Assessment of D-dimer for ruling out peripherally inserted central catheter-associated upper extremity venous thrombosis: a diagnostic accuracy study

Wanli Liu
Xiangya Hospital Central South University
Lianxiang He
Xiangya Hospital Central South University
Wenjing Zeng
Xiangya Hospital Central South University
Liqing Yue
Xiangya Hospital Central South University
Jie Wei
Xiangya Hospital Central South University
Shuangshuang Zeng
Xiangya Hospital Central South University
Xiang Wang
Xiangya Hospital Central South University
Zhicheng Gong (506017215@qq.com)
Xiangya Hospital Central South University https://orcid.org/0000-0002-7315-7856

Research

Keywords: D-dimer, deep vein thrombosis, superficial venous thrombosis, PICC, sensitivity and specificity, venous thrombosis

Posted Date: November 6th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-70098/v2

Abstract

Background: With the extensive use of peripherally inserted central catheter (PICC), PICC-associated venous thrombosis (VT) has become one of the most important complications in the hospital. To reduce unnecessary Color Doppler Ultrasound (CDU) or imaging tests, D-dimer values are usually used to exclude VT for patients with low VT risk. There is little evidence for the usefulness of the D-dimer level as an independent diagnostic marker for excluding PICC-associated VT.

Aims: To examine the effectiveness of D-dimer values to be used as an independent diagnostic marker for excluding PICC-associated Upper Extremity Venous Thrombosis(UEVT).

Methods: Records were reviewed for 281 patients who underwent PICC insertion over the two years period in Xiangya Hospital Central South University.The patients were categorized into the UEVT unlikely group (<2 points) and the UEVT likely group (≥2 points) according to the Constans Clinical Decision Score(Constans score) post PICC insertion, before extubation. After the score was determined, the patients underwent a D-dimer test and CDU within 7 days after D-dimer test.

Results: Among 281 patients, 180 patients (36%, 95%CI:30.6%-41.8%) had negative D-dimer results, 39 of 180 patients had VT despite having a negative D-dimer result, resulting in a failure rate of 21.7% (95% CI: 16.3–28.3%).The NPV of PICC-associated VT 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 DVT(Deep Venous Thrombosis) (84.9%,95% CI: 78.7–89.6%) was lower than that of the PICC-associated SVT(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 PICC-associated VT to avoid missed diagnosis of PICC-related VT, which may cause adverse consequences.

Introduction

In patients requiring infusion of corrosive drugs or long-term infusions, PICC is a convenient alternative to Central Venous Catheter (CVC). PICCs are easy to place, can be nurse-led, and do not have risks associated with CVC insertion [1]. However, PICCs have a risk of developing upper extremity superficial venous thrombosis (UESVT) and upper extremity deep venous thrombosis (UEDVT).UEDVT commonly affects inpatients and accounts for half of hospital-acquired DVT [2-4], which usually leads to treatment disruption, obvious scarring and occlusion of the deep veins of the upper extremity, impaired venous reflux and subsequent establishment of venous access, and increased hospital stay and cost [5,6] and may even cause pulmonary embolism [1,3]. Despite few studies on PICC-associated UESVT, the association between SVT and DVT is known to be variable[7].

The diagnostic criteria for thrombosis are recommended that patients determined to have a low risk for DVT, the negative D-dimer accurately ruled out UEDVT without the need for CDU or other imaging tests and helped avoid unnecessary anticoagulant treatment(Fig.1)[1,9-12]. However, the algorithm fails when low scores are assigned to patients with VT or when tests give false-normal D-dimer levels [13]. The latter may be the result of a small thrombus, reduced fibrinolysis, or D-dimer testing at a very early or late stage of the disease [14]. As we known,PICC-associated VT is different from the usual VT, as the former presents primarily as a mural thrombus[2-4]. This particular type of mural thrombus 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.

Method

Study Design

This was a retrospective case cohort study. The study included in inpatients between October 1, 2017, and October 1, 2019 on the all wards of Xiangya hospital Central South University in Hunan, China. The patients were categorized into the UEDVT unlikely group (<2 points) and the UEDVT likely group (≥2 points) according to the Constans score post PICC placement, before extubation. After the score was determined, the patients underwent a D-dimer test and CDU within 7 days after D-dimer test.To examine the effectiveness of D-dimer concentration to be used as an independent diagnostic marker for excluding PICC-associated UEVT.

Inclusion criteria were as follows: 1) patients aged≥18 years; 2) patients with PICC inserted via the upper arms; 3) <2 points on the Constans score；4) patients who underwent CDU and D-dimer values after PICC placement. Exclusion criteria were as follows: 1) PICC-associated lower extremity venous 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 Reasonable Safety Infusion Monitoring System of Xiangya Hospital of Central South University.

The study was approved by the ethics committee of Xiangya Hospital of Central South University (201907733) and was conducted according to the Helsinki Declaration of Ethical Principles for Medical Research involving Human Subjects.

The Constans score

A dichotomized Constans score are recommended by the American Society of Hematology 2018 guidelines to assess clinical probability of suspected UEDVT. It was composed of specific items that included venous material prensent(central venous catheter or pacemaker thread),localized pain,unilateral edema,other dignosis at least as plausible. The patients were categorized into the UEDVT unlikely group (<2 points) and the UEDVT likely group (≥ 2 points).

D-dimer

Blood samples for D-dimer testing were obtained before ultrasonography investigation. Blood was drawn by clean venipuncture from an antecubital vein with a 22-gauge butterfly needle and collected into 3 ml plastic tubes containing 0.3 ml 0.106 M trisodium citrate. After blood collection, the blood was gently reversed and mixed for 3-6 times.Whole blood was centrifuged at 2000 ×g for 20 min at 20 °C. The STA Liatest® D-dimer was employed which is an automated and rapid microlatex D-dimer assay. The STA Liatest® had higher sensitivity (median, ≥95%) which meet the US Food and Drug Administration (FDA) requirements could applied to rule out VT[15,16]. Use of the age-adjusted cutoffs wouldn't significantly impairing the NPV[17]. But it seems to be less useful with the STA-Liatest® assay [18] and the results obtained with specific D-dimer assays cannot be extrapolated from one test to another [18].So the results were expressed in mg/L, the cut-off value for DVT exclusion was 0.5mg/L.The blood laboratory of the hospital did not change the detection method or change the detection reagent between October 2017 and October 2019.

CDU

CDU was performed within 7 days after D-dimer detection.CDU was carried out with the Philips epic5 instrument , with a high-resolution broadband width 9-13 MHz linear array transducer by CDU technician who had adequate experience with CDU. The main criteria for the diagnosis of VT were as follows [19-21]: 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 brachial vein, axillary vein, subclavian artery, internal jugular vein, and brachial vein [19, 20]. Superficial veins of the upper limb included cephalic and cubital median veins and the basilic veins [2,21,22]. Patients with negative CDU did not undergo angiography.

Statistical analysis

The reliability and effectiveness of D-dimer level as an independent biomarker for PICC-associated VT was evaluated according to its sensitivity, specificity, NPV, and positive predictive value and the need for ultrasonography examinations. The patients were divided into the PICC-treated group, PICC-treated cancer group, and PICC-treated non-cancer group. The 95% confidence intervals (CI) were presented. All statistical analyses were performed using SPSS statistical software version 18.0.

Results

In total, 7454 patients underwent PICC placement during the study period. Of them, 3592 patients without CDU screening were excluded. Of the 3862 patients who underwent CDU screening, 769 developed VT and 3093 did not, yielding an incidence rate of 19.9%. After excluding 3212 patients with no D-dimer data within 7 days before CDU, 266 patients with LEVT, and 103 patients with Constans score ≥2 points, 281 patients were included in the final analysis (Fig. 2).

Among 281 patients, 101 patients (64%, 95%CI:58.2–69.4%) had positive D-dimer results, whereas 180 patients (36%, 95%CI:30.6%-41.8%) had negative D-dimer results .39 of 180patients had VT despite having a negative D-dimer result, resulting in a failure rate of 21.7% (95% CI: 16.3–28.3%)(Fig. 3).

The patients' clinicodemographic characteristics are shown in Table 1. The sensitivity of PICC-associated VT 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,required ultrasonography examinations was 35.9% (95% CI: 30.5–41.7%)(Table 2).

The NPV of PICC-associated VT 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 DVT(Deep Venous Thrombosis) (84.9%,95% CI: 78.7–89.6%) was lower than that of the PICC-associated SVT(Superficial Venous Thrombosis) (91.0% ,95% CI: 85.4–94.6%)(Table 2).

Discussion

Diagnostic guidelines for DVT recommend using Clinical prediction rules and D-dimer levels to initially screen for the risk of DVT before using CDU[8]. In this study, we investigated whether the D-dimer values could be used as a key diagnostic marker for excluding PICC-associated VT. We evaluated patients with a PICC who had a Constans score of DVT <2 points (DVT unlikely) and D-dimer <0.5mg/L and found that 21.7% of these patients had PICC-associated VT,15.1% of DVT,9.0% of SVT,This is difference to previous studies showing that the D-dimer level can accurately rule out DVT as the NPV of the D-dimer level for DVT ranged from 99.3% to 99.8% [23-25].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. UEDVT in cancer patients are usually associated with or triggered by vascular access devices[3,26-28].The prevalence of VT is increased (up to 20% of cancer patients develop VT) and the NPV is therefore reduced[29,30]. Not only that,Some hematological 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 [31]. Overall, the complexity of various factors in cancer patients, ranging from complications to drugs used for the cancer itself, may affect the sensitivity of D-dimer as a biomarker [10]. 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[32-34]. This may partly explain why the NPV of D-dimer in the non-cancer group was lower than that in the cancer group (60.0% [95% CI: 35.7–80.2%] vs. 80.0% [95% CI: 73.2–85.4%]).

Second, the type of VT is different. Due to the difference in pathogenesis and clinical processes between UEDVT and LEDVT [35,36], we only evaluated UEVT directly or indirectly caused by PICC. Some studies have shown that approximately 75% of UEDVT cases is associated with indwelling vascular catheters [35,36]. 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, placement of these devices satisfies the Virchow's triad, leading to increased risk of VT [37]. PICC-associated VT is unique, with most types being attached to wall thrombosis. A study found that D-dimer plasma levels correlated with the thrombotic burden in patients with LEDVT [38] and a normal D-dimer levels in UEVT can be ascribed to the low thrombotic burden associated with mural thrombus. Another study shows that D-dimer levels correlate with clot volume and surface area[39],the mural thrombus may be the result of a small thrombus causes tests give false-normal D-dimer levels[13,14]. This may be one of the important reasons for the lower NPV of D-dimer level for diagnosing PICC-associated VT in this study.

In this study, we discussed PICC-associated UEDVT and PICC-associated UESVT separately.PICC is placed in a much smaller vein than in CVC, and the risk of UEDVT in PICC is 2.5 times higher than that in CVC [3]. A case cohort study reported a 13-fold increased risk of thrombosis in patients receiving PICC [40]. Usually, PICC-associated UEDVT is clinically asymptomatic. In a recent randomized controlled clinical trial of PICC-associated UEDVT using CDU screening, it was found that up to 75% of patients with catheter had UEDVT, but only 4% of image-diagnosed patients with thrombosis developed clinical symptoms [41].Compared with UEDVT, UESVT is more prone to pain, reddening of the skin and swelling of the surrounding tissue and other clinical signs and symptoms because of its superficial location [42].Localized pain and unilateral edema are included in the Constans score [43] ,so

that the score of patients with UESVT is more than 2 points than that of patients with UEDVT.This may partly explain why the NPV of PICC-associated DVT was lower than that of the PICC-associated SVT.

This study also has some limitations. First, the single-center design may limit the generalizability of our findings. Further, our cutoff time was patient extubation, and follow-up data were not analyzed. 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, A duration of >7 days between D-dimer examination and CDU was another limitation. Finally, Patients with negative ultrasound did not undergo angiography, we were not able to establish whether such VT was a diagnostic failure or a intervening complication.

Conclusion

The D-dimer level as an independent biomarker has low NPV for PICC-associated VT in low-risk patients identified according to the Constans score. The D-dimer levels maybe should not be used as a diagnostic index to rule out PICC-associated VT to avoid missed diagnosis of PICC-related VT, which may cause adverse consequences.

Abbreviations

Constans score:Constans Clinical Decision Score

FP:False Positive

FN:False Negative

CI:Confidence Interval

CDU:Color Doppler Ultrasound

CVC:Central Venous Catheter

IQR:interquartile range

LEVT:Lower Extremity Venous Thrombosis

PICC: Peripherally Inserted Central Catheter

TP:True positive

TN:True negative

UEVT:Upper Extremity Venous Thrombosis

UESVT: Upper Extremity Superficial Venous Thrombosis

UEDVT:Upper Extremity Deep Venous Thrombosis

VT:Venous Thrombosis

NPV: Negative Predictive Value

Declarations

Acknowledgments

We are particularly grateful to the the Reasonable Safety Infusion Monitoring System of Xiangya Hospital of Central South University for providing technical and personnel support.

Funding

Funded by the Finance Department Project of Hunan Province, People's Republic of China (No. [2019] 60) and the Natural Science Foundation of Hunan Province (2020JJ5880).

Availability of data and material

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

Ethics approval and consent to participate

Approved by the Ethics Committee of Xiangya Hospital of Central South University (201907733)

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Teaching and Research Section of Clinical Nursing, Xiangya Hospital of Central South University, Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China

[2]Institute for Rational and Safe Medication Practices, National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China

[3]Department of Pharmacy, Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China

References

[1] Chopra V, Anand S, Hickner A, et al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. *Lancet*. 2013;382(9889):311-325.

[2] Winters JP, Callas PW, Cushman M, Repp AB, Zakai NA. Central venous catheters and upper extremity deep vein thrombosis in medical inpatients: the Medical Inpatients and Thrombosis (MITH) Study. *J Thromb Haemost*. 2015;13(12):2155-2160.

[3] Chopra V, Anand S, Hickner A, et al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. *Lancet*. 2013;382(9889):311-325.

[4] Malinoski D, Ewing T, Bhakta A, et al. Which central venous catheters have the highest rate of catheter-associated deep venous thrombosis: a prospective analysis of 2,128 catheter days in the surgical intensive care unit. *J Trauma Acute Care Surg*. 2013;74(2):454-460; discussion 461-462.

[5] Marnejon T, Angelo D, Abu Abdou A, Gemmel D. Risk factors for upper extremity venous thrombosis associated with peripherally inserted central venous catheters. *J Vasc Access*. 2012;13(2):231-238.

[6] Gonsalves CF1, Eschelman DJ, Sullivan KL, DuBois N, Bonn J. Incidence of central vein stenosis and occlusion following upper extremity PICC and port placement. *Cardiovasc Intervent Radiol*. 2003;26(2):123-127.

[7] Di Minno MN, Ambrosino P, Ambrosini F, Tremoli E, Di Minno G, Dentali F. Prevalence of deep vein thrombosis and pulmonary embolism in patients with superficial vein thrombosis: a systematic review and meta-analysis. *J Thromb Haemost*. 2016;14(5):964-972.

[8] Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv*. 2018;2(22):3226-3256.

[9] Fronas SG, Wik HS, Dahm AEA, et al. Safety of D-dimer testing as a stand-alone test for the exclusion of deep vein thrombosis as compared with other strategies. *J Thromb Haemost*. 2018;16(12):2471-2481.

[10] Qdaisat A, Wu CC, Yeung SJ. Normal D-dimer levels in cancer patients with radiologic evidence of pulmonary embolism. *J Thromb Thrombolysis*. 2019;48(1):174-179.

[11] Zhang D, Li F, Du X, et al. Diagnostic accuracy of biomarker D-dimer in patients after stroke suspected from venous thromboembolism: A diagnostic meta-analysis. *Clin Biochem*. 2019;63:126-134.

[12] Weitz JI, Fredenburgh JC, Eikelboom JW. A test in context: D-dimer. *J Am Coll Cardiol*. 2017;70(19):2411-2420.

[13] T.L. Fancher, R.H. White, R.L. KravitzCombined use of rapid D-dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: systematic review Brit Med J, 2004;329:821-824

[14] J. Kelly, A. Rudd, R.R. Lewis, B.J. HuntPlasma D-dimers in the diagnosis of venous thromboembolism Arch Intern Med, 2002;162:747-756

[15] CLSI. Quantitative D-dimer for exclusion of venous thromboembolic disease. CLSI document H59-A. Wayne, PA: Clinical and Laboratory Standard Institute; 2011.

[16] 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.

[17] Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. Jama. 2014;311:1117–1124.

[18] Pernod G, Maignan M, Marlu R. Questioning the use of an age-adjusted D-dimer threshold to exclude venous thromboembolism: analysis of individual patient data from two diagnostic studies: comment. J Thromb Haemost. 2016;14:2553–2554.

[19] 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.

[20] 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.

[21] 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.

[22] Kucher N. Clinical practice. Deep-vein thrombosis of the upper extremities. *N Engl J Med*. 2011;364(9):861-869.

[23] Schmaier AA, Ambesh P, Campia U. Venous thromboembolism and cancer. *Lancet*. 1998. 351(9109):1077-1080.

[24] Bates SM, Takach Lapner S, Douketis JD, et al. Rapid quantitative D-dimer to exclude pulmonary embolism: a prospective cohort management study. *J Thromb Haemost*. 2016;14(3):504-509.

[25] Nañez-Terreros H, Jaime-Perez JC, Muñoz-Espinoza LE, et al. D-dimer from central and peripheral blood samples in asymptomatic central venous catheter-related thrombosis in patients with cancer. *Phlebology*. 2018;34(1):52-57.

[26] 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):1-7

[27] Li J, Fan YY, Xin MZ, et al. A randomised, controlled trial comparing the long-term effects of peripherally inserted central catheter placement in chemotherapy patients using B-mode ultrasound with modified Seldinger technique versus blind puncture. *Eur J Oncol Nurs*. 2014;18(1):94-103.

[28] Patel GS, Jain K, Kumar R, et al. Comparison of peripherally inserted central venous catheters (PICC) versus subcutaneously implanted port-chamber catheters by complication and cost for patients receiving chemotherapy for non-haematological malignancies. *Support Care Cancer*. 2014;22(1):121-128.

[29] Angchaisuksiri, P., Cancer-associated thrombosis in Asia. Thrombosis Journal, 2016. 26(14):129-132.

[30] Giannitsis E, Mair J, Christersson C, et al. How to use D-dimer in acute cardiovascular care. Eur Heart J Acute Cardiovasc Care. 2017;6:69–80.

[31]Colombo R, Gallipoli P, Castelli R.Thrombosis and hemostatic abnormalities in hematological malignancies. Clin Lymphoma Myeloma Leuk .2014;14(6):441–450.

[32]Siragusa S, Terulla V, Pirrelli S, Porta C, Falaschi F, Anastasio R, Guarnone R, Scarabelli M, Odero A, Bressan MA.A rapid D-dimer assay in patients presenting at the emergency room with suspected acute venous thrombosis: accuracy and relation to clinical variables. Haematologica .2001;86(8):856–861

[33]Couturaud F, Kearon C, Bates SM, Ginsberg JS Decrease in sensitivity of D-dimer for acute venous thromboembolism after starting anticoagulant therapy. Blood Coagul Fibrinolysis. 2002;13(3):241–246

[34]Schutgens RE, Esseboom EU, Haas FJ, Nieuwenhuis HK, Biesma DH Usefulness of a semiquantitative D-dimer test for the exclusion of deep venous thrombosis in outpatients. Am J Med. 2002;112(8):617–621

[35] Lechner D, Wiener C, Weltermann A, Eischer L, Eichinger S, Kyrle PA. Comparison between idiopathic deep vein thrombosis of the upper and lower extremity regarding risk factors and recurrence. *J Thromb Haemost*. 2008;6(8):1269-1274.

[36] Adelborg K, Horváth-Puhó E, Sundbøll J, Prandoni P, Ording A, Sørensen HT. Risk and prognosis of cancer after upper-extremity deep venous thrombosis: A population-based cohort study. *Thromb Res*. 2018;161:106-110.

[37] Chopra V, Ratz D, Kuhn L,Lopus T, Lee A, Krein S. Peripherally inserted central catheter-related deep vein thrombosis: contemporary patterns and predictors. *J Thromb Haemost.* 2014;12(6):847-854.

[38] M. Sartori, E. Favaretto, M. Cini, C. Legnani, G. Palareti, B. CosmiD-dimer, FVIII and thrombotic burden in the acute phase of deep vein thrombosis in relation to the risk of post-thrombotic syndrome.Thromb Res.2014;134 (1):320-325

[39] Fraser DG,Moody AR,Marte A,Morgan P.Determinants of D-dimer level in patients presenting with deep venous thrombosis: assessment using magnetic resonance thrombus imaging. Abstracts from the European Haematology Association 5th Congress; June 27, 2000; Birmingham, Ala. Abstract 513.

[40] Winters JP, Callas PW, Cushman M, Repp AB, Zakai NA. Central venous catheters and upper extremity deep vein thrombosis in medical inpatients: the Medical Inpatients and Thrombosis (MITH) Study. J Thromb Haemost. 2015;13(12):2155-2160.

[41] Itkin M, Mondshein JI, Stavropoulos SW, Shlansky-Goldberg RD, Soulen MC, Trerotola SO. Peripherally inserted central catheter thrombosis–reverse tapered versus nontapered catheters: a randomized controlled study. J Vasc Interv Radiol. 2014;25(1):85-91.

[42] R.M. Bauersachs.Diagnosis and treatment of superficial vein thrombosis. Hamostaseologie,2013; 33 (1):232-240

[43] J. Constans, L.-R. Salmi, M.-A. Sevestre-Pietri, S. Perusat, M. Nguon, M. Degeilh, et al.A clinical prediction score for upper extremity deep venous thrombosis. Thromb Haemost, 2008;99 (1):202-207

Tables

Table 1. Clinicodemographic characteristics of the patients

	All patients N=281	No-VT patients N=200	DVT patients N=53	SVT patients N=28
Age (years), median (IQR)	44.9 (26.5)	42.7 (45.8)	51.6 (15.5)	47.3 (26.8)
Female sex, n (%)	131 (46.6)	95 (47.5)	27 (50.9)	9 (32.1)
Cancer	231 (82.2)	169 (84.5)	41 (77.4)	21 (75.0)
Infusion of corrosive/stimulant drugs	248 (88.3)	176 (88)	48 (90.6)	24 (85.7)
Consciousness	241 (85.8)	178 (89)	43 (81.1)	20 (71.4)
Hypertension	23 (8.2)	16 (8)	6 (11.3)	1 (3.6)
Diabetes mellitus	5 (1.8)	4 (2)	0 (0)	1 (3.6)
Coronary disease	11 (3.9)	9 (4.5)	2 (3.8)	0 (0)
Positive history of thrombus	3 (1.1)	1 (0.5)	0 (0)	2 (7.1)
Normal limb movement	242 (86.1)	176 (88)	45 (84.9)	21 (75)
Positive history of catheterization	16 (5.7)	13 (6.5)	2 (3.8)	1 (3.6)
With normal international normalized ratio	233 (82.9)	172 (86)	41 (77.4)	20 (71.4)
Normal thrombin time	240 (85.4)	175 (87.5)	43 (81.1)	22 (78.6)
Normal D-dimer level before catheterization	183 (65.1)	139 (69.5)	31 (58.5)	13 (46.4)
Normal fibrinogen level	155 (55.2)	112 (56)	29 (54.7)	14 (50)
Normal white blood cell count	181 (64.4)	130 (65)	30 (56.6)	21 (75)
Normal platelet count	185 (65.8)	128 (64)	35 (66)	22 (78.6)
Normal hemoglobin count	120 (42.7)	90 (45)	23 (43.4)	7 (25)
Normal glutamic-pyruvic transaminase level	220 (78.3)	156 (78)	42 (79.2)	22 (78.6)
Normal glutamic-oxalacetic transaminase level	201 (71.5)	147 (73.5)	37 (69.8)	17 (60.7)
Normal creatinine level	236 (84)	171 (85.5)	42 (79.2)	23 (82.1)
Cooperating with tube placement	241 (85.8)	176 (88)	44 (83)	21 (75)
Normal vital signs during catheterization	254 (90.4)	184 (92)	47 (88.7)	23 (82.1)
Normal amount of bleeding during puncture	272 (96.8)	193 (96.5)	51 (96.2)	28 (100)
One-time successful puncture	252 (89.7)	183 (91.5)	45 (84.9)	24 (84.7)
Catheterization vein is the basilic vein	240 (85.4)	174 (87)	42 (79.2)	24 (85.7)
X-ray positioning T5-T7	274 (97.5)	196 (98)	50 (94.3)	28 (100)
No catheter displacement	223 (79.4)	161 (80.5)	36 (67.9)	26 (92.9)
No other PICC-associated complications	270 (96.1)	192 (96)	51 (96.2)	27 (96.4)

*IQR, interquartile range

Table 2. Diagnostic performance of the different groups (n = 281)

	VT			DVT			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.–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	1.68	2.3	1.7	1.5	1.0
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
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

CI, Confidence Interval; FN, False Negative; FP, False Positive; TN, True Negative; TP, True Positive

Figures

Figure 1

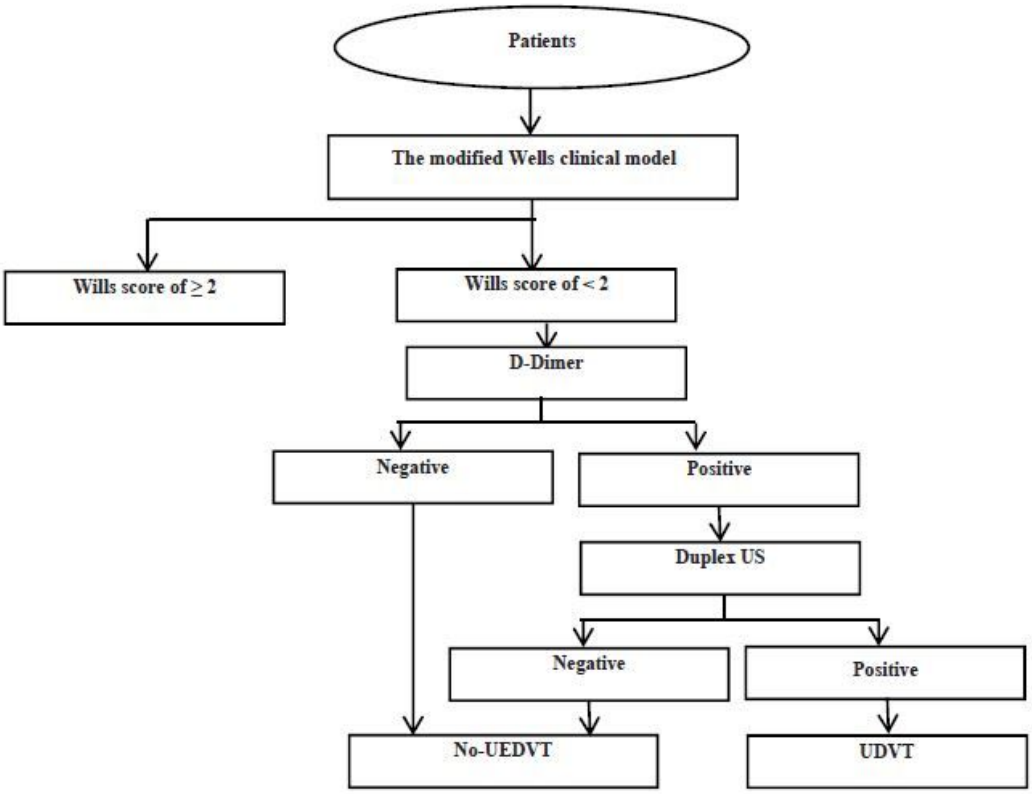

Figure 1

Diagnostic work-up of UEDVT

Figure 2

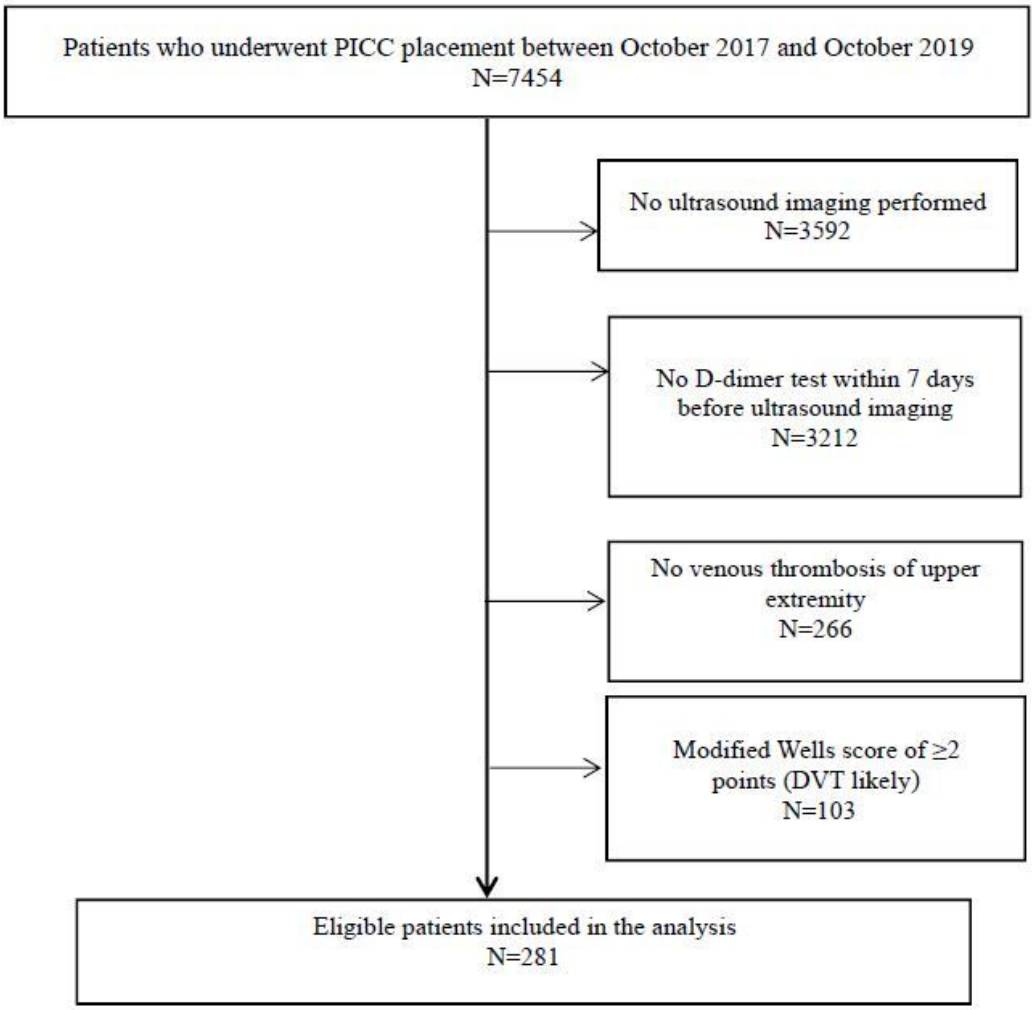

Figure 2

Flow diagram of study structure

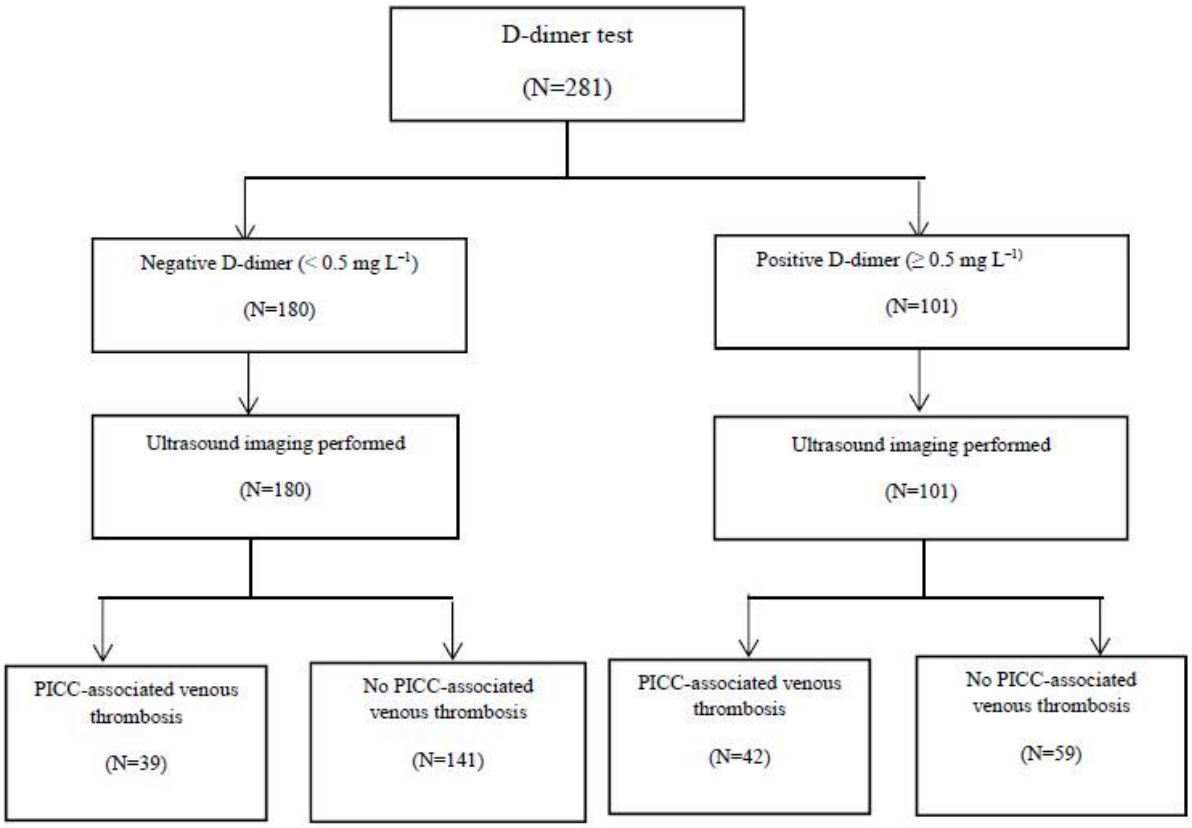

Figure 3

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