Lymphology 55 (2022) 178-187

UPPER LIMB LYMPHEDEMA IMPACTS THE RISK OF PERIPHERALLY INSERTED CENTRAL CATHETER-RELATED THROMBOSIS IN PATIENTS WITH BREAST CANCER

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ABSTRACT

There is little information on the risk for catheter-related thrombosis in patients with upper limb lymphedema following breast cancer treatment. We investigated the association between upper limb lymphedema and the risk of peripherally inserted central catheter-related thrombosis (PICC-RT) occurring in the contralateral limb of patients with breast cancer. A retrospective review analyzed all patients with breast cancer who underwent PICC insertion at a cancer hospital in Hunan Province from 2015 to 2019. Upper limb lymphedema was indexed from hospital information system (HIS) before the occurrence of PICC-RT developed in the contralateral limb. Cox regression analysis was used to evaluate the association of factors with outcome. A total of 1,262 patient records were found and 50 cases of PICC-RT were identified. Forty of these occurred in patients without lymphedema (n=1,236) and 10 in patients with upper limb lymphedema (n=26). After adjustment for various co-variables, Cox regression analysis showed that upper limb lymphedema was significantly associated with increased risk of PICC-RT (hazard ratio=12.128, 95% confidence interval=5.551-26.501; P<0.001). In breast cancer patients, upper limb lymphedema may be an important predictor for PICC-RT in the contralateral limb and information should be provided to patients.

Keywords: lymphedema, thrombosis, breast cancer, peripherally inserted central catheter

Breast cancer is currently the most common malignancy in females (1). As a common complication after comprehensive treatment for breast cancer, the topic of lymphedema has been increasingly discussed in the clinical setting (2,3). Peripherally inserted central catheter (PICC) is widely used for chemotherapy in patients with breast cancer, and its use can cause various adverse events. Among these, PICC-related thrombosis (PICC-RT) is one of the most frequent and serious complications (4). Whether there is a relationship between the two common complications is not clear.

Cancer-related lymphedema is due to treatments that lead to the obstruction of lymphatic system causing protein-rich lymph to accumulate in the tissue space (5). Failure to manage lymphedema effectively can result in chronic swelling and distortion of the shape of affected body part as well as pain, discomfort, infection, impaired sensation, and restricted

mobility (6). Thrombosis is affected by many factors. According to Virchow's triad theory of thrombosis, PICC insertion damages the integrity of vessel wall placing these patients at high risk for thrombosis (7). Impaired venous flow in the limb with lymphedema would in-crease the risk of venous thrombosis (6). In patients with high-risk state of thrombosis, such as cancer patients (7), lymphedema of the affected limb may increase the systemic burden of the blood circulation with a higher hypercoagulable state, and therefore increase the risk of limb thrombosis on the side of catheterization.

Some investigators have explored the risk factors of PICC-RT in breast cancer patients (8,9), however, the predictive variables didn't include lymphedema. Select reports have reported both thrombosis and lymphedema, but their focus was not on the association between the two complications (10,11). One study showed that lower extremity deep venous thrombosis was associated with postoperative lymphedema in patients with endometrial cancer (12). Another study reported the incidence of lymphedema and thrombosis in wound management demonstrating that in 11 cases of lymphedema, 3 cases (27%) has the co-morbidity of thrombosis (13). We may surmise that there is a relationship between the two complications. However, the article did not do further analysis to explore the association between the two complications under conditions that controlled other factors.

This study aimed to identify whether, after adjustment of other known risk factors for PICC-RT, including but not limited: ratio of catheter to vein, blood type, D-dimer, central venous catheter placement history, lymphedema still remained an independent association with PICC-RT.

METHODS

This single center retrospective cohort study was approved by the Medical Ethics Committee of Hunan Cancer Hospital, Hunan Province, China. Data were collected from the hospital information system (HIS) and the vascular access insertion center (VAIC) in the hospital. First, we obtained the PICC insertion data of breast cancer patients from VAIC, then we use inpatient number to search HIS to acquire other related data. We reviewed the data from January 2015 to August 2019. Data were included if cases (1) were diagnosed with breast cancer, (2) were female with age ≥18 years old, and (3) received PICC insertion in our hospital. Data would be excluded if the patient had bilateral upper limb lymph node dissection. According to the criteria, we included 1262 cases for analysis.

Data Collection

We collected related patient information from the points of insertion to extraction of the PICC. After obtaining PICC insertion data from VAIC, we then collected data including insertion vein, insertion side, placement attempts, and catheter/vessel diameter. Then we collect patient data from the HIS including (1) demographic data: age, body mass index (BMI), hypertension, diabetes, chronic obstructive pulmonary disease (COPD), smoking history, central venous catheter (CVC) placement history; (2) laboratory test results: ABO blood type, hemoglobin (Hb), platelet (PLT) count, fibrinogen (FIB) level, D-dimer, and activated partial thromboplastin time (APTT); and (3) breast cancer-specific data: menopause, cancer stage, pathological type, cancer side, lymphedema, use of anthracyclines, platinum-based drugs, trastuzumab, radiation therapy, and endocrine therapy. All data were extracted by two investigators independently. To protect patient privacy and confidentiality, we only used the patient number until all data for the study was obtained.

Outcome Measures

PICC-RT was the main outcome. When patients reported arm pain or swelling, ultra-sonography (Philipsiu22, Netherlands) was utilized. When lymphedema was identified, hospital records were examined to extract lymphedema related information. In our hospital, clinicians mainly utilize a method of 5-point circumference measurement to diagnose

lymphedema (14). Lymphedema would be diagnosed when the difference between the two sides was greater than 2cm. In examining the records from HIS, any records with "swelling", "lymphedema", or "heavy limb" on the operative side would be classified as lymphedema. For those cases with "limb swelling" or "heavy limb" on the operated side, we would then collect results of routine blood tests, blood coagulation test, and B-ultrasonic examination on the nearest date. If there was no clear indication of thrombosis, it would be classified as a case of lymphedema. For laboratory test results, the value of APTT, PLT, D-dimer, and FIB were extracted before insertion of PICC.

Quality Control

VAIC is a centralized place for hospital to provide PICC implantation with more than 3,000 PICCs insertion per year. The service is provided by two full-time personnel, both of whom are members of Infusion Nurses Society with rich experience in PICC placement which can ensure the quality of PICC placement.

Data Analysis

Statistical analysis was performed by SPSS software (version 22, SPSS Inc, IBM, NY, USA). Categorical data were presented as frequency and percentage (%). Continuous data were presented as mean and standard deviation (SD). Survival curves were estimated using Kaplan-Meier product-limited method and compared by the Mantel (15) (Log-rank test). Cox regression analysis was used to evaluate univariable and multivariable association of factors with PICC-RT. We used Cox regression models conditioned on the variables with P value <0.1 in the results of univariate analysis to estimate multivariable-adjusted hazards ratios (HR) and 95% confidence interval (CI) of the association between lymphedema and PICC-RT. all statistical tests were two-tailed. P<0.05 was considered statistically significant.

RESULTS

Characteristic of Sample

The average age of the patients was 47.5 (SD 8.8) with a range of 21-78 years, most of them (55.2%) were middle-aged. All patients were females, 2.8% of them had a low BMI (BMI<18.0). 23.7% of the patients (n=299) had chronic disease with hypertension most common (n=233). Detailed demographics are shown in *Table 1*.

All the catheters were inserted under the guidance of B-ultrasound. All catheters are made of silicon, and the distal end is designed with three valve openings. The ratio of catheter/vessel mostly was lower than 0.45 accounting for 84.2% of the patients (n=1062). Detailed PICC related information can be seen in *Table 1*.

Of the patients receiving chemotherapy, 78.9% (n=996) received Anthracyclines-based chemotherapy regimen and 7.2% (n=91) received platinum-based treatment. 89.1% of patients (n=1124) had breast surgery and of these, 98.3% (n=1105) had axillary lymph node dissection. Most patients were diagnosed with invasive ductal carcinoma. 11.9% of the patients (n=138) had a higher level of PT, and a low level of APTT was found in 0.6% of patients (n=7). 12.6% of the patients (n=159) had a higher level of D-dimer. Two patients had a history of deep venous thrombosis, 60 patients had records of anticoagulant drug use, and 9 had antiplatelet drug use. Detailed disease and laboratory test results related characteristics are showed in *Table 2*.

PICC-RT in Patients with Breast Cancer

A total of 50 breast cancer patients (3.96%) were diagnosed with PICC-RT by color Doppler ultrasound. Among 50 cases of catheter-related thrombosis, 62% (n=31) occurred in a single site including 38.7% (n=12) in basilic vein, 19.4% (n=6) in axillary veins, 12.9% (n=4) in internal jugular vein, and 12.9% (n=4) in the subclavian vein. The indwelling time of PICC ranged from 1 to 396

TABLE 1
Demographic and PICC- Related Characteristic of The Patients

Variable	Category	Total (n=1262)	PICC-RT (%)	
			Yes(n=50)	No(n=1212)
Age（years）	18~44	424(33.6)	14(28.0)	410(33.8)
	45~59	697(55.2)	26(52.0)	671(55.4)
	60 and above	141(11.2)	10(20.0)	131(10.8)
Body Mass Index (BMI)	＜18.5	35(2.8)	2(4.0)	33(2.7)
	18.5~23.9	679(53.8)	31(62.0)	648(53.5)
	≥24	548(43.4)	17(34.0)	531(43.8)
Blood type	A	440(34.9)	18（36.0）	422(34.8)
	B	299(23.7)	14（28.0）	285(23.5)
	O	407 (32.3)	12（24.0）	395(32.6)
	AB	116(9.2)	6（12.0）	110(9.1)
Hypertension	Yes	233(18.5)	12（24.0）	221(18.2)
Diabetes	Yes	100(7.9)	4（8.0）	96(7.9)
COPD	Yes	11(0.8)	3（6.0）	8(0.7)
Smoking history	Yes	13(1.0)	1（2.0）	12(1.0)
History of CVC placement history	Yes	9(0.7)	4（8.0）	5(0.4)
Vein selected for insertion	Basilic vein	1083(85.8)	41(82.0) ()	1042(86.0)
	Brachial vein	169(13.4)	8(16.0)	161(13.3)
	Other	10(0.8)	1(2.0)	9(0.7)
Insertion side	Left limb	674(53.4)	25(50.0)	649(53.5)
	Right limb	588(46.6)	25(50.0)	563(46.5)
Insertion attempts	1	1225(97.1)	48(96.0)	1177(97.1)
	≥2	37(2.9)	2(4.0)	35(2.9)
Catheter/vessel ratio	≤0.45	1062(84.2)	41(82.0)	1021(84.2)
	＞0.45	200(15.8)	9(18.0)	191(15.8)

days, with a median indwelling time of 122 days (IQR:81 days, 146 days). The indwelling time of PICC-RT ranged from 3 to 380 days, with a median time of 122.5 days (IQR: 46 days, 186 days). PICC-RT incidence in different groups can be seen in *Tables 1 and 2*.

Lymphedema and PICC-RT

HIS records identified 18 records of lymphedema records before PICC placement and 8 after catheterization. There were 10 PICC-RT in patients with lymphedema and 40 PICC-RT in patients without lymphedema. The PICC rate for lymphedema and non-lymphedema is demonstrated in *Fig. 1*. PICC-RT-free survival curves for patients with and without lymphedema are reported in *Fig. 2* and we identified a significant difference between the groups (P<0.01).

Factors Related to PICC-RT

Univariable analysis was performed to assess the association between risk of PICC-RT and the selected variable. This analysis showed that age group, CVC placement history, surgery on the breast, lymphedema, platinum-based chemotherapy, anthracyclines-based chemotherapy, endocrine therapy, PLT level, D-dimer level, FIB level, and APTT level were significantly associated with PICC-

TABLE 2
Disease and Laboratory Test Related Characteristics of the Patients

Variable	Category	Total (n=1262)	PICC-RT (%)	
			Yes(n=50)	No(n=1212)
Menopause	Yes	506(40.1)	32(64.0)	474(39.1)
Disease stage	I	193(15.3)	7(14.0)	186(15.3)
	II	597(47.3)	22(44.0)	575(47.4)
	III	332(26.3)	13(26.0)	319(26.3)
	IV	140(11.1)	8(16.0)	132(10.9)
Pathological type	Ductal carcinoma	1177(93.3)	47(94.0)	1130(93.2)
	Lobular carcinoma	39(3.1)	2(4.0)	37(3.1)
	Ductal and lobular carcinoma	14(1.1)	0(0)	14(1.2)
	other	32(2.5)	1(2.0)	31(2.6)
Breast surgery	Yes	1124(89.1)	27(54.0)	1097(90.5)
Limb lymphedema	Yes	26(2.1)	10(20.0)	16(1.3)
Platinum-based	Yes	91(7.2)	9(18.0)	82(6.8)
Anthracyclines-based	Yes	996(78.9)	27(54.0)	969(80.0)
Trastuzumab	Yes	198(15.7)	10(20.0)	188(15.5)
Radiation therapy	Yes	24(1.9)	2(4.0)	22(1.8)
Endocrine therapy	Yes	52(4.1)	11(22.0)	41(3.4)
Anticoagulant drug	Yes	60(4.9)	6(12.0%)	54(4.5)
Antiplatelet drug	Yes	9(0.7)	1(2)	8(0.7)
PLT(10^9/L)	＜100	20(1.6)	2（4.0）	18(1.5)
	100~300	1073(85.0)	30（60.0）	1043(86.1)
	＞300	169(13.4)	18（36.0）	151(12.5)
D-dimer(mg/L)	≤0.55	1103(87.4)	27（54.0）	1076(88.8)
	＞0.55	159(12.6)	23（46.0）	136(11.2)
PT(s)	＜10.0	150(11.9)	0（0.0）	15(1.2)
	10.0~13.5	1109(87.9)	44（88.0）	1065(87.9)
	＞13.5	138(10.9)	6（12.0）	132(10.5)
FIB(g/L)	＜1.8	29(2.3)	3（6.0）	26(2.1)
	1.8~3.5	943(74.7)	18（36.0）	925(76.3)
	＞3.5	290(23.0)	29（58.0）	261(21.5)
APTT(s)	＜20.0	7(0.6)	2（4.0）	5(0.4)
	20.0~40.0	1156(91.6)	47（94.0）	1109(91.5)
	＞40.0	99(7.8)	1（2.0）	98(8.1)

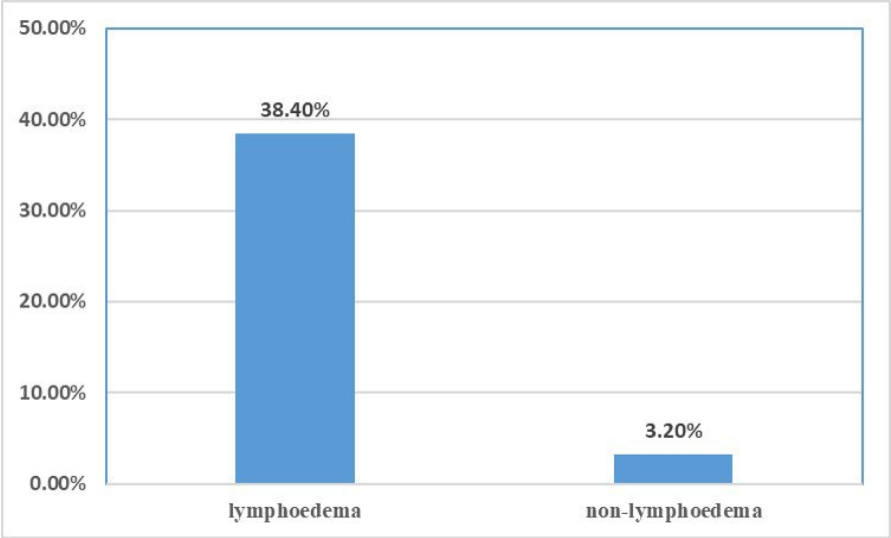

Fig. 1. PICC-RT rate (percentage) for patients with or without lymphedema

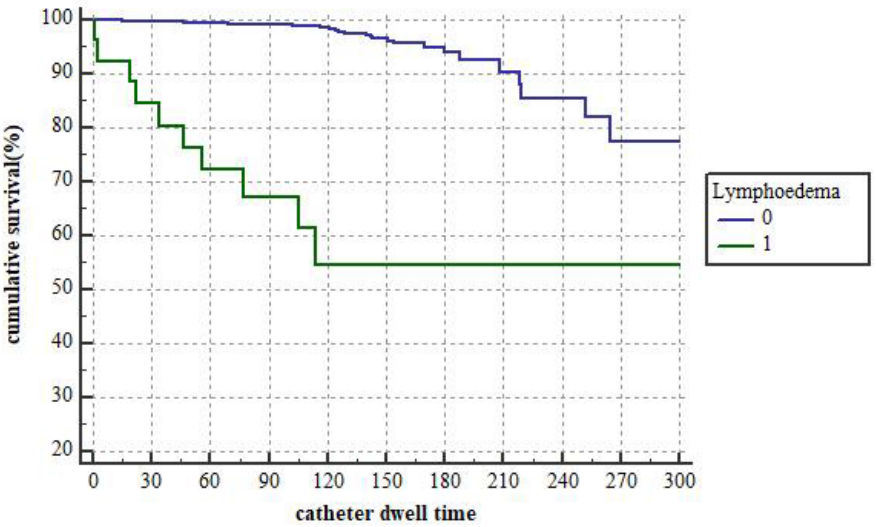

Fig. 2. PICC-RT-free Kaplan-Meier survival curves for patients with or without lymphedema

RT risk in breast cancer patients (*Table 3*). Other variables were neither associated nor tended to be associated with outcome (P>0.10).

We included the variables with P value lower than 0.10 into the multivariate Cox regression analysis. Results of the multivariate analysis are showed in *Table 4*. The results showed that CVC placement history, surgery on breast, limb lymphedema, and PLT level, D-dimer level were independent predictors of PICC-RT. Lymphedema remained an independent predictor of PICC-RT in patients with breast cancer (hazard ratio (HR) = 12.128; 95% confidence interval = 5.551-26.501; P<0.001).

TABLE 3
Univariate Cox Regression Analyses for PICC-RT

Variable	PICC-RT	
	HR (95%CI)	*P*
Age group (elders, year)	1.040 (1.006, 1.074)	0.019
BMI (higher level, kg/m2)	0.768(0.451,1.309)	0.332
O blood type	0.710(0.369,1.365)	0.304
Hypertension	1.665(0.861,3.221)	0.130
Diabetes	1.221(0.437,3.411)	0.703
COPD	2.729(0.786,9.480)	0.114
Smoking history	3.237(0.443,23.656)	0.247
CVC placement history	8.684(2.999,25.139)	<0.001
Insertion from basilic vein	0.860(0.416,1.779)	0.685
Insertion from right limb	1.093(0.627,1.904)	0.753
Insertion attempts>1	1.311(0.316,5.438)	0.709
Catheter/vessel ratio>0.45	0.829(0.396,1.733)	0.618
Menopause	2.257(1.258,4.049)	0.006
Disease stage (III-IV)	1.210(0.690,2.124)	0.506
Pathological type (Lobular carcinoma)	1.282(0.310,5.303)	0.732
Surgery on breast	0.221(0.120,0.407)	<0.001
Limb lymphedema	10.268(4.848,21.747)	<0.001
Platinum-based	2.057(0.976,4.336)	0.058
Anthracyclines-based	0.359(0.199,0.647)	0.001
Trastuzumab	0.769(0.378,1.562)	0.468
Radiation therapy	0.786(0.176,3.501)	0.752
Endocrine therapy	2.336(1.068,5.106)	0.034
Anticoagulant drug	0.753(0.304,1.864)	0.540
Antiplatelet drug	0.230(0.031,1.695)	0.149
PLT (higher level, 10^9/L)	2.701(1.496,4.876)	0.001
D-dimer(above 0.55mg/L)	4.619(2.622,8.136)	<0.001
PT (Higher level, s)	1.334(0.605,2.941)	0.474
FIB(g/L)	2.805(1.599,4.921)	<0.001
APTT(s)	0.417(0.153,1.133)	0.086

TABLE 4
Multivariate Cox Regression Analyses for PICC-RT

Variable	PICC-RT	
	HR (95%CI)	*P*
CVC placement history	5.367 (1.700, 16.947)	0.004
Surgery on breast	0.317(0.170,0.594)	<0.001
Limb lymphedema	12.128(5.551,26.501)	<0.001
PLT (higher level, 10^9/L)	3.274(1.726,6.210)	<0.001
D-dimer(above 0.55mg/L)	3.428(1.909,6.154)	<0.001

DISCUSSION

To our knowledge, this study is the first to examine the potential relationship between lymphedema and PICC-RT in patients with breast cancer. Among 1,262 breast cancer patients included in the study, PICC-RT occurred in 50 patients with lymphedema occurring in 26 patients. 10 PICC-RT cases (38.46%) occurred in lymphedema population. The ratio of PICC-RT in lymphedema case is high enough to test lymphedema as an independent predictor for PICC-RT, and multivariate analysis confirmed. Overall, the incidence of lymphedema or PICC-RT in breast cancer patients is relatively low in the extracted data, which may be a reason why previous studies did not carry out such research.

To our knowledge, the patients with both lymphedema and thrombosis were mostly reported in case reports (10,11) with the affected limb mainly in the ipsilateral limb. For PICC insertion in breast cancer, both international and domestic guidelines were recommended for PICC placement from the healthy side (16,17). The reported PICC related thrombosis mainly occurred on the catheterization side and lymphedema mainly occurred on the affected side (8,18,19). Whether lymphedema in the affected limb can increase the risk of catheter-related thrombosis in the opposite limb, and what is the mechanism are topics worthy of discussion.

The result showed that lymphedema on the affected side increased the risk of catheter-related thrombosis in the catheterized limb. The reason for that may include two aspects: First, the massive leakage of lymph in the affected limb could cause blood concentration, and the swelling of the limb further compresses the blood vessels, resulting in slower blood flow, and limited movement of both limbs, with these factors would result in increasing risk of thrombosis (7,20); Second, a large amount of protein components accumulate in the tissue space of limbs with lymphedema which allows increased substrates for infection and inflammation (21), and infection would further increase the risk of thrombosis (22). It should be noted that for breast cancer patients with lymphedema, medical staff should pay more attention to the risk assessment of catheter related thrombosis at the same time of improving management of lymphedema. It is important to make early intervention to reduce the risk of PICC-RT and thus to ensure the smooth progress of chemotherapy.

Other than lymphedema, we also find other factors playing important roles in the development of PICC-RT. Compared with other factors, surgery on the breast showed as a protective factor for the development of PICC-RT. This may because the tumor in the body could activate the coagulation chain and weaken the fibrinolysis system if not surgically removed, and then increase the risk of thrombosis (23). CVC history, higher level of PLT, and D-dimer showed higher risk for PICC-RT, these results are consistent with other research reports (24-26).

This study has some limitations. First, we studied only select population and our results may not be applied to other groups. Second, we applied a retrospective cohort research design to explore the relationship between the lymphedema and PICC-RT and since the diagnostic criteria of lymphedema may be inconsistent and the degree of lymphedema is unknown, the incidence of both may be underestimated.

Despite the above limitations, our study provides data support for exploring the relationship between lymphedema and catheter-related thrombosis. In the future, prospective studies can be carried out to further verify the relationship between lymphedema and catheter-related thrombosis with standardized evaluation criteria.

CONCLUSION

In breast cancer patients, upper limb lymphedema may be an independent predictor for PICC-RT in the contralateral limb. The significance of prevention and effective management of lymphedema is not only to improve the function of affected limbs, but it may also reduce the risk of catheter-related thrombosis and therefore ensure timely imple-

mentation of the chemotherapy regimen. The findings could provide a new topic for PICC-RT prevention, medical staff could inform breast cancer patients with both lymphedema and catheter about their risk for catheter related thrombosis and guidelines to reduce the risk and to emphasize the self-care activities for prevention could be developed.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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