancer patients may come with some side effects, such as major bleeding and heparin-induced thrombocytopenia. Therefore,

the evaluation of the risk of VTE is essential to select an appropriate prophylaxis strategy in lung cancer patients receiving ICIs.

Several risk assessment scores for VTE have been derived and validated in hospitalized patients. The Caprini, Padua and Khorana scores are the most widely studied, but there has been no consensus on which one is the best in patients with lung cancer [16–18]. The Caprini risk assessment score was originally developed and validated for predicting postoperative VTE in surgical patients. It contained 36 items and has been adopted to cancer patients [19–21]. The Padua score could help select patients at particularly high risk of VTE and has been recommended to evaluate the VTE risk among medical inpatients by the ACCP guideline [14]. However, the small number of VTE events in the derivation cohort and suboptimal validation led to limited clinical application of this risk score [22]. The Khorana score identified 5 different variables that were found to be independent predictors of chemotherapy-associated VTE in cancer patients [18]. Guidelines suggested that cancer patients with a Khorana score of 2 or higher might need primary pharmacological prophylaxis for VTE [23]. However, the predictive performances of these risk scores were not clear in patients with lung cancer receiving ICIs.

In this study, we aimed to validate and compare the performances of the Caprini, Padua and Khorana risk scores in patients with lung cancer receiving ICIs.

Methods

Study design and patients

This was a retrospective cohort study of lung cancer hospitalized patients at West China Hospital between January 2018 and March 2022. The inclusion criteria were as follows: histologically confirmed lung carcinoma, age ≥ 18 years, and had received at least one dose of an approved ICIs. The exclusion criteria were as follows: diagnosis of VTE within 48 hours following admission, receiving thromboprophylaxis or treatment with antiplatelets when treated with ICIs, and incomplete follow-up data. This study was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University in accordance with the Declaration of Helsinki. As all analyses were conducted using anonymized, de-identified patient data, the requirement for written informed consent was waived.

Data collection

The following parameters were collected: demographics (age, gender, body mass index (BMI)), cancer-related variables (past or active smoking status, histological subtype, TNM stage, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), PD-L1 status, number of distant metastatic sites, molecular alterations, cancer treatments), medical history (hypertension, diabetes, hyperlipemia, abnormal pulmonary function, severe lung disease, respiratory failure, atrial fibrillation, rheumatological disorder, arterial vascular events), variables associated with VTE risk (varicose veins, swollen legs, immobilization, recent (≤1 month) surgery, history of VTE), and laboratory findings (hemoglobin, white blood cell (WBC), platelet count). Patients were followed from the first day of treatment with ICIs until 12 months or death by rehospitalization, outpatient visits, or telephone.

Risk assessment scores

For the present study, the Caprini, Padua and Khorana risk scores were calculated using available data by trained physicians. The risk factors included in the three risk assessment scores, the points assigned, and the risk stratification were depicted in Supplemental Table S1. Based on commonly accepted definitions, patients with a Caprini score of 0 were at very low risk, 1–2 were low risk, 3–4 were moderate risk and ≥5 were high risk. The Padua score classified patients into low-risk (0–3) and high-risk (≥4) groups based on 11 risk factors. The Khorana risk score is composed of five objective parameters:

type of cancer (1 score for lung, lymphoma, gynecologic, bladder, testicular, or 2 scores for stomach, pancreas), pre-treatment platelet counts $\geq 350\times10^9$/L (1 score), hemoglobin < 10 g/dL (1 score), pre-treatment WBC count > 11×10^9/L (1 score), and BMI ≥ 35 kg/m^2 (1 score). Cancer patients were categorized into low-risk (score 0), intermediate-risk (score 1–2), and high-risk (score ≥ 3) groups based on the Khorana risk score.

Study outcomes

The main study outcome was VTE during 12 months of follow-up from the first day of treatment with ICIs. VTE was defined as symptomatic or asymptomatic, PE or DVT based on standardized radiographic findings. The clinical records and radiology reports of included patients were reviewed during follow-up.

Statistical analysis

Categorical variables were presented as frequencies and percentages and the chi-squared test was used to analyze group differences. Continuous variables were expressed as mean values with standard deviations or median plus quartile interval and were compared by the independent Student's t test (normal distribution) and the Mann–Whitney U test (skewed distribution). The risk factors for VTE in the cohort were explored by multivariate logistic regression and the odds ratio (OR) values and 95% confidence interval (CI) were reported. Kaplan–Meier curves were used to describe the time-courses for the occurrence of VTE after receiving ICIs in lung cancer patients with different risk levels by the Caprini, Padua and Khorana risk scores, and the log-rank test was used to make group comparisons. We estimated the discriminative power of each score in predicting VTE by calculating the area under the receiver operating characteristic curve (AUC). All collected data were analyzed with SPSS (Version 25.0), and a P value < 0.05 indicated a statistically significant difference.

Results

Patient characteristics and VTE incidence

Overall, 1253 patients with lung cancer receiving ICIs were initially identified for inclusion in this study, of which 138 patients were excluded for the following reasons: (1) diagnosis of VTE within 48 hours of admission ($n=39$), (2) received thromboprophylaxis or treated with antiplatelets when treated with ICIs ($n=10$), and (3) incomplete follow-up data for 12 months ($n=89$). Ultimately, 1115 patients were enrolled (Fig. 1). Overall, 105 patients (9.4%) experienced VTE during the 12-month follow-up period, of which 10 (9.5%) had definite isolated PE, 91 (86.7%) had isolated distal DVT and 4 (3.8%) had DVT complicated with PE. The median time from initial ICI treatment until VTE occurrence was 3 months.

Table 1 showed the baseline characteristics of patients with VTE and non-VTE cases. The mean age at diagnosis was 61.70±9.36 years, and 942 (84.5%) patients were men. Patients with adenocarcinoma tended to have a

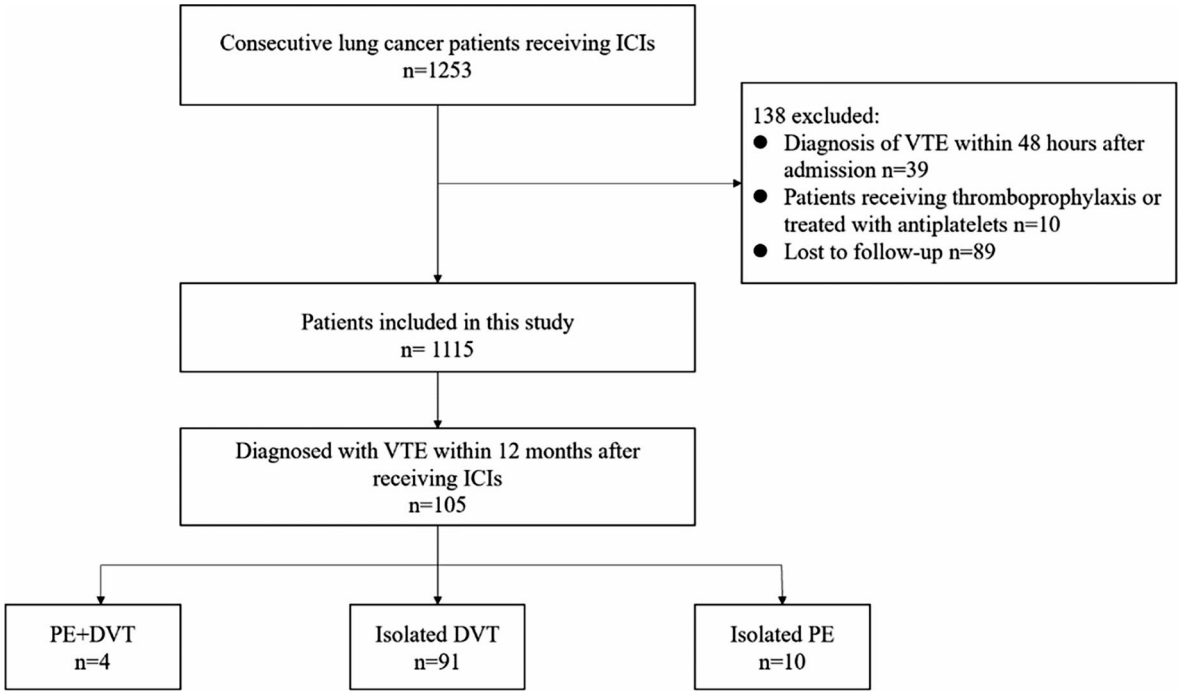

Fig. 1 Flow chart of the study. (Abbreviations: ICIs = immune checkpoint inhibitors; VTE = venous thromboembolism; PE = pulmonary embolism; DVT = deep venous thrombosis)

Table 1 Patient characteristics at baseline

Characteristics	All, *N* = 1115	Venous thromboembolism		*P*-Value
		No, *N* = 1010	Yes, *N* = 105	
Age, y	61.70 ± 9.36	61.63 ± 9.41	62.37 ± 8.93	0.439
Age ≥ 70 y	215(19.3)	194(19.2)	21(20.0)	0.845
Male	942(84.5)	855(84.7)	87(82.9)	0.628
BMI	23.05 ± 3.19	23.06 ± 3.21	22.99 ± 3.06	0.827
BMI ≥ 30 kg/m2	23(2.1)	22(2.2)	1(1.0)	0.716
Smoking (current or past)	719(65.0)	646(64.5)	73(69.5)	0.308
Histological subtype				
Squamous cell carcinoma	416(37.3)	387(38.3)	29(27.6)	0.031
Adenocarcinoma	427(38.3)	376(37.2)	51(48.6)	0.023
Small cell Carcinoma	197(17.7)	182(18.0)	15(14.3)	0.340
Other	75(6.7)	65(6.4)	10(9.5)	0.229
TNM stage				0.110
II-III	442(39.6)	408(40.4)	34(32.4)	
IV	673(60.4)	602(59.6)	71(67.6)	
ECOG PS				<0.001
0–1	1037(93.0)	960(95.0)	77(73.3)	
≥ 2	78(7.0)	50(5.0)	28(26.7)	
PD-L1 (TPS)				0.063
< 50%	286(84.4)	255(60.9)	31(75.6)	
≥ 50%	174(15.6)	164(39.1)	10(24.4)	
Number of distant metastatic sites				0.014
0–1	766(68.7)	705(69.8)	61(58.1)	
≥ 2	349(31.3)	305(30.2)	44(41.9)	
Molecular driver				
KRAS+	94(20.0)	77(18.5)	17(32.1)	0.020
ALK+	4(0.9)	3(0.7)	1(1.9)	0.939
EGFR+	76(16.2)	66(15.9)	10(18.9)	0.576
ROS1+	2(0.4)	2(0.5)	0(0.0)	1.000
ICI regimen given in line				0.019
1	731(65.6)	673(66.6)	58(55.2)	
≥ 2	384(34.4)	337(33.4)	47(44.8)	
Previous treatment before ICIs				
Platinum-based chemotherapy	298(26.7)	257(25.4)	41(39.0)	0.003
Chest radiotherapy	86(7.7)	75(7.4)	11(10.5)	0.265
Surgical resection	143(12.8)	128(12.7)	15(14.3)	0.638
Targeted therapy	85(7.6)	75(7.4)	10(9.5)	0.441
Bevacizumab	27(2.4)	20(2.0)	7(6.7)	0.003
Comorbidities				
Hypertension	269(24.1)	241(23.9)	28(26.7)	0.523
Diabetes	144(12.9)	132(13.1)	12(11.4)	0.633
Hyperlipemia	153(13.8)	137(13.6)	16(15.2)	0.647
Abnormal lung function	19(1.7)	13(1.3)	6(5.7)	0.001
Severe lung disease	31(2.8)	16(1.6)	15(14.3)	<0.001
Respiratory failure	21(1.9)	9(0.9)	12(11.4)	<0.001
Atrial fibrillation	19(1.7)	16(1.6)	3(2.9)	0.413
Rheumatological disorder	4(0.4)	4(0.4)	0(0.0)	1.000
Arterial vascular events	71(6.4)	64(6.3)	7(6.7)	0.895
Risk factors for VTE				
Varicose veins	27(2.4)	24(2.4)	3(2.9)	0.735
Swollen legs	14(1.3)	7(0.7)	7(7.6)	<0.001
Immobilization	12(1.1)	4(0.4)	8(7.6)	<0.001
Recent (≤ 1 month) surgery	11(1.0)	8(0.8)	3(2.9)	0.077

Table 1 (continued)

Characteristics	All, *N* = 1115	Venous thromboembolism		*P*-Value
		No, *N* = 1010	Yes, *N* = 105	
History of VTE	34(3.0)	13(1.3)	21(20.0)	<0.001
Central venous access	561(50.3)	503(49.8)	58(55.2)	0.289
Laboratory tests				
Hemoglobin (g/L)	125.69 ± 18.43	126.31 ± 18.12	119.70 ± 20.38	<0.001
Hemoglobin < 10 g/dL	95(8.5)	79(7.8)	16(15.2)	0.010
WBC($\times 10^9$/L)	7.08 ± 2.93	7.07 ± 2.88	7.13 ± 3.35	0.862
WBC > 11 × 10^9/L	88(7.9)	73(7.2)	15(14.3)	0.011
Platelet count($\times 10^9$/L)	229.27 ± 95.05	229.79 ± 93.25	224.31 ± 111.26	0.575
Platelet count ≥ 350 × 10^9/L	95(8.5)	86(8.5)	9(8.6)	0.987
Caprini score	5(4–6)	5(4–6)	6(5–7)	<0.001
Padua score	3(3–4)	3(3–4)	4(3–6)	<0.001
Khorana score	1(1–1)	1(1–1)	1(1–2)	0.034

Note Categorical variables were presented as number of patients (%); Continous variables were presented as mean (standard deviation) or median (interquartile range). Severe lung disease included symptomatic asthma, bronchiectasis, idiopathic pulmonary fibrosis, pneumoconiosis, active or destructive pulmonary tuberculosis, and pulmonary arterial hypertension

Abbreviations BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group Performance Status; PD-L1 = programmed cell death ligand 1; ICIs = immune checkpoint inhibitors; VTE = venous thromboembolism; WBC = white blood cell

higher prevalence of VTE within one year, whereas the opposite tendency was observed in squamous cell carcinoma. Patients who had PS ECOG ≥ 2 at start had an higher probability of developing VTE at 12 months. There was no significant difference in age, sex, BMI, smoking status, TNM stage, or PD-L1 expression between the two groups. Patients with higher number of metastatic sites before ICIs start and higher number of previous lines had a higher probability of developing VTE within 12 months. Among molecular subtypes, the KRAS-mut subset showed a significantly higher prevalence of VTE within one year . Additionally, among patients previously treated with platinum-based chemotherapy, and with bevacizumab, the prevalence of VTE was higher (both $P<0.05$). VTE within one year was more prevalent in patients with abnormal pulmonary function, severe lung disease, and respiratory failure (all $P<0.05$). In terms of variables associated with VTE risk, known risk factors for VTE as swollen legs, immobilization and personal history of VTE were associated with higher risk of VTE at one year. With respect to laboratory tests, VTE tended to occur more frequently in patients with anemia (defined as hemoglobin < 10 g/dL) and hyperleukocytosis (defined as WBC > 11 × 10^9/L). The median risk scores were significantly higher in the VTE group for all the risk assessment scores (all $P<0.05$).

Risk factors for VTE after initiation of ICIs

The clinical risk factors for VTE in lung cancer patients with ICIs therapy was explored. We performed a multivariate logistic regression analysis with histological subtype, ECOG PS, number of distant metastatic sites, previous treatment before ICIs, abnormal pulmonary function, severe lung disease, respiratory failure, swollen legs, immobilization, history of VTE, hemoglobin < 10 g/dL, and WBC > 11 × 10^9/L as candidate predictive factors based on the results of the univariate analysis (all $P<0.05$). We found that ECOG PS ≥ 2 (OR = 4.465; 95% CI: 2.393–8.331, $P<0.001$), previous platinum-based chemotherapy (OR = 1.759; 95% CI: 1.058–2.923, $P=0.029$), severe lung disease (OR = 6.906; 95% CI: 2.774–17.195, $P<0.001$), respiratory failure (OR = 3.835; 95% CI: 1.262–11.651, $P=0.018$), swollen legs (OR = 4.980; 95% CI: 1.354–18.313, $P=0.016$), immobilization (OR = 12.122; 95% CI: 2.490-59.016, $P=0.002$) and history of VTE (OR = 19.380; 95% CI: 8.723–43.058, $P<0.001$) were independent predictors of VTE (Table 2).

Table 2 Multivariate analysis for predictors of VTE in lung cancer patients receiving ICIs

Risk factors	OR	95% CI	*P*-Value
Adenocarcinoma	1.375	0.850–2.225	0.195
ECOG PS ≥ 2	4.465	2.393–8.331	<0.001
Number of distant metastatic sites ≥ 2	1.351	0.824–2.215	0.233
Previous chemotherapy	1.759	1.058–2.923	0.029
Abnormal lung function	2.862	0.766–10.700	0.118
Severe lung disease	6.906	2.774–17.195	<0.001
Respiratory failure	3.835	1.262 – 11.651	0.018
Swollen legs	4.980	1.354–18.313	0.016
Immobilization	12.122	2.490–59.016	0.002
History of VTE	19.380	8.723–43.058	<0.001
Hemoglobin < 10 g/dL	1.209	0.582–2.514	0.611
WBC > 11 × 10^9/L	1.827	0.866 – 3.855	0.114

Abbreviations VTE = venous thromboembolism; ICIs = immune checkpoint inhibitors; ECOG PS = Eastern Cooperative Oncology Group Performance Status; OR = odd ratio; CI = confidence interval

Incidence of VTE by risk levels and the three risk assessment scores

Table 3 showed the incidence of VTE based on risk levels of Caprini, Padua and Khorana scores in the cohort. For the Caprini risk assessment score, 0 (0%) patients were in the lowest-risk group, 5 (0.4%) patients were in the low-risk group, 370 (33.2%) patients were in the moderate-risk group, and 740 (66.4%) patients were in the high-risk group. The respective VTE incidence in the different risk levels were 0%, 3.5%, and 12.4%. There was a significant difference in the increased VTE incidence ($P<0.001$). For the Padua risk score, 54.3% of the study population were classified as low risk with 0–3 score, and 45.7% as high risk with more than 4 cumulative risk score. A higher risk level indicated a greater incidence of acquired VTE within 12 months: 4.5% of low-risk patients acquired a VTE; among the high-risk patients, 15.5% acquired a VTE ($P<0.001$). However, based on the Khorana score, 95.6% of the study patients with lung cancer were categorized as moderate risk, and 9.3% acquired VTE. There were no statistically significant differences in VTE incidence between moderate-risk and high-risk levels for the Khorana score ($P=0.488$) (Fig. 2).

Performances of risk assessment scores in the overall cohort

The 12-month cumulative incidences of VTE based on the risk levels of Caprini, Padua and Khorana risk scores were shown in Fig. 3. In the time-to-event analysis, there was a significant difference in the cumulative incidence of VTE between patients with different risk levels by Caprini and Padua scores (all $P<0.001$). However, for the Khorana score, the cumulative incidence of VTE did not show a significant difference between the patients with moderate-risk scores and those with high-risk scores ($P>0.05$).

Figure 4 presented the discriminative performances of the Caprini, Padua and Khorana scores. The AUC decreased for almost all scores compared with the original cohorts, with AUCs ranging from 0.553 to 0.745. The Caprini and Padua scores yielded good discriminative performances (AUC 0.743, 95% CI 0.688 - 0.799 for Caprini score; AUC 0.745, 95% CI 0.687 - 0.803 for Padua score). The AUC of the Khorana score was 0.553 (95% CI, 0.493 - 0.613), which was significantly lower than that of the Caprini and Padua scores ($P<0.05$).

Performances of risk assessment scores in the subgroup of ICIs monotherapy

A total of 152 patients received ICIs monotherapy in the study; 11 (7.2%) experienced VTE during the 12-month follow-up period, of which 1 (9.1%) had isolated PE, 9 (81.8%) had isolated distal DVT and 1 (9.1%) had DVT complicated with PE. The median time until VTE occurrence was 5 months. Based on the ROC curve analysis, the AUC was 0.762 (95% CI, 0.583–0.942) for the Caprini score, which exhibited good performance in predicting 12-month VTE in lung cancer patients receiving ICIs monotherapy. However, the discrimination performances of the Padua and Khorana scores for predicting VTE were poor (AUC 0.656, 95% CI 0.458-0.854 for Padua score; AUC 0.549, 95% CI 0.367-0.731 for Khorana score) (Supplementary Figure S1).

Discussion

In this study, we validated and compared the performances of the Caprini, Padua and Khorana risk scores for predicting VTE in patients with lung cancer receiving ICIs. We found that the Caprini and Padua scores performed better than the Khorana score in identifying patients who were at high risk of VTE. Additionally, the Caprini score showed the best accuracy for predicting 12-month VTE in lung cancer patients receiving ICIs monotherapy. These findings indicated that the Khorana score may be not suitable for evaluating VTE in lung cancer patients receiving ICIs. On the other hand, the

Table 3 Incidence of 12-month VTE based on risk levels of Caprini, Padua and Khorana scores

Score	Risk level	*n*, %	12-month VTE	*P*-Value
Caprini				
	Lowest risk (0)	0 (0%)	-	< 0.001
	Low risk (1–2)	5(0.4%)	0/5(0.0%)	
	Moderate risk (3–4)	370(33.2%)	13/370(3.5%)	
	High risk (≥ 5)	740(66.4%)	92/740(12.4%)	
Pauda				
	Low risk (0–3)	605(54.3%)	26/605(4.5%)	< 0.001
	High risk (≥ 4)	510(45.7%)	79/510(15.5%)	
Khorana				
	Low risk (0)	0 (0%)	-	0.488
	Moderate risk (1–2)	1066(95.6%)	99/1066(9.3%)	
	High risk (≥ 3)	49(4.4%)	6/49(12.2%)	

Abbreviations VTE = venous thromboembolism

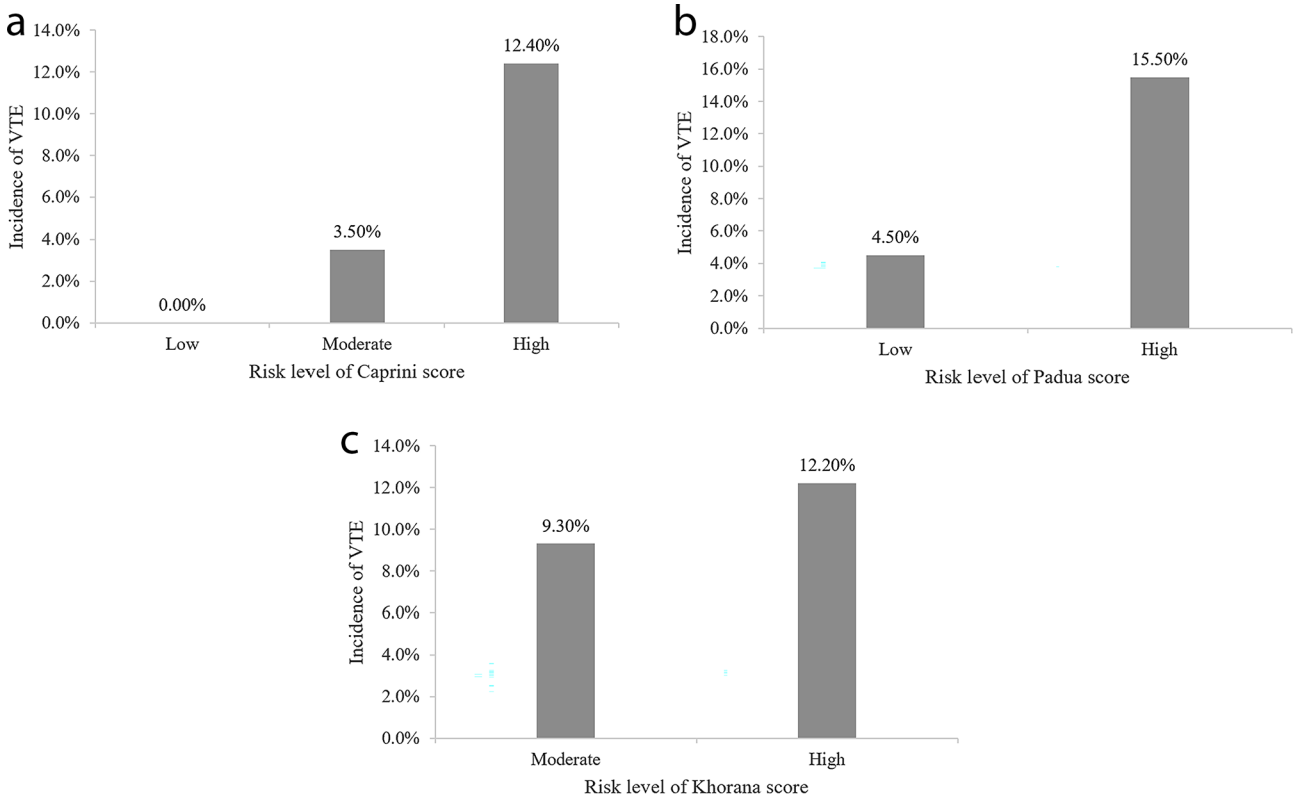

Fig. 2 Incidence of 12-month VTE by risk levels of Caprini, Padua and Khorana scores. (**a**) Caprini score (**b**) Padua score (**c**) Khorana score. (Abbreviations: VTE = venous thromboembolism)

Caprini score may be useful in predicting VTE in lung cancer patients receiving ICIs monotherapy.

The incidence of VTE was reported to be relatively high in cancer patients treated with ICIs, most likely because ICIs enhanced the prothrombotic state by activation of coagulation and platelets and impairment of fibrinolysis [24–26]. An Israeli observational cohort study observed that the 6-month cumulative incidence of VTE in a cohort of 176 lung cancer patients receiving single-agent ICIs was 4.5% [9]. In a large investigation using Health-Core Integrated Research Environment - Oncology data, the VTE incidence rate (95% CI) per 100 person-years was 17.8 (95% CI 16.0 to 19.5) with a median follow-up of 9.1 months [11]. In our study, the 12-month VTE incidence was 9.4% in lung cancer patients who received immunotherapy. This was consistent with the findings of a recent monocentric observational study conducted in France, which reported that the incidence of VTE was 9.8% in lung cancer patients treated with ICIs [27]. VTE development during ICIs treatment had significant impact on overall survival. Therefore, more attention should be focused on VTE during ICIs therapy in order to optimize both the prevention and management of VTE.

Most guidelines recommend risk stratification for VTE using clinical risk scores in hospitalized cancer patients, followed by appropriate prophylaxis measures [14, 15]. Several risk assessment scores have been proposed and validated for risk stratification in cancer patients. The most widely used clinical risk scores were Caprini, Padua and Khorana scores, but they were not equivalent. The three risk scores for VTE were targeted to different populations, the Caprini score concerned patients undergoing surgery, Padua score was realized for inpatients, whereas Khorana score for ambulatory patients with cancer [17, 18, 28]. The Caprini score was originally developed for surgical patients and could be used to risk stratify patients effectively [29]. Zhou et al.. attempted to preliminarily assess the predictive ability of the Caprini risk assessment score among unselected hospitalized patients with VTE and found that the score provided an accurate, practical, and effective method for selection of high-risk patients who may benefit from thromboprophylaxis [30]. However, Paul et al. validated the Caprini score in 63,548 medical patients across 48 Michigan hospitals, and found that the Caprini risk assessment score had limited ability to identify medical patients who were at high risk for VTE [31]. Barbar et al. developed the Padua risk assessment score based on a single cohort study conducted in Italy [17]. Some flaws in this score have been mentioned by some researchers, for example, there were limited VTE events, the model performance characteristics were

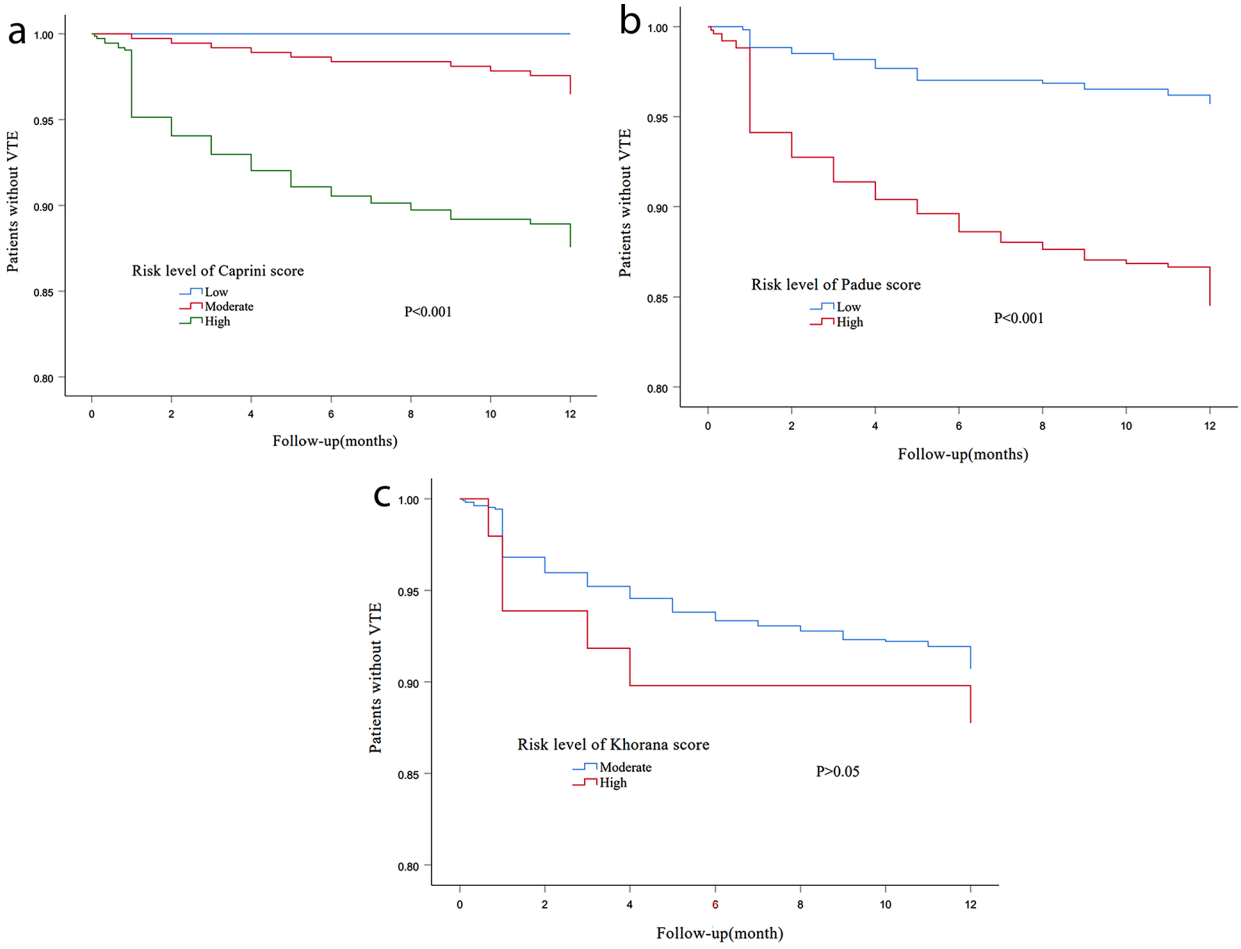

Fig. 3 Cumulative incidence of VTE in patients with different risk levels of Caprini, Padua and Khorana scores (P-value by the log-rank test for comparison of the outcome among groups at 12 months) (**a**) Caprini score (**b**) Padua score (**c**) Khorana score. (Abbreviations: VTE = venous thromboembolism)

not presented, and external validation is suboptimal [32, 33]. The Khorana score, an established tool, helps identify patients receiving chemotherapy who were at risk for VTE [18]. The score is heavily weighted on the type of cancer; thus, all patients with lung cancer were classified as (at least) moderate risk for VTE [34]. The three risk scores are widely used in clinical practice, but it is not yet clear which one is the best among lung cancer patients receiving ICIs. In our study, we compared the performance of these risk scores and found that the Caprini and Padua scores performed better than the Khorana score in identifying lung cancer patients receiving ICIs who were at high risk of VTE. In this cohort of lung cancer patients receiving ICIs, the incidence of VTE increased with higher risk levels according to the Caprini and Padua risk scores. These results revealed that both the Caprini and Padua risk scores could be effectively used to stratify VTE risk among lung cancer patients receiving ICIs. Additionally, for the subgroup of lung cancer patients receiving ICIs monotherapy, the Caprini score showed the best accuracy for predicting VTE compared with the other scores. There were mainly three explanations for this phenomenon. Firstly, the Caprini score covered a broad range of risk factors and provided a personalized and quantifiable strategy for assessing VTE risk. The independent risk factors for VTE in patients with lung cancer receiving ICIs, such as swollen legs, severe lung disease, immobilization, and history of VTE were included in the Caprini score. Secondly, approximately 28.4–39.8% of lung cancer patients were complicated with chronic obstructive pulmonary disease (COPD) [35]. The factor of COPD was unique to the Caprini score, which was also found to be an independent risk factor for VTE in patients with lung cancer [36]. Third, the Caprini score performed a more detailed stratification of VTE risk, which might obtain a better effect on thromboprophylaxis. These findings suggested that the Caprini score may be applied as a useful tool in lung cancer patients receiving ICIs monotherapy.

The Khorana score has been used for VTE risk assessment in cancer patients, but its predictive validity to identify high-risk patients among lung cancer patients

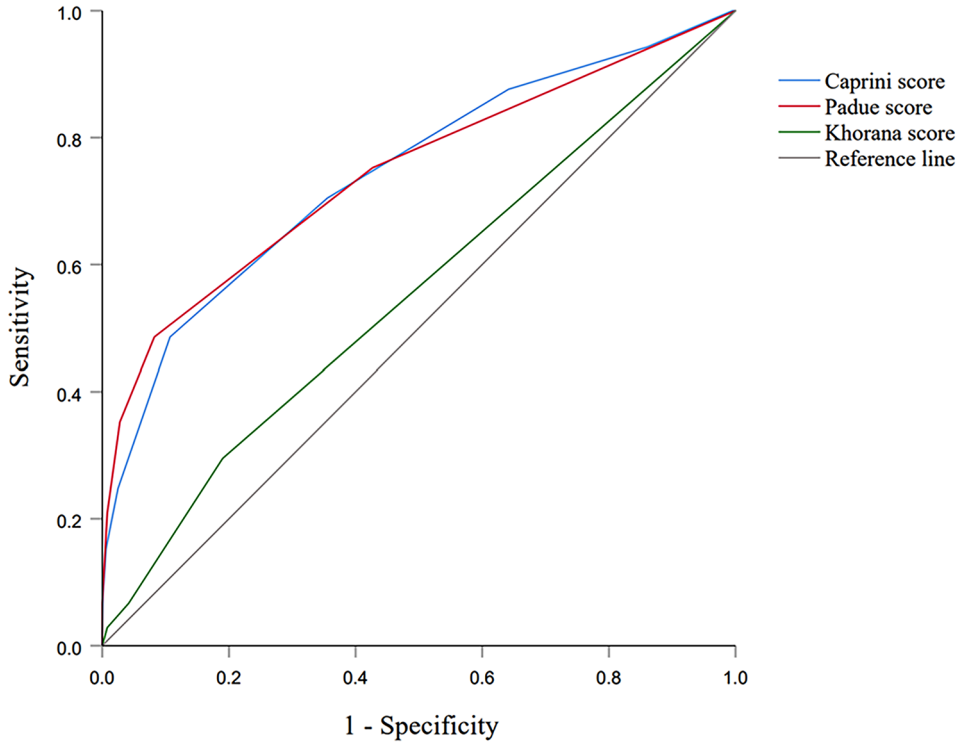

Fig. 4 Receiver operating characteristic (ROC) curve of the Caprini, Padua and Khorana scores

treated with ICIs remains unclear [34, 37, 38]. Recent studies have acknowledged that the Khorana score is associated with VTE in patients treated with ICIs. For example, Gong et al. found that patients with VTE had a higher Khorana risk score, and a Khorana score≥2 could indicate cancer patients at high risk of VTE for thromboprophylaxis [39]. In a retrospective cohort study of cancer patients receiving ICIs therapy with a median follow-up of 27.3 months, a Khorana score≥1 was reported to be significantly associated with VTE [40]. In contrast, the Khorana score showed poor performance with poor accuracy in our study population. It may be due to the difference in the study population, our study only enrolled hospitalized cancer patients but did not include outpatients. Alma et al. reached the same conclusion with our study [27]. No significant difference was observed in the rate of VTE between patients with a Khorana score<2 and ≥2, the Khorana score did not effectively predict VTE in lung cancer patients receiving ICIs [27]. Thus, it is crucial to improve the Khorana score for VTE risk stratification and to guide primary prevention strategies.

Strengths and limitations

To our knowledge, this study was the first attempt to validate and compare the Caprini, Padua and Khorana risk scores among patients with lung cancer receiving ICIs. The data quality in our study was relatively high because of large number of patients and integral 12-month follow-up data. Nevertheless, our study was associated with several limitations. First, this was a retrospective cohort study of patients with lung cancer, and some variables, including PD-L1 expression levels and laboratory tests, were not available for all patients. Fortunately, the proportion of patients was small, and the impact on our results can be neglected. Second, our study was performed in a single center, and the majority of patients we included had previously received chemotherapy for locally advanced or metastatic cancer; thus, its generalizability might be limited. Therefore, multicenter prospective studies should be conducted to further validate the performance of existing risk stratification tools in lung cancer patients receiving ICIs.

Conclusion

In summary, the Caprini and Padua scores showed better performances in predicting the risk of VTE in lung cancer patients receiving ICIs than the Khorana score. Further studies were needed to develop and validate an ICI-specific risk assessment score in patients with lung cancer.

Abbreviations

VTE	venous thromboembolism
ICIs	immune checkpoint inhibitors

PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
DVT	deep venous thrombosis
PE	pulmonary embolism
ACCP	American College of Chest Physicians
NCCN	National Comprehensive Cancer Network
BMI	body mass index
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
WBC	white blood cell
OR	odds ratio
95% CI	95% confidence interval
AUC	area under the receiver operating characteristic curve

Supplementary Information

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Supplementary Material 1

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Author contributions
JZ and YX contributed to the curation and analysis of the data and drafted the manuscript. DL contributed to the design of the study and revised or critically reviewed the article. LY, MY, and RX all contributed to the acquisition and interpretation of the data and gave final approval of the version to be published.

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Data availability
The original data of this manuscript are available on reasonable request by contacting the correspondence author.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review board of the West China Hospital of Sichuan University in accordance with the Declaration of Helsinki. The informed consent was waived by the Ethics Review Committee of West China Hospital of Sichuan University.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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