Peripherally inserted central venous catheter in upper extremities leads to an increase in D-dimer and deep vein thrombosis in lower extremities

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Research

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Abstract

Background: The purpose of this study is to elucidate the association between peripherally inserted central venous catheter (PICC) in upper extremities and lower extremity deep venous thrombosis (LEDVT) by observing the changes in D-dimer.

Methods: This was a retrospective cohort study of 3452 patients (104 inserted with PICCs and 3348 without PICC) enrolled at the neurology department from April 1, 2017 to April 1, 2020. The patients underwent color Doppler ultrasound (CDU) and D-dimer examinations. LEDVT-related factors and the D-dimer value were analyzed before and after PICC insertion. The predictive value of D-dimer for LEDVT was also evaluated.

Results: Univariate logistic regression analysis showed that PICC insertion increased the risk of LEDVT by 9 times and promoted the increase of D-dimer by 5 times. After risk adjustment, multivariate logistic regression analysis showed that PICC insertion tripled the risk of LEDVT and doubled the risk of D-dimer increase. The concentration of D-dimer was significantly increased after PICC insertion. D-dimer was unsuitable for excluding venous thrombosis in patients inserted with PICCs.

Conclusion: PICC insertion increases the level of D-dimer and the risk of LEDVT. The risks of venous thrombosis need to be assessed in patients inserted with PICCs to ensure the expected clinical outcomes.

Introduction

A peripherally inserted central venous catheter (PICC) is a tube that extends to the superior vena cava or inferior vena cava through superior limb basilic vein, median cubital vein, cephalic vein, brachial vein or external jugular vein. A PICC can enter the body of a newborn at great saphenous vein of lower limb, temporal vein of head or retroauricular vein. The use of PICC can reduce the pain of repeated puncture and the incidence of drug extravasation, which is welcomed by clinical medical staff, patients and family members [1]. However, PICC insertion and displacement may damage the vascular intima [2]. PICC insertion-induced endothelial injury and stasis of blood flow coupled with medication-induced hypercoagulability constitute the Virchow's triad for thrombosis [3]. Deep venous thrombosis (DVT) is a venous thromboembolic disorder defined as "the formation of a blood clot within a deep vein" [4]. The incidence of PICC-related symptomatic upper extremity DVT (UEDVT) varies between 6% and 18%, but it can reach 25% in a few circumstances such as malignancies [5, 6]. The prevalence of asymptomatic thrombosis ranges from 35% to 71.9% [7-11].

PICC-related venous thrombosis is mainly mural thrombus and limited to the venous route where the catheter is located [12-14]. Increasing evidence has suggested that PICC insertion also increases the incidence of lower extremity DVT (LEDVT), and that PICC-related venous thrombosis can even exceed the range of infusion route [2, 3, 15-16]. However, there is no explanation for this clinical phenomenon.

D-dimer is a specific degradation product of cross-linked fibrin. An increase in D-dimer reflects the enhancement of coagulation and fibrinolysis system, which can be used as a sensitive indicator of hypercoagulability [12, 17]. D-dimer is augmented in catheter-related venous thrombosis [18, 19], and the normal value of D-dimer can be used to exclude venous thrombosis [18, 20-23]. Nonetheless, it is not clear whether D-dimer is the medium or by-product of catheter-related venous thrombosis [24]. In this study, the association between PICC in upper extremities and LEDVT was investigated by observing the changes in D-dimer.

Materials And Methods

Patients and study design

The study was approved by the ethics committee of Xiangya Hospital of Central South University (202004327) and conducted according to the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects.

This retrospective case cohort study involved 3452 patients who received color Doppler ultrasound (CDU) in the neurology department of Xiangya Hospital of Central South University, Hunan Province from April 1, 2017 to April 1, 2020. The clinical characteristics of the patients are listed in Table 1.

Table 1 Clinical characteristics of all patients

Factors	PICC	NO PICC
	n = 104	n = 3348
Age (year, $\bar{X} \pm s$)	62.0 ± 14.0	61.5 ± 13.6
Male	61 (58.7%)	2036 (60.8%)
Malignant tumor	7 (6.7%)	120 (3.6%)
Recent surgery	18 (17.3%)	222 (6.6%)
Cerebral hemorrhage	30 (28.8%)	206 (6.2%)
Ischemic stroke	32 (30.8%)	1581 (47.2%)
Parkinson's disease	2 (1.9%)	228 (6.8%)
Infection	6 (5.8%)	331 (9.9%)
BMI ≥ 25	9 (8.6%)	22 (6.83%)
Unconsciousness	80 (76.9%)	847 (25.3%)

Note: malignant tumor refers to cases treated within the prior six months; recent surgery refers to neurosurgery (over two hours) performed within six months

The inclusion criteria of research objects were as follows: aged ≥ 18 years, admitted to the neurology department and receiving CUD from April 1, 2017 to April 1, 2020. The exclusion criteria were: 1) under 18 years old; 2) pregnant; 3) inserted with a PICC in the lower extremity; 4) diagnosed with venous thromboembolism within six months before admission. All the 3452 patients were given a Caprini score and routine D-dimer test at admission to the neurology department. CDU was performed at admission on unconscious patients or on those with a high-risk score or suspected symptoms of DVT such as swelling,

pain, tenderness and pyrexia of lower extremities. During hospitalization, CDU was performed on patients when they showed thrombotic symptoms of lower extremities or on long-term bedridden patients. PICCs were used for long-term infusion in patients having poor vascular conditions such as unclear superficial veins of upper extremities and difficulty in peripheral short catheter insertion. Only 104 of the 3452 patients were inserted with PICCs.

All the 3452 patients underwent CDU, among which 1360 patients received D-dimer test within seven days before the CDU examination. Only 101 of the 1360 patients were inserted with PICCs

.D-dimer test

D-dimer test was performed within seven days after catheterization. Blood samples for D-dimer test were obtained before CDU examnination. The blood was drawn from the antecubital vein with a clean 22-gauge butterfly needle to a 3-ml plastic tube containing 0.3 ml of 0.106 M trisodium citrate. The tube was gently inverted to mix the blood with trisodium citrate for three to six times. The whole blood was centrifuged at 2000 ×g for 20 min at 20°C. The automated and rapid STA Liatest® D-dimer assay was used for measurement of D-dimer. The STA Liatest® assay has high sensitivity (median value ≥ 95%) which meets the requirements of the Food and Drug Administration and can be used to rule out venous thrombosis [25,26]. The cut-off value for negative DVT was 0.5 mg/L. The detection methods or reagents adopted by the blood laboratory of the hospital remained unchanged during the research period.

CDU

CDU was performed within seven days after D-dimer test by an experienced CDU technician using Philips Epiq 5 and a high-resolution linear array transducer (9-13 MHz). The criteria for the diagnosis of venous thrombosis were as follows [27-29]: the lumen cannot be compressed despite firm compression with the transducer probe; defective blood flow signal in the lumen; solid return in the lumen sound; disappearance or weakening of the spent response; phase change in the loss of blood spectrum; disappearance or weakening of the blood flow in the distal limb by squeezing.

Statistical analysis

Descriptive statistics for continuous variables and categorical variables were recorded as mean ± standard deviation. Categorical variables were compared using Pearson's c2 test. Continuous variables were compared using Student's *t*-test or Mann-Whitney rank sum test according to the normality of their distribution. Risk factors for LEDVT and D-dimer increase were studied by univariate and multivariate logistic regression analysis. A Student's *t*-test was used to compare the D-dimer value before and after PICC insertion. Risk assessments were presented as odds ratios (ORs) with 95% confidence intervals (CIs). The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used to evaluate the diagnostic capability and accuracy of D-dimer. All statistical analyses were conducted with

SPSS (Version 18; SPSS, Central South University, Hunan, China). A *P*-value < 0.05 (two-tailed) was considered significant.

Results

PICC insertion increases the risk of LEDVT

Among the 3452 patients, 270 patients (7.82%, including 43 patients inserted with PICCs) were diagnosed with LEDVT by ultrasound. Among the 3182 patients (92.18%) without LEDVT, 61 patients were inserted with PICCs. LEDVT occurred in 43 of 104 patients inserted with PICCs 6.8 days (an average value) after catheterization. The median time from index to LEDVT was five days. Univariate logistic regression analysis showed that malignancy, PICC insertion, recent surgery, body mass index (BMI ≥ 25), unconsciousness and diseases including ischemic stroke and Parkinson's disease were associated with the increased risk of LEDVT (Table 2). PICC insertion increased the risk of LEDVT by 9 times (Table 2, OR = 9.692 [95% CI: 6.414-14.646], *P* = 0.000). After adjustment of the risk factors, multivariate logistic regression analysis showed that PICC insertion increased the risk of LEDVT by 3 times (Table 2, OR = 3.271 [95% CI: 1.936-5.525], *P* = 0.000).

Table 2 Logistic regression analysis of LEDVT-related factors

Factors	LEDVT	NO LEDVT	Univariate		Multivariate	
	n = 270	n = 3182	OR (95% CI)	*P*	OR (95% CI)	*P*
PICC	43	61	9.692 (6.414-14.646)	0.000	3.271 (1.936-5.525)	0.000
Age (year, $\bar{X} \pm s$)	61.27 ± 12.63	61.57 ± 13.71	0.998 (0.989-1.007)	0.724	1.006 (0.997-1.016)	0.197
Male	156	1941	0.875 (0.680-1.125)	0.298	1.002 (1.014-3.130)	0.987
Malignant tumor	48	79	8.493 (5.787-12.464)	0.000	1.782 (1.014-3.130)	0.045
Recent surgery	80	160	7.593 (5.857-10.797)	0.000	3.670 (2.295-5.868)	0.000
Cerebral hemorrhage	26	210	1.508 (0.983-2.313)	0.060	0.878 (0.532-1.449)	0.612
Ischemic stroke	74	1539	0.403 (0.306-0.531)	0.000	0.889 (0.643-1.228)	0.476
Parkinson's disease	8	222	0.407 (0.199-0.834)	0.014	0.394 (0.189-0.820)	0.013
Infection	26	311	0.984 (0.646-1.499)	0.939	1.704 (1.082-2.682)	0.021
BMI ≥ 25	29	209	1.712 (1.136-2.579)	0.010	1.329 (0.846-2.089)	0.217
Unconsciousness	78	549	1.948 (1.474-2.575)	0.000	1.539 (1.106-2.143)	0.011

Note: malignant tumor refers to cases treated within the prior six months; recent surgery refers to neurosurgery (over two hours) performed within six months

PICC insertion is associated with the increased risk of D-dimer

Patients with a high-risk Caprini score were inserted with PICCs. Among the 3452 patients, 1360 patients underwent D-dimer test within seven days after PICC insertion. Among the 1360 patients, 597 patients (43.90%, including 80 patients inserted with PICCs) had a D-dimer value > 0.5mg/L, and 763 patients (56.10%, including 21 patients inserted with PICCs) had a D-dimer value ≤ 0.5mg/L. Univariate logistic regression analysis showed that age, male sex, malignancy, PICC insertion, recent surgery, unconsciousness and diseases including cerebral hemorrhage, ischemic stroke, Parkinson's disease and

infection were associated with the increased risk of D-dimer value (Table 3). PICC insertion promoted the increase of D-dimer value by 5 times (Table 3, OR = 5.467 [95% CI: 3.338-8.956], P = 0.000). After adjustment of the risk factors, multivariate logistic regression analysis showed that PICC insertion promoted the increase of D-dimer value more than twofold (Table 3, OR = 2.828 [95% CI: 1.511-5.293], P = 0.001).

Table 3 Logistic regression analysis of D-dimer-related factors

Factors	D-dimer (> 0.5 mg/L)	D-dimer (≤ 0.5 mg/L)	Univariate		Multivariate	
	n = 597	n = 763	OR (95% CI)	P	OR (95% CI)	P
PICC	80	21	5.467 (3.338-8.956)	0.000	2.828 (1.511-5.293)	0.001
Age (year, $\overline{X} \pm s$)	61.91 ± 15.50	60.17 ± 14.46	1.008 (1.001-1.015)	0.033	1.016 (1.008-1.024)	0.000
Male	339	486	0.749 (0.602-0.932)	0.010	0.806 (0.633-1.025)	0.079
Malignant tumor	85	38	3.167 (2.126-4.720)	0.000	0.769 (0.422-1.401)	0.390
Recent surgery	158	64	3.931 (2.872-5.381)	0.000	4.527 (2.763-7.417)	0.000
Cerebral hemorrhage	58	41	1.895 (1.251-2.870)	0.003	1.469 (0.906-2.383)	0.119
Ischemic stroke	192	330	0.622 (0.497-0.778)	0.000	0.767 (0.586-1.004)	0.053
Parkinson's disease	19	64	0.359 (0.213-0.606)	0.000	0.380 (0.219-0.659)	0.001
Infection	121	85	2.028 (1.500-2.740)	0.000	3.468 (2.465-4.879)	0.000
BMI ≥ 25	42	57	0.937 (0.620-1.148)	0.759	0.639 (0.400-1.020)	0.061
Unconsciousness	126	127	1.340 (1.019-1.762)	0.036	1.056 (0.765-1.458)	0.741

Note: malignant tumor refers to cases treated within the prior six months; recent surgery refers to neurosurgery (over two hours) performed within six months

D-dimer value before and after PICC insertion

Ninety-two patients underwent D-dimer tests within seven days before and after catheterization. During the testing period, none of the patients were pregnant, took oral contraceptive, underwent major surgery, or had new tumor, heart failure, infection or trauma/fracture. The D-dimer value was significantly increased within seven days after the PICC insertion (Table 4, P < 0.05).

Table 4 D-dimer changes before and after PICC insertion

	N	D-dimer (mg/L)	t	P
Before PICC insertion	92	0.86 ± 0.84	-7.07	0.000
After PICC insertion	92	1.78 ± 1.45		

Analysis of the predictive value of D-dimer for LEDVT

ROC curves were plotted to evaluate the diagnostic sensitivity and specificity of D-dimer for LEDVT in patients with or without PICCs. The AUC of D-dimer in patients inserted with PICCs was 0.657 (Table 5, Figure 1, 95% CI: 0.549-0.765, *P* < 0.05). The optimal critical value of D-dimer in patients inserted with PICCs was 0.675 mg/L, and the sensitivity, specificity, positive predictive value and negative predictive value of D-dimer were 48.28%, 86.05%, 55.22% and 82.35%, respectively (Table 5).

Table 5 Analysis of the predictive value of D-dimer for LEDVT

	Optimal critical value	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under ROC curve	95% confidence interval
The level of D-dimer in patients with PICC	0.675	48.28%	86.05%	55.22%	82.35%	0.657	0.549-0.765
The level of D-dimer in patients without PICC	0.665	72.01%	75.89%	36.82%	93.25%	0.800	0.769-0.830

The AUC of D-dimer in patients without PICC was 0.800 (Table 5, Figure 2, 95% CI: 0.769-0.830, *P* < 0.05). The optimal critical value of D-dimer in patients without PICC was 0.665 mg/L, and the sensitivity, specificity, positive predictive value and negative predictive value of D-dimer were 72.01%, 75.89%, 36.82% and 93.25%, respectively (Table 5).

The results show that the sensitivity, specificity, and positive predictive value of D-dimer are not high. Generally, the negative predictive value of D-dimer is used to exclude thrombosis. The negative predictive value of D-dimer in patients inserted with PICCs (82.35%) is lower than in patients without PICC, suggesting D-dimer as an inappropriate predictor for thrombosis in patients inserted with PICCs.

Discussion

Venous thrombosis is a common vascular disorder in the general population. The annual incidence of venous thromboembolism in people of European descent is estimated to be 104 to 183 per 100,000 people [30]. DVT more often happens in lower extremities than in upper extremities. In USA, LEDVT has an annual incidence in about 187,000 individuals and is considered as the third common vascular disease following myocardial infarction and stroke [31]. Registro Informatizado de Enfermedad Trombo Embólica (RIETE) enrolled 37366 patients with DVT, among which 35094 (93.9%) cases were LEDVT and the other 2272 (6.1%) were UEDVT [32]. A recent retrospective cohort study of 83 patients hospitalized for DVT showed that 72 cases were LEDVT and 11 cases were UEDVT [33]. Foreign bodies in the vascular system are the most important independent risk factors of DVT [34-36]. A study of the general population

showed that LEDVT occurred in 372 of 3790 patients inserted with PICCs during hospitalization [3]. In this study, 43 of the 270 LEDVT patients were inserted with PICCs. Consistently, we found that PICC insertion tripled the risk of LEDVT after risk adjustment. LEDVT occurred in 43 of 104 patients inserted with PICCs 6.8 days (an average value) after catheterization. The median time from index to LEDVT was five days, which is similar to the time for UEDVT. PICC-related UEDVT occurs within 12 days after catheterization, and the median time for UEDVT is 8 days [37]. In addition to the PICC insertion, factors including malignancy, recent surgery, infection, BMI ≥ 25 and unconsciousness were also associated with the increased risk of LEDVT.

The concentration of D-dimer is considered a gold biochemical standard for assessing both coagulation activation and fibrin digestion [38] and for ruling out venous thrombosis in patients with low-median clinical probability [39-41]. Other conditions such as infection, cancer, chronic inflammation, aging, pregnancy, recent surgery, and trauma can also increase the concentration of D-dimer by accelerating fibrin production or breakdown [42]. A retrospective study of 1647 patients showed that the most common cause of positive D-dimer was infection, followed by venous thrombosis, syncope, heart failure, trauma, and cancer [43]. After excluding these factors, we investigated the D-dimer concentration within seven days before PICC catheterization. Evidence showed that the risk of PICC line-related DVT was increased in the first two weeks after PICC insertion [15]. We found that the concentration of D-dimer within seven days after PICC insertion was higher than that before PICC insertion, indicating a PICC-induced increase in D-dimer. Moreover, recent surgery, infection, and cerebral hemorrhage were also associated with the increase in D-dimer. D-dimer cannot be used to exclude venous thrombosis in patients inserted with PICCs. Thrombosis is a natural process activated by internal and external pathways which stimulatea series of coagulation in the body and eventually lead to fibrin rich thrombus. Endothelial injury is a coagulation inciting event. Fibrinolysis and destruction of the blood clot are induced following coagulation to maintain homeostasis. DVT occurs when the coagulation process is not restrained or the mechanism of decomposing blood clots is overloaded [44]. A PICC occupies nearly half of the inner diameter of a vein, which causes a slowing of the local blood flow. The stasis of blood flow can induce micro venous thrombosis and activate the coagulation system in the process of reflux, leading to a larger range of DVT [44]. We suspect that PICC insertion is a risk factor of LEDVT and results in a general increase in D-dimer concentration. By the joint action of other risk factors, DVT can spread beyond the PICC vascular bed.

This study provides novel insights for the clinical evaluation of LEDVT. The concentration of D-dimer was first used to explain the possible relationship between PICC inserted in upper extremities and LEDVT. A PICC inserted in upper extremities increases the risk of LEDVT, which inspires clinicians to consider the complications of PICC insertion. For patients with a high risk of thrombosis, it is necessary for a specialized nursing team to weigh the side-effect and benefit of PICC or to consider an alternative vascular access. Moreover, clinicians are suggested to use a prophylactic anticoagulant regimen in patients at high risk of thrombosis who need PICC insertion.

Despite the significance, limitations exist in this study. Firstly, the data of asymptomatic UEDVT was not collected to determine whether PICC insertion conferred a greater risk of DVT in upper extremities than in lower extremities. Secondly, this study was limited to the neurology department. Finally, the study was retrospective without follow-up data.

Conclusion

PICC insertion increases the value of D-dimer and is an important risk factor of LEDVT. The predictive value of D-dimer in patients inserted with PICCs is lower than in patients without PICC. D-dimer is unsuitable for routine examination to exclude LEDVT in patients inserted with PICCs.

Abbreviations

PICC: Peripherally Inserted Central venous Catheter; LEDVT:lower extremity deep venous thrombosis; UEDVT:upper extremity deep venous thrombosis

Declarations

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Wanli Liu participated in data acquisition and management of the study, analyzed and interpreted the data, and drafted and revised the manuscript. Lianxiang He and Wenjing Zeng and Liqing Yue participated in data interpretation, and revision of the manuscript. Jie Wei and Shuangshuang Zeng participated in protocol drafting, study management. Zhicheng Gong was trial manager, designed, initiated and managed the study, participated in data acquisition and interpretation, and revised the manuscript.All authors read and approved the final manuscript.

Ethical Approval and Consent to participate The study was approved by the ethics committee of Xiangya Hospital of Central South University(202004327) and was conducted according to the Helsinki Declaration of Ethical Principles for Medical Research involving Human Subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

[1]   Commission, N.H.A.F., Technical operation specifications for intravenous therapy nursing. China nursing management, 2014. 1(14): p. 1-4.

[2]   Song, L., et al., Malposition of peripherally inserted central catheter: experience from 3012 cancer patients. Int J Nurs Pract, 2014. 20(4): p. 446-9.

[3]   Chopra V, G.M.B.S., The Association between Upper and Lower Extremity Deep Vein Thrombosis and Peripherally Inserted Central Catheters: Think Below the Waist Annual Scientific Conference Abstract. Society of Hospital Medicine, 2014(Las Vegas, NV.).

[4]   Olaf, M, et al., Deep Venous Thrombosis. Emerg Med Clin North Am, 2017. 35(4): p. 743-770.

[5]   O'Brien J, et al. Insertion of PICCs with minimum number of lumens reduces complications and costs. J Am Coll Radiol. 2013;10:864−8.

[6]   Aw A, et al. Incidence and predictive factors of symptomatic thrombosis related to peripherally inserted central catheters in chemotherapy patients. Thromb Res. 2012;130(3):323−6.

[7]   Chemaly RF, et al. Venous thrombosis associated with peripherally inserted central catheters: a retrospective analysis of the Cleveland Clinic experience. Clin Infect Dis. 2002;34(9):1179−83.

[8]   Cortelezzia A, et al. Central venous catheter-related complications in patients with hematological malignancies: a retrospective analysis of risk factors and prophylactic measures. Leuk Lymphoma. 2003;44(9):1495−501.

[9]   King MM, et al. Peripherally inserted central venous catheter-associated thrombosis: retrospective analysis of clinical risk factors in adult patients. South Med J. 2006;99(10):1073–7.

[10]   Paauw JD, et al. The incidence of PICC line-associated thrombosis with and without the use of prophylactic anticoagulants. JPEN J Parenter Enteral Nutr. 2008;32(4):443–7.

[11]   Itkin M, et al. Peripherally inserted central catheter thrombosis – reverse tapered versus nontapered catheters: a randomized controlled study. J Vasc Interv Radiol. 2014;25(1):85–91.

[12]   Liem, T.K., et al., Peripherally inserted central catheter usage patterns and associated symptomatic upper extremity venous thrombosis. Journal of Vascular Surgery, 2012. 55(3): p. 761-767.

[13]   Olson, J.D., D-dimer: An Overview of Hemostasis and Fibrinolysis, Assays, and Clinical Applications. Adv Clin Chem, 2015. 69(2): p. 1-46.

[14]   Easaw, J.C., et al., Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: treatment. Curr Oncol, 2015. 22(2): p. 144-55.

[15]   Greene, M.T., et al., The Association Between PICC Use and Venous Thromboembolism in Upper and Lower Extremities. The American Journal of Medicine, 2015. 128(9): p. 986-993.e1.

[16]   Al-Asadi, O., M. Almusarhed and H. Eldeeb, Predictive risk factors of venous thromboembolism (VTE) associated with peripherally inserted central catheters (PICC) in ambulant solid cancer patients: retrospective single Centre cohort study. Thrombosis Journal, 2019. 17(2): p. 1-7.

[17]   van der Straaten Mark Roest Fred Haas Philip G. De Groot Rob Fijnheer, F.H.J.H., Elevated levels of D-dimer and fragment 1+2 upon central venous catheter insertion and factor V Leiden predict subclavian vein thrombosis. the hematology journal, 2005. 4(90): p. 499-504.

[18]   Chen Q, Z.Z.D.H. and Z.F.A.Z. Zhi., Perioperative Venous Thromboembolism (VTE) Prophylaxis in Thoracic Cancer Patients: Chinese Experts Consensus - Interpretation of Clinical Significance of D-dimer. Zhongguo Fei Ai Za Zhi, 2019. 12(22): p. 761-766.

[19]   Kanno, Y., et al., Elevation of plasma D-dimer is closely associated with venous thrombosis produced by double-lumen catheter in pre-dialysis patients. Nephrology Dialysis Transplantation, 2007. 22(4): p. 1224-1227.

[20]   Zhang, D., et al., Diagnostic accuracy of biomarker D-dimer in patients after stroke suspected from venous thromboembolism: A diagnostic meta-analysis. Clinical Biochemistry, 2019. 63(2): p. 126-134.

[21]   Jeffrey I. Weitz, M.A.B.C., A Test in Context : D-Dimer. JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, 2017. 70(19): p. 2411-2419.

[22]   Lim, W., et al., American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. Blood Adv, 2018. 2(22): p. 3226-3256.

[23]   Chopra, V., et al., Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. Lancet, 2013. 382(9889): p. 311-25.

[24]   Greene, M.T., et al., The Association Between PICC Use and Venous Thromboembolism in Upper and Lower Extremities. The American Journal of Medicine, 2015. 128(9): p. 986-993.e1.

[25]   CLSI. Quantitative D-dimer for exclusion of venous thromboembolic disease. CLSI

document H59-A. Wayne, PA: Clinical and Laboratory Standard Institute; 2011.

[26]   Di Nisio M, Squizzato A, Rutjes AW, et al. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007;5:296–304.

[27]   Stein PD, Beemath A, Meyers FA, Skaf E, Sanchez J, Olson RE. Incidence of venous

thromboembolism in patients hospitalized with cancer. Am J Med. 2006;119(1):60-68.

[28]   Menéndez JJ, Verdú C, Calderón B, et al. Incidence and risk factors of superficial and deep

vein thrombosis associated with peripherally inserted central catheters in children. J Thromb Haemost. 2016;14(11):2158-2168.

[29]   .   Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315-352.

[30]   Heit, J. A. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12(8):464-74.

[31]   Heit, J. A. The epidemiology of venous thromboembolism in the community: implications for prevention and management. J Thromb Thrombolysis. 2006;21(1):23-9.

[32]   Cote, L. P., et al. Comparisons Between Upper and Lower Extremity Deep Vein Thrombosis: A Review of the RIETE Registry. Clin Appl Thromb Hemost. 2017;23(7):748-754.

[33]   Rokosh, R. S., et al. High Prevalence and Mortality Associated with Upper Extremity Deep Venous Thrombosis in Hospitalized Patients at a Tertiary Care Center. Ann Vasc Surg. 2020;65:55-65.

[34]   Frolova, A.I., et al., Complications of peripherally inserted central catheters in pregnancy: a systematic review and meta-analysis. J Matern Fetal Neonatal Med, 2020.https://doi.org/10.1080/14767058.2020.1769591

[35]   Jiang, M., et al., Risk of venous thromboembolism associated with totally implantable venous access ports in cancer patients: a systematic review and meta-analysis. J Thromb Haemost,

2020. https://doi.org/10.1111/jth.14930

[36]   Heil, J., et al., Deep Vein Thrombosis of the Upper Extremity. Dtsch Arztebl Int, 2017. 114(14): p. 244-249.

[37]   Fletcher, J. J., et al. The clinical significance of peripherally inserted central venous catheter-related deep vein thrombosis. Neurocrit Care. 2011;15(3):454-60.

[38]   Gaffney PJ, Lane DA, Kakkar VV, et al. Characterisation of a soluble D dimer-E complex in crosslinked fibrin digests. Thromb Res. 1975;7:89–99.

[39]   Thachil J, Lippi G, Favaloro EJ. D-dimer testing: laboratory aspects and current issues. Methods Mol Biol. 2017;1646:91–104

[40]   Lippi G, Cervellin G, Casagranda I, et al. D-dimer testing for suspected venous thromboembolism in the emergency department. Consensus document of AcEMC, CISMEL, SIBioC, and SIMeL. Clin Chem Lab Med. 2014;52:621–628.

[41]   Karnrawee Kamolratanapiboon, Chaicharoen Tantanate. (2019) Inappropriate use of D-dimer and impact on the test characteristics for deep vein thrombosis exclusion. Scandinavian Journal of Clinical and Laboratory Investigation.2019;79(6):431-436.

[42]   Linkins LA, Takach Lapner S. Review of D-dimer testing: good, bad, and ugly. Int J Lab Hematol. 2017;39 (Suppl 1):98–103.

[43]   Lippi G, Bonfanti L, Saccenti C, et al. Causes of elevated D-dimer in patients admitted to a large urban emergency department. Eur J Intern Med. 2014;25:45–48.

[44]   Hattab, Y., et al., Deep Venous Thrombosis of the Upper and Lower Extremity. Crit Care Nurs Q, 2017. 40(3): p. 230-236.

Figures
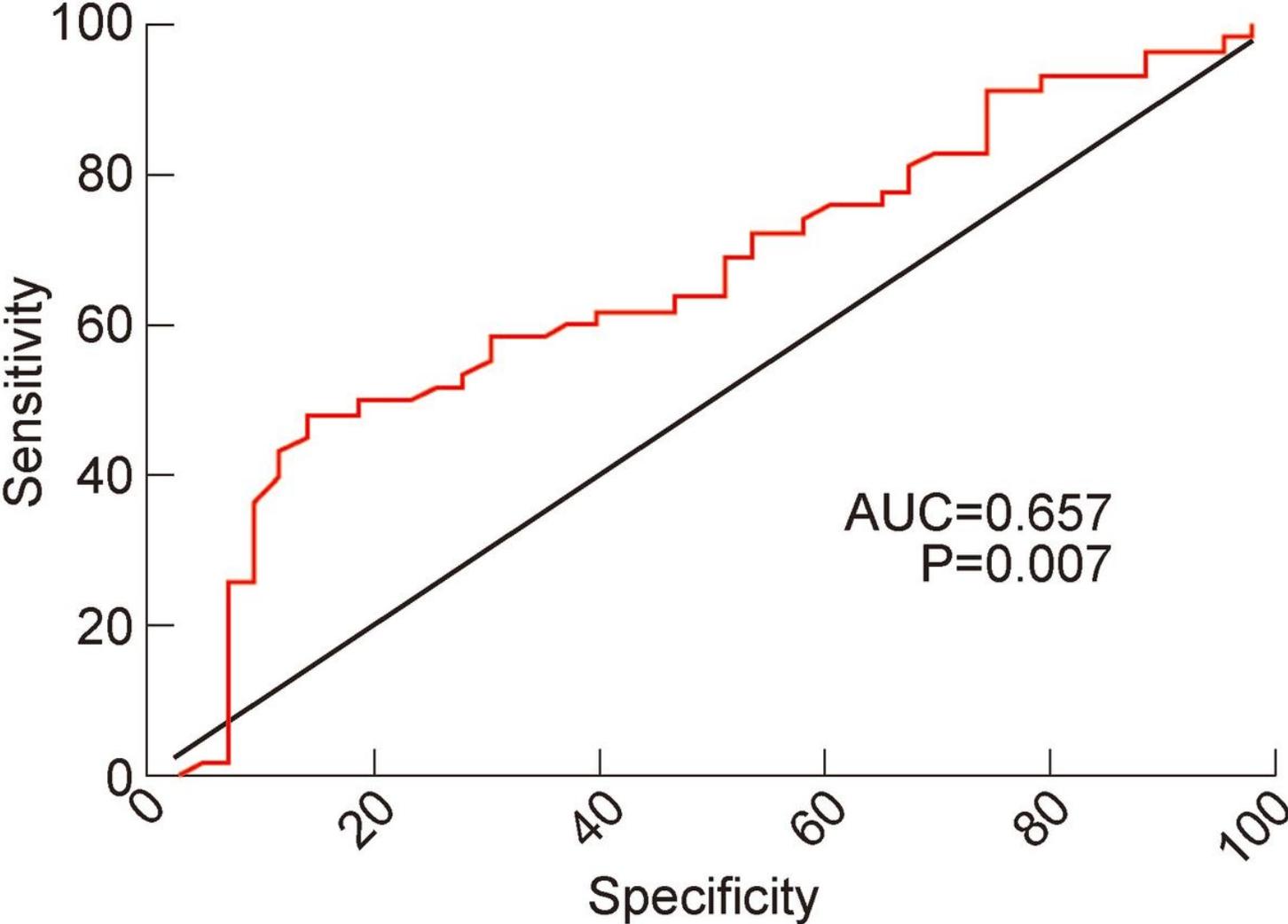
Figure 1

Area under ROC curve of D-dimer for diagnosis of LEDVT in patients inserted with PICCs
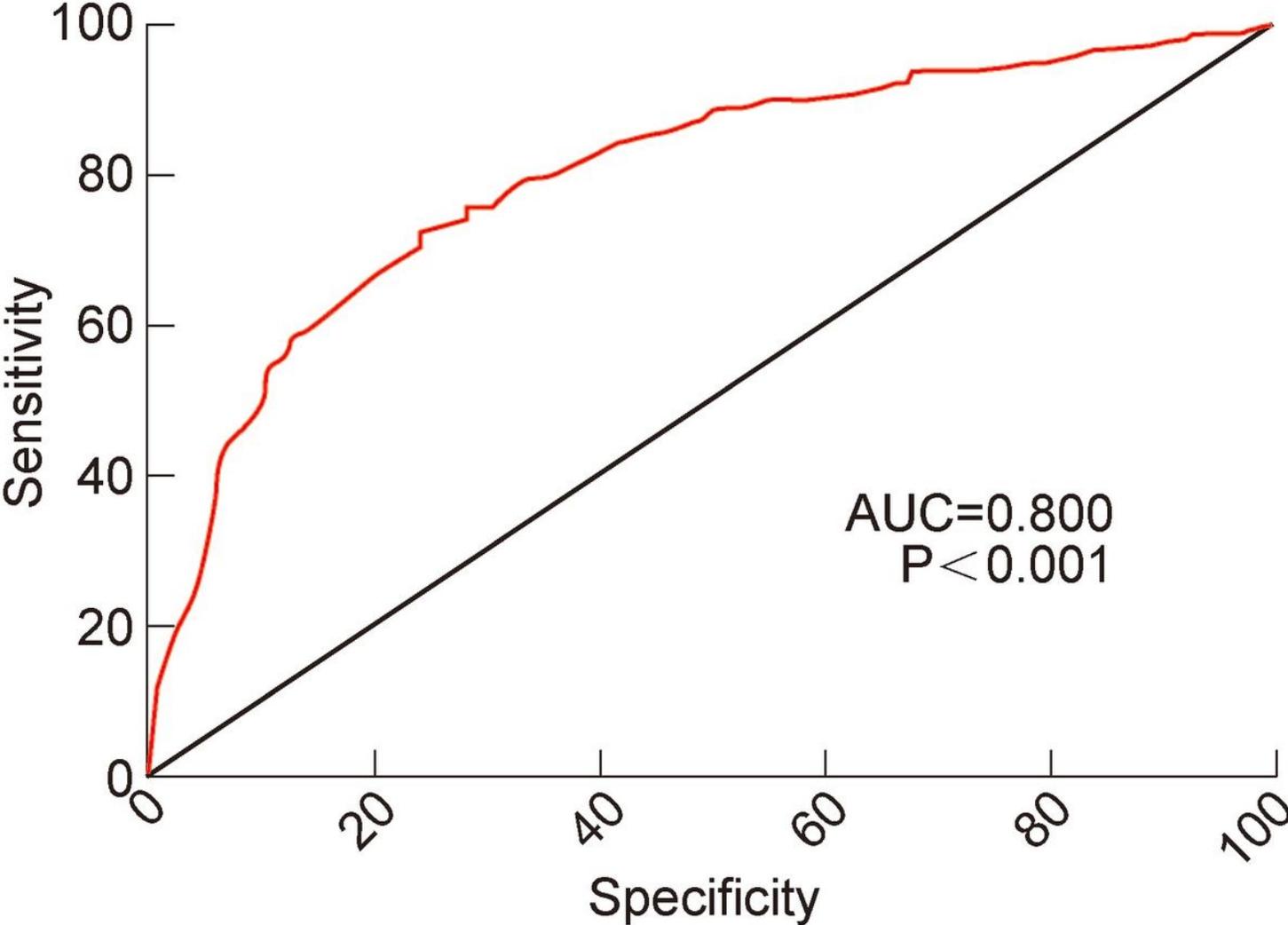
Figure 2

Area under ROC curve of D-dimer for diagnosis of LEDVT in patients without PICC