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

Si-yi Peng (pengsiyi@hnca.org.cn)
Affiliated Cancer Hospital of School of Medicine Central South University Xiangya: Hunan Cancer Hospital
https://orcid.org/0000-0003-3342-9981

Tao WEI
Affiliated Cancer Hospital of School of Medicine Central South University Xiangya: Hunan Cancer Hospital

Xu-ying LI
Affiliated Cancer Hospital of School of Medicine Central South University Xiangya: Hunan Cancer Hospital

Zhong YUAN
Hunan cancer hospital

Qin LIN
Affiliated Cancer Hospital of School of Medicine Central South University Xiangya: Hunan Cancer Hospital

Research Article

Keywords: Breast cancer, peripherally inserted central catheter, risk, prediction, thrombosis

DOI: https://doi.org/10.21203/rs.3.rs-330758/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
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 role 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 (Philipsiu22, 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 (Philipsiu22, 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 \( \leq 0.10 \) in univariate analysis (including Fisher exact test, \( \chi^2 \) 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 \( \geq 0.70 \) 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  | %  | derivation sample (n=978) | validation sample (n=284) | Statistics value | P     |
|------------------------|------------|----|----|--------------------------|---------------------------|-----------------|-------|
| 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)                  |                           |                 |       |
| Category                                      | Municipal Medical Insurance | At One's Own Expense | Habitation | Township / Rural | Vein Selected For Insertion | Insertion Side | Venipuncture Method | Placement Complication | Placement Attempts | Catheter Diameter / Vessel Diameter | BMI | Blood Type |
|----------------------------------------------|------------------------------|----------------------|------------|-----------------|-----------------------------|----------------|---------------------|-----------------------|-------------------|-------------------------------------|-----|------------|
|                                              | 41.04.20                      | 17.06.00             | 4.0.40     | 1.0.40          | Basilic vein                | Left limb      | Ultrasound guidance | Yes                   | 1                 | ≥0.45                               | 18.5| A          |
|                                              |                              |                      |            |                 |                             |                | Tradition           | No                    | 913.93.40         | 0.45                               |     | B          |
|                                              |                              |                      |            |                 |                             |                | Tradition           | No                    | 913.93.40         | 0.45                               |     | O          |
|                                              |                              |                      |            |                 |                             |                | Tradition           | No                    | 913.93.40         | 0.45                               |     | AB         |
| Condition                        | Yes | No  | Median | IQR | P-value | 95% CI of median |
|---------------------------------|-----|-----|--------|-----|---------|------------------|
| Hypertension                    | Yes | 185 | 18.9   | 48  | 0.593   | 0.441            |
| Diabetes                        | Yes | 79  | 8.1    | 21  | 0.141   | 0.707            |
| Coronary heart disease          | Yes | 7   | 0.7    | 10  | -       | 0.692            |
| Hyperlipidemia                  | Yes | 119 | 12.2   | 29  | 0.814   | 0.367            |
| Chronic kidney disease          | Yes | 5   | 0.5    | 0   | -       | 0.593            |
| COPD                            | Yes | 8   | 0.8    | 3   | -       | 0.718            |
| Operation history               | Yes | 363 | 37.1   | 117 | 1.555   | 0.212            |
| Radiation therapy history       | Yes | 34  | 3.5    | 10  | 0.001   | 0.971            |
| Endocrine therapy history       | Yes | 56  | 5.7    | 19  | 0.366   | 0.545            |
| Smoking history                 | Yes | 11  | 1.1    | 2   | -       | 0.744            |
| Drinking history                | Yes | 20  | 2.0    | 6   | 0.005   | 0.944            |
| CVC placement history           | Yes | 7   | 0.7    | 2   | -       | 1.000            |
| Anticoagulant                   | Yes | 11  | 1.1    | 2   | -       | 0.744            |
| Anticoagulant drugs             | Yes | 46  | 4.7    | 14  | 0.025   | 0.875            |
| Antiplatelet drugs              | Yes | 7   | 0.7    | 2   | -       | 1.000            |
| WBC                             | ≤4.0| 44  | 4.5    | 7   | 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  | 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      |
| PT     | 0.55 | 128.13.1 | 31.10.9 |
|--------|------|----------|---------|
| 10.0   | 10.10.1 | 5.1.8 | 1.816 0.403 |
| 10.0~13.5 | 865.88.4 | 244.85.9 |
| 13.5   | 103.10.5 | 35.12.3 |
| FIB    | 1.8 | 25.26.1 | 4.14.1 | 3.006 0.222 |
| 1.8~3.5 | 737.75.4 | 206.72.5 |
| 3.5    | 216.22.1 | 74.26.1 |
| APTT   | 20.0 | 6.0.6 | 10.0.4 | 0.301 0.860 |
| 20.0~40.0 | 896.91.6 | 260.91.5 |
| 40.0   | 76.7.8 | 23.8.1 |
| Menopause | Yes | 402.41.1 | 104.36.6 | 1.843 0.175 |
| No     | 576.58.9 | 180.63.4 |
| Disease stage | I | 154.15.7 | 39.13.3 | 2.925 0.403 |
| II     | 451.46.1 | 146.51.4 |
| III    | 265.27.1 | 67.23.6 |
| IV     | 108.11.0 | 32.11.3 |
| Pathological type | Infiltrative specific cancer | | 14.1.4 | 6.2.1 | 1.519 0.468 |
| Infiltrative non specific cancer | 961.98.3 | 278.97.9 |
| Other | 3.0.3 | 0.0.0 |
| Metastasis | Yes | 609.62.3 | 176.62.0 | 0.008 0.927 |
| Tumor location 1 | Left side | 504.51.5 | 142.50.0 | 0.489 0.783 |
| Right side | 467.47.8 | 139.48.9 |
| Bilateral | 7.0.7 | 3.1.1 |
| Tumor location 2 | Outer upper quadrant | 572.58.5 | 145.51.1 | 6.621 0.250 |
| Outer lower quadrant | 110.11.2 | 41.14.4 |
| Inner upper | 196.20.0 | 60.21.1 |
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 value ≤ 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 (years)       | 21~30           | 1~3.1%            | 31~96.9%          | 7.358           | 0.118^a|
|                   | 31~40           | 7~4.2%            | 158~95.8%         |                 |         |
|                   | 41~50           | 12~2.8%           | 417~97.2%         |                 |         |
|                   | 51~60           | 12~4.6%           | 250~95.4%         |                 |         |
|                   | ≥61             | 8~8.9%            | 82~91.1%          |                 |         |
| Marital status    | Married         | 40~4.1%           | 929~95.9%         | 0.387           | 0.824^a|
|                   | Unmarried       | 0~0.0%            | 7~100.0%          |                 |         |
|                   | Divorce         | 0~0.0%            | 2~100.0%          |                 |         |
| Education levels  | Primary or below| 22~3.4%           | 620~96.6%         | 4.813           | 0.090^a|
|                   | Secondary       | 14~6.8%           | 193~93.2%         |                 |         |
|                   | Tertiary or above| 4~3.1%         | 125~96.9%         |                 |         |
| Profession        | Farmer          | 12~3.4%           | 338~96.6%         | 10.922          | 0.142^a|
|                   | Worker          | 6~7.8%            | 71~92.2%          |                 |         |
|                   | Businessman     | 2~10.0%           | 18~90.0%          |                 |         |
|                   | Enterprise employees | 9~5.8%   | 145~94.2%         |                 |         |
|                   | Teacher         | 1~1.9%            | 53~98.1%          |                 |         |
|                   | Medical staff   | 1~7.1%            | 13~92.9%          |                 |         |
|                   | Civil servant   | 2~10.0%           | 18~90.0%          |                 |         |
|                   | Other           | 7~2.4%            | 282~97.6%         |                 |         |
| Medical insurance | Rural medical insurance | 16~2.7% | 584~97.3% | 12.389 | 0.015^a|
|                   | Urban medical insurance | 18~5.7% | 300~94.3% |                 |         |
|                   | Provincial medical insurance | 1~6.7% | 14~93.3% |                 |         |
|                   | Municipal medical insurance | 5~12.2% | 36~87.8% |                 |         |
|                   | At one's own expense | 0~0.0%   | 4~100.0%          |                 |         |
| Habitation        | City            | 25~6.2%           | 376~93.8%         | 7.968           | 0.005^a|
| Parameter                                      | Township /Rural | 15·2.6 | 562·97.4 |
|------------------------------------------------|-----------------|--------|----------|
| Vein selected for insertion                    | Basilic vein    | 33·3.9 | 816·96.1 |
|                                                | Brachial vein   | 60·4.9 | 117·95.1 | 2.703  | 0.259<sup>a</sup> |
|                                                | Other           | 1·16.7 | 5·83.3   |
| Insertion side                                 | Left limb       | 20·3.9 | 491·96.1 | 0.085  | 0.771<sup>a</sup> |
|                                                | Right limb      | 20·4.3 | 447·95.7 |
| Venipuncture method                            | Ultrasound guidance | 40·4.1 | 932·95.9 | -      | 1.000<sup>b</sup> |
|                                                | Tradition       | 0·0.0  | 6·100.0  |
| Placement complication                         | Yes             | 3·4.6  | 62·95.4  | -      | 0.744<sup>b</sup> |
| Placement attempts                             | 1               | 38·4.0 | 909·96.0 | -      | 0.365<sup>b</sup> |
|                                                | ≥2              | 2·6.5  | 29·93.5  |
| Catheter/vessel ratio                          | ≤0.45           | 33·4.0 | 784·96.0 | 0.033  | 0.857<sup>a</sup> |
|                                                | ≥0.45           | 7·4.3  | 154·95.7 |
| Body Mass Index (BMI)                          | ≤18.5           | 2·6.9  | 27·93.1  | 1.152  | 0.562<sup>c</sup> |
|                                                | 18.5~23.9       | 23·4.4 | 495·95.6 |
|                                                | ≥24             | 15·3.5 | 416·96.5 |
| Blood type                                     | A               | 14·4.2 | 318·95.8 | 1.521  | 0.677<sup>a</sup> |
|                                                | B               | 11·4.8 | 217·95.2 |
|                                                | O               | 10·3.1 | 314·96.9 |
|                                                | AB              | 5·5.3  | 89·94.7  |
| Hypertension                                   | Yes             | 10·5.4 | 175·94.6 | 1.006  | 0.316<sup>a</sup> |
| Diabetes                                       | Yes             | 4·5.1  | 75·94.9  | -      | 0.557<sup>b</sup> |
| Coronary heart disease                         | Yes             | 0·0.0  | 7·100.0  | -      | 1.000<sup>b</sup> |
| Hyperlipidemia                                 | Yes             | 7·5.9  | 112·94.1 | -      | 0.319<sup>b</sup> |
| Chronic kidney disease                         | Yes             | 2·40.0 | 3·60.0   | -      | 0.015<sup>b</sup> |
| COPD                                           | Yes             | 3·37.5 | 5·62.5   | -      | 0.003<sup>b</sup> |
|                               |       |       |       |       |       |
|-------------------------------|-------|-------|-------|-------|-------|
| **Operation history**         | Yes   | 23±6.3 | 340±93.7 | 7.424 | 0.006^a |
| **Chemotherapy history**      | Yes   | 16±18.4 | 71±81.6 | - | 0.000^b |
| **Radiation therapy history** | Yes   | 7±20.6 | 27±79.4 | - | 0.000^b |
| **Endocrine therapy history** | Yes   | 13±23.2 | 43±76.8 | - | 0.000^b |
| **Smoking history**           | Yes   | 1±9.1  | 10±90.9 | - | 0.370^b |
| **Drinking history**          | Yes   | 0±0.0  | 20±100.0 | - | 1.000^b |
| **CVC placement history**     | Yes   | 3±42.9 | 4±57.1 | - | 0.002^b |
| **Anticoagulant**             | Yes   | 2±18.2 | 9±81.8 | - | 0.071^b |
| **Antiplatelet drugs**        | Yes   | 1±14.3 | 6±85.7 | - | 0.254^b |
| **WBC**                       |       | 4.0±4.5 | 42.95.5 | 14.809 | 0.001^c |
|                               | 4.0~10.0 | 33±3.6 | 874±96.4 | |
|                               | 10.0   | 5±18.5 | 22±81.5 | |
| **Hb**                        |       | 110±3.4 | 114±96.6 | 10.943 | 0.004^c |
|                               | 110~150 | 33±3.9 | 813±96.1 | |
|                               | 150    | 3±21.4 | 11±78.6 | |
| **PLT**                       |       | 100±12.5 | 14±87.5 | 21.865 | 0.000^c |
|                               | 100~300 | 24±2.9 | 812±97.1 | |
|                               | 300    | 14±11.1 | 112±88.9 | |
| **D-dimer**                   | ≤0.55 | 24±2.8 | 826±97.2 | 26.555 | 0.000^a |
|                               | 0.55   | 16±12.5 | 112±87.5 | |
| **PT**                        |       | 10.0±0.0 | 10±100.0 | 0.583 | 0.747^c |
|                               | 10.0~13.5 | 35±4.0 | 830±96.0 | |
|                               | 13.5   | 5±4.9 | 98±95.1 | |
| **FIB**                       |       | 1.8±12.0 | 22±88.0 | 32.344 | 0.000^c |
|                               | 1.8~3.5 | 15±2.0 | 722±98.0 | |
|                          | 3.5 | 22 | 194 | 89.8 |
|--------------------------|-----|----|-----|------|
| APTT                     | 20.0| 33.3| 66.7| 14.60| 0.001<sup>c</sup> |
|                          | 20.0~40.0 | 37.4 | 859 | 95.9 |
|                          | 40.0 | 11.3| 75 | 98.7 |
| Menopause                | Yes | 27.6 | 375 | 93.3 |
| Disease stage            | I   | 53.2 | 149 | 96.8 |
|                          | II  | 19.4 | 432 | 95.8 |
|                          | III | 93.4 | 256 | 96.6 |
|                          | IV  | 76.5 | 101 | 93.5 |
| Pathological type        | Infiltrative specific | 0 | 100 | 7.14 |
|                          | Infiltrative non-specific | 39 | 4.1 | 922 | 95.9 |
|                          | Other | 133.3 | 266.7 |
| Metastasis               | Yes | 34.5 | 575 | 94.4 |
| Tumor location 1         | Left side | 20 | 4.0 | 484 | 96.0 |
|                          | Right side | 19 | 4.1 | 448 | 95.9 |
|                          | Bilateral | 114.3 | 85.7 |
| Tumor location 2         | Outer upper quadrant | 24 | 4.2 | 548 | 95.8 |
|                          | Outer lower quadrant | 6.5 | 104 | 94.5 |
|                          | Inner upper quadrant | 6.3 | 190 | 96.9 |
|                          | Inner lower quadrant | 36.4 | 44 | 93.6 |
|                          | Areola area | 0 | 100 | 34 |
|                          | Other | 5.3 | 18 | 94.7 |
| Breast surgery           | Yes | 22 | 2.5 | 849 | 97.5 |
| Upper limb lymphedema    | Yes | 84.4 | 10 | 55.6 |
| Anthracyclines           | Yes | 23 | 2.9 | 757 | 97.1 |
| Platinum-based           | Yes | 69.0 | 61 | 91.0 |
| Trastuzumab              | Yes | 85.3 | 143 | 94.7 | 0.664 | 0.415<sup>a</sup>
After the initial univariate screening, the potential predictive factors associated with PICC-RVT were retain 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

| 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

**Funding:**

This work were partly supported by the funds from Science and Technology Planning Project of Hunan Province, China [NO.2020JJ8018 (Xu-ying Li)], Science and Technology Planning Project of Hunan Province, China [NO.2020JJ8065 (Zhong Yuan)], Science and Technology Planning Project of Hunan Province, China [NO.2018JJ8089 (Qin Lin)].

**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

References

1. International Agency for Research on Cancer. (2020). Latest global cancer data
   https://www.iarc.fr/faq/latest-global-cancer-data-2020-qa/

2. National Cancer Institute (2018). Surveillance Epidemiology and End Results (SEER) program. Cancer
   query system: SEER survival statistics. https://https://seer.cancer.gov/canques/survival.html.
   Accessed 15 June 2020.

3. Fallouh, N., McGuirk, H. M., Flanders, S. A., & Chopra, V. (2015). Peripherally Inserted Central Catheter-
   associated Deep Vein Thrombosis: A Narrative Review. Am J Med, 128(7), 722-738.
   https://doi.org/10.1016/j.amjmed.2015.01.027

4. Iriondo, J., Iarra, O., Sarriegui, B., Sanz, N., & Ceberio, I. (2020). Peripherally inserted central catheter (picc)
   related deep venous thrombosis: a retrospective cohort study on incidence and risk factors in a single center.
   Blood, 136(Supplement 1), 30-31. https://doi.org/10.1182/blood-2020-139506

5. Bertoglio, S., Faccini, B., Lalli, L., Cafiero, F., & Bruzzi, P. (2016). Peripherally inserted central catheters
   (PICCs) in cancer patients under chemotherapy: A prospective study on the incidence of complications and
   overall failures. J Surg Oncol, 113(6), 708-714. https://doi.org/10.1002/jso.24220

6. Garrino, C., Gennaro, C., Monasterolo, G., Pischedda, F., & Mussa, B. (2012). Feasibility, efficacy and
   advantages of an early diagnosis and treatment of picc-related thrombosis in cancer patient. European Journal
   of Surgical Oncology (EJSO), 38(10), P1009-1010.

7. Gorski L A, Hadaway L, Hagle M, & McGoldrick, M. (2016). 2016 Infusion therapy standards of practice.
   Journal of Infusion Nursing, 39(1 Suppl.), S1-S159.

8. Seeley, M. A., Santiago, M., & Shott, S. (2007). Prediction tool for thrombi associated with peripherally
   inserted central catheters. Journal of Infusion Nursing, 30(5), 286.
   https://doi.org/10.1097/01.nan.0000292570.62763.3f

9. Chopra, V., Kaatz, S., Conlon, A., Paje, D., Grant, P. J., Rogers, M. A. M., ... Flanders, S. A. (2017). The
   michigan risk score to predict peripherally inserted central catheter-associated thrombosis. Journal of
   Thrombosis and Haemostasis, 15(10), 1951-1962. https://doi.org/10.1111/jth.13794

10. Feng, Y., Zheng, R., Fu, Y., Xiang, Q., Yue, Z., & Li, J., et al. (2021). Assessing the thrombosis risk of
    peripherally inserted central catheters in cancer patients using caprini risk assessment model: a
    prospective cohort study. Support Care Cancer. https://doi.org/10.1007/s00520-021-06073-4

11. Marnejon, T., Angelo, D., Abdou, A. A., & Gemmel, D. (2012). Risk Factors for Upper Extremity Venous
    Thrombosis Associated with Peripherally Inserted Central Venous Catheters. The Journal of Vascular
    Access, 13(2), 231–238. https://doi.org/10.5301/jva.5000039
12. Bonizzoli, M., Batacchi, S., Cianchi, G., Zagli, G., Lapi, F., Tucci, V., ... Peris, A. (2010). Peripherally inserted central venous catheters and central venous catheters related thrombosis in post-critical patients. Intensive Care Medicine, 37(2), 284-289. https://doi.org/10.1007/s00134-010-2043-x

13. Xing, L., Adhikari, V. P., Liu, H., Kong, L., Liu, S., Li, H. Y., ... & Wu, K. N. (2012). Diagnosis prevention and treatment for PICC-related upper extremity deep vein thrombosis in breast cancer patients. Asia-pacific Journal of Clinical Oncology, 8(3), e12–e16. https://doi.org/10.1111/j.1743-7563.2011.01508.x

14. Shi, Y., Wen, L., Zhou, Y., & Tao, S. (2014). Thrombotic risk factors in patients undergoing chemotherapy via peripherally inserted central catheter. Journal of International Medical Research, 42(3), 863-869. https://doi.org/10.1177/0300060514527061

15. Lee, Y. G., Lee, E., Kim, I., Lee, K. W., Kim, T. M., & Lee, S. H. (2015). Cisplatin-based chemotherapy is a strong risk factor for thromboembolic events in small-cell lung cancer. Cancer Research & Treatment, 10 (4), 4143-4148. https://doi.org/10.4143/crt.2014.045

16. Gao, Y., Liu, Y., Chen, W., Wei, L., Song, L., & Ma, X. (2015). Peripherally inserted central catheter thrombosis incidence and risk factors in cancer patients: a double-center prospective investigation. Therapeutics & Clinical Risk Management, 11, 153-160.

17. Hao, N., Xie, X., Zhou, Z., Li, J., Kang, L., Wu, H., ... Zhang, H. (2017). Nomogram predicted risk of peripherally inserted central catheter related thrombosis. Scientific Reports, 7(1), 6344. https://doi.org/10.1038/s41598-017-06609-x

18. Jiang, S. L., & Li, G. H. (2014). Causes analysis and nursing research progress of PICC related complications in breast cancer patients undergoing chemotherapy. Chinese Journal of Modern Nursing, 20(9), 1012-1015. https://doi.org/10.3760/cma.j.issn.1674-2907.2014.09.007

19. Mailhe, M., Aubry, C., Brouqui, P., Michelet, P., & Lagier, J. C. (2020). Complications of peripheral venous catheters (pvcs): the need to propose alternative route of administration. International Journal of Antimicrobial Agents, 55(3), 105875. https://doi.org/10.1016/j.ijantimicag.2020.105875

20. Kang, J., Sun, W., Li, H., Ma, E., Wang, K., & Chen, W. (2016). Peripherally Inserted Central Catheter-Related Vein Thrombosis in Breast Cancer Patients. The Journal of Vascular Access, 17(1), 67–71. https://doi.org/10.5301/jva.5000457

21. Kang, J. R., Chen, W., Li, H. L., Sun, W. Y., Wang, K., Song, Q., Liu, B., & Ma, E. L. (2013). Diagnosis and treatment of peripherally inserted central venous catheter-associated symptomatic upper extremity vein thrombosis in breast cancer patients undergoing chemotherapy. Chinese Journal of Clinical Nutrition, 21(6), 380-383. https://doi.org/10.3760/cma.j.issn.1674-635X.2013.06.012

22. Canonico, M., Plu-Bureau, G., Lowe, G. D. O., & Scarabin, P-Y. (2008). Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ, 336(7655), 1227–1231. https://doi.org/10.1136/bmj.39555.441944.be
23. Cui, C. J., & Cui, W. (2019). Risk prediction of malignant tumor related venous thrombosis. Chinese Journal of Laboratory Medicine, 42(4), 236-240. https://doi.org/10.3760/cma.j.issn.1009-8158.2019.04.003

24. Zhu, Y.Q., Xie, Y. H., Liu, F. H., Guo, Q., Shen, P. P., & Tian, Y. (2014). Systemic analysis on risk factors for breast cancer related lymphedema. Asian Pacific Journal of Cancer Prevention, 15(16), 6535-41. https://doi.org/10.7314/APJCP.2014.15.16.6535

25. Thomet, C., Belgrado, J. P., Vankerckove, S., Grijseels, S., Heijmans, S., De Smet, S., & Vandermeeren, L. (2016). The Chondroepitrochlearis Muscle: A Rare Cause of Axillary Vein Thrombosis and Lymphedema. Lymphology, 49(3), 133-139.

26. Kunze, G., & Staritz, M. (2017). Lymph Vessel Thrombus Detection in Cervical Lymphedema: A Case Series. Journal of Ultrasound in Medicine, 36(9), 1955–1960. https://doi.org/10.1002/jum.14249

27. Liu, F., Lu, Q., & OuYang, Q. (2015). The relationship between lymphedema status and lymphedema symptoms in breast cancer survivors. Chinese Journal of Nursing, 51(5), 518-522. https://doi.org/10.3761/j.issn.0254-1769.2016.05.001

28. Clemence, B. J., & Maneval, R. E. (2014). Risk factors associated with catheter-related upper extremity deep vein thrombosis in patients with peripherally inserted central venous catheters: literature review: part 1. Journal of Infusion Nursing, 37(3), 187. https://doi.org/10.1097/NAN.0000000000000037.

29. Onitilo, A. A., Doi, S. A. R., Engel, J. M., Glurich, I., Johnson, J., & Berg, R. (2012). Clustering of venous thrombosis events at the start of tamoxifen therapy in breast cancer: A population-based experience. Thrombosis Research, 130(1), 27–31. https://doi.org/10.1016/j.thromres.2011.11.025

30. Valérie, Olié, Marianne, Canonico, Pierre-Yves, & Scarabin. (2010). Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women. Current Opinion in Hematology, 17(5), 457-463. https://doi.org/10.1097/MOH.0b013e32833c07bc

31. Burstein, H. J., Lacchetti, C., Anderson, H., Buchholz, T. A., Davidson, N. E., Gelmon, K. A., ... Griggs, J. J. (2018). Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update. Journal of Clinical Oncology, 37(5), 423-438. https://doi.org/10.1200/JCO.18.01160

Figures
**Figure 1**

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