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The Alfalfa-inpatient-CAT assessment model: a thrombotic risk assessment model for inpatient cancer patients

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Abstract

Purpose To construct a venous thromboembolism (VTE) risk assessment model specifically for inpatients with cancer.

Method Patients were included according to the inclusion criteria. Univariate and multivariate analyses of all variables were included to develop a VTE risk assessment model applicable to the derivation cohort. Hosmer–Lemeshow test and receiver operating characteristic (ROC) curve were used to test the fit degree and identification validity of the model. The patient data from separate validation cohorts verified the external population.

Result A total of 944 cancer patients were included in this study. Alfalfa-inpatient-CAT model, a risk assessment model for VTE in hospitalized cancer patients, was established, which mainly includes hypertension, surgical history (nearly one month), history of VTE, peripherally inserted central venous catheters (PICC), chemotherapy, PT < 12.85 s, D-dimer ≥ 1.805 μg/mL, hemoglobin ≤ 114.5 g/L, CRP ≥ 7.575 mg/L. Hosmer–Lemeshow test results showed $P = 0.353 > 0.05$, ($\chi^2 = 8.872$, Df = 8). The area under ROC curve was 0.906 [95%CI (0.881–0.930), $P < 0.001$]. The authenticity evaluation in the model database showed that the risk of thrombosis in the high-risk group (score ≥ 3) was 72.63%, significantly higher than that in the low-risk group (score 0–2) (27.37%) [$\chi^2 = 144.00$, Df = 1, $P < 0.001$].

Conclusion This study developed a new VTE risk assessment model – Alfalfa-inpatient-CAT model – for hospitalized cancer patients at high risk of thrombosis. This model has a good fitting degree and discriminant validity. It is expected to provide some reference for the clinical treatment of inpatients with cancer through continuous optimization.

Keywords Venous thromboembolism, Cancer-associated thrombosis, Inpatients, Risk assessment, Cancer

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Introduction

VTE is one of the common complications in patients with cancer, and the cancer is also a high-risk factor for thrombosis. The occurrence of tumor-related VTE accounted for 23% of the total VTE events [1]. Cancer patients have a 4–sevenfold increased risk of thrombosis than non-cancer patients [2]. A population-based cohort study even suggests that cancer increases the risk of VTE by ninefold [3]. More importantly, VTE can significantly increase mortality and decrease the overall survival rate of cancer patients. Cancer-associated VTE has become the second leading cause of death in cancer patients, second only to cancer itself [4]. So a pressing clinical issue is how to reliably predict which cancer patients are at higher risk for VTE, i.e., which factors are risk factors for VTE in cancer patients.

According to the characteristics of different populations, many risk assessment models for VTE have been established, but the risk assessment models for hospitalized cancer patients are very limited. At present, experts and scholars at home and abroad have constructed some models to assess the risk of VTE in hospitalized cancer patients. Caprini [5] constructs a thrombosis risk assessment model. Khorana et al.[6] constructed a chemotherapy-related thrombosis prediction model. Barbar et al. [7] constructed Padova prediction score to identify the risk of venous thromboembolism in hospitalized medical patients. Above model have been used to assess the risk of VTE in hospitalized cancer patients. In some studies, they have been proved to help assess the risk of VTE in cancer patients, but there are still deficiencies. For example, relevant studies point out that the sensitivity and specificity of Khorana are low, and the applicable population needs to be further confirmed [8, 9]. And the latter two models are not specifically designed for cancer patients, which have a bias in the accuracy of their assessments for cancer-associated VTE with more complex mechanisms.

Therefore, this study aimed to construct a model to predict the risk of thrombosis in hospitalized cancer patients.

Data and methods

Research Data

We conducted a retrospective analysis to collect medical records of inpatients with cancer from January 2015 to December 2020 at Fujian Medical University Union Hospital through an electronic medical record system.

Inclusion and exclusion criteria

Thrombus group, that is, cancer patients with VTE.

Inclusion criteria: (1) Patients over 18 years of age, regardless of gender; (2) Hospitalized patients with cancer confirmed by cytological examination or histopathological analysis; (3) Patients with VTE (including DVT, catheter-associated thrombosis, and PE) confirmed by enhanced CT, color doppler ultrasound, or pulmonary angiography.

Exclusion criteria: (1) Received anticoagulant medication in the past month; (2) Incomplete data. Patients were hospitalized simultaneously, with the same gender, diagnosis, and stage as the control group, namely, cancer patients without VTE. The cases in the control group were randomly screened in the same department and period. Patients (including DVT and PE) excluded by enhanced CT, color doppler ultrasound, or pulmonary angiography were included in the control group, and other criteria were the same as those in the thrombosis group.

Data collection

Patient data is reviewed and collected from the hospital's electronic database, timely collated, and clinically recorded by professional doctors or nurses. Clinical variables known to be associated with VTE as well as potential risk factors include the general information of the population (such as age, gender, ethnicity, BMI index, smoking history, history of drinking), merged disease (e.g., hypertension, coronary heart disease, diabetes, stroke, nephrotic syndrome), cancer-related information (e.g., tumor type, stage, chemotherapy, chemotherapy drugs), surgical history (nearly one month); history of VTE, peripherally inserted central venous catheters (PICC), central venous catheters, peripheral venous catheters, combined medications, blood clotting tetrachoric, D-dimer, blood routine, and type of thrombus.

Derivation and validation of the model

The derivation and validation of the model are based on the split sample method. 85% of study participants were randomly assigned to a model derivation cohort ($n=800$), and 15% ($n=144$) were retained as a separate validation cohort. Clinical and laboratory variables were compared between the two cohorts.

Univariate analysis of variables included in the empirical model database was performed using Pearson Chi-square or Fisher's exact test. Variables associated with an increased risk of VTE ($P<0.20$) in the univariate analysis and variables selected a priori based on known relevance were included in the pool of variables for the forward stepwise regression model.

Once the final model was developed, it was assessed in the model derivation and separate validation cohorts. The Hosmer–Lemeshow statistic was used to assess model calibration or fit the data based on the agreement between predicted risk score probabilities using

the model and the observed probabilities. For overall assessment, discrimination was evaluated using the ROC curve test representing the area under the receiver operating characteristic curve with larger values indicating better discrimination (when the area of the ROC curve is between 0.5 and 0.7, the diagnostic value is small; between 0.7–0.9, diagnosis good value; over 0.9, the diagnostic value is high).

Results

Patient characteristics

A total of 944 patients were included, including 472 in the thrombosis group and 472 in the control group, with 52.01% of men. The number of patients diagnosed with lung cancer (21.19%) accounted for a large number of patients, followed by gastric cancer (14.41%), breast cancer (9.86%), and rectal cancer (7.31%), and pancreatic cancer (4.44%). The tumor staging of 363 patients was I-II (38.45%), and 581 cases were III-IV (61.55%). The specific distribution is shown in Table 1. In the thrombosis groups, the number of patients with deep venous thrombosis in the lower limbs accounted for the largest proportion, followed by deep venous thrombosis of the upper limb.

Establishment and comparison of model database and model verification database

Analysis of the differences in the clinical variables in the model derivation cohort and the separate validation cohort showed that the randomization of the patients in this study was essentially completely randomized. These avoided the bias of the two databases due to differences in the distribution of clinical variables. (Supplementary Table 1–2 for details).

Table 1 General information of the thrombosis group and the control group

General data	Thrombosis group ($n=472$)	Control group ($n=472$)	*P
Sex, n(%)			0.397
Male	252(53.39)	239(50.64)	
Female	220(46.61)	233(49.36)	
Tumor types, n(%)			0.993
Lung cancer	100(21.19)	95(20.13)	
Gastric cancer	71(15.04)	65(13.77)	
Breast cancer	44(9.32)	49(10.38)	
Colorectal Cancer	38(8.05)	43(9.11)	
Rectum cancer	33(6.99)	36(7.63)	
Esophageal cancer	31(6.57)	27(5.72)	
Pancreatic cancer	21(4.45)	21(4.45)	
Liver cancer	16(3.39)	18(3.81)	
Others	118(25)	118(25)	
Tumor Stages, n(%)			0.052
I-II	196(41.53)	167(35.38)	
III-IV	276(58.47)	305(64.62)	

* $P<0.05$, indicating statistical significance

Development of risk model

Using the ROC curve analysis, the dichotomous variable's clinical cut-off value is obtained (Supplementary Table 3–4). In univariate analysis, the following covariates were statistically significantly associated with the development of symptomatic VTE: age, smoking, hypertension, coronary heart disease, diabetes, stroke, history of surgery (nearly 1 month), history of VTE, history of central venous catheterization ($P=0.084$), PICC, chemotherapy, PT, INR, TT, D-dimer, white blood cell count, neutrophil count, lymphocyte neutrophil ratio, lymphocyte ratio, monocyte ratio, red blood cell count, hemoglobin, blood platelet count, CRP (Supplementary Table 5–7).

In the final multivariate analysis, the following variables were independently associated with the risk of VTE: Hypertension、surgical history (nearly one month); History of VTE, PICC, chemotherapy, PT < 12.85 s, D-dimer ≥ 1.805 μg/mL, hemoglobin ≤ 114.5 g/L、CRP ≥ 7.575 mg/L (Supplementary Table 8). The formula is as follows:

$\ln(P/1\text{-}P) = -4.504 + 1.005X_1 + 1.468X_2 + 1.737X_3 + 1.042X_4 + 1.032X_5 - 0.798X_6 + 1.834X_7 + 0.774X_8 + 1.071X_9$

(Supplementary Table 9 Show the independent variable assignment method in the logistic regression model).

Hosmer–Lemeshow test showed that $P=0.353>0.05$ ($\chi^2=8.872$, Df = 8), and the area under the ROC curve was 0.906, 95%CI was (0.881–0.930), $P<0.001$(Fig. 1). In conclusion, this model has a good fitting degree and good discriminant validity, accurately evaluating and distinguishing VTE risk in cancer patients.

According to the regression coefficients from the final multivariate model, establish a scoring model to predict VTE risk for hospitalized cancer patients. Among the risk factors for VTE in hospitalized cancer patients, the minimum absolute value of β with hemoglobin ≤ 114.5 g/L was 0.774, so hemoglobin ≤ 114.5 g/L was taken as the standard, and the score was recorded as 1. Scores of other variables = absolute value of beta value of each variable/absolute value of beta value of hemoglobin. For example, the score of Hypertension = ß (Hypertension) /ß (Haemoglobin) = 1.005/0.774 = 1.298, the score of Hypertension is 1 point without retaining the decimal point. The specific scoring is shown in Table 2. Based on our early research foundation on anticoagulant drugs, the Alfalfa-inpatient-CAT model is named.

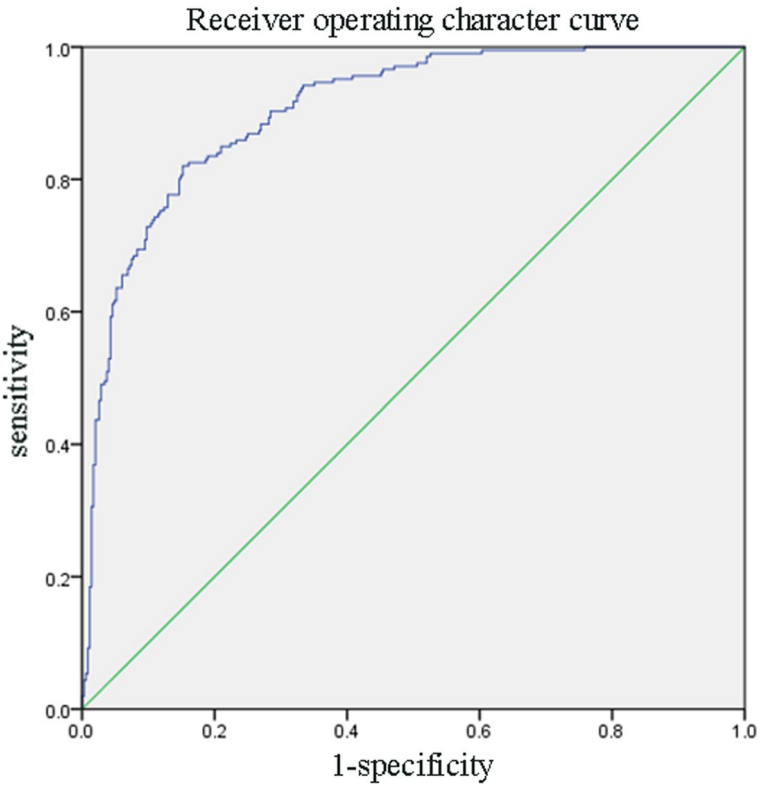

Fig. 1 ROC curve analysis for logistic regression models

$$\text{Score} = \frac{|\beta\ (\textit{Clinical variables})|}{|\beta\ (\text{hemoglobin})|}$$

According to the Alfalfa-inpatient-CAT model, the tumor patients in the model derivation cohort are scored, and the score results are used as a diagnostic variable to perform the ROC curve analysis of the model. As a result, when the score was greater than or equal to 3 points, they were recorded as VTE high-risk people, otherwise VTE low-risk people.

Accuracy and validation of risk model

Identification validity verification

Alfalfa-inpatient-cat evaluation model was analyzed by ROC curve using scores of patients in separate validation cohorts as diagnostic variables. Results show that the area under the ROC curve was 0.757, 95%CI was (0.724–0.790), $P<0.001$, indicating that the scoring system had good discriminant validity and could accurately distinguish the risk of VTE in hospitalized cancer patients (Fig. 2).

Authentic assessment

Based on the Alfalfa-inpatient-CAT assessment model, patients in the separate validation cohort were scored, and they were divided into VTE low-risk people and high-risk groups. Among them, 72.63% of the high-risk group (score ≥ 3) had thrombosis, which was significantly higher than the low-risk group (27.37%)($\chi^2=144.00$, Df = 1, $P<0.001$) (Table 3).

Discussion

VTE is one of the most preventable diseases. VTE prevention is effective in patients with a high incidence of VTE, such as inpatients or postoperative patients [10]. However, VTE prevention was less effective in cancer patients identified as high risk by a single factor, such as the primary cancer site or intravenous access devices. Our study aimed to develop a multivariable risk assessment model to allow better clinical identification of cancer patients at high risk of VTE. At present, there is insufficient research on the risk assessment model of VTE for inpatients with cancer. Therefore, based on the actual situation of hospitalized tumor patients, this study constructed a thrombosis risk assessment model for them, which was named the Alfalfa-inpatient-CAT assessment model. In this study, we finally identified 9 clinical and laboratory parameters: Hypertension、surgical history (nearly one month), History of VTE, peripherally Inserted Central Venous catheters (PICC), chemotherapy, PT < 12.85 s,

Table 2 Risk assessment scale for concurrent VTE in oncology patients

Variables	β	OR (95% CI)	*P	Score
Hypertension				
Yes	1.005	2.732 (1.579–4.724)	< 0.001	1
No		1		0
History of surgery				
Yes	1.737	5.682 (3.366–9.590)	< 0.001	2
No		1		0
History of VTE				
Yes	1.468	4.339 (1.065–17.677)	0.041	2
No		1		0
PICC				
Yes	1.042	2.836 (1.709–4.704)	< 0.001	1
No		1		0
Chemotherapy				
Yes	1.032	2.806 (1.675–4.703)	< 0.001	1
No		1		0
PT, sec				
≥ 12.85	-0.798	2.222 (1.254–3.939)	0.006	0
< 12.85		11		1
D-Dimer, μg/mL				
≥ 1.805	1.834	6.258 (3.685–10.626)	< 0.001	2
< 1.805		1		0
Haemoglobin, g/L				
≤ 114.5	0.774	2.168 (1.115–4.217)	0.023	1
> 114.5		1		0
CRP(mg/L)				
≥ 7.575	1.071	0.343 (0.142–0.824)	0.017	1
< 7.575		1		0

* $P < 0.05$, indicating statistical significance. *CI*, confidence interval. *VTE*, venous thromboembolism. *PICC*, peripherally inserted central catheter. *PT*, prothrombin time. *CRP*, C-reactive protein

D-dimer ≥ 1.805 μg/mL, hemoglobin ≤ 114.5 g/L, CRP ≥ 7.575 mg/L, which are considered to predict the risk of thrombosis in hospitalized tumor patients independently. These parameters are merged with Alfalfa-inpatient-CAT, which allows patients to be divided into two discrete categories, corresponding to the risk of VTE-related VTE during the hospitalization. This model is verified in the separate validation cohort from the same observation research.

Some risk factors in this study are consistent with early research. Khorana et al. [6] built a VTE risk prediction model for outpatient cancer patients treated with chemotherapy, which is widely used internationally. Chemotherapy and hemoglobin were included in the model and considered independent factors affecting thrombogenesis in tumor patients. Starting from the patients in the hospitalized tumor, this study confirmed that chemotherapy (OR = 2.806; 95%CI: 1.675–4.703; $P < 0.001$), hemoglobin ≤ 114.5 g/L (OR = 2.168; 95%CI:1.115–4.217; $P = 0.023$) are also considered to be independently associated with risk of VTE for hospitalized tumor patients. In addition, in the study of Ay [11] et al., the efficacy could be significantly improved when soluble p-selectin and D-dimer were added to the Khorana model. These are consistent with the results of our study. The risk of thrombosis could be higher when a patient's D-dimer is ≥ 1.805 μg/mL (OR = 6.258; 95% CI: 3.685–10.626; $P < 0.001$). As one of the important treatment methods for tumor patients, surgery is also an important factor leading to thrombosis, especially pelvic and abdominal surgery. Lower limb orthopedic surgery is also considered a high-risk operation for VTE [12, 13]. And our study also confirmed a significantly increased risk of VTE in hospitalized tumor patients with a history of surgery within the past one month (OR = 5.682; 95% CI: 3.366–9.590; $P < 0.001$). For those with a history of VTE (OR = 4.339; 95% CI: 1.065–17.677; $P = 0.041$), more attention should be paid to preventing thrombosis during treatment, which is consistent with Padua [7] and Caprini models[5]. In addition, catheterization, which can increase the morbidity and mortality of VTE [14], is becoming more and more popular in chemotherapy for solid tumor patients. In our study, central vein catheterization and PICC were included in the analysis process of influencing factors. In univariate analysis, both of them were considered the influencing factors of VTE for hospitalized tumor patients. And in multivariate analysis, PICC was considered a risk factor for VTE occurrence in hospitalized tumor patients (OR = 2.836; 95%CI: 1.709–4.704; $P < 0.001$), while central vein catheterization was not.

In the Alfalfa-inpatient-CAT assessment model, a history of hypertension, PT < 12.85 s, and CRP ≥ 7.575 mg/L were also included as independent factors influencing the development of thrombosis in hospitalized oncology patients. These factors have been proved to be the key factors affecting the occurrence of thrombosis, but there are few relevant studies. For hypertensive patients, blood pressure is often fluctuating, leading to spontaneous aggregation of platelets. The large aggregation of platelets makes hypertensive patients more prone to VTE, leading to vascular occlusion [15]. In the study of Yuan Huijun et al. [15], hypertension was confirmed to be an independent risk factor for lower extremity deep vein thrombosis (OR: 2.634; 95%CI: 5.03–16.54). In this study, hypertension was confirmed as a risk factor for VTE in hospitalized tumor patients (OR = 2.732; 95% CI: 1.579–4.724; $P < 0.001$). PT is the most commonly performed coagulation test in clinical laboratories. When PT is shortened, it is believed that the activity of coagulation factors in plasma is fine, which may lead

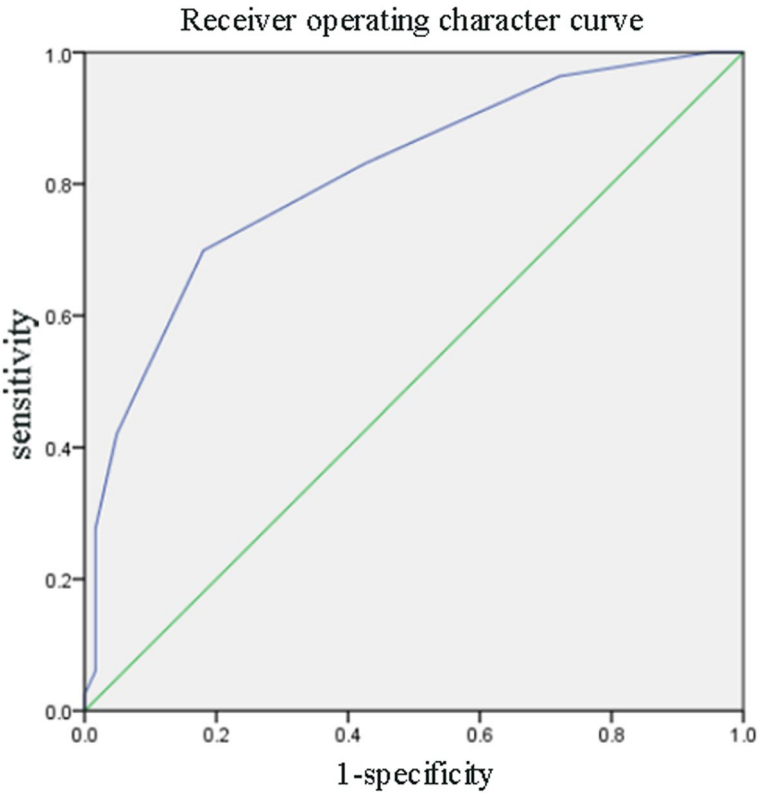

Fig. 2 ROC curve to validate the total thrombotic risk score in the database

Table 3 Incidence of thrombosis in different risk groups in the model validation database

Type of people	Grouping		Total
	Thrombosis group	Control group	
Low risk (score < 3)	14(28.57%)	35(71.43%)	49(34.03%)
High risk (score ≥ 3)	69(72.63%)	26(27.37%)	95(65.97%)
Total	83(57.64%)	61(42.36%)	144

to the state of hypercoagulation and promote the occurrence of thrombi. In the study of Guo Yuan et al. [16], it was confirmed that the occurrence of VTE could significantly shorten the prothrombin time. The PT value could evaluate the risk of VTE in tumor patients to a certain extent. Our results also showed that PT < 12.85 s (OR = 2.222; 95% CI: 1.254–3.939; $P = 0.006$) was an independent risk factor for VTE in hospitalized tumor patients. In evaluating cancer and VTE studies [17], CRP was used as one of the laboratory biomarkers affecting tumor-associated VTE. Results showed that patients with CRP > 1.8 mg/dL had an increased risk of VTE in the first 12 months after enrollment (11.7% vs. 4.9%, $P = 0.030$) [17]. However, CRP was no longer an independent predictor of VTE when multivariate models were analyzed (adjusting for chemotherapy, radiation, surgery, tumor stage, and SP-selectin levels). In this study, CRP ≥ 7.575 mg/L (OR = 0.343; 95% CI: 0.142–0.824; $P = 0.017$) is an important risk factor for VTE in hospitalized tumor patients in both univariate analyses and multivariate analyses. Acute infection, which is associated with a significantly increased risk of VTE at hospital diagnosis or in community care, is a frequent and strong trigger of VTE. And this association is strongest in the first 2–4 weeks (sometimes as high as 12 weeks) after infection and then decreases gradually [18]. As an indicator of acute inflammation, the CRP of normal people is very small and can increase rapidly in acute inflammation. Therefore, it is reliable to predict the risk of thrombosis in hospitalized tumor patients by CRP level. The reasons for the inconsistency between the two studies are as follows: Firstly, the inclusion of multiple factors in the two studies is different. This study analyzes the general risk factors, co-diseases, coagulation indicators, and blood routine of hospitalized tumor patients. Second, the two studies target different research groups, which may also lead to different results.

According to the H–L test and ROC curve analysis, the Alfalfa-inpatient-CAT evaluation model had

goodness-of-fit and good discriminant validity. Although validation of an external population is an ideal method to validate the model, we were unable to identify a dataset of cancer patients that reliably collected VTE data and the variables identified in the model. Therefore, we chose to perform split-sample validation. The Alfalfa-inpatient-CAT model was used to evaluate the occurrence of thrombosis in the separate validation cohort. According to the scoring model, the population was divided into low-risk and high-risk groups. In the low-risk population, the proportion of patients with thrombosis was 28.57%, and the risk of thrombosis was low. Therefore, cancer patients are less likely to benefit from thromboprophylaxis because of their increased risk of bleeding complications. For the high-risk group, 72.63% of the patients had thrombosis. Thromboprophylaxis in these populations will effectively reduce the incidence of thrombosis, but prevention safety still needs to be evaluated in clinical trials. The authenticity evaluation results show that the model can better predict the high risk of thrombosis for Hospitalized tumor patients, which provides a certain reference for clinical treatment of patients with hospitalization. Taking preventive measures in time can reduce the occurrence of thrombosis.

The risk of VTE is also affected by the site and stage of the primary tumor. Pancreatic cancer, gastric cancer, lung cancer, and hematologic malignancies (including lymphoma and myeloma) have the strongest correlation with VTE [19]. In this study, patients with lung cancer (21.19%) and stomach cancer (14.41%) had a high incidence of VTE, which was consistent with the existing conclusion. The risk of VTE increases with the cancer stage, and patients with advanced cancer have a greater risk of VTE [20]. The relative risk of I, II, III, and IV cancers was 2.9, 2.9, 7.5, and 17.1, respectively [21]. In this study, patients with stages III and IV also had a significantly higher risk of thrombosis than those with I and II (58.47% vs. 41.53%, $P<0.5$). Although the effects of tumor type and cancer stage on thrombosis are well established, because this study was primarily a differential comparison between hospitalized tumor patients who had thrombosis and hospitalized tumor patients who did not have thrombosis regarding risk factors affecting thrombosis, these two factors were not included in the study to maintain consistency between the two populations at baseline. However, these two factors can be combined clinically to improve the accuracy of thrombotic risk assessment in hospitalized oncology patients.

Although we have a relatively large sample of patients ($N=800$), a large amount of data is still needed to compare the validity of Alfalfa-inpatient-CAT for continuous optimization. Large and multicenter prospective data for clinical validation of Alfalfa-inpatient-CAT are also necessary. In summary, cancer-related thrombosis, which can be prevented, is an important cause of death in cancer patients. In this study, based on the actual situation of hospitalized tumor population, an Alfalfa-inpatient-CAT evaluation model was developed to evaluate the risk of VTE in hospitalized tumor patients. The main subjects included: chemotherapy, hypertension, history of VTE, history of surgery in recent 1 month, PICC, D-dimer ≥ 1.805(μg/mL), PT < 12.85(s), hemoglobin ≤ 114.5(g/L), and CRP ≥ 7.575 (mg/L). This model can reliably predict VTE risk in hospitalized tumor patients and provide a reference for clinical.

Supplementary Information

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Additional file 1:

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None.

Authors' contributions
JZ initiated the study. WC, GW, PN, SW, JS, ML, TW and SJ performed data collation. WC, GW, PN and SW performed data extraction, and analyses. WC, GW drafted the first version of the manuscript. WC, GW, PN, SW, JS and JZ critically reviewed the manuscript and revised it. TW and ML worked on data validation. WC, PN and SJ performed the graphical revisions. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used during this study are available on reasonable request to corresponding author.

Declarations

Ethics approval and consent to participate
The study complies with the Declaration of Helsinki and was authorized by The Ethics Committee of Fujian Medical University Union Hospital. The requirement for patient consent was waived due to its retrospective nature.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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