Construction and Validation of a Nomogram Prediction Model for Catheter Related Thrombosis Risk of Central Venous Access Devices in Cancer Patients -- Prospective, Machine Learning Study

Guiyuan Ma, Shujie Chen, Sha Peng, Nian Yao, Jiaji Hu, Letian Xu, Tingyin Chen, Jiaan Wang, Xin Huang, Jinghui Zhang

Submitted to: Journal of Medical Internet Research
on: February 25, 2024

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Guiyuan Ma[1, 2]; Shujie Chen[2, 3]; Sha Peng[1, 2]; Nian Yao[1, 2]; Jiaji Hu[1, 2]; Letian Xu[4]; Tingyin Chen[5]; Jiaan Wang[6]; Xin Huang[7]; Jinghui Zhang[1, 8]

[1]Teaching and Research Section of Clinical Nursing Xiangya Hospital of Central South University Changsha, Hunan CN
[2]Xiangya School of Nursing Central South University Changsha, Hunan CN
[3]Health and Wellness Bureau of Nanming District Guiyang, Guizhou CN
[4]Department of Ultrasound Xiangya Hospital of Central South University Changsha, Hunan CN
[5]Network Information Department Xiangya Hospital of Central South University Changsha, Hunan CN
[6]Vascular Access Department Hainan Provincial People's Hospital Hainan CN
[7]Department of Nursing , Affiliated Hospital of Qinghai University Qinghai CN
[8]National Clinical Research Center for Geriatric Diseases Xiangya Hospital Central South University Changsha, Hunan CN

Corresponding Author:
Jinghui Zhang
Teaching and Research Section of Clinical Nursing
Xiangya Hospital of Central South University
No. 87, Xiangya Road
Changsha, Hunan
CN

Abstract

Background: Central venous access devices (CVADs) play a crucial role in providing treatment and supportive care for cancer patients. However, catheter-related thrombosis (CRT) poses a significant risk to patient safety., which will interrupt patient treatment, delay the patient's therapeutic period, prolong hospitalization, and increase the patient's physical, mental, and economic burden. Identifying independent risk factors for CRT in cancer patients, proactively utilizing high-quality risk assessment tools in high-risk groups, and implementing precise prevention and treatment can effectively reduce the occurrence of CRT.

Objective: Construction and validation of a prediction model for predicting the risk of catheter-related thrombosis (CRT) in cancer patients' central venous access devices (CVADs).

Methods: Using a prospective study design, cancer patients with CVADs in Xiangya Hospital of Central South University were followed up from January 2021 to December 2022 until catheter removal and 539 cases of CVADs-CRT occurred. Five hundred patients who met the inclusion and exclusion criteria were taken as the case group. Two cases of cancer patients without CRT were taken according to the number of CRTs/number of non-CRTs (1:2) in the same month in which a case of cancer patient with CRT was diagnosed by using the random number table method, for a total of 1,000 cases of cancer patients without CRT as the control group. Patient data were randomly divided into a training group (n=1050) and a testing group (n=450) according to the ratio of 7:3. Univariate and Least Absolute Shrinkage and Selection Operator (LASSO) algorithm was used to determine the risk factors for CRT formation. Risk prediction models were constructed based on Logistic Regression, Random Forest, and Support Vector Machine and evaluated by area under the curve (AUC). Data from patients with CVADs placement in Qinghai University Affiliated Hospital and Hainan Provincial People's Hospital (January 2023 to June 2023) were applied to externally validate the optimal model's differentiation, calibration, and clinical applicability.

Results: The incidence of CVADs-CRT in cancer patients was 5.02%. There was a difference in the occurrence of CRT in patients with different cancers (P<.05), and the top three highest risks of occurrence were in patients with head and neck tumors (9.66%), haematological tumors (6.97%) and respiratory tumors (6.58%). There was a difference in the occurrence of CRT in patients with different catheters placed (P<.05), with the top three highest risks occurring in hemodialysis catheters (13.91%), CVC (8.39%), and PICC (4.68%). Eleven independent risk factors were screened for age, catheter method, catheter valve,

catheter material, infection, catheter history, D-Dimer, operation history, anemia, diabetes, and targeted drugs. The Logistic prediction model had the best discriminative ability among the three machine learning-constructed models, with AUCs of 0.868 (0.846-0.890) for the training group. The externally validated AUC was 0.708 (0.618-0.797), the Nomogram model calibration curve was consistent with the ideal curve, and the Hosmer-Lemeshow test showed a good fit (P > .05) and a high net benefit value for the clinical decision curve.

Conclusions: The Nomogram constructed in this study can be personalised to predict the risk of developing CVADs-CRT in cancer patients, which can help in the early identification and screening of patients at high risk of cancer CVADs-CRT.

(JMIR Preprints 25/02/2024:57709)
DOI: https://doi.org/10.2196/preprints.57709

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[1] Teaching and Research Section of Clinical Nursing, Xiangya Hospital of Central South University, Changsha, Hunan, China

[2] Xiangya School of Nursing, Central South University, Changsha, Hunan, China

[3]Health and Wellness Bureau of Nanming District, Guiyang, Guizhou, China

[4] Department of Ultrasound, Xiangya Hospital of Central South University, Changsha, Hunan, China

[5] Network Information Department, Xiangya Hospital of Central South University, Changsha, Hunan, China

[6] Vascular Access Department, Hainan Provincial People's Hospital, Hainan, China

[7] Department of Nursing, Affiliated Hospital of Qinghai University, Qinghai, China

[8] National Clinical Research Center for Geriatric Diseases, Xiangya Hospital, Central South University, Changsha, Hunan, China

Correspondence: Jinghui Zhang, Teaching and Research Section of Clinical Nursing, Xiangya Hospital of Central South University, Number 87 Xiangya Road, Kaifu District, Changsha, Hunan, 410008, China
Phone: +86 15874032339
Email: 401212@csu.edu.cn

[Abstract]

Background: Central venous access devices (CVADs) play a crucial role in providing treatment and supportive care for cancer patients. However, catheter-related thrombosis (CRT) poses a significant risk to patient safety., which will interrupt patient treatment, delay the patient's therapeutic period, prolong hospitalization, and increase the patient's physical, mental, and economic burden. Identifying independent risk factors for CRT in cancer patients, proactively utilizing high-quality risk assessment tools in high-risk groups, and implementing precise prevention and treatment can effectively reduce the occurrence of CRT.

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the optimal model's differentiation, calibration, and clinical applicability.
Result: The incidence of CVADs-CRT in cancer patients was 5.02%. There was a difference in the occurrence of CRT in patients with different cancers (*P*<.05), and the top three highest risks of occurrence were in patients with head and neck tumors (9.66%), haematological tumors (6.97%) and respiratory tumors (6.58%). There was a difference in the occurrence of CRT in patients with different catheters placed (*P*<.05), with the top three highest risks occurring in hemodialysis catheters (13.91%), CVC (8.39%), and PICC (4.68%). Eleven independent risk factors were screened for age, catheter method, catheter valve, catheter material, infection, catheter history, D-Dimer, operation history, anemia, diabetes, and targeted drugs. The Logistic prediction model had the best discriminative ability among the three machine learning-constructed models, with AUCs of 0.868 (0.846-0.890) for the training group. The externally validated AUC was 0.708 (0.618-0.797), the Nomogram model calibration curve was consistent with the ideal curve, and the Hosmer-Lemeshow test showed a good fit (*P* > .05) and a high net benefit value for the clinical decision curve.
Conclusion: The Nomogram constructed in this study can be personalised to predict the risk of developing CVADs-CRT in cancer patients, which can help in the early identification and screening of patients at high risk of cancer CVADs-CRT.
[Key Words] cancer; central venous access devices; thrombosis; risk factors; prediction model; LASSO; Nomogram

Introduction

Central venous access devices (CVADs) include central venous catheter (CVC), peripherally inserted central catheter (PICC), implantable venous access port (IVAP), and hemodialysis catheter[1]. CVADs are essential lifelines for cancer patient’s treatment and supportive care[2]. Still, certain risks are associated with their use, including complications such as catheter occlusion, catheter dislocation, and catheter-related thrombosis (CRT)[3]. CRT refers to the clotting of blood cells, platelets, and fibrin in the veins of the limb on the side of the patient's catheter[4]. The incidence of CRT varies from approximately 5% to 28%[5-7], and the risk of CRT in cancer patients is 4-5 times higher than that in non-cancer patients[6]. Meanwhile, CRT is also the main reason for the unplanned extubation of CVADs[8]. Once CRT occurs, it will interrupt patient treatment, delay the patient's therapeutic period, prolong hospitalization, and increase the patient’s physical, mental, and economic burden. In more severe cases, it will lead to the occurrence of pulmonary embolism and even sudden death[2]. Therefore, identifying independent risk factors for CRT in cancer patients, early application of high-quality risk assessment tools in high-risk groups, and adopting precise prevention and treatment can effectively reduce the occurrence of CRT[9].

Many risk factors, including patients, catheterization, and catheter dimensions, lead to CRT. Studies have shown that previous venous thromboembolism (VTE) history[10], catheterization history[11], trauma history[7], higher level of D-dimer[11], and catheter-related infection[10] are risk factors for CRT in cancer patients in terms of patient-related factors. In the catheterization factors, CRT is closely related to the puncture method (with the help of visualization technology)[12] and the puncture site[13]. In terms of catheter-related factors, studies have shown that catheter type[14], catheter lumens[10], ratio of catheter diameter to vessel diameter[15], and position of catheter tip are related to CRT[14]. However, there are differences in the risk factors identified by different studies, which are related to inconsistent study subjects and small sample sizes[16]. In addition, the research on risk factors are cross-sectional or retrospective studies at present[14,17], and there is still a lack of solid evidence for the type of cancer, combined with other underlying

diseases, postoperative infection, and the choice of chemotherapy drugs on thrombosis. The causal relationship between other vital factors, such as laboratory indicators and catheter-related thrombosis, must be clarified further.

At present, there are many risk prediction models for CRT in cancer patients, such as the Seeley risk assessment tool[18], the Autor scale[19], the Michigan risk score[9]. The risk factors considered by these risk models focus on the clinical data of patients, and the catheter and catheterization risk factors of CRT are rarely considered. Therefore, the risk prediction of CRT in cancer patients is lack of specificity[9, 17, 18]. At the same time, the source of the study population is mainly the local population, so it needs to be further verified in the Chinese population. Liu et al. constructed a thrombosis prediction model for Chinese cancer patients involving sex, cancer type, catheter type, position of the catheter tip, chemotherapy status, and antiplatelet/anticoagulation status at baseline predictors, but the type of catheters were CVC catheters and the samples were retrospectively collected[11, 14]. Many researchers have applied machine learning algorithms to construct prediction models with high accuracy[20]. However, these prediction models are complex and inaccurate, challenging to implement in clinical practice for nurses. Therefore, more straightforward, accurate, and feasible models are needed, especially for clinical practical settings.

Currently, the detection of CRT is still dominated by vascular ultrasound, and ultrasound findings during the period of unthrombosed thrombosis have limited predictive value for CRT[5]. Although there have been previous studies on the risk prediction of CRT in cancer patients[9, 11, 14], most were retrospective case-control studies with small sample sizes, single catheter type, limited variables included in the analyses, and a lack of multiple machine-learning modeling comparisons. Given this, this study will rely on a large-sample prospective cohort, integrate patients' pre-hospital, in-hospital and post-hospital data, and apply the Least Absolute Shrinkage and Selection Operator (LASSO) algorithm[21] to screen the risk factors of CVADs-CRT in cancer patients. Three ML methods to construct CVADs-CRT prediction models, then screening optimal model to develop a Nomogram model, and use external data to evaluate the Nomogram model, to provide an assessment tool for preventing the formation of CVADs-CRT in cancer patients and early intervention.

Methods

Participants

The study subjects for model construction were from Xiangya Hospital of Central South University, where prospective data on cancer patients with CVADs placed from January 2021 to December 2022 were collected. The study subjects for external validation of the model were from Qinghai University Affiliated Hospital and Hainan Provincial People's Hospital from January 2023 to June 2023. Inclusion criteria: (1) pathological tissue sections confirmed the diagnosis of cancer; (2) indwelling CVADs catheter; (3) ultrasound did not find CRT the day before tube placement; (4) vascular ultrasound before tube removal to check CRT results. Exclusion criteria: (1) previous persistent atrial fibrillation; (2) previous history of coronary artery disease and percutaneous coronary intervention, stent implantation; (3) taking anticoagulant drugs during the period of catheterisation; (4) incomplete follow-up data; (5) patients who did not have an angiographic ultrasound during the period of catheterisation or before the extraction of the catheter. A total of 500 patients with CVADs-CRT who met the inclusion and exclusion criteria were included in the prospective data from Xiangya Hospital as a case group. In the same month of treatment in which

CRT was diagnosed in a cancer patient, two cancer patients without diagnosis of CRT were randomly selected using a non-duplicated sampling method as a control group for the construction of the model (500 case group, 1000 control group). External validation was obtained from the Qinghai University Affiliated Hospital and the Hainan Provincial People's Hospital, with 300 cases of data provided by each hospital, for a total of 600 cases of data for external validation. This study was approved by the Ethics Review Committee of Xiangya Hospital of Central South University (approval number: 202112658), which observed informed consent and followed the principle of confidentiality.

The sample size was calculated according to the formula for cohort design. We set $\alpha=0.05$ $\beta=0.10$ $\mu_{\frac{\alpha}{2}}=1.96$ $\mu_{\beta}=1.282$. A previous study identified several risk factors for CRT in cancer patients. Of these risk factors, the risk factor with the largest minimum sample size required for the case group was a previous history of Deep vein thrombosis (DVT)[3], where the proportion of previous history of DVT in the group with no CRT was 14.1%, p0 = 0.141 (103/730). The proportion of DVT in the group with CRT thrombosis was 20.8%, p1 = 0.208 (30/144)[3]. So the study's case group requires a minimum sample size of 186. The incidence of CRT is reported as 19.3%(106/549) [10]. Based on this value, the initial sample size needed for a prospective study was 870. After accounting for the possibility of missed visits and increasing the sample size by 20%, the required sample size is at least 1150.

CRT diagnostic method

The diagnosis of CVADs-CRT is determined by ultrasound specialists in combination with Doppler ultrasound[4, 22], and the diagnostic criteria are (1) the lumen cannot be deflated; (2) solid echoes in the lumen; (3) filling defects of blood flow signals in the lumen; (4) loss of period-phase changes in the blood flow spectrum; (5) disappearance or diminution of the lack of response; and (6) disappearance or diminution of blood flow enhancement of the distal limb of the extruded limb.

Data collection tool

The research team conducted a literature review of CVADs-CRT risk factors [3, 5, 7, 8, 9, 10, 22-24], combined with focus group discussions and two rounds of Delphi expert consultations; based on this, the research team discussed the formation the information collection form and finally included in the data analysis of the relevant factors of a total of 21 items. (1) the patient's factors: gender, age, body mass index (BMI) (weight, height); (2) catheter-related factors: catheter type, catheter way, catheter vein, catheter limb side, puncture times, catheter lumen, catheter valves, catheter material, infection, insertion history. (3) disease-related factors: cancer types, targeted drugs, chemotherapy, operation history, deep venous thrombosis (DVT) history, diabetes, anemia. (4) laboratory index: D-Dimer concentration.

Data collection method

The researchers were uniformly trained before data collection. The data were collected according to the data collection form. We strictly screened the study subjects based on the inclusion and exclusion criteria and introduced in detail the purpose of this study, the methodology, the process of implementation, and the benefits gained to the eligible subjects or their family members to obtain their consent. Patient's general information, clinical information, tube placement information, examination and test reports can be collected through the safe infusion system, Lis, Pacx, Emr, His, pathology and other systems; follow-up visits are arranged according to the follow-

up table, and patients are observed or asked about systemic and local symptoms on the day of tube placement, 1d, 7d, 7*(n+1)d after tube placement. On the day of extubation, patients are immediately asked about the symptoms of CRT if they are suspected to have CRT symptoms or signs. Vascular ultrasound was used to detect CRT, all patients must have vascular ultrasound to screen for CRT before extubation, and all patients with symptoms or signs of suspected CRT have vascular ultrasound to screen for CRT. To ensure stable data quality, missing or NA values under the database were removed, and the final data included in the statistical calculations and model analyses were completed.

Statistical analysis

SPSS 22.0 and R Studio 4.0.2 software were used for statistical description and statistical interpretation. Numerical data were presented as the number of cases and rate, and χ^2 test or Fisher exact test was used; quantitative data were presented as $\bar{x}\pm s$ one-way and LASSO algorithms were used to explore the influencing factors of CRT in cancer patients, and two-sided $P<0.05$ was considered as a statistically significant difference. The samples were randomly divided into a training group and a testing group in a ratio of 7:3. The training group was used for the construction and training of the risk prediction model, and the testing group was used to verify the prediction accuracy of the model. We used Logistic Regression (LR), Random Forest (RF), and Support Vector Machine (SVM) to construct the prediction models for PICC-CRT in cancer patients. The optimal model was selected based on the discriminative power of the model (AUC, and 95% confidence interval, CI). The external validation dataset was disrupted according to the shuffling algorithm so that the data were evenly distributed, and the model was evaluated by differentiation, calibration, and clinical applicability. (1) Differentiation: the evaluation index that the prediction model can distinguish the high and low risk of CVADs-CRT in the population, the area under the ROC curve (AUC) was applied to evaluate, when the AUC value is greater than 0.7, the diagnostic accuracy of the model is good. (2) Calibration: an indicator reflecting the degree of conformity between predicted and actual results, the Hosmer-Lemeshow (H-L) test and calibration curve are applied for evaluation, the smaller the χ^2 value obtained by the H-L test, and the more the fitted line tends to coincide with the reference line in the calibration curve, the better the calibration degree is[25]. (3) Clinical applicability: refers to the diagnostic accuracy of the model applied in the clinic, which is evaluated by using the clinical Decision Curve Analysis (DCA), and the curve contains two extreme situations; the grey line indicates that all patients receive CRT preventive interventions, and the black line indicates that all patients do not receive CRT interventions, and the clinical Decision Curve is farther away from the two extreme situations, the better [26].

In RStudio software, LASSO is calculated using the "glmnet" package, the penalty function is defined using the ten-fold orthogonal method, the minimum deviation value is taken. LR, RF, and SVM use the "caret", "randomForest", and "e1071" packages, respectively. The ROC curve was plotted using the "pROC" package, the Hosmer-Lemeshow test was performed using the "hoslem. test" package, and the Nomogram and DCA decision curves were plotted using the "rms" and "rmda" packages.

Results

Population demographic

From January 2021 to December 2022, a prospective cohort of 10736 patients was established

at Xiangya Hospital of Central South University, and a total of 539 cases (5.02%) of CVADs-CRT occurred, 15 patients with incomplete follow-up data and 24 patients taking anticoagulants during the time of the tube period were excluded. A total of 500 patients with data on CVADs-CRT were included in the final model construction, and 1,000 patients without CVADs-CRT patient data were included. Table 1 shows the demographic and clinical characteristics of all patients, comparing the differences between the case group and the control group and between the training group and the testing group. A total of 600 cases of data were externally validated, including 38 in the case group and 562 in the control group. Tables 2 and 3 show the occurrence of CRT in prospectively collected patients with CVADs at Xiangya Hospital of Central South University from January 2021 to December 2022, with different catheters and different diseases.

Table 1 Univariate analysis of the control group and case group, training group and testing group

Variables		Non-CVADs-CRT[a] (n=1000)	CVADs-CRT[a] (n=500)	*p-value*	Training group (n=1050)	Testing group (n=450)	*p-value*
Gender	Male	584 (58.4)	253 (50.6)	.004[*]	585 (55.7)	252 (56.0)	.919
	Female	416 (41.6)	247 (49.4)		465 (44.3)	198 (44.0)	
Age (years)	2-11	14 (1.4)	1 (0.2)	.000[** f]	11 (1.0)	4 (0.9)	.883[f]
	12-18	7 (0.7)	1 (0.2)		7 (0.7)	1 (0.2)	
	19-35	51 (5.1)	13 (2.6)		44 (4.2)	20 (4.4)	
	36-59	573 (57.3)	255 (51.0)		581 (55.3)	247 (54.9)	
	60-75	342 (34.2)	208 (41.6)		381 (36.3)	169 (37.6)	
	≥76	13 (1.3)	22 (4.4)		26 (2.5)	9 (2.0)	
BMI (kg/□)	<18.5	114 (11.4)	60 (12.0)	0.666	128 (12.2)	46 (10.2)	.172
	18.5-23.9	594 (59.4)	305 (61.0)		637 (60.7)	262 (58.2)	
	≥24.0	292 (29.2)	135 (27.0)		285 (27.1)	142 (31.6)	
Catheter type	CVC[b]	156 (15.6)	91 (18.2)	.002[*]	170 (16.2)	77 (17.1)	.795
	Hemodialysis catheter	88 (8.8)	19 (3.8)		72 (6.9)	35 (7.8)	
	PICC[c]	538 (53.8)	293 (58.6)		590 (56.2)	241 (53.6)	
	IVAP[d]	218 (21.8)	97 (19.4)		218 (20.8)	97 (21.6)	
Catheter method	Blind	6 (0.6)	20 (4.0)	□.001[**]	23 (2.2)	3 (0.7)	.081
	Blind-MST[e]	54 (5.4)	24 (4.8)		51 (4.9)	27 (6.0)	
	ultrasound-MST[e]	940 (94.0)	456 (91.2)		976 (93.0)	420 (93.3)	
Catheter vein	Upper extremity vein	917 (91.7)	437 (87.4)	□.001[**]	941 (89.6)	413 (91.8)	.196
	Jugular vein	7 (0.7)	24 (4.8)		26 (2.5)	5 (1.1)	
	Lower extremity vein	76 (7.6)	39 (7.8)		83 (7.9)	32 (7.1)	
Catheter limb side	Right	328 (32.8)	206 (41.2)	.001[*]	369 (35.1)	165 (36.7)	.572
	Left	672 (67.2)	294 (58.8)		681 (64.9)	285 (63.3)	
Puncture times	1	981 (98.1)	483 (96.6)	.08[g]	1025 (97.6)	439 (97.6)	.057[g]
	2	12 (1.2)	14 (2.8)		21 (2.0)	5 (1.1)	
	≥3	7 (0.7)	3 (0.6)		4 (0.4)	6 (1.3)	
Catheter	Single	876 (87.6)	426 (85.2)	.195	912 (87.9)	390 (86.7)	.92

lumen	Double	124 (12.4)	74 (14.8)		138 (13.1)	60 (13.3)	
Catheter valves	None	409 (40.9)	285 (57.0)	□.001**	474 (45.1)	220 (48.9)	.182
	Yes	591 (59.1)	215 (43.0)		576 (54.9)	230 (51.1)	
Catheter material	Silicon	219 (43.8)	413 (41.3)	□.001**	442 (42.1)	190 (42.2)	.953
	polyurethane	138 (27.6)	216 (21.6)		250 (23.8)	104 (23.1)	
	Pressure-resistance polyurethane	143 (28.6)	371 (37.1)		358 (34.1)	156 (34.7)	
Infection	None	856 (85.6)	293 (58.6)	□.001**	796 (75.8)	353 (78.4)	.269
	Yes	144 (14.4)	207 (41.4)		254 (24.2)	97 (21.6)	
Insertion history	None	734 (73.4)	287 (57.4)	□.001**	709 (67.5)	312 (69.3)	.491
	Yes	266 (26.6)	213 (42.6)		341 (32.5)	138 (30.7)	
Cancer type	Digestive system cancer	267 (26.7)	96 (19.2)	□.001**	253 (24.1)	110 (24.4)	.531
	Respiratory system cancer	237 (23.7)	107 (21.4)		240 (22.9)	104 (23.1)	
	genitourinary system cancer	194 (19.4)	112 (22.4)		212 (20.2)	94 (20.9)	
	Hematological malignances	119 (11.9)	57 (11.4)		123 (11.7)	53 (11.8)	
	Head and neck cancer	83 (45.4)	41 (8.2)		87 (8.3)	37 (8.2)	
	Skin tumors and others	100 (10.0)	87 (17.4)		135 (12.9)	52 (11.6)	
Targeted drugs	None	398 (39.8)	140 (28.0)	□.001**	371 (35.3)	167 (37.1)	.511
	Yes	602 (60.2)	360 (72.0)		679 (64.7)	283 (62.9)	
Chemotherapy	None	16 (1.6)	21 (4.2)	.002*	22 (2.1)	15 (3.3)	.157
	Yes	984 (98.4)	479 (95.8)		1028 (97.9)	435 (96.7)	
Operation history	None	701 (70.1)	164 (32.8)	□.001**	591 (56.3)	274 (60.9)	.098
	Yes	299 (29.9)	336 (67.2)		459 (43.7)	176 (39.1)	
DVT history	None	910 (91.0)	391 (78.2)	□.001**	902 (85.9)	399 (87.7)	.352
	Yes	90 (9.0)	109 (21.8)		148 (14.1)	56 (12.3)	
Diabetes	None	174 (17.4)	75 (15.0)	.239	171 (16.3)	78 (17.3)	.617
	Yes	826 (82.6)	425 (85.0)		879 (83.7)	372 (82.7)	
Anemia	None	703 (70.3)	237 (47.4)	□.001**	661 (63.0)	279 (62.0)	.727
	Yes	297 (29.7)	263 (52.6)		389 (37.0)	171 (38.0)	
D-Dimer (mg/L)	≤0.5	740 (73.6)	211 (42.2)	□.001**	668 (63.6)	279 (62.0)	.551
	>0.5	265 (26.4)	289 (57.8)		382 (36.4)	171 (38.0)	

[a]CVADs-CRT: catheter-related thrombosis of central venous access devices.
[b]CVC: Central Venous Catheter.
[c]PICC: Peripherally Inserted Central Catheter.
[d]IVAP: Implantable Venous Access Port.
[e]MST: Modified Seldinger Technique.
[f]Fisher exact test.
*P□.05
**P□.001

Table 2 Occurrence of CVADs-CRT for different diseases

Cancer type	CRT[a]	Non-CRT[a]	All	Incidence (%)	χ^2	*P-value*
Digestive system cancer	96	3668	3764	2.55	107.593	□0.001

Respiratory system cancer	138	1960	2098	6.58
genitourinary system cancer	63	1458	1521	4.14
Hematological malignances	93	1241	1334	6.97
Head and neck cancer	69	645	714	9.66
Skin tumors and others	80	1225	1305	6.13
All	539	10197	10736	5.02

[a]CRT: catheter-related thrombosis.

Table 3 Occurrence of CVADs-CRT for different catheters

Catheter type	CRT[a]	Non-CRT[a]	All	Incidence (%)	χ^2	*P*
CVC[b]	92	1004	1096	8.39	52.061	0.001
Hemodialysis catheter	16	99	115	13.91		
PICC[c]	358	7294	7652	4.68		
IVAP[d]	73	1800	1873	3.90		
All	539	10197	10736	5.0		

[a]CRT: catheter-related thrombosis.
[b]CVC: Central Venous Catheter.
[c]PICC: Peripherally Inserted Central Catheter.
[d]IVAP: Implantable Venous Access Port.

Risk factors of CVADs-CRT in cancer patients

Univariate analysis showed that a total of 17 risk factors, including gender, age, catheter type, catheter way, catheter vein, catheter limb side, catheter valve, catheter material, infection, catheter history, cancer type, targeted agents, chemotherapy, operation history, DVT history, anemia, and D-Dimer, were statistically significant ($P < .05$) for the development of CVADs-CRT, as shown in Table 1.

With the occurrence of CVADs-CRT as the dependent variable, 17 variables with statistically significant results from the univariate analysis, as well as diabetes and BMI, which the group discussed and the effects of clinical reality and confounding factors were considered, for a total of 19 variables were screened for prediction using the LASSO algorithm with a 10-fold orthogonal method. The line of one colour in Figure1 represents the trend of a variable, with the variables incorporated in the model decreasing as the penalty coefficient λ changes. The dashed line on the left in Figure 2 represents the value of λ and the number of features screened corresponding to the maximum AUC, and the dashed line on the right represents the further reduction in the number of elements remaining in the model when the standard error is increased by a factor of 1 over the maximum AUC, at which point the error is minimised (1SE = 0.020 for the minimum value of λ). The 11 predictor variables screened at this time included age, catheter method, catheter valve, catheter material, infection, catheter history, D-Dimer, operation history, anemia, diabetes, and targeted drugs.

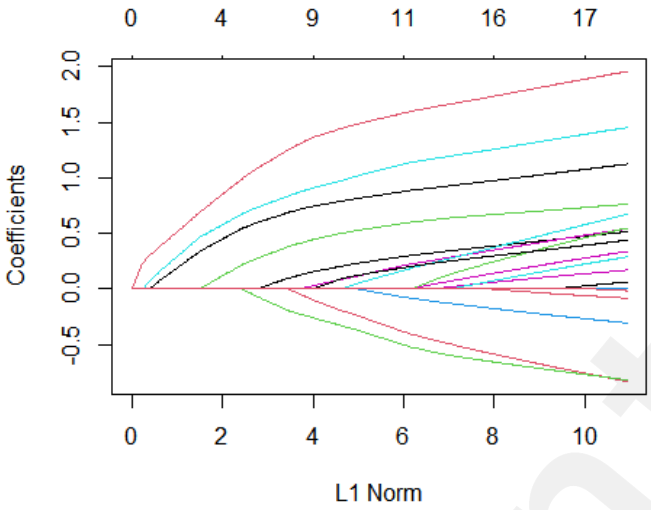

Figure 1 Plot of the LASSO regression coefficients on the different penalty parameters

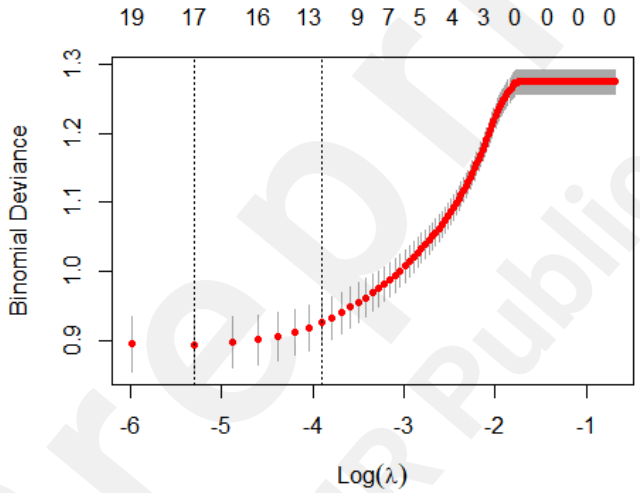

Figure 2 Cross-validation plot of the LASSO penalty term

Construction and validation of the prediction model for CVADs-CRT in cancer patients

The 11 variables screened by univariate analysis and the LASSO algorithm, combined with the dependent variable (whether CVADs-CRT occurred), were incorporated into the three ML algorithms for each. Three risk prediction models for cancer patients were established. In the multivariable logistic regression prediction model, we set α in=0.05 and α out=0.10, with the backward LR method(χ^2=513.783, P<0.001). Comparing the partial regression coefficients, the operation history was the most associated risk factor, as shown in Table 4. In the RF prediction model, ntree=217, mtry=3, based on this parameter to classify the training group, the model prediction accuracy is 89.97%, and the out-of-bag error is 19.43%. By comparing the four kernel functions of SVM, the radial was the best model constructed with a prediction accuracy of 0.826 and the number of support vectors of 633.

Among the three CVADs-CRT prediction models, the LR model had the best predictive efficacy, with AUCs of 0.868 (0.846-0.890) for the training group. The AUCs was 0.762 (0.730-0.793) for the RF training group, and 0.796 (0.767-0.825) for the SVM training group (Figure3). The Nomogram

column-line diagram model constructed from the Logistic prediction model is shown in Figure 4. According to the scale above the column-line diagram corresponding to each risk factor, a single score for the element was obtained, and all the scores were added to get a total score. The higher the total score, the higher the likelihood that the patient would have a CRT.

External data were used for validation, and the AUC for external validation was 0.708 (0.618-0.797) (Figure 5), and the Hosmer-Lemeshow test showed a high agreement between the actual and predicted values of the calibration curves at $P > .05$, see Figure 6. The DCA of the model is shown in Figure 7, where the red line indicates the net benefit rate of the prediction model, and the red line is not close to the two extreme case lines of both receiving the intervention and neither receiving the intervention, and is overall relative to the upper right corner, indicating that the use of the present risk prediction model to intervene in the population at high risk of CVADs-CRT for cancer has a clinical application, with the threshold probability being in the range of 3% to 100%, and with a high value of the net benefit.

Table 4 Logistic Regression analysis of CVADs-CRT in cancer patients

Variables	β	SE	Z	OR	95% CI	*P-value*
Constant	-9.836	1.330	19.257	0.000	-	<.001
Age	0.523	0.128	17.194	1.686	1.313-2.166	<.001
Catheter method	-1.011	0.248	27.503	0.364	0.224-0.592	<.001
Catheter value	-0.739	0.197	34.599	0.478	0.325-0.702	<.001
Catheter material	-0.276	0.117	30.235	0.759	0.603-0.955	.019
Infection	1.741	0.217	53.578	5.700	3.727-8.719	<.001
Catheter history	0.622	0.185	17.044	1.863	1.296-2.677	.001
D-Dimer	1.149	0.176	3.910	3.156	2.234-4.459	<.001
Operation history	2.195	0.195	3.985	8.982	6.134-13.151	<.001
Anemia	0.948	0.182	95.341	2.580	1.805-3.688	<.001
Diabetes	0.750	0.265	6.461	2.116	1.258-3.560	.005
Targeted drugs	0.489	0.211	23.161	1.631	1.079-2.464	.02

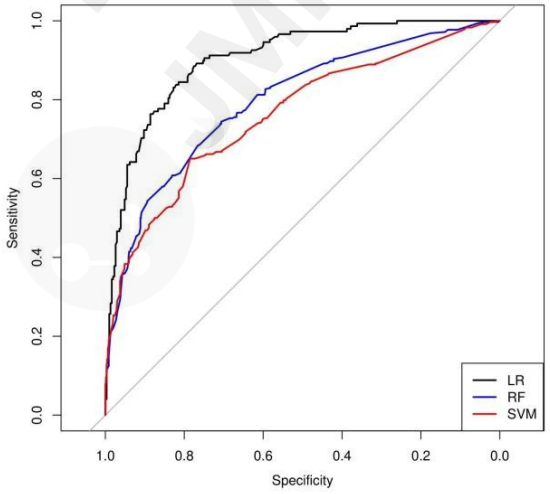

Figure3 AUC (95% CI) plots of 3 prediction models

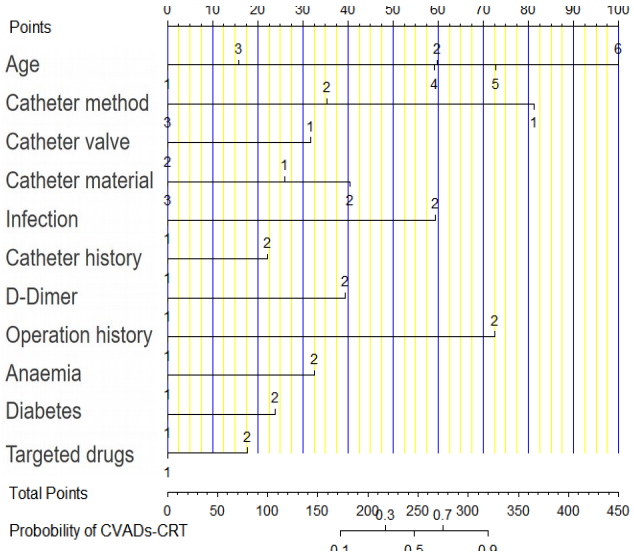

Figure 4 The Nomogram prediction model

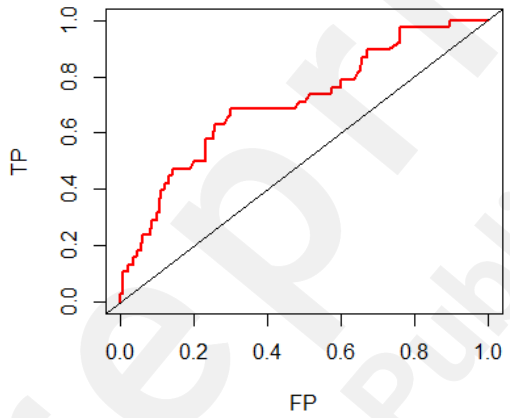

Figure 5 The ROC curve of the prediction model in the external validation

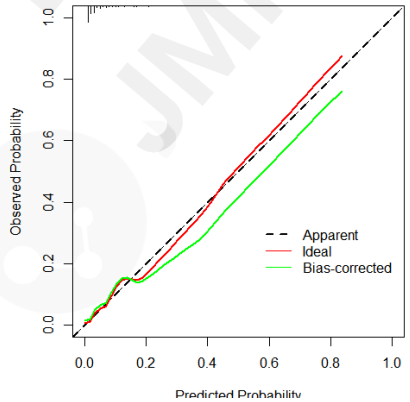

Figure 6 The calibration curve of the prediction model in the external validation

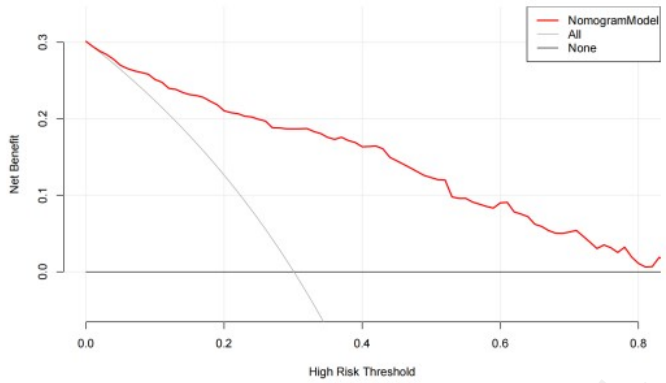

Figure 7 The DCA curve of the prediction model in the external validation

Discussion

This study constructed and validated a prediction model based on ML algorithm for CVADs-CRT in cancer patients. The model constructed based on Logistic regression had the best predictive efficacy, and the Nomogram model had a high level of discrimination, calibration, and clinical applicability.

Studies have found that the incidence of CVADs-CRT in cancer patients ranges from 5% to 28%[5-7]. This prospective data shows that the incidence of CVADs-CRT in our cancer patients is about 5.02%, lower than the incidence reported in most literature[5-7]. This may be related to the standardized training of nursing staff in vascular access and maintenance, the pre-, mid-, and post-catheterization quality control of patients with vascular access catheters, quality control management of intravenous therapy before, during, and after hospitalization, strengthening patient education for patients and their families. It is also related to the differences in the inclusion criteria, follow-up method, duration, and sample size of the study population[3].

Among the occurrence of CVADs-CRT in different diseases, the highest was in head and neck tumor patients in our hospital (9.66%). Most head and neck tumor patients underwent surgical treatment, with long operation time and limb immobilization[16]. In addition, the intravenous input of viscous nutrient solution, intracranial pressure-reducing dehydrating medication, etc., are all prone to causing slow venous blood flow and stagnation of blood[16]. Additional influences are reduced muscle tone due to anesthetics and muscle relaxants[16]. The subsequent highest incidence was in hematological tumor patients (6.97%). Immunomodulators and hormones may lead to an increased risk of CRT [13, 27]. In addition, patients with hematological tumors have higher use of recombinant human granulocyte stimulating factors, which decreases leukocytes and neutrophils, contributing to an increased risk of thrombosis[28]. The incidence in patients with respiratory tumors was comparable to patients with hematological tumors (6.58%). Lung cancer cells can produce tissue factors, cancerous procoagulant substances, and inflammatory factors, which directly activate the coagulation system[17]; and the hypoxia caused by surgery, postoperative hemostatic medications, anti-angiogenic and targeted drugs can cause blood hypercoagulation[29].

In the comparison of the incidence of different types of CVADs-CRT, hemodialysis catheters have the highest risk, with an incidence of 13.91%; the reasons may related to that hemodialysis catheters have a large diameter and are primarily double-lumen catheters, which have a greater impact on the vascular and hemodynamic indexes of the patients[28]. Patients who need dialysis

tend to suffer from chronic renal diseases; these patients have a high risk of thromboembolism due to the nephrin- activation of the angiotensin-aldosterone system, aortic or vascular calcification, and impaired calcium and phosphorus mineral metabolism[30]. The second is CVCs (8.39%); the reason is that most CVC used in our hospital are made of ordinary polyurethane, which is irritates to the endothelium of the blood vessels[31]. The diameter of the CVC is relatively thick, primarily a double-lumen or triple-lumen, which has a greater impact on the blood flow rate, resulting in slow blood flow and thrombus formation.

Slow blood flow, vascular endothelial damage and hypercoagulable state of blood are the three main elements of venous thrombosis[31]. We found that the older the patient, the higher the risk of CRT, which is similar to the results of SONG Y's study[10], and this may be related to the reduced smoothness of the vessel wall, the increase in blood viscosity, and the relatively low blood flow in older adults[14]. We found that the catheter method, catheter valve, and catheter material were associated with the risk of CRT occurrence. Blind or blind-sedinger puncture is prone to endothelial damage due to repeated punctures and increased number of catheter repositioning, increasing the risk of CRT [10]. The risk of CRT in catheters with valves is lower than that in catheters without valves, which is related to that catheter valves can effectively prevent luminal blood reflux and reduce the formation of CRT in the catheter lumen[13]. It was found that the risk of CRT was lower in the new pressure-resistant polyurethane catheters than in silicone catheters, probably due to the addition of a surface-active macromolecule based on fluorine-atom doping to the new polyurethane material, which inhibits platelet adhesion, avoids blood coagulation, and reduces CRT formation[31].

The study also found that patients with diabetes, infection, anemia, catheter history, operation history, usage of targeted drugs, and increased concentration of D-dimer were all risk factors for developing CRT. A hyperglycemic environment is prone to slow blood flow and microcirculatory disorders[23]. At the same time, diabetes is an inflammatory state that causes oxidative stress, damages vascular endothelial cells, and induces vascular endothelial dysfunction, and abnormalities in the anticoagulant and fibrinolytic systems[23]. Inflammatory reactions associated with infections in patients tend to lead to acidosis, leading to the down-regulation of anticoagulant mechanisms, and the enhancement of coagulation factors and platelet activity[32], resulting in a blood hypercoagulable state. Iron deficiency due to anemia stimulates increased production of megakaryocytes and erythropoietin, resulting in increased platelet production and hypercoagulability of the blood[24]. Meanwhile, surgical treatment and tube placement may easily cause endothelial damage and release of large amounts of coagulation factors[20, 31], leading to the formation of CRT. Targeted drugs can increase vascular resistance and limit endothelial cell self-renewal while inhibiting cancer cells, leading to endothelial cell disorders[33] and increasing the risk of CRT. D-dimer is produced by hydrolysis of fibrin by fibrinolytic proteins and has been identified as a sensitive biomarker of activation of the fibrinolytic system[24]. Elevated levels are considered to be in a state of hypercoagulability in the organism[24].

In the CVADs-CRT risk prediction model for cancer patients constructed in this study, having a surgical history was most closely associated with the risk of CVADs-CRT occurrence. The risk of CVADs-CRT in patients with operation history was significantly increased, surgery activates some coagulation factors, and the fibrinolytic system is altered, leading to a systemic hypercoagulable state[20, 33]. At the same time, prolonged postoperative bed rest slows blood flow and increases the overall risk of CVADs-CRT[34]. The seven risk factors for CVADs-CRT, namely, gender, catheter

type, catheter vein, limb side of the catheter, catheter material, placement history, and cancer type, were excluded from the univariate analysis by LASSO regression. The reasons for the exclusion were related to the size of the sample and the differences in the definition of the classification of the variables[14], e.g., the classification of the veins of catheter placement as upper extremity veins, internal jugular veins and lower extremity veins, which resulted in a significant risk of CVADs-CRT in some specific sites of the cannulated veins. Nevertheless, the risk factors screened in this study had high predictive accuracy, and the constructed Nomogram column-line diagram model was concise and diagnostic.

Our study constructed a comprehensive and more predictive model through LASSO algorithm screening features and three machine-learning model comparisons. LASSO algorithm is a variable dimension reduction analysis method capable of screening non-zero coefficient predictors [22], and logistic regression is a nonlinear probabilistic prediction method [14,21]. Recently, the method of determining disease risk factors through LASSO and Logistic regression has been widely used in the medical field [14,21]. The logistic regression prediction model we constructed showed high efficacy in both the training and test groups regarding discrimination, calibration accuracy, and clinical applicability. Nomogram graphs can provide better-individualized prediction and risk assessment intuitively and visually [14]. The Nomogram we constructed can be used to distinguish high-risk and low-risk PICC-CRT cancer patients and can be used to adjust the risk limits of medical decisions up or down according to the risk tolerance of patients and medical workers. The PICC-CRT prediction model built based on the ML algorithm in this study also provides some hints for related research. Previous related studies only used traditional statistical methods, while our study used multiple ML methods [4,9]. ML algorithms can fully explore the data and process high-dimensional variables and their complex interactions. Moreover, in our study, the test group can better predict the occurrence of PICC-CRT based on the results of the training group, which has obvious superiority in prediction performance. The best prediction model was selected by model precision, and a Nomogram model was constructed to classify high-risk groups to provide a theoretical basis for the etiological prevention of PICC-CRT in cancer patients. Stepwise regression analysis was used to solve the multicollinearity between variables. The Nomogram prediction model for cancer patients performed well in the training and test groups, which can be considered for future clinical application under multi-center and large sample data verification.

Limitations and future research

The Nomogram model constructed in this study can predict the risk of CVADs-CRT occurrence early, quickly and accurately. It provides a reference for clinical personnel to analyze individual risk intuitively, and improves the utilization of limited medical resources. However, this study only applied epidemiological methods for risk factor prediction and lacked the analysis of genetic genes. We will consider the CVADs-CRT susceptibility genes and their localities in cancer patients and use Machine Learning Integration Algorithm to integrate genetic and environmental factors further to explore the risk prediction of CVADs-CRT in cancer patients. Later, the group will consider implanting the Nomogram model into the safety infusion system. Through the interconnection of the hospital safety infusion system and the electronic medical record system, the relevant data will be obtained automatically to realize the intelligent warning of CVADs-CRT.

Conclusion

The establishment of risk prediction models can assist the clinic in accurately predicting the risk of adverse events and assist in scientifically formulating the next step of treatment. The prediction

models constructed in this study have a certain degree of predictive ability for the risk of CVADs-CRT occurrence in cancer patients. The built Nomogram model indicators are simple to obtain, operable, with good predictive efficacy, and have high clinical applicability.

Acknowledgments

We are grateful for the assistance and support of all those responsible for the data collection process in the selected hospitals, as well as the nurses who also participated in the data collection. We also thank all the patients who participated in this study.This work was supported by the National Natural Science Foundation of China (grant number 72174210), the Hunan Natural Science Foundation (grant number 2022JJ70168), the Clinical Research Fund of the National Clinical Research Center for Geriatric Disorders (grant number 2021LNJJ09).

Data Availability

The data sets generated or analyzed during this study are not publicly available due to the terms of consent and permission to which the participants agreed but are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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