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Original Article

Incidence and risk factors for peripherally inserted central catheter-related vein thrombosis in lung cancer patients

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Abstract: Objective: To explore the incidence of peripherally inserted central catheters (PICC)-related venous thrombosis (VT) in lung cancer patients, and risk factors for PICC-related VT. Methods: This retrospective study included 347 lung cancer patients who underwent chemotherapy via PICC placement in our hospital between May 2013 and April 2015. Demographics, medical history, clinical, catheter-related and insertion-related characteristics, and complications of the patients were collected. The color Doppler ultrasound was used to confirm PICC-related VT (PRVT). The risk factors for symptomatic PRVT in patients with lung cancer were identified by multivariate logistic regression analysis. Results: Among 347 lung cancer patients undergoing chemotherapy via PICC, 6.63% developed VT and the median time from PICC placement to presence of VT was 13.56 days. Results from uni-variate analysis found that gender, smoking, stage, diabetes mellitus, D-dimer level before placement, previous thrombus, indwelling arm, indwelling vein, catheter tip mal-position were potential risk factors associated with PRVT. On the multivariate logistic regression analysis, such factors as advanced stage, elevated D-dimer level before placement, previous thrombus and catheter tip mal-position significantly increased the risk for PRVT, with adjusted odds ratio (OR) of 2.76 (95% CI: 1.53-4.94), 1.89 (95% CI: 1.22-2.43), 2.19 (95% CI: 1.54-3.24) and 2.47 (95% CI: 1.42-5.04) respectively. Conclusion: Advanced stage, elevated D-dimer level before placement, previous thrombus and catheter tip mal-position were independent risk factors for PRVT. Therefore, it is advisable for high risk patients to undergo individual early intervention to reduce the incidence of PICC-related VT.

Keywords: Lung cancer, peripherally inserted central venous catheter, venous thrombosis, risk factor

Introduction

In China, lung cancer has become one of the most common malignancies, and its mortality ranks first in all kinds of cancers [1]. As most cancer patients are at advanced stage when they are clinically diagnosed and confirmed, they have missed the optimum opportunity for surgery. Venous chemotherapy is currently one of the major procedures for treatment of lung cancer. However, chemotherapy can cause great damage to the intravenous endothelium, so it is crucial to choose a safe and reliable venous access for chemotherapy for lung cancer [2]. In recent years, peripherally inserted central catheter (PICC) has been increasingly extensively used in cancer patients because of its advantages in reducing frequent venipuncture, protecting the peripheral veins and allowing longer indwelling time [3, 4]. However, as an invasive intervention operation, PICC may result in complications. For example, after catheter insertion, the patient's own condition or vascular intima injury attributed to puncture/catheterization results in the presence of blood clots in the catheter-located vessel or catheter wall, which develops into catheter-related thrombosis, even fatal pulmonary embolism if severe [5, 6]. The reported incidence of PICC-related venous thrombosis (VT) in patients with tumors varies greatly with study methods and population, with the incidence of symptomatic PICC-related VT (PRVT) ranging from 1% to 29.5% [7, 8]. A meta-analysis showed that lung cancer is one of malignant tumors with the highest risk for the development of venous thrombosis [9].

Table 1. Baseline and clinical characteristics of patients in the Non-PRVT group and the PRVT group

Variable	Non-PRVT (n=324)	PRVT (n=23)	x^2/t	P
Age	58.7±8.4	60.2±9.7	0.785	0.43
Gender			3.813	0.051
Male	202 (62.3)	19 (82.6)		
Female	122 (37.3)	4 (17.4)		
Smoking			4.112	0.042
No	91 (28.1)	2 (8.7)		
Yes	233 (71.9)	21 (91.3)		
BMI	25.3±4.4	26.2±5.7	0.891	0.374
Diabetes history				0.041*
No	289 (89.2)	17 (73.9)		
Yes	35 (10.8)	6 (26.1)		
Hypertension			0.528	0.467
No	194 (59.9)	12 (52.2)		
Yes	130 (40.1)	11 (47.8)		
COPD				0.752*
No	281 (86.7)	19 (82.6)		
Yes	43 (13.3)	4 (17.4)		
Hyperlipidemia			0.047	0.828
No	246 (75.9)	17 (73.9)		
Yes	78 (24.1)	6 (26.1)		
Previous thrombus				0.002*
No	301 (92.9)	16 (69.6)		
Yes	23 (7.1)	7 (30.4)		

Note: *The Fisher's exact test.

The reports concerning the incidence and risk factors for PRVT in lung cancer patients undergoing chemotherapy are rare and the findings are not completely consistent with each other [10, 11]. Therefore, the purpose of our study was to conduct a retrospective cohort study to investigate the incidence and risk factors for upper-extremity venous thrombosis in lung cancer patients undergoing chemotherapy during the PICC period, so as to provide a basis for the prevention of PRVT.

Materials and methods

Study subjects

This study included 347 lung cancer patients who underwent chemotherapy via PICC placement in our hospital between May 2013 and April 2015 as subjects. All the eligible patients were divided into the venous thrombosis (PRVT) group and the non-venous thrombosis (Non-PRVT) group according to the presence or absence of PRVT after PICC placement. The patients were included in the study if they had confirmed lung cancer; chemotherapy via PICC insertion and complete data on catheter insertion; an age of older than 18 years; available ultrasonography during catheterization period; informed written consents. The patients were excluded if their ultrasonography was not carried out after catheterization as planned and if they had hematological disorders. The study protocol was approved by the Hospital Ethics Committee.

PICC placement

Three-way valve PICC (BD Company, US) was adopted for the PICC placement. Before catheter placement, the patients and their families were informed of precautions, the patient's vascular conditions were assessed by trained nurses and the appropriate vessel was selected for PICC placement under local anesthesia. The vessel for catheter placement was preferred to be basilica vein, followed by elbow vein. The tip of the catheter was placed in the superior vena cava. And the puncture site was covered with sterile dressing. The postoperative elastic bandage was applied with pressure for 2 hours. Postoperative chest X-ray examination was performed to verify that the tip was located within the superior vena cava.

Determination of PRVT

During the PICC indwelling period, the patient's arms or neck were closely observed for such clinical symptoms as swelling, pain and redness. For those patients with clinical symptoms of suspected venous thrombosis, color Doppler ultrasound was performed to determine whether there was the development of venous thrombosis [12].

Data collection

All data were pooled from the paper and electronic medical records, including demographics, clinical, catheter- and insertion-related characteristics of the patients. Individual data included age, gender, smoking, drinking, previ-

Table 2. Clinical characteristics of patients in the Non-PRVT group and the PRVT group

Variable	Non-PRVT (n=324)	PRVT (n=23)	x^2/t	P
Histological subtype				0.589*
Non-small-cell lung cancer	261 (80.6)	20 (87.0)		
Small-cell lung cancer	63 (19.4)	3 (13.0)		
Stage			5.921	0.015
I-IIIa	209 (64.5)	9 (39.1)		
IIIb/IV	115 (35.5)	14 (60.9)		
Leukocyte counts (10^9/L)	8.5±4.5	8.8±3.9	8.8±3.9	0.756
Platelet count (10^9/L)	242.8±78.4	267.5±98.12	1.434	0.152
Prothrombin time				0.648*
Normal	304 (93.8)	21 (91.3)		
Increased	20 (6.2)	2 (8.7)		
Fibrinogen D-Dimer				
Normal	261 (80.6)	13 (56.5)		0.01*
Elevated	63 (18.4)	10 (43.5)		

Note: *The Fisher's exact test.

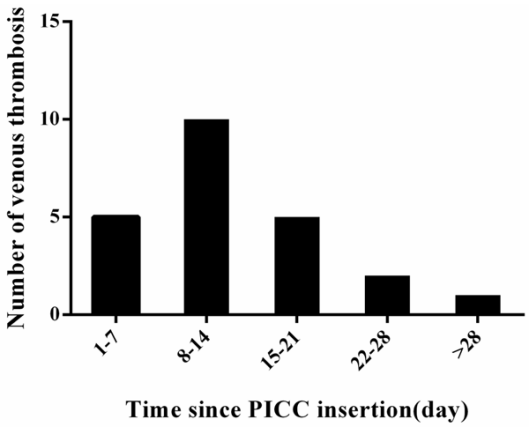

Figure 1. Time from PICC insertion to presence of PRVT in lung cancer patients. 96.7% of PRVT occurred within one month after PICC in lung cancer patients, 65.22% of which occurred within the first two weeks after PICC. The initial episode of thrombosis was present at two days after PICC, and the last episode was present at 78 days, with the median time of 13.56 days.

ous or present thrombus, blood test prior to PICC (leukocyte and platelet counts, prothrombin time, fibrinogen, D-dimer level). Catheter and catheterization data covered catheter gauge, number of lumens, indwelling extremities and veins.

Statistical analysis

Statistical analysis was carried out with the use of SPSS statistical software, version 19.0. In the study, the significance of differences in categorical variables between the PRVT group and the Non-PRVT group were assessed using the two-tailed chi-square test or the Fisher's exact test, whereas the mean of continuous variables was compared using the two independent samples t-test. Multivariate logistic regression analysis was performed to assess the risk factors for PRVT. The variables with significant level less than 0.1 assessed by uni-variate analysis were reassessed by multivariate logistic regression analysis. In the multivariate analysis, the likelihood-ratio test was conducted based on the maximum-partial likelihood. And independent variables were identified with the use of forward stepwise logistic regression analysis. A two-tailed *P* value <0.05 was considered to be statistically significant.

Results

Individual and clinical characteristics of patients

During the study period, among 347 lung cancer patients who had undergone chemotherapy via PICC replacement, 29 had the symptoms of swelling and pain in the catheter-arm, and 23 were confirmed with venous thrombosis by Doppler ultrasound.

Table 1 shows baseline characteristics of the PRVT group and the Non-PRVT group. No significant differences were showed in the mean age (60.2±9.7 in the PRVT group vs. 58.7±8.4 in the Non-PRVT group, respectively) and body mass index (BMI, 26.2±5.7 in the PRVT group vs. 25.3±4.4 in the Non-VT group, respectively) between the two groups (P>0.05). The proportion of male patients in the PRVT group (82.6%) was higher than that in the non-VT group (62.3%; P=0.051). The two groups were not significantly different in previous hypertension and hyperlipidemia. The rates of 91.3% of smoking rate, 26.1% of diabetes mellitus and 69.6% of previous thrombosis were found in

Table 3. Factors for PRVT of patients in the Non-PRVT group and the PRVT group

Variable	Non-PRVT (n=324)	PRVT (n=23)	x^2/t	P
Gauge (French)			0.141	0.707
4	196 (60.5)	13 (56.5)		
5	128 (39.5)	10 (43.5)		
Lumen number			0.066	0.797
1	178 (54.9)	12 (52.2)		
2	146 (45.1)	11 (47.8)		
IA				
Right	214 (66.0)	10 (43.5)	4.781	0.029
Left	110 (34.0)	13 (56.5)		
IV				0.045*
334 Basilica	288 (88.9)	17 (73.9)		
Other	36 (11.1)	6 (26.1)		
CTP				0.018
1/3 below the SVA	319 (98.5)	21 (91.3)	5.558	
2/3 upper or beyond the SVA	5 (1.5)	2 (8.3)		
PM				0.020
Conventional	131 (40.4)	15 (65.2)	5.431	
Ultrasound	193 (56.9)	8 (34.8)		
PN				0.596*
1	257 (79.3)	17 (73.9)		
>1	67 (20.7)	6 (26.1)		

Note: *The Fisher's exact test. IA denotes indwelling arm; IV denotes indwelling vein; CTP denotes catheter tip position; SVA denotes superior vena cava; PM denotes puncture method; PN denotes puncture number.

Table 4. Multivariate logistic regression analysis on risk factors for PRVT in lung cancer patients undergoing chemotherapy

Variable	Adjusted OR*	95% CI	P
Stage			0.012
I/IIIa	Reference		
IIIb/IV	2.76	1.53-4.94	
D-Dimer			0.032
Normal	Reference		
Elevated	1.89	1.22-2.43	
Previous thrombus	Reference		0.014
No			
Yes	2.19	1.54-3.24	
CTP			0.015
Inside SVA	Reference		
Outside SVA	2.47	1.42-5.04	

Note: *Adjusted gender, smoking, stage, diabetes mellitus, indwelling arm, and indwelling vein. CTP denotes catheter tip position, and SVA denotes superior vena cava.

the VT group, which were significantly higher than those in the Non-VT group (P<0.05).

In addition, for the proportion of non-small cell lung cancer, the PRVT group (87.0%), and the Non-VT group (80.6%) showed no significant differences (P= 0.589). The proportion of elevated D-dimer levels was significantly higher in the PRVT group (43.5%) than in the Non-VT group (18.4%; P<0.05). In contrast, 39.1% of I-IIIa venous thrombosis occurred in the patients with venous thrombosis, which was significantly lower than that of patients without venous thrombosis (P=0.005). The factors including leukocytes counts, platelet counts, and prothrombin time were not significantly different between the two groups (**Table 2**).

PRVT outcomes

The incidence of PRVT was 6.63%. Thrombosis all occurred in the upper-extremity deep veins of the patients, including four cases in the basilica vein, five cases in the brachial vein, four cases in the subclavian vein, two cases in the internal jugular vein, three cases in the axillary vein, two cases in the median cubital vein. In addition, three cases were concurrently involved in two veins.

Of the 23 patients with venous thrombosis, 96.7% occurred within one month after PICC, 65.22% of which occurred within the first two weeks after PICC. The initial episode of thrombosis was present at two days after PICC, and the last episode was present at 78 days, with the median time of 13.56 days (**Figure 1**).

Multivariate logistic regression analysis on risk factors for PRVT

Tables 1-3 show that gender, smoking, stage, diabetes mellitus, D-dimer level, previous thrombus, indwelling arm, indwelling vein, catheter tip mal-position and puncture method are potential risk factors for PRVT. On the logistic

regression analysis covering the above-mentioned factors, advanced stage, elevated D-dimer level before PICC, previous thrombus and catheter tip positioned beyond the superior vena cava were independent risk factors for PRVT, with adjusted odds ratio (OR) of 2.76 (95% CI: 1.53-4.94), 1.89 (95% CI: 1.22-2.43), 2.19 (95% CI: 1.54-3.24) and 2.47 (95% CI: 1.42-5.04) respectively (**Table 4**).

Discussion

Chemotherapy is one of the main treatment methods for tumors, and intravenous administration is a conventional route of administration. PICC is advantageous in easy operation, easy care, and high safety and compliance, which are favorable for chemotherapy. As a result, it has been extensively used in chemotherapy for cancer patients. However, there is a high risk for PRVT in cancer patients. Studies have demonstrated that identified malignancy before catheterization is an independent risk factor for PRVT [13]. Lung cancer patients are more predisposed to venous thrombosis than other cancer patients in PICC use. In this study, the incidence of PRVT was 6.63% in lung cancer patients, which is in accord with the results of other studies, but slightly higher than that of a retrospective study [10, 11, 14]. This may be associated with different study populations. In addition, in this study, the median time from PICC placement to presence of PRVT was 13.56 days. Most of VT occurred within half a month after PICC, which was close to the results of other studies [5, 15]. Therefore, taking preventive measures within the first half month after PICC is crucial to reduce the incidence of PRVT.

The hypercoagulable status of tumor patients has proved to be a risk factor for PRVT. A retrospective analysis on 2313 patients with PICC procedures showed that D-dimer level more than 5 mg/L and OR value as high as 36.651 were the major risks factors for PRVT [16]. D-dimer is a specific marker in the fibrinolytic process. An elevation in D-dimer level reflects the enhancement of the secondary fibrinolytic activity, which can be used as a molecular marker for hypercoagulability and fibrinolysis *in vivo*. Many studies have further documented that elevated D-dimer level is an independent risk factor for venous thrombosis in patients with cancers including lung cancer [14, 17, 18]. Our study has provided further evidence for the association of D-dimer levels with PRVT. In addition, the history of venous thrombosis also significantly increased the risk of PRVT, which is consistent with that of the previous studies [19].

This study indicated that patients with advanced lung cancer had a significantly higher risk for PRVT, which is in accord with other studies [10, 18, 20]. Other studies have also demonstrated that metastatic tumors are closely related to venous thrombosis [21]. Most metastatic tumors occur in patients at advanced stage. The patients' coagulation predictors including platelet counts, fibrinogen, D-dimer levels gradually increase with the stage progression and metastasis of tumors, suggesting that high coagulation level also shows the trend of elevation [22].

Other factors of the patients may be related to the occurrence of PRVT, such as smoking, adenocarcinoma, and other complications including diabetes mellitus, hypertension [23-26]. In our study, the differences in the rates of PRVT were not compared among different cell types due to the small sample size. In addition, a significant association between diabetes mellitus and PRVT was observed only in the uni-variate analysis. Additional studies are required for exploring the association of the above factors with PRVT.

PICC-related factors can influence the development of venous thrombosis. Studies have reported that the catheter diameter can reduce the incidence of venous thrombosis, but the results are not completely consistent [6, 27]. However, we did not find the catheter gauge is associated with the development of PRVT. During the PICC use, some factors may also affect the development of PRVT. For example, catheter indwelling in the right extremities, basilica vein puncture and ultrasound guidance can reduce the incidence of PRVT while the catheter tip mal-position may increase the risk of PRVT [28]. It is generally believed that the catheter tip is preferred to be placed at the site of 1/3 of the superior vena cava close to the right atrium, whereas the catheter-tip beyond the superior vena cava is deemed to be an independent risk predictor for venous thrombosis, which is similar to our results [8, 10, 20]. This may be mainly due to the facts that the

blood flow is large at this site and the incidence of PRVT is low when the catheter tip is placed at the site.

In our study, a comprehensive analysis was made on risk factors for PRVT in lung cancer patients undergoing chemotherapy from the three aspects of patients, catheter and catheter insertion. There are still some limitations, however, such as a retrospective study design. Moreover, we only assessed symptomatic venous thrombosis in the analysis. A report showed that the incidence of PRVT was higher when asymptomatic patients were included [29]. Therefore, this study may underestimate the real incidence of the PRVT. In addition, due to the small sample size, no analysis was made according to diverse pathological types of lung cancer.

In conclusion, the incidence of PRVT remains high in lung cancer patients undergoing chemotherapy via PICC access. However, the findings regarding the risk factors for development of PRVT in previous studies are not consistent, which may be attributed to the smaller size in some studies, and most of the studies were retrospective. As a result, additional multi-centered, large-sample prospective studies are needed to explore the incidence of PRVT and associated risk factors, so as to lay a basis for planning effective preventive measures.

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Disclosure of conflict of interest

None.

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