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RESEARCH ARTICLE

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D-dimer level for ruling out peripherally inserted central catheter-associated upper extremity deep vein thrombosis and superficial vein thrombosis

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Abstract

Aims: To examine the effectiveness of D-dimer values to be used as an independent diagnostic marker for excluding peripherally inserted central catheter-associated upper extremity deep vein thrombosis and superficial vein thrombosis.

Design: This was a retrospective case–cohort study.

Methods: Records were reviewed for 281 patients who underwent peripherally inserted central catheter insertion between 1 October 2017 and 1 October 2019. According to the modified Wells score after peripherally inserted central catheter insertion, the patients who had low vein thrombosis risk underwent a D-dimer test and colour Doppler ultrasound.

Results: Among 281 patients, 180 patients (64%, 95% CI: 58.2%–69.4%) had negative D-dimer results and 39 of 180 patients had vein thrombosis despite having a negative D-dimer result, resulting in a failure rate of 21.7% (95% CI: 16.3%–28.3%). The negative predictive value of peripherally inserted central catheter-associated vein thrombosis in the cancer group (80.0%, 95% CI: 73.2%–85.4%) was higher than that of the non-cancer group (60.0%, 95% CI: 35.7%–80.2%). The negative predictive value of peripherally inserted central catheter-associated deep venous thrombosis (84.9%, 95% CI: 78.7%–89.6%) was lower than that of the PICC-associated superficial venous thrombosis (91.0%, 95% CI: 85.4%–94.6%).

Conclusion: The D-dimer levels maybe should not be used as a diagnostic index to rule out peripherally inserted central catheter-associated upper extremity vein thrombosis.

KEYWORDS

D-dimer, deep vein thrombosis, diagnosis, negative predictive value, peripherally inserted central catheter, superficial vein thrombosis

1 | INTRODUCTION

In patients requiring an infusion of corrosive drugs or long-term infusions, peripherally inserted central catheter (PICC) is a convenient alternative to a central venous catheter (CVC). PICCs are easy to place, can be nurse-led and do not have risks associated with CVC insertion (Chopra et al., 2013). However, PICCs have a risk of developing upper extremity superficial vein thrombosis (UESVT) and deep vein thrombosis (UEDVT). A considerable proportion of patients with UEDVT develops serious complications such as recurrent thrombosis, post-thrombotic syndrome and pulmonary embolism (Potere et al., 2021). Despite a few studies on UESVT, the association between UESVT and UEDVT is known to be variable. DVT and pulmonary embolism occur in 18.1% and 6.9% of SVT patients, respectively (Minno et al., 2016).

1.1 | Background

The standard diagnostic modality for PICC-associated vein thrombosis (VT) is colour Doppler ultrasound (CDU). However, its use remains controversial. The American Society of Hematology 2018 guidelines (Lim et al., 2018) for the diagnosis and management of venous thromboembolism recommend the D-dimer test as the initial screening modality for patients with low venous thromboembolism (VTE) risk (unlikely) as it reduces the need for diagnostic imaging. Negative D-dimer may exclude UEDVT and indicate the needlessness of other tests or anticoagulation therapy (Chopra et al., 2013).

D-dimer, the minimal degradation product of fibrin, is produced by fibrinolytic protein hydrolysis of fibrin. It has been established as a sensitive biomarker for the activation of the fibrinolytic system (Lim et al., 2018). In VTE events, D-dimer levels can rise abnormally; accordingly, the diagnosis of VTE can be assisted by determining the D-dimer levels. Among patients determined to have a low risk for DVT, a D-dimer level of <0.5 mg/L accurately ruled out DVT without the need for CDU or other imaging tests and helped avoid unnecessary anticoagulant treatment (Chen et al., 2019; Chopra et al., 2013; Fronas et al., 2018; Qdaisat et al., 2019; Weitz et al., 2017; Zhang et al., 2019). Further, the risk of VTE in these patients was very low over the next three months (<1%) (Chen et al., 2019; Weitz et al., 2017; Zhang et al., 2019). The majority of patients who undergo PICC placement in China are cancer chemotherapy patients (Liu et al., 2018). Moreover, PICC-associated upper extremity vein thrombosis (UEVT) is different from the usual vein thrombus, as the former presents primarily as a mural thrombus (Liu et al., 2021; Winters et al., 2015). The different study population and the different types of VT may affect D-dimer levels, and the question of whether they are also sensitive to rule out PICC-associated UEVT remains unclear. Thus, this study aimed to investigate whether the D-dimer concentration could also be used as an independent diagnostic marker for excluding PICC-associated UEVT.

2 | AIM

To examine the effectiveness of D-dimer values to be used as an independent diagnostic marker for excluding PICC-associated UESVT and UEDVT.

3 | METHODS

3.1 | Design

This was a retrospective case–cohort study. The patients were categorized into the DVT unlikely group (<2 points) and the DVT likely group (≥2 points) according to the modified Wells score post-PICC placement, before extubation. After the modified Wells score was determined, the patients underwent a D-dimer test and CDU within seven days after the D-dimer test. To examine the effectiveness of D-dimer concentration to be used as an independent diagnostic marker for excluding PICC-associated UESVT and UEDVT.

3.2 | Setting and participants

The study was conducted between 1 October 2017 and 1 October 2019 on the oncological ward, breast ward, neurology ward, haematology ward, respiratory ward and other wards of a teaching hospital in Hunan, China. The teaching hospital is a 3500-bed urban tertiary facility, which is consistently ranked as a top hospital in South China and provides state-of-the-art diagnosis and treatment services.

Inclusion criteria were as follows: 1) patients aged ≥18 years; 2) patients with PICC via the upper arms; 3) <2 points on the modified Wells score; and 4) patients who underwent CDU and D-dimer values after PICC placement. Exclusion criteria were as follows: 1) PICC-associated lower extremity vein thrombosis (LEVT); 2) a duration of >7 days between D-dimer examination and CDU; and 3) outpatient management. Subjects were excluded from the study for incomplete data. Data, including basic demographic characteristics, PICC, test results, disease course and medications, were collected using the standard form in the infusion monitoring system.

3.3 | Diagnosis of vein thrombosis

The modified Wells score for DVT is the best-known clinical probability assessment tool for clinically suspected DVT. It is a straightforward point-score system with a maximum of eight score points. Two points are subtracted if an alternative diagnosis is at least as probable as DVT. A score of ≥2 points indicates that the probability of DVT is likely, whereas a score of <2 points indicates that the probability of DVT is unlikely.

After determining the modified Wells score, the patients underwent a D-dimer test and CDU, with the latter conducted within seven days after the former. A subsequent D-dimer test was conducted, and D-dimer results were defined as negative (i.e. D-dimer <0.5 mg/L) and positive (i.e. D-dimer ≥0.5mg/L) (Figure 1) (Chen et al., 2019). The main criteria for the diagnosis of VT were as follows (Kearon et al., 2016; Stein et al., 2006): for probe after compression, the lumen cannot be compressed; the blood flow signal in the lumen is filled with defects; solid return can be seen in the lumen sound; disappearance or weakening of the spent response; phase change in the loss of the blood spectrum; and weakening or disappearance of the blood flow of the distal limb by squeezing. Deep veins of the upper limb included axillary vein, subclavian artery, internal jugular vein and brachial vein (Menéndez et al., 2016; Stein et al., 2006). Superficial veins of the upper limb included cephalic and cubital median veins and the basilic veins (Kearon et al., 2016; Kucher, 2011; Winters et al., 2015). In cases of inconclusive CDU diagnosis, another physician conducted a second CDU. Differences in diagnosis between the two CDU physicians were resolved according to the opinion of a third CDU physician. If the diagnosis cannot be established on CDU, venography or computed tomography was used.

3.4 | Procedure

The primary outcome of interest was CDU results of UESVT and UEDVT. PICC-associated UESVT and UEDVT were defined as events after the PICC placement date and before extubation. D-dimer levels were determined after catheterization. Since the risk of VTE is dynamic and changes during hospitalization (Winters et al., 2015), only D-dimer data collected within seven days prior to CDU were analysed. The primary outcome measure was the failure rate of the primary diagnostic strategy. This was defined as the proportion of patients in whom PICC-associated VT was ruled out based on the assessment of lower VTE probability and negative D-dimer levels but were diagnosed with PICC-associated VT on CDU. The outcome indexes were PICC-associated VT, PICC-associated DVT and PICC-associated SVT. The patients were further divided into two subgroups, namely, the cancer and non-cancer subgroups.

3.5 | Analysis

Descriptive statistics for continuous variables were recorded as mean ± standard deviation. ANOVA test was used to compare the age of patients with non-VT, PICC-associated DVT and PICC-associated SVT. Chi-square test was used to compare the gender, cancer, consciousness and other factors in non-VT, PICC-associated DVT and PICC-associated SVT. The reliability and effectiveness of the D-dimer level as an independent biomarker for PICC-associated VT was evaluated according to its sensitivity, specificity, negative predictive value and positive predictive value and the need for ultrasonography examinations. The 95% confidence intervals (CI) were presented. A p-value <.05 (two-tailed) was considered significant. All statistical analyses were conducted with SPSS (Version 18; SPSS, Central South University, Hunan, China).

3.6 | Ethics

The study was approved by the ethics committee and was conducted according to the Helsinki Declaration of Ethical Principles for Medical Research involving Human Subjects.

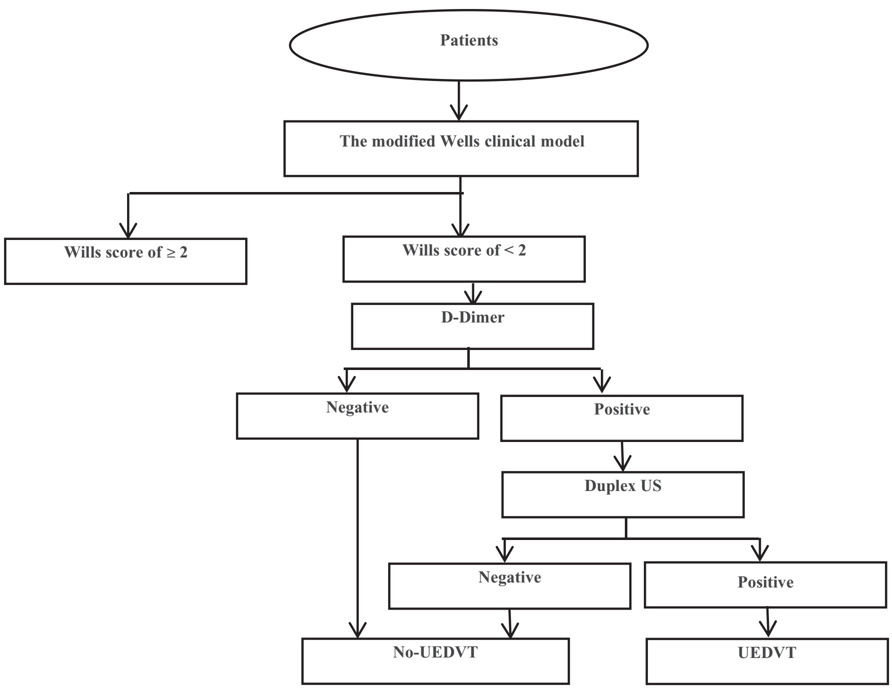

FIGURE 1 Diagnostic work-up of UEDVT

4 | RESULTS

In total, 7,454 patients underwent PICC placement during the study period. Of them, 3,592 patients without CDU screening were excluded. Of the 3,862 patients who underwent CDU screening, 769 developed VT and 3,093 did not, yielding an incidence rate of 19.9%. After excluding 3,212 patients with no D-dimer data within 7 days before CDU, 266 patients with LEVT and 103 patients with the modified Wells score ≥2 points, 281 patients were included in the final analysis (Figure 2).

Among 281 patients, 101 patients (36%, 95% CI: 30.6%-41.8%) had positive D-dimer results, whereas 180 patients (64%, 95% CI: 58.2%–69.4%) had negative D-dimer results. Thirty-nine of 180 patients had VT despite having a negative D-dimer result, resulting in

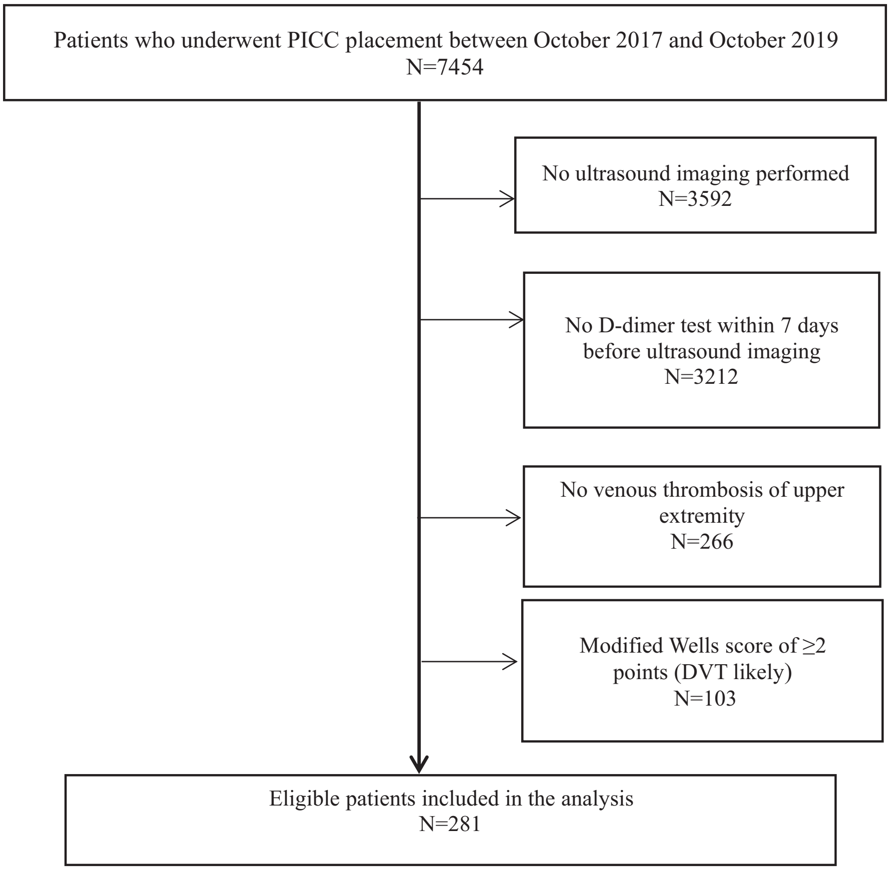

FIGURE 2 Flow diagram of study structure. DVT, deep vein thrombosis

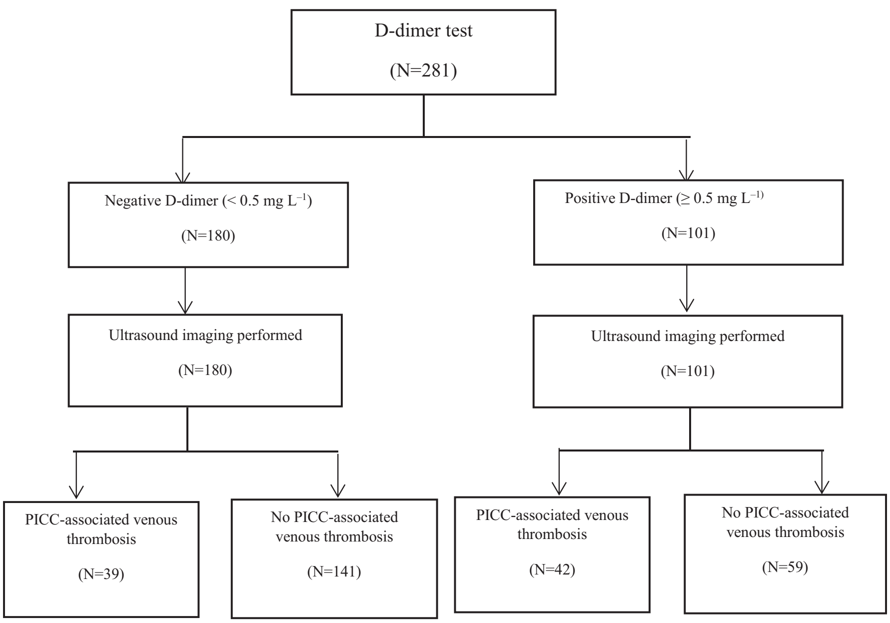

FIGURE 3 D-dimer level as an independent biomarker for excluding PICC-associated VT

TABLE 1 Clinicodemographic characteristics of the patients

	No-VT patients $N = 200$	DVT patients $N = 53$	SVT patients $N = 28$	*p*
Age (years), mean (Std)	44.9 (26.5)	42.7 (45.8)	51.6 (15.5)	**.010**
Female sex, *n* (%)	95 (47.5)	27 (50.9)	9 (32.1)	.244
Cancer	169 (84.5)	41 (77.4)	21 (75.0)	.277
Infusion of corrosive/stimulant drugs	176 (88)	48 (90.6)	24 (85.7)	.795
Consciousness	178 (89)	43 (81.1)	20 (71.4)	**.011**
Hypertension	16 (8)	6 (11.3)	1 (3.6)	.473
Diabetes mellitus	4 (2)	0 (0)	1 (3.6)	.465
Coronary disease	9 (4.5)	2 (3.8)	0 (0)	.515
Positive history of thrombus	1 (0.5)	0 (0)	2 (7.1)	**.004**
Normal limb movement	176 (88)	45 (84.9)	21 (75)	.077
Positive history of catheterization	13 (6.5)	2 (3.8)	1 (3.6)	.657
With normal international normalized ratio	172 (86)	41 (77.4)	20 (71.4)	.205
Normal thrombin time	175 (87.5)	43 (81.1)	22 (78.6)	.327
Normal D-dimer level before catheterization	139 (69.5)	31 (58.5)	13 (46.4)	.069
Normal fibrinogen level	112 (56)	29 (54.7)	14 (50)	.996
Normal white blood cell count	130 (65)	30 (56.6)	21 (75)	.166
Normal platelet count	128 (64)	35 (66)	22 (78.6)	.113
Normal haemoglobin count	90 (45)	23 (43.4)	7 (25)	.166
Normal glutamic-pyruvic transaminase level	156 (78)	42 (79.2)	22 (78.6)	.842
Normal glutamic-oxalacetic transaminase level	147 (73.5)	37 (69.8)	17 (60.7)	.440
Normal creatinine level	171 (85.5)	42 (79.2)	23 (82.1)	.460
Cooperating with tube placement	176 (88)	44 (83)	21 (75)	.149
Normal vital signs during catheterization	184 (92)	47 (88.7)	23 (82.1)	.132
Normal amount of bleeding during puncture	193 (96.5)	51 (96.2)	28 (100)	.595
One-time successful puncture	183 (91.5)	45 (84.9)	24 (84.7)	.287
Catheterization vein is the basilic vein	174 (87)	42 (79.2)	24 (85.7)	.363
X-ray positioning T5-T7	196 (98)	50 (94.3)	28 (100)	.212
No catheter displacement	161 (80.5)	36 (67.9)	26 (92.9)	**.023**
No other PICC-associated complications	192 (96)	51 (96.2)	27 (96.4)	.992

a failure rate of 21.7% (95% CI: 16.3%–28.3%) (Figure 3). Patients who developed PICC-associated SVT and PICC-associated DVT were similar to those who did not with respect to clinicodemographic characteristics such as gender, cancer, infusion of corrosive/stimulant drugs and hypertension. However, differences in age, consciousness, positive history of thrombus, catheter displacement between the three groups on bivariate, unadjusted comparisons were noted ($p < .05$) (Table 1).

The sensitivity of PICC-associated UEVT was 51.9% (95% CI:14.2%–62.4%), the specificity was 70.5% (95% CI:63.8%–76.4%), the NPV was 78.3% (95% CI: 71.7%–83.7%), the positive likelihood ratio was 41.6% (95% CI: 32.5%–51.3%), the positive likelihood ratio was 2.0, the negative likelihood ratio was 0.7, and required ultrasonography examinations were 35.9% (95% CI: 30.5%–41.7%) (Table 2). The NPV of PICC-associated UEVT in the cancer group (80.0%, 95% CI: 73.2%–85.4%) was higher than that of the non-cancer group (60.0%, 95% CI: 35.7%–80.2%). The NPV of PICC-associated UEDVT (84.9%, 95% CI: 78.7%–89.6%) was lower than that of the PICC-associated UESVT (91.0%, 95% CI: 85.4%–94.6%) (Table 2).

5 | DISCUSSION

In this study, we investigated whether the D-dimer concentration could be used as a key diagnostic marker for excluding PICC-associated UEVT. Our result is contrary to previous results showing that the D-dimer level can accurately rule out DVT (Lim et al., 2018).

TABLE 2 Diagnostic performance of the different groups ($n = 281$)

	PICC-associated VT			PICC-associated DVT			PICC-associated SVT		
	All patients	Cancer group	Non-cancer group	All patients	Cancer group	Non-cancer group	All patients	Cancer group	Non-cancer group
Sensitivity									
TP/(TP +FN)	42/81	29/62	13/19	28/53	20/41	8/12	14/28	9/21	5/7
Estimate (%)	51.9	46.8	68.4	52.8	48.8	66.7	50.0	42.9	71.4
95% CI	41.2–62.4	34.9–59.0	46.0–84.6	39.0–65.66	34.3–63.5	39.1–86.2	32.6–67.4	24.5–63.5	35.9–91.8
Specificity									
TN/(TN +FP)	141/200	132/169	9/31	141/200	132/169	9/31	141/200	132/169	9/31
Estimate (%)	70.5	78.1	29.0	70.5	78.1	71.0	70.5	78.1	29.0
95% CI	63.8–76.4	71.3–83.7	16.1–46.6	63.8–76.4	71.3–83.7	53.4–83.9	63.8–76.4	71.3–83.7	16.1–46.6
NPV									
TN/TN +FN	141/180	132/165	9/15	141/166	132/153	9/13	141/155	132/144	9/11
Estimate (%)	78.3	80.0	60.0	84.9	86.3	69.2	91.0	91.7	81.8
95% CI	71.7–83.7	73.2–85.4	35.7–80.2	78.7–89.6	80.0–90.9	42.3–87.3	85.4–94.6	86.0–95.2	52.3–94.9
Positive predictive value									
TP/TP +FP	42/101	29/66	13/35	28/87	20/57	8/30	14/73	9/46	5/27
Estimate (%)	41.6	43.9	37.1	32.2	35.1	26.7	19.2	19.6	18.5
95% CI	32.5–51.3	32.6–55.9	23.1–53.6	23.3–42.6	24.0–48.1	14.2–44.5	11.8–29.7	10.7–33.2	8.2–36.7
Positive likelihood ratio									
Sensitivity/(1 – specificity)	0.519/(1–0.705)	0.468/(1–0.781)	0.684/(1–0.29)	0.528/(1–0.705)	0.488/(1–0.781)	0.667/(1–0.710)	0.5/(1–0.705)	0.429/(1–0.781)	0.714/(1–0.29)
Estimate (ratio)	2.0	2.1	1.0	1.8	2.2	2.3	1.7	2.0	1.0
95% CI	1.3–2.4	1.4–3.2	0.7–1.4	1.3–2.5	1.5–3.4	1.3–3.9	1.1–2.6	1.1–3.5	0.6–1.7
Negative likelihood ratio									
(1–sensitivity)/specificity	(1–0.519)/0.705	(1–0.468)/0.78	(1–0.684)/0.29	(1–0.528)/0.705	(1–0.488)/0.781	(1–0.667)/0.710	(1–0.5)/0.705	(1–0.429)/0.781	(1–0.714)/0.29
Estimate (ratio)	0.7	0.7	1.1	0.7	0.7	0.5	0.7	0.7	1.0
95% CI	0.5–0.9	0.5–0.9	0.5–2.6	0.5–0.9	0.5–0.9	0.2–1.1	0.5–1.0	0.5–1.1	0.3–3.6
Required ultrasonography examinations[†]									
TP +FP/TP +FN + FP +TN	101/281	66/231	35/50	87/253	57/210	30/43	73/228	46/190	27/38
Estimate (%)	35.9	28.6	70.0	34.4	27.1	69.8	32.0	24.2	71.1
95% CI	30.5–41.7	23.2–34.7	56.2–80.9	28.8–40.4	21.5–33.5	54.9–81.4	26.3–38.3	18.7–30.8	55.3–83.0

Abbreviations: and TP, true positive; CI, confidence interval; FN, false negative; FP, false positive; TN, true negative.

[†]According to the criteria warranting ultrasonography in each strategy.

In these previous studies, the overall negative predictive values of the D-dimer level for DVT ranged from 99.3% to 99.8% (Bates et al., 2016; Nañez-Terreros et al., 2019). The possible reasons are as follows: first, the study population are different. We evaluated a specific PICC population, whereas the majority of patients who undergo PICC placement in China are cancer chemotherapy patients (Liu et al., 2018). VT events in cancer patients are usually associated with or triggered by vascular access devices (Al-Asadi et al., 2019; Kang et al., 2020). Some haematological malignancies also are known to secrete proteolytic factors, and we speculate that some patients with malignancies and DVT have normal D-dimer levels because of accelerated degradation of D-dimer (Colombo et al., 2014, Qdaisat et al., 2019). In this study, non-cancer patients were mainly from the neurology and neurosurgery departments. The age of these patients, thrombotic burden and fibrinolytic activity, duration of symptoms, previous VT and inflammatory status, and use of anticoagulants may affect the accuracy of D-dimer levels.

Second, the type of VT is different. Due to the difference in pathogenesis and clinical processes between UEDVT and LEDVT (Adelborg et al., 2018), we only evaluated UEVT directly or indirectly caused by PICC. A meta-analysis enrolled ten studies comprising 1591 participants with 1592 PICCs showed that the incidence of asymptomatic PICC-associated VT in adults was 22% (95% CI, 0.17–0.29) and in cancer patients was 19% (95% CI, 0.13–0.26) (Chen et al., 2021). Some studies have shown that approximately 75%-86% of UEDVT cases are associated with indwelling vascular catheters (Adelborg et al., 2018, Ploton et al., 2020). This association is not surprising as catheter insertion leads to endothelial damage, occupies the vein lumen (promoting venous stasis) and is often required in patients with hypercoagulability because of intercurrent illness or malignancy. Thus, the placement of these devices satisfies the Virchow's triad, leading to an increased risk of VTE (Chopra et al., 2014). PICC is placed in a much smaller vein than in CVC, and the risk of DVT in PICC is 2.5 times higher than that in CVC (Chopra et al., 2013). A case–cohort study reported a 13-fold increased risk of thrombosis in patients receiving PICC (Winters et al., 2015). Usually, PICC-associated VT is clinically asymptomatic (Chen et al., 2021). In a randomized controlled clinical trial of PICC-DVT using CDU screening, it was found that up to 75% of patients with catheters had VT, but only 4% of image-diagnosed patients with thrombosis developed clinical symptoms (Itkin et al., 2014). Asymptomatic PICC-associated VT mainly occurred in superficial veins (Chen et al., 2021). Concurrently, PICC-associated VT is unique, with most types being attached to wall thrombosis (Liu et al., 2021). This may be one of the important reasons for the lower negative predictive value of the D-dimer level for diagnosing PICC-associated VT in this study.

The advantages of our research include the use of the Reasonable Safety Infusion Monitoring System, which increases data accuracy owing to its forward-looking design and the structured, standardized collection of data. Further, all the D-dimer test results were confirmed using CDU within seven days. To reduce the bias, the type of thrombus was divided into PICC-associated VT, PICC-associated DVT and PICC-associated SVT. Each type had positive and negative indicators of a certain proportion of samples, and the results were relatively reliable. To evaluate the impact of cancer on VT and to reduce the impact of confounders, we also divided the population into all inpatients, cancer patients and non-cancer patients.

5.1 | Limitations

This study also has some limitations. First, the single-centre design may limit the generalizability of our findings. Further, our cut-off time was patient extubation, and follow-up data were not analysed. As a retrospective study, our data may underestimate the true number of cases of PICC-associated SVT and DVT because our institution does not have a systematic CDU screening protocol. In addition, our population was limited only to the patients with a PICC, and further analysis in non-cancer patients was not conducted. Finally, diagnostic bias was not evaluated, which may lead some clinicians to lean towards using CDU for diagnosing PICC.

6 | CONCLUSION AND IMPLIC ATIONS FOR CLINICAL PRACTICE

According to this study, the D-dimer level as an independent biomarker has low negative predictive value for PICC-associated VT. These results need to be confirmed among a wider group of patients receiving PICCs in the hospital setting, and these studies would need to be prospective and included both high- and low-risk patients, to avoid the selection bias of including only patients who ended up with D-dimer and US.

The results of this study could recommend against the use of D-dimer to rule out PICC-associated UEVT. This result could help nurses to realize the NPV of D-dimer level for PICC-associated UESVT is higher than that for UEDVT and the NPV of D-dimer level for PICC-associated UEVT in the cancer population is higher than that in the non-cancer population.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Wanli Liu participated in data acquisition and management of the trial, analysed and interpreted the data, and drafted and revised the manuscript. Lianxiang He, Wenjing Zeng and Liqing Yue participated in protocol drafting and study management. Jie Wei, Shuangshuang Zeng and Xiang Wang participated in data acquisition and daily management of the study. Zhicheng Gong was the trial manager and designed, initiated and managed the study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of Xiangya Hospital of Central South University (201,907,733).

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

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

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