A Model to Assess the Risk of Peripherally Inserted Central Venous Catheter-related Thrombosis in Patients with Breast Cancer: A Retrospective Cohort Study

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Abstract

Purpose: Limited risk assessment tool to stratify the risk of PICC-related thrombosis (PICC-RVT) in breast cancer patients. This study developed a model to assess the risk of PICC-RVT in breast cancer patients.

Methods: We conducted a retrospective cohort study of 1284 breast cancer patients receiving PICC insertion during 1 January 2015 - 31 August 2019 at a cancer specialized hospital in Hunan province, China. The entire population is divided into two groups at a ratio of 3:1 which included a derivation sample (n=978), and a validation sample (n=284). PICC-RVT was confirmed by ultrasonography in the presence of clinical symptoms and signs.

Results: PICC-RVT occurred in 40 (4.09%) of the derivation sample patients. Multivariable analysis identified 9 variables: chronic obstructive pulmonary disease, prior central venous catheter placement, higher level of Platelets, higher level of D-dimer, lower level of Activated partial thromboplastin time, menopause, no prior breast surgery, upper extremity lymphedema, and endocrine therapy. Points were assigned to each variable according to regression coefficient. The model had an area under the receiver operating characteristics curve (AUC) of 0.850 (95% CI 0.776 to 0.924), The Hosmer-Lemeshow goodness of fit was 4.781 (p=0.572). At a cutoff value of 3.5, the sensitivity and specificity were 75% and 83%, respectively.

Conclusion: Several disease-specific factors of breast cancer (e.g., menopause, endocrine therapy and upper extremity lymphedema) play important roles in the development of PICC-RVT. Patients at higher PICC-RVT risk could be candidates for close post-insertion monitoring and interventions to prevent PICC-RVT.

Introduction

Breast cancer is the most common cancer in female patients [1]. With the development of medical service, the 5-year survival rate of breast cancer is as high as 90.9%. [2] Chemotherapy is one of the main treatment methods for breast cancer. It is very important for breast cancer treatment to ensure the safe infusion of chemotherapy drugs. Peripherally inserted central venous catheter (PICC) is a kind of catheter inserted from peripheral vein such as basilica or brachial vein to central venous, which can effectively prevent the extravasation of chemotherapy drugs, and provide a safe 'life access' for breast cancer patients[3]. Despite these advantages, the application of PICC can also cause some catheter-related complications, among which PICC-related thrombosis (PICC-RVT) has been the most common and detrimental complications that could cause discomfort experience such as swelling and pain in the limb, and even cause pulmonary embolism which can endanger patients' life[4]. Fortunately, it can be reversible by early detection and timely intervention [5–6]. However, current guidelines do not recommend routine preventive anticoagulation therapy [7]. Many researchers have assessed PICC-RVT risk prediction models to guide medical staff to take measures as early as possible [8–10]. Nevertheless, it was lacking in specific cancer patients. Study showed that the risk of PICC-RVT in different cancer patients were

inconsistent [11]. Disease-specific factors in specific cancer patients may play a role in the development of PICC-RVT. Breast cancer patients generally select the healthy-side upper-limb for chemotherapy drugs infusion which makes it difficult for second catheter placement if the first catheter fails to infusion. Besides, the female blood vessels are generally thinner than male's, and hormone levels and blood components changes in different physiological stage are more complicated than that in male. Furthermore, the specificity of breast cancer-related treatments such as endocrine therapy and chemotherapy may play roles in the development of PICC-RVT [12–13]. There is a need to develop a simple prediction rule for peripherally inserted central venous catheter-related symptomatic thrombosis (PICC-RVT) in patients with breast cancer.

The incidence of PICC-RVT varies by patient population [3]. A review showed that the incidence of PICC-RVT in cancer patients was 8 times higher than that in non-cancer patients [14], and the incidence of thrombosis in tumor patients undergoing chemotherapy was 6.5 times higher than that in non-chemotherapy cancer patients[15].A study reported that the incidence of PICC-RVT in cancer patients was as high as 51.4%, and asymptomatic thrombosis accounted for about half of that[16]. Without ultrasound examination, it is difficult to detect thrombosis. Therefore, the prevention of PICC-RVT in cancer patients is important for reduction of its occurrence.

Building mathematical models based on big data to predict the risk of diseases or symptoms has been widely used in clinical practice. In recent five years, some prediction models have been constructed for PICC-RVT. Seeley and Chopra team from the United States reported PICC-RVT prediction model respectively. Both of their target population was patients who had a PICC insertion, and most of them were cancer patients [8–9]. Since 2016, scholar from China began to explore the construction of predictive models for PICC-RVT. Hao's team first reported PICC-RVT risk prediction nomogram models for cancer patients[17]. However, these models have not been widely used, and their clinical effectiveness needs further exploration.

Few scholars have gone deep into the construction of PICC-RVT prediction model in specific cancer patients. In order to explore the risk of PICC-RVT in patients with specific tumor, we should not only consider the factors related to catheter, operator and general condition of patients, but also consider the role of tumor-specific factors in the development of PICC-RVT.

For breast cancer patients after surgery, the affected side of the upper limb lymphatic reflux is blocked, it is not suitable for further puncture, and the main infusion procedure would be completed by the healthy side of the limb[18]. If we apply the short peripheral venous catheter for infusing chemotherapeutic drug, it is easy to cause chemotherapeutic drug extravasation, which would increase the risk of chemotherapy delay and greatly increase the medical expenses of patients [19]. If the vascular condition of the healthy limb is poor, repeated peripheral vein puncture would increase the pain of the patient, and may delay the optimal treatment time of the patient. The PICC selection for breast cancer patients is a better choice for solving these problems. However, during the retention of PICC, in addition to the tumor itself, breast cancer may have other disease and treatment specific factors leading to thrombosis. At present, few

research were reported on the risk factors of PICC-RVT in breast cancer patients[20], and the research on the specific PICC-RVT prediction tool for breast cancer patients has not been reported. Thus, it is necessary to build a PICC-RVT risk scoring system for breast cancer patients which would help guide the clinical decision-making regarding thromboprophylaxis strategies.

Methods

Study design and patients

A retrospective, cohort study was conducted in patients with breast cancer receiving PICC insertion during 1 January 2015 - 31 August 2019 at Tier-3A (Grade A tertiary hospital) cancer specialized hospital in Hunan province, China. Patients were included if they: (1) were diagnosed with breast cancer; (2) were female with age ≥ 18 years old; (3) received PICC insertion in our hospital. Patients were excluded if they did not have the catheter removed in our hospital. A total of 1375 PICCs were inserted in 1375 patients with breast cancer at the vascular access clinic. The final sample size included in this study was 1262 after excluded 113 cases for no record of catheter removal.

Data collection

We obtained the patients ID number from the Vascular Access Clinic in which most of breast cancer patients have their PICC inserted. Then, we enter the Hospital Information System (HIS) to collect potential related factors for PICC-RVT, which consisted of five parts: 1) General information: age, marital status, residence, type of medical insurance, etc; 2) PICC insertion data: date of PICC insertion, puncture site of PICC, arm of PICC insertion, vein diameter, times of puncture, etc; 3) Patients' disease and treatment related data: chronic disease, treatment history, medication history, laboratory test results before insertion(e.g., Platelet count, Fibrinogen level, and D-dimer), etc; 4) Breast cancer specific data: menopause, cancer stage, pathological type, tumor location, treatment, lymphedema, etc; 5) Follow-up information of PICC-RVT: date and result of color Doppler ultrasound, occurrence of other PICC related complications, catheter removal data, etc. Trained nurses regularly checked missing data to ensure data quality. When patients reported arm pain or swelling limb, we would use ultra-sonography (Philipsu22, Netherlands) for further diagnostic. All data were extracted by two investigators independently. To protect patient privacy and confidentiality, we just use the inpatient number as the unique identifier to extract the data needed for this study as listed above.

Primary outcome

The primary outcome was the incidence of symptomatic PICC-RVT. This outcome was selected primarily because it can cause patients' discomfort which affects patients' quality of life seriously. When patients reported arm pain or swelling limb, qualified sonographer would use ultrasonography (Philipsu22, Netherlands) for further diagnostic.

Statistical Analysis

Data analysis was performed using SPSS software (version 18, SPSS Inc, IBM, NY, USA). We randomly selected 75% of the total samples for model derivation, and the remaining 25% samples for model validation. Patients demographic and clinical variable were compared between the two sample groups. Then we abstracted the data of model derivation for further analysis. Patients demographic and clinical variable were screened for possible inclusion into the risk prediction model. The dependent variable in the analysis was the development of symptomatic PICC-RVT. Those with P value ≤ 0.10 in univariate analysis (including Fisher exact test, χ^2 test and Mann-Whitney U test, as appropriate) were retained for further consideration. Multivariable logistic regression analysis was used in a stepwise entry process with the P-value set at <0.05 to identify the relevant predictive factors.

From the logistic regression statistical outputs, the contribution of the individual PICC-RVT risk factors was weighted by beta-coefficients of the final model. To simplify calculations using these weights in the risk scoring system, the beta-coefficients were rounded to the nearest unit value. A summary PICC-RVT risk scoring system in breast cancer was then assigned to each patient by simply adding up transformed beta-coefficients values for each risk factor they possessed.

The predictive accuracy of the final risk scoring system was then determined by testing the specificity, sensitivity, and area under the receiver-operating characteristic (ROC) curve. We did these testing both in the case of model derivation and model validation. A predictive instrument with an ROC of ≥ 0.70 is considered to have good discrimination.

Results

Sample characteristics

PICC-RVT developed in 4.09% (40/978) of the validation sample and in 3.52% (10/284) of the deviation sample. The peak incidence of PICC-RVT occurred after post-insertion day 180 (range, 3 to 380 days). Table 1 describes the baseline characteristics of the derivation (n=978) and validation (n=284) samples. The derivation and validation samples were similar in all characteristics.

Table 1

Data comparison between derivation sample and validation sample

Variable	Group	N(%)		Statistics value	P
		derivation sample n=978	validation sample n=284		
Age(years)	21~30	32(3.3)	10(3.5)	1.007	0.909
	31~40	165(16.9)	53(18.7)		
	41~50	429(43.9)	127(44.7)		
	51~60	262(26.8)	70(24.6)		
	≥61	90(9.2)	24(8.5)		
Marital status	Married	969(99.1)	283(99.6)	2.242	0.326
	Unmarried	7(0.7)	0(0.0)		
	Divorce	2(0.2)	1(0.4)		
Education levels	Primary or below	642(65.6)	182(64.1)	0.806	0.668
	Secondary	207(21.2)	67(23.6)		
	Tertiary or above	129(13.2)	35(12.3)		
Profession	Farmer	350(35.8)	113(39.8)	9.378	0.227
	Worker	77(7.9)	20(7.0)		
	Businessman	20(2.0)	10(3.5)		
	Enterprise employees	154(15.7)	54(19.0)		
	Teacher	54(5.5)	10(3.5)		
	Medical staff	14(1.4)	4(1.4)		
	Civil servant	20(2.0)	3(1.1)		
	Other	289(29.6)	70(24.6)		
Medical insurance	Rural medical insurance	600(61.3)	179(63.0)	2.607	0.626
	Urban medical insurance	318(32.5)	84(29.6)		
	Provincial medical insurance	15(1.5)	3(1.1)		

	Municipal medical insurance	4104.20	1706.00		
	At one's own expense	400.40	100.40		
Habitation	City	401041.00	113039.80	0.134	0.714
	Township /Rural	577059.00	171060.20		
Vein selected for insertion	Basilic vein	849086.80	234082.40	4.410	0.110
	Brachial vein	123012.60	46016.20		
	Other	600.60	401.40		
Insertion side	Left limb	511052.20	163057.40	2.341	0.126
	Right limb	467047.80	121042.60		
Venipuncture method	Ultrasound guidance	972099.40	282099.30	-	1.000
	Tradition	600.60	200.70		
Placement complication	Yes	6506.60	1304.60	1.624	0.202
	No	913093.40	271095.40		
Placement attempts	1	947096.80	278097.90	0.864	0.353
	≥2	3103.20	602.10		
Catheter diameter / vessel diameter	≤0.45	817083.50	245086.30	1.230	0.267
	0.45	161016.50	39013.70		
BMI	018.5	2903.00	602.10	1.563	0.458
	18.5023.9	518053.00	161056.70		
	≥24	431044.10	117041.20		
Blood type	A	332033.90	108038.00	3.189	0.363
	B	228023.30	71025.00		
	O	324033.10	83029.20		
	AB	9409.60	2207.70		

Hypertension	Yes	185±18.9	48±16.9	0.593	0.441
Diabetes	Yes	79±8.1	21±7.4	0.141	0.707
Coronary heart disease	Yes	7±0.7	1±0.4	-	0.692
Hyperlipidemia	Yes	119±12.2	29±10.2	0.814	0.367
Chronic kidney disease	Yes	5±0.5	0±0.0	-	0.593
COPD	Yes	8±0.8	3±1.1	-	0.718
Operation history	Yes	363±37.1	117±41.2	1.555	0.212
Radiation therapy history	Yes	34±3.5	10±3.5	0.001	0.971
Endocrine therapy history	Yes	56±5.7	19±6.7	0.366	0.545
Smoking history	Yes	11±1.1	2±0.7	-	0.744
Drinking history	Yes	20±2.0	6±2.1	0.005	0.944
CVC placement history	Yes	7±0.7	2±0.7	-	1.000
Anticoagulant	Yes	11±1.1	2±0.7	-	0.744
Anticoagulant drugs	Yes	46±4.7	14±4.9	0.025	0.875
Antiplatelet drugs	Yes	7±0.7	2±0.7	-	1.000
WBC	≥4.0	44±4.5	7±2.5	3.339	0.188
	4.0~10.0	907±92.7	272±95.8		
	≥10.0	27±2.8	5±1.8		
Hb	≥110	118±12.1	38±13.4	0.351	0.839
	110-150	846±86.5	242±85.2		
	≥150	14±1.4	4±1.4		
PLT	≥100	16±1.6	4±1.4	1.016	0.602
	100~300	836±85.5	237±83.5		
	≥300	126±12.9	43±15.1		
D-dimer	≤0.55	850±86.9	253±89.1	0.943	0.331

	0.55	12813.1	3110.9		
PT	10.0	101.0	51.8	1.816	0.403
	10.0~13.5	86588.4	24485.9		
	13.5	10310.5	3512.3		
FIB	1.8	252.6	41.4	3.006	0.222
	1.8~3.5	73775.4	20672.5		
	3.5	21622.1	7426.1		
APTT	20.0	60.6	100.4	0.301	0.860
	20.0~40.0	89691.6	26091.5		
	40.0	767.8	238.1		
Menopause	Yes	40241.1	10436.6	1.843	0.175
	No	57658.9	18063.4		
Disease stage	I	15415.7	3913.7	2.925	0.403
	II	45146.1	14651.4		
	III	26527.1	6723.6		
	IV	10811.0	3211.3		
Pathological type	Infiltrative specific cancer	141.4	62.1	1.519	0.468
	Infiltrative non specific cancer	96198.3	27897.9		
	Other	30.3	000.0		
Metastasis	Yes	60962.3	17662.0	0.008	0.927
Tumor location 1	Left side	50451.5	14250.0	0.489	0.783
	Right side	46747.8	13948.9		
	Bilateral	70.7	31.1		
Tumor location 2	Outer upper quadrant	57258.5	14551.1	6.621	0.250
	Outer lower quadrant	11011.2	4114.4		
	Inner upper	19620.0	6021.1		

	quadrant				
	Inner lower quadrant	47	4.8	17	6.0
	Areola area	34	3.5	15	5.3
	Other	19	1.9	6	2.1
Breast surgery	Yes	871	89.1	253	89.1
Upper limb lymphedema	Yes	18	1.8	8	2.8
Anthracyclines	Yes	780	79.8	216	76.1
Platinum-based drugs	Yes	67	6.9	24	8.5
Trastuzumab	Yes	151	15.4	47	16.5
Radiation therapy	Yes	18	1.8	6	2.1
Endocrine therapy	Yes	42	4.3	10	3.5
				0.000	0.990
				1.040	0.308
				1.810	0.179
				0.842	0.359
				0.205	0.651
				0.087	0.768
				0.333	0.564

Univariate and multivariate analyses for PICC-RVT

The bivariable analysis comparing the risk factors in those with and without PICC-RVT in the derivation sample is displayed in Table 2. Univariate analysis screened out 25 variables related to PICC-RVT with $P \text{ value} \leq 0.10$, which included: education level, medical insurance type, residence, chronic kidney disease, COPD, operation history, chemotherapy history, radiotherapy history, endocrine treatment history, CVC placement history, use of coagulant, WBC, Hb, PLT, D-dimer, FIB, APTT, pathological type, menopause, tumor metastasis, breast operation, upper limb lymphedema, anthracycline chemotherapy, platinum chemotherapy and endocrine therapy.

Table 2

Univariate analyses for PICC-RT

Variables	Group	PICC-RT n=40	Non- PICC-RT n=938	Statistic value	P value
Age ^a years ^a	21~30	13.1	3196.9	7.358	0.118 ^a
	31~40	74.2	15895.8		
	41~50	122.8	41797.2		
	51~60	124.6	25095.4		
	≥61	88.9	8291.1		
Marital status	Married	404.1	92995.9	0.387	0.824 ^a
	Unmarried	00.0	7100.0		
	Divorce	00.0	2100.0		
Education levels	Primary or below	223.4	62096.6	4.813	0.090 ^a
	Secondary	146.8	19393.2		
	Tertiary or above	43.1	12596.9		
Profession	Farmer	123.4	33896.6	10.922	0.142 ^a
	Worker	67.8	7192.2		
	Businessman	210.0	1890.0		
	Enterprise employees	95.8	14594.2		
	Teacher	11.9	5398.1		
	Medical staff	17.1	1392.9		
	Civil servant	210.0	1890.0		
	Other	72.4	28297.6		
Medical insurance	Rural medical insurance	162.7	58497.3	12.389	0.015 ^a
	Urban medical insurance	185.7	30094.3		
	Provincial medical insurance	16.7	1493.3		
	Municipal medical insurance	512.2	3687.8		
	At one's own expense	00.0	4100.0		
Habitation	City	256.2	37693.8	7.968	

					0.005 ^a
	Township /Rural	152.6%	56297.4%		
Vein selected for insertion	Basilic vein	333.9%	81696.1%		
	Brachial vein	64.9%	11795.1%	2.703	0.259 ^a
	Other	116.7%	583.3%		
Insertion side	Left limb	203.9%	49196.1%	0.085	0.771 ^a
	Right limb	204.3%	44795.7%		
Venipuncture method	Ultrasound guidance	404.1%	93295.9%	-	1.000 ^b
	Tradition	00.0%	6100.0%		
Placement complication	Yes	34.6%	6295.4%	-	0.744 ^b
Placement attempts	1	384.0%	90996.0%	-	0.365 ^b
	≥2	26.5%	2993.5%		
Catheter/vessel ratio	≤0.45	334.0%	78496.0%	0.033	0.857 ^a
	0.45	74.3%	15495.7%		
Body Mass Index (BMI)	18.5	26.9%	2793.1%	1.152	0.562 ^c
	18.5~23.9	234.4%	49595.6%		
	≥24	153.5%	41696.5%		
Blood type	A	144.2%	31895.8%	1.521	0.677 ^a
	B	114.8%	21795.2%		
	O	103.1%	31496.9%		
	AB	55.3%	8994.7%		
Hypertension	Yes	105.4%	17594.6%	1.006	0.316 ^a
Diabetes	Yes	45.1%	7594.9%	-	0.557 ^b
Coronary heart disease	Yes	00.0%	7100.0%	-	1.000 ^b
Hyperlipidemia	Yes	75.9%	11294.1%	-	0.319 ^b
Chronic kidney disease	Yes	240.0%	360.0%	-	0.015 ^b

COPD	Yes	337.5	562.5	-	0.003 ^b
Operation history	Yes	236.3	34093.7	7.424	0.006 ^a
Chemotherapy history	Yes	1618.4	7181.6	-	0.000 ^b
Radiation therapy history	Yes	720.6	2779.4	-	0.000 ^b
Endocrine therapy history	Yes	1323.2	4376.8	-	0.000 ^b
Smoking history	Yes	19.1	1090.9	-	0.370 ^b
Drinking history	Yes	00.0	20100.0	-	1.000 ^b
CVC placement history	Yes	342.9	457.1	-	0.002 ^b
Anticoagulant	Yes	218.2	981.8	-	0.071 ^b
Antiplatelet drugs	Yes	114.3	685.7	-	0.254 ^b
WBC	4.0	24.5	4295.5	14.809	0.001 ^c
	4.0~10.0	333.6	87496.4		
	10.0	518.5	2281.5		
Hb	110	43.4	11496.6	10.943	0.004 ^c
	110~150	333.9	81396.1		
	150	321.4	1178.6		
PLT	100	212.5	1487.5	21.865	0.000 ^c
	100~300	242.9	81297.1		
	300	1411.1	11288.9		
D-dimer	≤0.55	242.8	82697.2	26.555	0.000 ^a
	0.55	1612.5	11287.5		
PT	10.0	00.0	10100.0	0.583	0.747 ^c
	10.0~13.5	354.0	83096.0		
	13.5	54.9	9895.1		
FIB	1.8	312.0	2288.0	32.344	0.000 ^c

	1.8~3.5	1502.0	722098.0		
	3.5	2210.2	194089.8		
APTT	20.0	2033.3	4066.7	14.560	0.001 ^c
	20.0~40.0	3704.1	859095.9		
	40.0	101.3	75098.7		
Menopause	Yes	2706.7	375093.3	12.003	0.001 ^a
Disease stage	I	503.2	149096.8	2.196	0.533 ^a
	II	1904.2	432095.8		
	III	903.4	256096.6		
	IV	706.5	101093.5		
Pathological type	Infiltrative specific	000.0	140100.0	7.140	0.028 ^a
	Infiltrative non-specific	3904.1	922095.9		
	Other	1033.3	2066.7		
Metastasis	Yes	3405.6	575094.4	9.171	0.002 ^a
Tumor location 1	Left side	2004.0	484096.0	1.875	0.392 ^a
	Right side	1904.1	448095.9		
	Bilateral	1014.3	6085.7		
Tumor location 2	Outer upper quadrant	2404.2	548095.8	3.214	0.667 ^a
	Outer lower quadrant	605.5	104094.5		
	Inner upper quadrant	603.1	190096.9		
	Inner lower quadrant	306.4	44093.6		
	Areola area	000.0	340100.0		
	Other	105.3	18094.7		
Breast surgery	Yes	2202.5	849097.5	-	0.000 ^b
Upper limb lymphedema	Yes	8044.4	10055.6	-	0.000 ^b
Anthracyclines	Yes	2302.9	757097.1	12.792	0.000 ^a
Platinum-based	Yes	609.0	61091.0	-	0.05 ^b

Trastuzumab	Yes	8[5.3]	143[94.7]	0.664	0.415 ^a
Radiation therapy	Yes	2[11.1]	16[88.9]	-	0.165 ^b
Endocrine therapy	Yes	6[14.3]	36[85.7]	-	0.006 ^b
a: χ^2 , b: Fisher exact test, c:Mann-Whitney U testing					

After the initial univariate screening, the potential predictive factors associated with PICC-RVT were retained for further analysis using multivariable logistic regression analysis in a stepwise entry process with the P-value set at <0.05 to identify the relevant predictive factors. The final nine variables retained in the model that were considered as significant PICC-RVT predictive factors, including: CVC placement history, COPD, PLT, D-dimer, APTT, menopause, breast cancer surgery, upper limb lymphedema, and endocrine therapy (P <0.05) (Table 3). These variables were selected for the development of the prediction rule. In addition, the time of PICC retention could not be determined until PICC removal, therefore, it was not included in the risk prediction rule.

Table 3
multivariate logistic analysis for PICC-RT

Characteristic	Estimate	SE	Wald	OR	95% CI for OR		P value
CVC placement history (vs. None)	2.315	0.892	6.740	10.120	1.763	58.081	0.009
COPD(vs. None)	2.075	1.033	4.034	7.967	1.051	60.367	0.045
PLT (vs. Per unit increase)	1.330	0.392	11.546	3.783	1.756	8.149	0.001
D-dimer (vs. Per unit increase)	1.301	0.394	10.923	3.673	1.698	7.946	0.001
APTT(vs. Per unit decrease)	1.962	0.876	5.018	7.112	1.278	39.571	0.025
Menopause(vs. None)	0.808	0.405	3.984	2.242	1.015	4.955	0.046
breast operation (vs. None)	-1.085	0.445	5.943	0.338	0.141	0.808	0.015
upper limb lymphedema (vs. None)	3.334	0.597	31.187	28.040	8.703	90.344	0.000
endocrine therapy (vs. None)	1.475	0.598	6.095	4.372	1.355	14.105	0.014

Derivation of the Prediction Rule

Based on the results of the multivariable modeling, a final prediction rule was developed by adding parameter score if it is present. Score values are the regression beta-coefficients rounded to the nearest unit value for the specific parameter. An individual patients' score is calculated in the following manner: If a parameter is present, the corresponding score value is multiplied by 1, if not by 0. Adding these values results in the patients' total score. Table 4 shows the parameters and the weights.

Table 4

Risk scoring system for PICC-RVT in breast cancer patients

Characteristic	Group	Points
PLT	>300	2
	100~300	1
	<100	0
D-dimer	≤ 0.55	0
	> 0.55	1
APTT	0	0
	2	2
	4	4
COPD	Yes	2
	No	0
Menopause	Yes	1
	No	0
CVC placement history	Yes	2
	No	0
Breast surgery	Yes	-1
	No	0
Upper limb lymphedema	Yes	3
	No	0
Endocrine therapy	Yes	1
	No	0

The final product was a scoring system with summation between 0 and 15, a higher score was associated with an increased risk for PICC-RVT in breast cancer. The model was continued with a ROC curve analysis and a test of the area under the curve (AUC). The findings indicated that the AUC was acceptable at 0.850 (95%CI: 0.776, 0.924), indicating a good accuracy of the scoring system (Figure 1). Applying this scoring system to the deviation sample and using a cut-point of 3.5 or more to identify high-risk patients, sensitivity was 75% and specificity was 83.2%.

Validation of the scoring system

Applying the PICC-RVT risk scoring system derived from deviation sample to the validation sample and using a cut-point of 3.5 or more to identify high risk patients in PICC-RVT, we find the AUC was 0.882 (95%CI: 0.781, 0.984) (Figure 1), with sensitivity 70%, specificity 84.7%, respectively.

Discussion

The study is the first to develop a simple and validated prediction tool to assess PICC-RVT in breast cancer patients, to our knowledge. Among the 1262 breast cancer patients included in this study, 50 developed symptomatic PICC-RVT, the incidence was 3.96%. This finding was consistent with the findings of other studies on the incidence of PICC-RVT in breast cancer patients [20–21]. In recent years, the relevant studies of PICC-RVT in breast cancer patients were all retrospective studies, and there may be a certain degree of positive events missed, meaning that the incidence might be underestimated. Despite the inherent limitations of this retrospective study design, the present study provided important reference for PICC-RVT risk prediction in breast cancer patients.

In this study, the specific characteristic of breast cancer was included in the final model, which has not yet been reported. The variables indentified as being important predictors for PICC-RVT in breast cancer patients included: COPD, history of CVC, PLT level, APTT level, D-dimer level, menopause, breast surgery, upper limb lymphedema, endocrine therapy, all of which were objectively measurable, and the last four variables were the specific characteristic for breast cancer. The results showed that patients with menopause were more likely to develop venous thrombosis, this may be attributed to menopausal hormone therapy [22]. The risk of PICC-RVT in breast cancer patients without breast surgery was three times than that in patients with breast surgery. This may because the tumor in the body activate the coagulation system and weaken the fibrinolysis system when the breast tumor is not surgically removed, which would lead to thrombosis development [23]. Most breast cancer patients will have axillary lymph node dissection on the affected side, and a few people will have opposite lymph node dissection, which would cut off the pathway of lymphatic reflux and cause lymphedema [24]. This study found that the risk of PICC-RVT in breast cancer patients with lymphedema was 28 times than that without lymphedema. After lymphedema, a large amount of lymph leakage will cause blood concentration. Swelling of the limbs will compress the blood vessels and slow down the blood flow. Besides, the limited mobility of the limbs with lymphedema increases the risk of thrombosis [25–26]. Meanwhile, lymphedema patients are

prone to infection and inflammation [27]. It has been reported that the more serious the infection, the higher the risk thrombosis [28]. In this study, we found that the risk of PICC related thrombosis in patients with endocrinotherapy was more than 4 times than that in patients without endocrinotherapy, which may be related to the significantly increased risk of venous thrombosis [29–30]. Endocrine therapy is one of the main means of systemic treatment for breast cancer, and it is also the treatment method that making breast cancer specific to other tumors [31].

We developed the scoring system with score ≥ 3.5 indicated high risk of PICC-RVT in breast cancer patients. The results show that the AUC in both sample were greater than 0.8, and the sensitivity and specificity were more than 70%, and the Hosmer-Lemeshow goodness of fit test showed that there was no significant difference between the prediction results of PICC-RVT of the scoring systems and the actual results, the scoring system has acceptable prediction accuracy. The scoring system developed in the current study allows the corporation of breast cancer specific factors that will identify patients at high risk and ensure they are receiving appropriate prophylaxis. The scoring system is applicable to breast cancer patients, which is the most common cancer in female. Besides, it can discriminate between high and low risk patients. The risk threshold for medical decision making can also be shifted up or down, depending on a patients' or clinician's risk tolerance. The primary use of this tool as we see it is to modify current anti-thrombosis prophylaxis to avoid unnecessary thrombosis, identify patients who require additional education regarding PICC-RVT management, and to monitor current antiemetic protocols.

Despite the potential benefits of the PICC-RVT risk model in breast cancer patients, several limitations in the current study that need to be acknowledged. Even though we have validated the risk scoring system, it was carried out in the same institution, which may lead to a certain degree of bias in the selection of patients. The model should undergo external prospective validation on a new sample of patients. In addition, we applied a retrospective design to develop the model, it is generally accepted that this kind of research design could lead to underreporting the incidence of PICC-RVT, so the actual rate of PICC-RVT may be higher than we reported.

Despite the above limitations, this study has important implications for future research and clinical practice. Patients who are stratified into high risk for PICC-RVT would benefit from frequent PICC-RVT screening and implementation of prevention strategies. Importantly, this PICC-RVT prediction rule in patients with breast cancer provides a method to stratify at-risk patients before insertion for such interventions to ultimately reduce PICC-RVT occurrence and cost of PICC-RVT.

Conclusion

In this study, we developed a PICC-RVT risk prediction scoring system in breast cancer patients. The disease-specific factors of breast cancer, such as endocrine therapy, lymphedema of upper extremity play important roles in the development of PICC-RVT. The clinical application of the scoring system will be important source of individual patient risk information for oncology clinician and may enhance patient care by optimizing the use of the anticoagulation in a proactive manner.

Declarations

Authors' contributions

1. Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data (LX, WT, PS,YZ, LQ)
2. Drafting the manuscript or revising it critically for important intellectual content (LX, WT, PS)

All authors approved the final version and agreed to be accountable for all aspects of the work

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Conflict of Interest/Competing interests:

No conflict of interest has been declared by the author(s)

Availability of data and material:

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request

Authors' contributions:

1. Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data (LX, WT, PS,YZ, LQ)
2. Drafting the manuscript or revising it critically for important intellectual content (LX, WT, PS)

All authors approved the final version and agreed to be accountable for all aspects of the work

Ethical approval

The work was conducted in accordance with the Declaration of Helsinki. The study was approved by Medical Ethics Committee of Hunan Cancer Hospital.

Consent to participate:

N/A

Consent for publication:

N/A

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Figures

Figure 1

ROC curves showing score function. A for derivation cohort, B for validation cohort