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Original Article

Development, validation, and clinical utility of risk prediction models for cancer-associated venous thromboembolism: A retrospective and prospective cohort study

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ABSTRACT

Objectives: This study aims to develop cancer-associated venous thromboembolism (CA-VTE) risk prediction models using survival machine learning (ML) algorithms.

Methods: This study employed a double-cohort study design (retrospective and prospective). The retrospective cohort ($n = 1036$) was used as training set (70.0%, $n = 725$) and internal validation set (30.0%, $n = 311$); while the prospective cohort ($n = 321$) was used as external validation set. Seven survival ML algorithms, including COX regression, classification, regression and survival tree, random survival forest, gradient boosting survival machine tree, extreme gradient boosting survival tree, survival support vector analysis, and survival artificial neural network, were applied to train CA-VTE models.

Results: Univariate analysis and LASSO-COX regression both selected five predictors: age, previous VTE history, ICU/CCU, CCI, and D-dimer. The seven survival ML models (C-index: 0.709–0.760; Brier Score: 0.212–0.243) all outperformed Khorana Score (C-index: 0.632; Brier Score: 0.260) in external validation set. Among all models, the COX_DD model (COX regression + D-dimer) performed best. However, ML models and Khorana Score predicted CA-VTE risk on ≥ 7 days of hospitalization with an increase in Brier Score ≥ 0.25, showing poor calibration.

Conclusions: In this study, the CA-VTE risk prediction models developed in seven survival ML algorithms outperformed Khorana Score. Combining with D-dimer can improve model performance. Applying the nomogram based on the optimal COX_DD model allows oncology nurse to reassess CA-VTE risk once a week. The prediction models developed using survival ML algorithms in this study may contribute to the dynamic and accurate risk assessment of CA-VTE for cancer survivors.

Introduction

Cancer-associated venous thromboembolism (CA-VTE), was one of the most common complications in cancer patients.[1] Approximately 4%–20% of patients diagnosed with cancers will develop CA-VTE, which is relatively higher than that of none-cancer patients.[2–4] CA-VTE directly affects the quality of life and long-term prognosis of cancer patients, seriously endangering their safety of life by increasing the risk of CA-VTE recurrence, major bleeding, and mortality.[1,5,6] CA-VTE is the second leading cause of death in cancer patients, second only to tumor progression.[2] The occurrence of CA-VTE was associated with multiple risk factors, including patient-related, cancer-specific, and treatment-related factors.[7,8]

Considering the serious consequences caused by CA-VTE, it is essential to conduct risk assessment and precise stratification using CA-VTE predictive models.[9] Multiple prevention and treatment guidelines for CA-VTE recommend the use of cancer-specific risk prediction models,

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such as the Khorana Score, to assess the risk of CA-VTE and guide the next steps in prevention and treatment strategies.[9–11]

Since the development of the Khorana Score to predict risk of CA-VTE,[12] numerous modified cancer-specific CA-VTE risk prediction models, including Vienna Score,[13] Protecht Score,[14] CONKO Score,[15] ONKOTEV Score,[16] COMPASS-CAT Score,[17] TiC-Onco Score,[18] and Nomogram Score,[19] have been proposed and partly validated.[20–22] Khorana Score was the earliest, most widely used cancer-specific model, which only used five clinically available variables.[12] Unfortunately, Khorana Score and other models still share some limitations to be improved,[23,24] including moderate or low model accuracy (area under the curve [AUC] $\leq$ 0.7), lack of potential sensitive biomarkers (e.g., D-dimer, soluble P-selection, tissue factor positive microparticles, etc.) and clinical-genetic predictors, lack of multi-center or cross-ethnic external validation.[1,23,25–27] On the basis of Khorana Score, Vienna Score combined D-dimer and soluble P-selectin to improve the predictive accuracy.[13] However, soluble P-selectin is not a routine indicator for clinical testing. D-dimer is an important coagulation indicator which is routinely tested for almost all cancer patients. A meta-analysis study also showed that D-dimer has predictive value for CA-VTE.[28] Therefore, it is necessary to combine D-dimer as an important predictor when developing CA-VTE predictive models.

In recent years, machine learning (ML) algorithms have been preliminarily applied in CA-VTE risk prediction, which may have the potential to improve the performance of Khorana Score and other models.[29–31] Lei et al.[32] used five algorithms, including random forest (RF), Adaboost, Xgboost, logistic regression (LR), and k-nearest neighbor (KNN), to develop CA-VTE predictive models for lung cancer patients and RF model had the highest AUC (AUC: 0.870, 95%CI: 0.802–0.917). Meng et al.[33] developed CA-VTE predictive models using three different ML algorithms, including support vector machine (SVM), RF, and Xgboost, and logistic regression for VTE risk among hospitalized cancer patients. In Meng et al.'s study, Xgboost model achieved the best performance (AUC: 0.818). In our past study,[34] a retrospective cohort study was designed and five ML algorithms including linear discriminant analysis (LDA), LR, classification tree (CT), RF, and SVM were selected to develop CA-VTE predictive models.

Most of the above models are based on binary outcomes of CA-VTE, which can be able to provide a specific risk probability value. However, the underlying etiology of CA-VTE was multifaceted and the CA-VTE risk was in highly dynamic states instead of always being static.[35] The one-time prediction based on baseline variables and binary outcomes in existing models, either traditional statistical or ML models, may lead to bias and have an adverse to precise prevention of CA-VTE. Thus, the fact that the probability of CA-VTE is a time-dependent variable should be highlighted, considering the time-to-event outcomes of CA-VTE.[36] Survival ML algorithms, such as COX regression (COX),[37] classification, regression and survival tree (CARST),[38] random survival forest (RSF),[39] gradient boosting survival machine tree (GBSM),[40] extreme gradient boosting survival tree (XGBS),[41] survival support vector machine (SSVM),[42] and survival artificial neural network (SANN),[43,44] not only can predict the time-to-event outcome of CA-VTE, but also can utilize the high-precision advantages of ML algorithm. However, there were few studies using survival ML algorithms to predict CA-VTE risks.

Therefore, this study aims to conduct a retrospective and prospective cohort study to develop CA-VTE risk assessment models using seven survival ML algorithms, including COX, CARST, RSF, GBSM, XGBS, SSVM, and SANN, and comprehensively evaluate model performance based on whether D-dimer was combined.

Methods

Study design and participants

The retrospective and prospective cohorts

This study consists of two cohorts, the retrospective and prospective cohorts. The retrospective cohort of 1036 cancer patients who were treated in a tertiary hospital in Beijing from January 2017 to October 2019 was used as training set (70%, 725 cases) and internal validation set (30%, 311 cases) for model development and internal validation; The prospective cohort of 321 cancer patients who were treated in the same hospital from November 2019 to October 2021 was used as external validation set to evaluate the model performance.

The inclusion and exclusion criteria

The inclusion criteria have six items: i) patients $\geq$ 18 years old; ii) hospital stay $\geq$ 48 hours; iii) patients with a confirmed pathological diagnosis of a malignant tumor before being diagnosed with CA-VTE; iv) having at least one test result of blood routine and D-Dimer; v) having at least one screen result of CA-VTE; vi) informed consent (only required for the prospective cohort).

The exclusion criteria include four items: i) having a diagnosis of acute leukemia; ii) being pregnant or lactating; iii) having a diagnosis of VTE (DVT or PE) upon admission or receiving anticoagulation treatment instead of thromboprophylaxis.

Sample size

This study will include 30 alternative predictive variables, and the sample sizes of three datasets were estimated separately. For training set, according to the 5–10 events per variable (EPV) rule of thumb,[45] 158 patients developed CA-VTE, which reached 5 EPV. For internal and external validation sets: a study[46] suggested that the sample size for validation sets should be at least 200 cases, with 100 positive cases and 100 negative cases. The sample size of negative group basically meets the requirements, while the sample size of positive group is slightly lower than the requirement.

Candidate predictors

Based on the literature review of CA-VTE related risk factors, this study included a total of 30 candidate predictive factors from four dimensions: patients-related factors, cancer-specific factors, treatment-related factors, and laboratory variables (Supplementary Fig. S1). More details about candidate predictors can be found in our past study.[34]

Outcomes

The outcomes of this study included "whether CA-VTE occurred" and "when CA-VTE occurred". The diagnosis of CA-DVT was objectively confirmed by color Doppler ultrasonography during hospitalization. The diagnostic methods of CA-PE included computed tomography, magnetic resonance imaging (MRI), pulmonary arteriography, radionuclide lung ventilation or blood flow perfusion scanning, etc. The definition of the CA-VTE occurrence time was as follows: CA-VTE occurred on *t* days since admission. Patients who until discharge without CA-VTE or death before CA-VTE were defined as censored.

Data collection, model development, and model validation

Data collection

All data were manually collected in an electronic medical record system (EMRS) from a tertiary hospital by two well-trained researchers using identical standard case report form (CRF). To control the data quality, all CRFs were recorded twice and double-checked in the Epidata software (v 3.1). Both in the retrospective and prospective cohorts, all candidate predictors were recorded before the screen for CA-VTE.

Data preprocessing

Before model development, missing rate for candidate variables were calculated. Categorical variables had no missing values. Missing rate of continuous variables were low (0.2% to 0.9%) and the median values were used to fill the missing continuous variables.

Data splitting

The retrospective cohort was randomly split into training set (n = 725) and internal validation set (n = 311) in a 7:3 ratio. The prospective cohort was regarded as external validation set (n = 321). Supplementary Fig. S2 shows the study flowchart.

Statistical description and statistical inference

Continuous variables were described by median with interquartile range. Categorical variables were described by frequency and percentage. The χ^2 test, Mann–Whitney test, Kruskal–Wallis test, and one-way ANOVA were appropriately used to conduct univariable analysis and compare the characteristics of three datasets.

Predictors selection

Predictors selection was conduct in training set using univariable analysis and Lasso-COX regression. Variables with a P-value < 0.1 in univariable analysis and having a non-zero coefficient in the Lasso-COX regression were entered into the model.

Hyperparameter tuning and model training

To determine the best hyperparameters of CARST, RSF, GBSM, XGBS, SSVM, and SANN, five-fold cross-validation (repeated three times) and grid research method were used in training set.

Model performance

Model performances were compared among seven survival ML models and Khorana Score based on whether D-dimer was combined. This study comprehensively evaluated model performance from four dimensions: discrimination, calibration, clinical utility, and model improvement. i) Model discrimination: C-index[47] and time dependent C-index, the range of C-index is from 0 to 1, and the higher the C-index, the better the model discrimination; C-index ≤ 0.500 indicates poor discrimination; C-index ≥ 0.700 indicates good discrimination; C-index ≥ 0.800 indicates excellent discrimination[48]; ii) Model calibration: Brier Score and time dependent Brier Score, the range of Brier Score is from 0 to 1, and the lower the Brier Score, the better the model calibration; Brier Score < 0.250 indicates good or excellent discrimination; Brier Score ≥ 0.250 indicates poor calibration.[49] iii) Clinical utility: Decision curve analysis (DCA) curve, the x-axis of the DCA curve represents the probability threshold (0–1), and the y-axis represents the clinical net benefit (−1 to 1); Under the same probability threshold, the greater the clinical net benefit, the better the clinical utility[50]; iv) Model improvement: Category based net reclassification index (Category based NRI) and integrated discrimination improvement (IDI), the range of Category based NRI and IDI are both from −200% to 200%, and the higher the Category based NRI and IDI, the better the model improvement; $P < 0.05$ indicates that model A has significant improvement than model B.[51]

Model presentation and report

In this study, nomogram was used to present the best model. Cut off was determined according to the maximized Youden's Index from the receiver operating characteristic (ROC) curve and CA-VTE risk stratification (low risk and high risk) was carried out for cancer patients. We used Statistical Package for Social Sciences 20.0 and R 3.6.1 (https://www.r-project.org/) to conduct statistical analysis. A two-sided P value < 0.05 was regarded as statistically significant.

Results

Description and comparison of variable characteristics of three datasets

The comparisons of variable characteristics among three datasets are detailed in Table 1. The proportion differences of variables such as gender, age $\geq$ 65 years old, smoking, and bed rest $\geq$ 3 days reached a statistically significant level ($P < 0.05$). The incidences of CA-VTE are similar among three datasets (21.8% vs 26.4% vs 24.3%, $P = 0.258$).

Univariate analysis between CA-VTE and none CA-VTE patients in training set

The univariate analysis results are shown in Supplementary Table S1. In the training set, there are 13 predictive factors with $P < 0.100$, including age, bed rest, chemotherapy, PICC, NSAID, previous VTE history, ICU/CCU, CCI, WBC, PLT, Hb, PT, and D-dimer.

Results of predictors selection

The process of using LASSO-COX to select predictors is shown in Supplementary Fig. S3. LASSO-COX selected 10 variables with non-zero regression coefficients, including gender, age, tumor stage, transfusion, previous VTE history, ICU/CCU, varicose veins, edema, CCI, and D-dimer. Finally, five variables were both selected, including age, previous VTE history, ICU/CCU, CCI, and D-dimer. Therefore, these five variables are used as predictors for model training.

Results of hyperparameter tuning and model training

This study trained seven models in training set, including COX, CARST, RSF, GBSM, XGBS, SSVM, and SANN. Six models, except for COX, are optimized for hyperparameters in training set The results of hyperparameter tuning are shown in Supplementary Table S2.

Results of model performance

Model discrimination

The C-indexes of seven models and Khorana Score in three datasets are shown in Table 2. In the same model, the model combing with D-dimer has a higher C-index compared to the model without D-dimer. Among different models, the C-indexes of all models are higher than the Khorana Score. The C-indexes in internal validation set are slightly lower than those in training set, while the C-indexes in external validation set are higher than those in the training set. Supplementary Table S3 presents the C-indexes of seven models and Khorana Score for predicting CA-VTE risk on the 5th, 7th, 10th, and 15th days of hospitalization. Fig. 1A–1C respectively present time dependent C-indexes of all models in three datasets, dynamically presenting the C-indexes for predicting CA-VTE risk on days 1–35 of hospitalization.

Model calibration. The Brier Scores of seven models and Khorana Score in three datasets are shown in Table 2. In training set, models that combined with D-dimer have slightly higher Brier Scores and lower calibration compared to models that without D-dimer. While in internal validation set, the models combined with D-dimer have lower Brier Scores and better calibration. In external validation set, some models (COX, XGBS, and SSVM) combined with D-dimer show a decrease in Brier Scores, while CARST and SANN combined with D-dimer show no change in Brier Scores. Other models combined with D-dimer show an increase in Brier Scores. In all datasets, Brier Scores of seven models are lower than Khorana Score, and model calibration are better than Khorana Score. The Brier Scores of all models in internal validation set are lower than those in training set, while the Brier Scores in external validation set are higher than those in training set. Supplementary Table S3 presents Brier Scores for predicting CA-VTE risk on the 5^{th}, 7^{th}, 10^{th}, and 15^{th} days of hospitalization using seven models and Khorana Score. Fig. 1D–1F respectively show the time dependent Brier Scores of all models in three datasets, dynamically presenting Brier Scores for predicting CA-VTE risk on days 1–35 of hospitalization.

Model utility. The DCA curves of seven models and Khorana Score for predicting CA-VTE risk on the 7^{th} day of hospitalization are shown in Supplementary Fig. S4. Overall, DCA curves of all models are superior to the None-treatment curves and the All-treatment curves in all three datasets. For the same model, the DCA curves of the combined D-dimer model have higher clinical net benefit than the model without D-dimer. In all three datasets, the DCA curves of seven models have higher clinical net benefit than Khorana Score.

Table 1
Comparison of variable characteristics of three datasets, *n* (%) / M [*P*25, *P*75] (*N* = 1357).

Variables	Values	Training set (*n* = 725)	Internal validation set (*n* = 311)	External validation set (*n* = 321)	*P*
Sex	Men	343 (47.3)	160 (51.4)	194 (60.4)	<0.001***
	Women	382 (52.7)	151 (48.6)	127 (39.6)	
Age	< 65 years old	468 (64.6)	200 (64.3)	171 (53.3)	0.001**
	≥ 65 years old	257 (35.4)	111 (35.7)	150 (46.7)	
Smoking	Yes	88 (12.1)	47 (15.1)	24 (7.5)	0.010**
	No	637 (87.9)	264 (84.9)	297 (92.5)	
Drinking	Yes	83 (11.4)	37 (11.9)	23 (7.2)	0.077
	No	642 (88.6)	274 (88.1)	298 (92.8)	
Bed rest	< 3 days	324 (44.7)	142 (45.7)	235 (73.2)	<0.001***
	≥ 3 days	401 (55.3)	169 (54.3)	86 (26.8)	
Site of tumor	Low risk	123 (17.0)	56 (18.0)	34 (10.6)	0.068
	High risk	393 (54.2)	169 (54.3)	184 (57.3)	
	Very high risk	209 (28.8)	86 (27.7)	103 (32.1)	
Tumor type	Colorectal cancer	202 (27.9)	87 (28.0)	111 (34.6)	<0.001***
	Gastric cancer	84 (11.6)	39 (12.5)	76 (23.7)	
	Gynecological cancer	98 (13.5)	37 (11.9)	27 (8.4)	
	Peritoneal cancer	100 (13.8)	41 (13.2)	5 (1.6)	
	Lung cancer	48 (6.6)	22 (7.1)	19 (5.9)	
	Hepatobiliary	39 (5.4)	18 (5.8)	23 (7.2)	
	Pancreatic cancer	25 (3.4)	6 (1.9)	22 (6.9)	
	Urinary system cancer	8 (1.1)	5 (1.6)	4 (1.2)	
	Other cancers[a]	121 (16.7)	56 (18.0)	34 (10.6)	
Tumor stage	I-III	171 (23.6)	66 (21.2)	108 (33.6)	<0.001***
	IV	460 (63.4)	190 (61.1)	183 (57.0)	
	X	94 (13.0)	55 (17.7)	30 (9.3)	
Chemotherapy	Yes	364 (50.2)	142 (45.7)	133 (41.4)	0.027*
	No	361 (49.8)	169 (54.3)	188 (58.6)	
Surgery	Yes	463 (63.9)	203 (65.3)	136 (42.4)	<0.001***
	No	262 (36.1)	108 (34.7)	185 (57.6)	
Radiotherapy	Yes	9 (1.2)	4 (1.3)	1 (0.3)	0.343
	No	716 (98.8)	307 (98.7)	320 (99.7)	
Targeted or immunotherapy	Yes	54 (7.4)	21 (6.8)	118 (36.8)	<0.001***
	No	671 (92.6)	290 (93.2)	203 (63.2)	
CVC	Yes	254 (35.0)	102 (32.8)	19 (5.9)	<0.001***
	No	471 (65.0)	209 (67.2)	302 (94.1)	
PICC	Yes	125 (17.2)	54 (17.4)	71 (22.1)	0.148
	No	600 (82.8)	257 (82.6)	250 (77.9)	
Transfusion	Yes	377 (52.0)	153 (49.2)	79 (24.6)	<0.001***
	No	348 (48.0)	158 (50.8)	242 (75.4)	
NSAID	Yes	363 (50.1)	165 (53.1)	155 (48.3)	0.477
	No	362 (49.9)	146 (46.9)	166 (51.7)	
Lymphadenopathy	Yes	54 (7.4)	28 (9.0)	21 (6.5)	0.494
	No	671 (92.6)	283 (91.0)	300 (93.5)	
Previous VTE history	Yes	22 (3.0)	14 (4.5)	34 (10.6)	<0.001***
	No	703 (97.0)	297 (95.5)	287 (89.4)	
Varicose veins	Yes	42 (5.8)	26 (8.4)	9 (2.8)	0.010**
	No	683 (94.2)	285 (91.6)	312 (97.2)	
Edema	Yes	30 (4.1)	12 (3.9)	101 (31.5)	<0.001***
	No	695 (95.9)	299 (96.1)	220 (68.5)	
ICU/CCU	Yes	88 (12.1)	36 (11.6)	15 (4.7)	0.001**
	No	637 (87.9)	275 (88.4)	306 (95.3)	
CCI	< 3	90 (12.4)	31 (10.0)	21 (6.5)	0.016*
	≥ 3	635 (87.6)	280 (90.0)	300 (93.5)	
BMI	< 24 kg/m^2	477 (65.8)	193 (62.1)	230 (71.7)	0.035*
	≥ 24 kg/m^2	248 (34.2)	118 (37.9)	91 (28.3)	
WBC	< 3.5 × 10^9/L	65 (9.0)	26 (8.4)	35 (10.9)	0.712
	3.5–9.5 × 10^9/L	578 (79.7)	252 (81.0)	256 (79.8)	
	> 9.5 × 10^9/L	82 (11.3)	33 (10.6)	30 (9.3)	
PLT	< 100 × 10^9/L	65 (9.0)	30 (9.6)	33 (10.3)	0.733
	100-300 × 10^9/L	549 (75.7)	241 (77.5)	247 (76.9)	
	> 300 × 10^9/L	111 (15.3)	40 (12.9)	41 (12.8)	
Hb	< 115 g/L	288 (39.7)	150 (48.2)	139 (43.3)	0.037*
	115–150 g/L	386 (53.2)	145 (46.6)	170 (53.0)	
	> 150 g/L	51 (7.0)	16 (5.1)	12 (3.7)	
PT	< 8.8 s	0 (0.0)	0 (0.0)	0 (0.0)	<0.001***
	8.8–11.8 s	349 (48.1)	129 (41.5)	186 (57.9)	
	≥ 11.8 s	376 (51.9)	182 (58.5)	135 (42.1)	
APTT	< 24 s	9 (1.2)	6 (1.9)	4 (1.2)	0.804
	24–37 s	688 (94.9)	295 (94.9)	308 (96.0)	
	> 37 s	28 (3.9)	10 (3.2)	9 (2.8)	
TT	< 11 s	5 (0.7)	0 (0.0)	0 (0.0)	0.149
	11–17.8 s	706 (97.4)	300 (96.5)	312 (97.2)	
	> 17.8 s	14 (1.9)	11 (3.5)	9 (2.8)	

(*continued on next page*)

Table 1 (*continued*)

Variables	Values	Training set ($n = 725$)	Internal validation set ($n = 311$)	External validation set ($n = 321$)	*P*
FIB	< 2 g/L	29 (4.0)	10 (3.2)	11 (3.4)	<0.001***
	2–4.5 g/L	544 (75.0)	232 (74.6)	284 (88.5)	
	> 4.5 g/L	152 (21.0)	69 (22.2)	26 (8.1)	
D-dimer	< 243 μ g/L	277 (38.2)	112 (36.0)	114 (35.5)	0.643
	≥ 243 μ g/L	448 (61.8)	199 (64.0)	207 (64.5)	
Khorana score		2.0 [1.0, 2.0]	2.0 [1.0, 2.0]	2.0 [1.0, 2.0]	0.643
Khorana Score + D-dimer		2.0 [2.0, 3.0]	2.0 [2.0, 3.0]	3.0 [2.0, 3.0]	0.474
Khorana risk level	Low risk	48 (6.6)	19 (6.1)	20 (6.2)	0.921
	Moderate risk	499 (68.8)	217 (69.8)	230 (71.7)	
	High risk	178 (24.6)	75 (24.1)	71 (22.1)	
Khorana + D-dimer risk level	Low risk	21 (2.9)	9 (2.9)	9 (2.8)	0.458
	Moderate risk	346 (47.7)	148 (47.6)	134 (41.7)	
	High risk	358 (49.4)	154 (49.5)	178 (55.5)	
CA-VTE	Yes	158 (21.8)	82 (26.4)	78 (24.3)	0.258
	No	567 (78.2)	229 (73.6)	243 (75.7)	

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

CVC, Central venous catheter; PICC, Peripherally inserted central catheter; NSAID, Nonsteroidal Anti-inflammatory Drugs; ICU/CCU, intensive care unit or cardiology intensive care; CCI, Charlson Comorbidity Index; BMI, body mass index; WBC, white blood cell count; PLT, platelet count; Hb hemoglobin; PT, Prothrombin time PT; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen.

[a] Other cancers, including breast cancer, lymphoma cancer, esophageal cancer, head and neck cancer, small intestine, and appendiceal cancer.

Table 2

Discrimination and calibration of seven models and Khorana Score ($N = 1357$).

	Training set ($n = 725$)				Internal validation set ($n = 311$)				External validation set ($n = 321$)			
	C-index		Brier Score		C-index		Brier Score		C-index		Brier Score	
D-dimer	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
COX	0.690	0.636	0.136	0.133	0.668	0.643	0.111	0.122	0.760	0.703	0.214	0.217
CARST	0.695	0.624	0.128	0.128	0.658	0.666	0.109	0.115	0.734	0.666	0.219	0.219
RSF	0.673	0.601	0.140	0.131	0.656	0.652	0.110	0.127	0.746	0.706	0.231	0.225
GBSM	0.687	0.626	0.140	0.132	0.674	0.671	0.108	0.117	0.756	0.710	0.221	0.216
XGBS	0.691	0.625	0.134	0.128	0.636	0.672	0.111	0.117	0.739	0.699	0.212	0.213
SSVM	0.689	0.618	0.135	0.132	0.661	0.647	0.114	0.121	0.756	0.691	0.232	0.242
SANN	0.647	0.608	0.135	0.133	0.644	0.609	0.112	0.116	0.709	0.648	0.243	0.243
Khorana score	0.601	0.553	0.141	0.137	0.517	0.486	0.117	0.118	0.632	0.565	0.260	0.250

COX, COX regression; CARST, classification, regression and survival tree; RSF, random survival forest; GBSM, gradient boosting survival machine tree; XGBS, extreme gradient boosting survival tree; SSVM, survival support vector machine; SANN, survival artificial neural network.

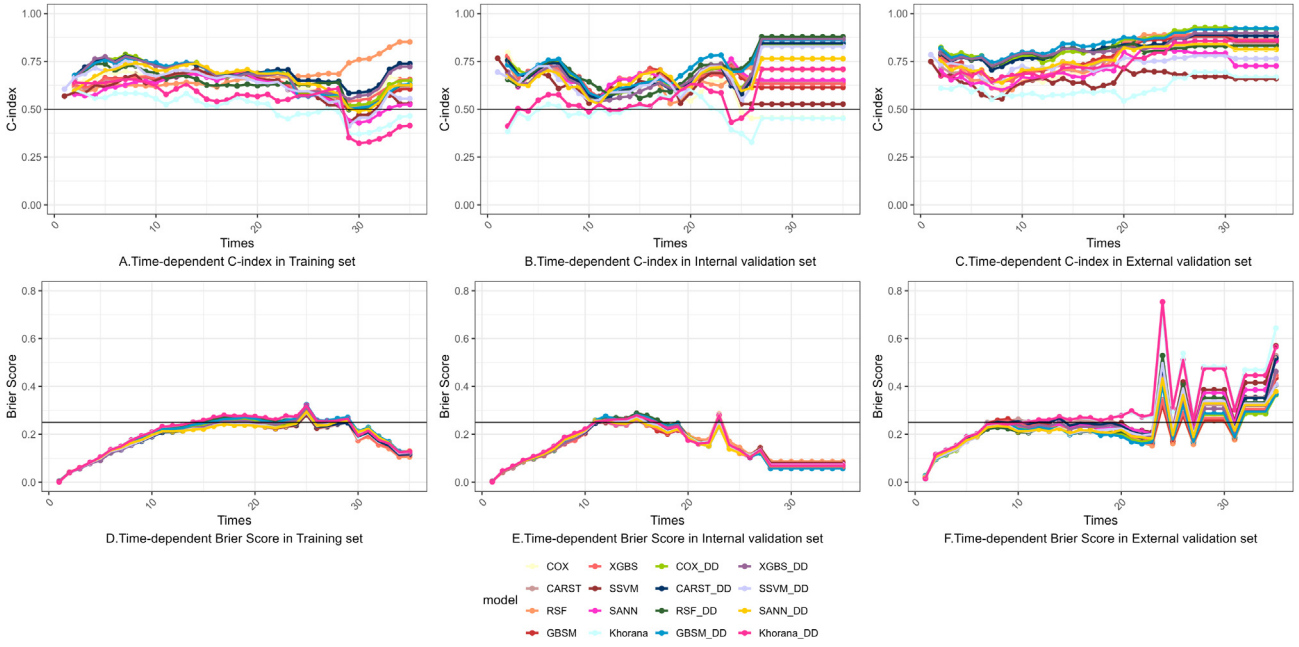

Fig. 1. Discrimination and calibration of seven models and Khorana Score in predicting CA-VTE risk for different hospital stays. †Figures A, B, and C show time dependent C-index in training set, internal validation set, and external validation set, respectively; Figures D, E, and F show time dependent Brier Score in training set, internal validation set, and external validation set, respectively. ‡COX, COX regression; CARST, classification, regression and survival tree; RSF, random survival forest; GBSM, gradient boosting survival machine tree; XGBS, extreme gradient boosting survival tree; SSVM, survival support vector machine; SANN, survival artificial neural network; §'DD' indicates models combing with D-dimer.

Model improvement. In external validation set, the Category-based NRI and IDI for predicting CA-VTE risk on the 7th day of hospitalization between any two models are calculated. The results are shown in Supplementary Table S4 and Supplementary Table S5, respectively. COX_DD, RSF_DD, GBSM_DD, XGBS_DD, and SSVM_DD model, all have a significant improvement in Category based NRI comparing to Khorana Score ($P < 0.05$). COX_DD, RSF_DD, GBSM_DD, XGBS_DD, SVM_DD, and ANN_DD model, all show significant improvement in IDI ($P < 0.05$) comparing to Khorana Score.

Presenting for the optimal model

Taking into account model discrimination, calibration, clinical utility, and model improvement, the COX_DD model is recommended as the optimal model. The COX_DD model is shown in Supplementary Table S6. Fig. 2 is the nomogram developed based on COX_DD model. The score range of the nomogram is 0–335. In training set, cut off is determined as 161.5, 0–161.5 is the low-risk group, while 162–335 is the high-risk group.

Discussion

In this study, retrospective and prospective cohorts were established and CA-VTE risk prediction models were developed using seven survival ML algorithms, comparing to Khorana Score based on whether D-dimer was combined. In addition, based on survival ML algorithms, we dynamically evaluated the model performance of predictive models.

The characteristics of three datasets

The incidence of CA-VTE in three datasets was similar ($P = 0.258$), with 21.8% (158/725), 26.4% (82/311), and 24.3% (78/321), respectively. The characteristics of training set and internal validation set were basically similar, but there were significant differences ($P < 0.05$) in some variables, compared to external validation set. The differences among three datasets might cause the different model performance. Khorana Score[12] used two similar datasets for model development and internal validation. The advantage of this study was that both internal and external validation were completed.

Predictors selected into the survival ML models

This study ultimately selected five predictors for model training. Previous studies had shown that cancer patients with ≥ 65 years old,[52,53] previous history of VTE,[17,54] transferred to ICU/CCU during hospitalization,[54] more comorbidities (CCI ≥ 3),[52,55] and an increase in D-dimer[13,56] were related to increased risk of CA-VTE. Moreover, these five variables were clinically available.

Model discrimination, calibration, and clinical improvement

In this study, seven survival ML algorithms were used to develop CA-VTE risk prediction models, and these models were better than Khorana Score from four dimensions of discrimination, calibration, clinical utility, and model improvement. Among seven models, COX_DD model was the optimal model. Currently, there was few research that applied multiple survival ML algorithms to develop CA-VTE risk prediction models. Two studies[30,57] applied SVM algorithm to develop and validate CA-VTE models in cancer patients. SVM model outperformed Khorana score (AUC: 0.716 vs 0.589). In our study, the SSVM model outperformed the Khorana Score as well.

This study also compared model performance of seven models and Khorana Score in both combined and non-combined D-dimer. Overall, the combination of D-dimer improved the model discrimination and

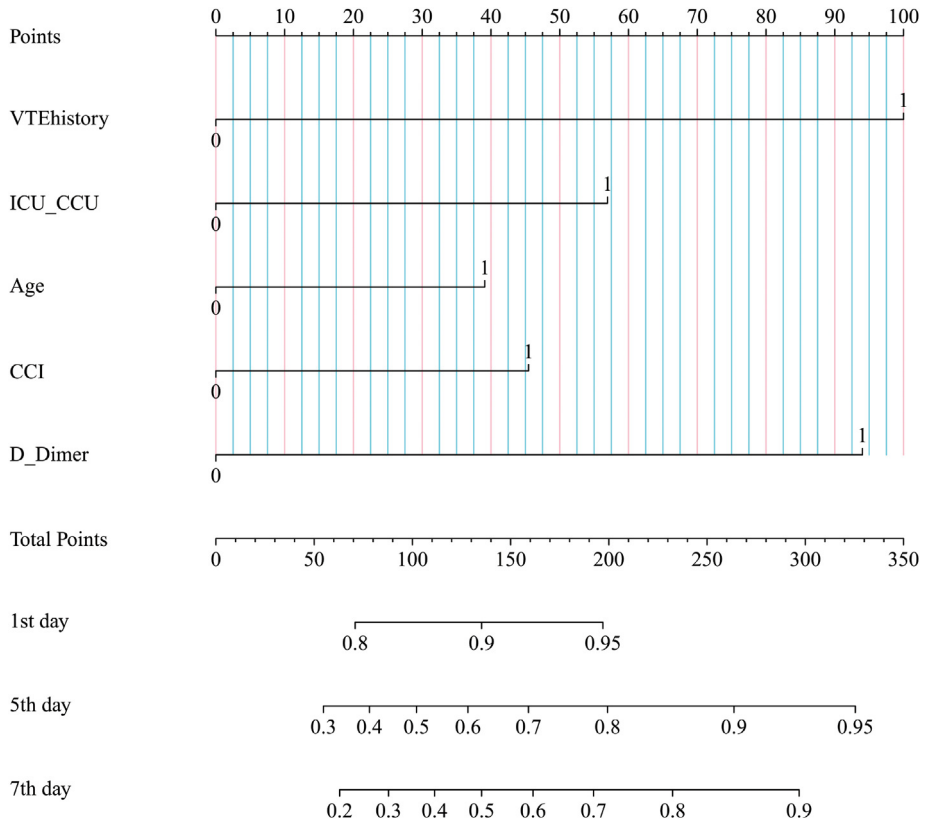

Fig. 2. The nomogram of COX_DD model. †VTE history, Previous VTE history, 1 = yes, score 100; ICU_CCU, ICU/CCU, 1 = yes, score 57; Age, 1 was ≥ 65 years old, score 39; CCI, Charlson Comorbidity Index, 1 was ≥ 3, score 45; D_Dimer, D-dimer, 1 was ≥ 243 μ g/L, score 94. Total score was 0–335 and cut off was 161.5.

clinical utility, but the improvement in calibration was relatively small. The predictive effect of D-dimer on CA-VTE has received widespread attention. Vienna Score added two coagulation biomarkers (D-dimer and soluble P Selectin) into Khorana Score to improve model performance.[13,58,59] The CATS/MICA Score only included two variables, one was site of tumor, and the other was D-dimer.[19] This study further validated the predictive effect of D-dimer on CA-VTE.[28,58]

This study also compared model performance in predicting CA-VTE risk at different times of hospitalization. Khorana et al.[35] and Carmona Bayonas et al.[36] believed that CA-VTE risk changes with anti-cancer treatment or tumor progression, and dynamic assessment should be conducted. The relevant guidelines also recommend dynamic assessment of CA-VTE risk.[9–11,60,61] This study found that, with the extension of prediction time ($\geq$ 7 days of hospitalization), model calibration lost accuracy (Brier Score $\geq$ 0.25). Thus, it is recommended that clinical professionals reassess the CA-VTE risk once a week.

Implications for nursing practice and research

The risk assessment of CA-VTE is one of the important tasks for oncology nurses. The prediction models developed using survival ML algorithms in this study may contribute to the dynamic and accurate risk assessment of CA-VTE. Moreover, taking the risk prediction of CA-VTE as an example, this study presents a relatively standardized process for developing clinical prediction models using survival ML algorithms, which can provide reference for nursing researchers to conduct similar research.

Study advantages and limitations

This study has the following advantages: i) Double cohort study design: this study completed internal and external validation; ii) Candidate predictors: a total of 30 variables from four dimensions were included; iii) Model development: seven survival ML algorithms were used to train the CA-VTE model; iv) Model evaluation: this study comprehensively evaluated model performance from four dimensions: model discrimination, calibration, clinical utility, and model improvement. This study also has the following limitations: i) This study is a single center study, and we are conducting a multi-center, prospective cohort study to validate and improve the model generalizability; ii) The sample size may be relatively limited. However, the slightly lower sample size of the prospective cohort did not lead to overfitting problems when the models were validated. Take the COX_DD model for example, in the case of overfitting, the C-index of the COX-DD model may be 0.800 and 0.600 in the training and prospective validation sets, respectively. In fact, the C-index of the COX-DD model were 0.690 and 0.760, respectively. The C-index of the COX-DD model did not decrease when the model was validated.

Conclusions

In this study, seven survival ML algorithms are used to develop CA-VTE risk prediction model. These seven models are all superior to Khorana Score and COX_DD model has the best model performance. Combining with D-dimer can improve model performance. Applying the nomogram based on COX_DD model allows health care professionals to reassess CA-VTE risk once a week. In the future, multi-center, prospective cohort study is still needed to further validate the model performance.

CRediT authorship contribution statement

Shuai Jin: Data curation, Formal analysis, Visualization, Writing-original draft, Writing-review & editing, and Funding acquisition; **Dan Qin:** Data curation, Writing-original draft, and Writing-review & editing; **Chong Wang:** Data curation, Writing-original draft, and Writing-review & editing; **Baosheng Liang:** Conceptualization, Methodology, and Writing-Review & Editing; **Lichuan Zhang:** Data curation, Writing-original draft, and Writing-review & editing; **Weiyin Gao:** Data curation and Writing-review & editing; **Xiao Wang:** Data curation and Writing-review & editing; **Bo Jiang:** Conceptualization, Methodology, Resources, and Writing-review & editing; **Benqiang Rao:** Conceptualization, Resources, and Writing-review & editing; **Hanping Shi:** Conceptualization, Resources, Writing-review & editing, and Supervision; **Lihui Liu:** Resources, Writing-review & editing, and Supervision; **Qian Lu:** Conceptualization, Funding acquisition, Writing-original draft, Writing-review & editing, Supervision, and Project administration. All authors have read and approved the final manuscript.

Ethics statement

This study was approved by the Institutional Review Board of Peking University (IRB No. 00001052–18037) and was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants provided written informed consent.

Declaration of competing interest

The authors declare no conflict of interest. The corresponding author, Prof. Qian Lu, is an editorial board member of *Asia–Pacific Journal of Oncology Nursing*. The article was subject to the journal's standard procedures, with peer review handled independently of Prof. Lu and their research groups.

Data availability statement

The data and code that support the findings of this study are available from the corresponding author, QL, upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apjon.2025.100691.

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