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ORIGINAL ARTICLE

Peripherally inserted central catheter-related deep vein thrombosis: contemporary patterns and predictors

V. CHOPRA,*†‡ D. RATZ,* † L. KUHN,* † T. LOPUS,† A. LEE§ and S. KREIN*†‡

The Patient Safety Enhancement Program, The Center for Clinical Management Research; †The VA Ann Arbor Healthcare System; ‡The University of Michigan Health System, Ann Arbor, MI, USA; and §The Division of Hematology, University of British Columbia, Vancouver, BC, Canada

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Summary. *Background:* Despite growing use, peripherally inserted central catheters (PICCs) are associated with risk of deep vein thrombosis (DVT). We designed a study to determine patient, provider and device factors associated with this outcome. *Methods:* This was a retrospective cohort study of adults who underwent PICC placement between 1 June 2009 to 30 June 2012. Symptomatic PICC-associated DVT was confirmed by ultrasound. Because PICCs are also recognized risk factors for lower-extremity DVT, lower-extremity DVT occurring while the PICC was *in situ* was included. Multivariable logistic and Cox-proportional hazards regression models were fit to examine the association between covariates specified *a priori* and PICC-DVT. Odds ratios (ORs) and hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were generated. *Results:* Of 966 unique PICC placements, 33 patients developed symptomatic PICC-associated DVT and 9 developed lower-extremity DVT, accounting for 42 thrombotic events. On bivariate analysis, recent diagnosis of cancer, interventional radiology placement, chemotherapy administration, number of lumens and PICC-gauge were associated with PICC-DVT. Following multivariable adjustment, recent cancer diagnosis (OR 1.95 [95% CI 1.01–3.76]) and PICC gauge (HR 2.21 [95%CI 1.04–4.70] and HR 3.56 [95%CI 1.31–9.66] for 5-Fr and 6-Fr PICCs, respectively) remained associated with thrombosis. *Conclusions:* Recent diagnosis of cancer and PICC gauge are associated with PICC-DVT. These findings have important clinical ramifications and suggest that placement of large gauge PICCs or PICCs in patients with cancer may provoke thrombosis. Improved policies and procedural oversights in these areas appear necessary to prevent PICC-DVT.

Keywords: central venous catheter thrombosis; central venous catheters; deep vein thrombosis; peripheral venous catheterization; upper extremity deep vein thrombosis; venous thromboembolism.

Correspondence: Vineet Chopra, 2800 Plymouth Road, Building 16 Room 432W, Ann Arbor, MI 48109, USA.
Tel.: +1 734 936 5216; fax: +1 734 689 1844.
E-mail: vineetc@umich.edu

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Introduction

The use of peripherally inserted central catheters (PICCs) has grown rapidly in the United States [1]. Because these devices are inserted in the arm and avoid many of the iatrogenic, mechanical complications associated with central venous catheter insertion in the neck or chest, they are often considered safer than their traditional counterparts. Furthermore, with the advent of vascular access nursing teams, who provide high rates of insertion success and evidence-based insertion and maintenance, PICCs have become more accessible to hospitals across the country, often serving as a bridge for intravenous therapies from the inpatient to the outpatient setting [2].

Despite these advantages, PICCs are increasingly associated with deep vein thrombosis of the arm (PICC-DVT), a complication that has important consequences [3,4]. For example, PICC-DVT often leads to interruptions in treatment, creating a conundrum for providers who rely on these devices for venous access, while increasing length of stay and cost [5.] This adverse event also leads to significant scarring and obliteration of upper extremity deep veins, impairing venous return and subsequent venous access. Thrombosis associated with PICCs often resolves with residual venous stenosis of the upper extremities [6] and has been recognized as a key predictor of arteriovenous graft failure in patients on hemodialysis [7]. In its most severe form, PICC-DVT may cause pulmonary embolism, an outcome that is especially frequent in critically ill and cancer populations [3]. Finally, the thrombogenic burden associated with PICCs is known to

extend beyond veins of the arm, as PICCs are increasingly recognized as one of the strongest risk factors for in-hospital, lower-extremity DVT [8,9]. Given all of these risks, both the Society of General Internal Medicine and the American Society of Nephrology have suggested caution with the use of PICCs in their national Choosing Wisely® initiatives [10,11].

To better inform clinical practice and reduce the risk of PICC-DVT, factors associated with this adverse event must be identified. Early studies have demonstrated that a number of modifiable and non-modifiable factors are associated with PICC thrombosis [5,12–15]. However, there remains a paucity of data regarding which of these may be targeted to reduce venous thromboembolism. Therefore, we conducted a retrospective study to examine patterns, incidence, timing and predictors of PICC-DVT. In accordance with a previously published framework [16], we hypothesized that specific patient-, provider-, and device-related characteristics would be associated with PICC-DVT. We were most interested in factors that could be modified to reduce the risk of thrombosis associated with these devices.

Patients and methods

Using records obtained from our vascular access nursing team, we assembled a cohort of consecutive, adult, hospitalized patients who underwent insertion of a PICC between 1 June 2009 and 30 June 2012 at our 145-bed, academic Veterans Affairs (VA) Medical Center. Clinical data, such as indication for insertion, number of insertion attempts, vein and arm of insertion, and details regarding the type of PICC (lumens, gauge, coating), were directly abstracted from electronic medical records. Information regarding patient co-morbidities, medications and dosages, disposition and admission/discharge diagnoses was obtained from administrative datasets. Because data regarding device details and insertion were missing from patients who had PICCs placed at another institution, such patients were excluded from our study.

PICC-DVT was identified through a combination of vascular access nursing records, ICD-9 codes and chart review. DVTs were classified as being PICC-associated when B-mode or Doppler ultrasound revealed the presence of thrombus in the deep veins of the arm (brachial, axillary and subclavian veins) while a PICC was *in situ*. In all cases, testing was performed in the presence of clinical signs or symptoms (e.g. arm pain, swelling or shortness of breath); further evaluation for extension in the superior vena cava or pulmonary embolism was only performed if symptoms suggest the same. Difficulties flushing the line prompted vascular access nursing referral for a 'declot' evaluation, but only led to ultrasound testing if clinical signs suggestive of thrombosis were present. Because the presence of a PICC is a known risk factor for lower-extremity DVT [8,9,17], we also included thrombosis involving the deep veins of the leg if it occurred when the PICC was in place. Patients were followed until the PICC was removed (regardless of whether this occurred in the hospital or the home setting), as our vascular access team is responsible for all device removals. Only patients with PICCs for whom complete data were available, from insertion to removal, were included in the final cohort.

PICC insertion and care

All PICC insertions by our vascular access nursing team and interventional radiologists employ standard aseptic precautions. Portable ultrasonography is routinely performed prior to PICC placement to identify a suitable vein for insertion. All PICCs are placed in veins that are deemed to have an appropriate size and location (above the elbow and at least twice the size of the maximal PICC diameter). Should bedside PICC placement prove difficult (e.g. coiling or kinking of the catheter despite several attempts) or technically unfeasible (e.g. no visible veins for insertion), patients are referred to interventional radiology for PICC placement. Following insertion, PICC-tip position at the cavoatrial junction is verified by chest x-ray or fluoroscopy, with subsequent adjustments made according to radiologist interpretation of catheter-tip position. No PICCs are used prior to verification of central termination of the tip. Surveillance imaging for incorrect position or thrombosis is not performed at our facility.

Routine device and site checks are performed weekly by the vascular access team or earlier if malfunction occurs. All PICC lumens are flushed with 10 mL normal saline and 5 mL heparin daily according to a defined maintenance protocol. In the event of luminal occlusion (failure to flush or withdraw from the PICC), 2 mg mL^{-1} of tissue plasminogen-activator is instilled in each lumen to 'declot' the device. At our hospital, patients with PICCs do not receive pharmacologic DVT prophylaxis on account of the device itself, but most patients tend to receive prophylaxis due to coexisting medical co-morbidities.

Variables and definitions

Duration of PICC use was calculated in days by subtracting the date of removal from the date of PICC placement, whereas time to DVT was calculated by subtracting the date of the positive ultrasound study from the date of PICC insertion. Patients with recent diagnosis of cancer were identified by searching for ICD9-specific codes for cancer in the inpatient or outpatient setting in the 6 months prior to the PICC-related admission using a validated algorithmic approach [18]. Similarly, active chemotherapy was flagged when patients received an oral or intravenous chemotherapeutic agent during, or 6 months prior to, PICC insertion. We defined ICU status as includ-

ing patients who received care in any ICU setting at any point during hospitalization. PICC dislodgements were defined as accidental removal of the PICC by either the patient or provider. Antibiotic use was defined as administration of any oral or intravenous antimicrobial within 30 days of PICC insertion. We included chemotherapy, and steroid use if any of these events occurred within 6 months of PICC placement. Surgery was defined as any operation lasting ≥ 1 h during the index admission (before the PICC was put in place, on the same day as PICC insertion or while the PICC was *in situ*).

Statistical analysis

The unit of analysis was PICC insertion. The study population was first characterized using descriptive statistics. Bivariate logistic regression was used to estimate unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between all risk factors and PICC-DVT. We used our previously published conceptual model of predictors of PICC complications to structure our multivariable analytic approach [16]. In brief, this model was derived by systematically synthesizing the published evidence and identified the risk of PICC-related complications as being related to patient-, provider-, and device-related characteristics (Fig. 1). Because we were specifically interested in time-to-DVT in addition to standard predictors, we constructed multivariable logistic regression and Cox proportional hazards regression models to estimate ORs and hazard ratios (HRs) with 95% CIs, respectively. Adjustment for baseline characteristics was made on scientific grounds in all models. Standard errors were adjusted to account for within-patient clustering of observations (e.g. patients with multiple lines). Covariate correlations and variance inflation factors were assessed to ensure absence of collinearity. SAS for Windows (Version 9.3, SAS Inc., Cary, NC, USA) and Stata MP SE (StataCorp Version 13, College Station, TX, USA) were used for analyses. All statistical tests were two-tailed; $P < 0.05$ was considered statistically significant.

The Institutional Review Board of the Veterans Affairs Ann Arbor Healthcare System granted ethical and regulatory approval for the study.

Results

Between 1 June 2009 and 30 June 2012, 1241 PICCs were inserted at our academic VA medical center. Of these 1241 PICCs: 71 were removed without a documented removal date; 46 had no matching inpatient visits; and 158 had no matching administrative data. Therefore, our final study cohort included 966 PICCs that were inserted in 747 unique patients, accounting for a total of 26 887 catheter days (Fig. 2). The majority of patients who underwent insertion were male (98%), with a median duration of PICC use of 21 days (95% CI, 19–23 days). Most PICCs were placed by vascular access nurses (85%, $n = 823$); only 15% ($n = 143$) were placed by interventional radiology when bedside insertion was not successful or appropriate. Over one-third of our inpatient cohort ($n = 301$; 40%) had a cancer diagnosis in the 6 months prior to PICC insertion; 145 were receiving active chemotherapy at the time of hospitalization (Tables 1 and 2). Over 95% ($n = 713$) of included patients were prescribed pharmacologic DVT prophylaxis with either subcutaneous heparin or daily enoxaparin while the PICC was in place.

The most common indications for PICC insertion included: long-term antibiotic administration (52%, $n = 503$), venous access (21%, $n = 201$), total parenteral nutrition (16%, $n = 155$) and delivery of chemotherapy (11%, $n = 107$). With respect to PICC characteristics, almost half of all PICCs inserted were single-lumen devices (48%, $n = 459$) and many were POWER-PICCs (52%, $n = 500$), specialized devices capable of withstanding high-pressure injections for radiographic studies. While the majority of PICCs were placed in patients on medical or surgical units, 171 (18%) were inserted in intensive care unit patients. PICCs were most commonly

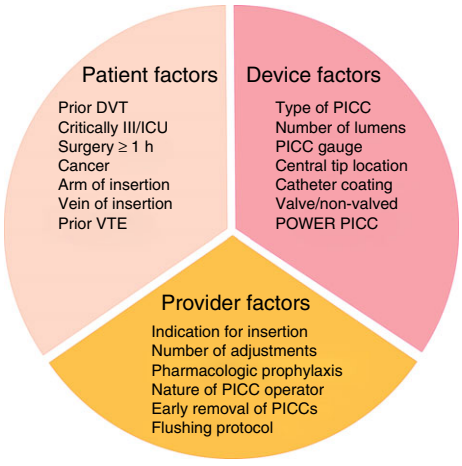

Fig. 1. Conceptual model for PICC-Related Deep Vein Thrombosis.

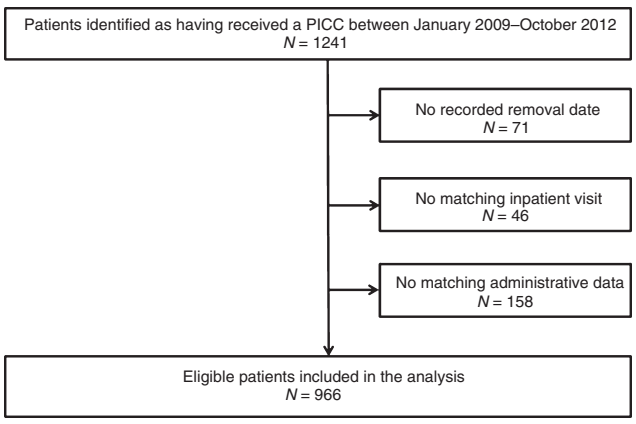

Fig. 2. Flow diagram illustrating generation of final study cohort.

Table 1 Characteristics of upper and lower extremity thrombosis in patients with PICC

Variable	PICC-DVT ($N = 33$)	LE DVT ($N = 9$)	No DVT ($N = 924$)
Age	64.2 ± 8.0	64.4 ± 3.9	65.5 ± 10.3
Male gender	32 (97.0)	9 (100)	897 (97.1)
Acute LOS	12.0 ± 11.7	26.3 ± 23.1	11.0 ± 11.9
ICU LOS	6.5 ± 12.4	2.6 ± 4.8	5.6 ± 16.4
Cancer (6 months)	16 (48.5)	5 (55.6)	280 (30.3)
Prior DVT	1 (3.0)	1 (11.1)	31 (3.4)
Prior surgery (> 1 h)	12 (36.4)	0 (0)	267 (28.9)
Prior PICC use	0.24 ± 0.44	0.67 ± 1.12	0.27 ± 0.59
Anticoagulant use			
Heparin	27 (81.8%)	7 (77.8%)	679 (73%)
Enoxaparin	11 (33.3%)	4 (44.4%)	124 (13%)
Warfarin	7 (21.2%)	0 (0%)	112 (12%)
CLABSI	0 (0%)	1 (11.1%)	57 (6.2%)
Mortality	4 (12.1%)	0 (0%)	54 (5.8%)
No. of insertion attempts	1.18 ± 0.53	1.78 ± 0.83	1.25 ± 0.64
Adjustments during insertion			
Yes	6 (18.2)	0 (0)	196 (21.2)
Number of adjustments	0.18 ± 0.39	0.0 ± 0.0	0.27 ± 0.58
Dislodgements			
Yes	0 (0)	0 (0)	46 (5.0)
Duration of PICC use (days)	37.3 ± 69.7	28.2 ± 18.6	27.5 ± 25.9
Operator			
IR	9 (27.3)	3 (33.3)	131 (14.2)
Nursing	24 (72.7)	6 (66.7)	793 (85.8)
Therapy			
ABX	12 (36.4)	3 (33.3)	488 (52.8)
Access	9 (27.3)	3 (33.3)	189 (20.5)
Chemo	9 (27.3)	3 (33.3)	95 (10.3)
TPN	3 (9.1)	0 (0)	152 (16.5)
Lumens			
1	8 (24.2)	3 (33.3)	448 (48.5)
2	19 (57.6)	5 (55.6)	390 (42.2)
3	6 (18.2)	1 (11.1)	86 (9.3)
Power-PICC			
Yes	22 (66.7)	5 (55.6)	473 (51.2)
Tunneled PICC			
Yes	0 (0)	0 (0)	12 (1.3)
French (gauge)			
4	8 (24.2)	3 (33.3)	422 (45.7)
5	19 (57.6)	5 (55.6)	404 (43.7)
6	6 (18.2)	1 (11.1)	98 (10.6)
Admitting bed section			
ICU	3 (9.1)	1 (11.1)	113 (17.5)
Medical	20 (60.6)	7 (77.8)	516 (55.8)
NH	2 (6.1)	1 (11.1)	79 (8.6)
Surgery	7 (21.2)	0 (0)	154 (16.7)
Other	1 (3.0)	0 (0)	62 (6.7)
Insertion vein			
Basilic	23 (69.7)	4 (44.4)	715 (77.4)
Brachial	7 (21.2)	3 (33.3)	138 (14.9)
Cephalic	3 (9.1)	2 (22.2)	53 (5.7)
Other	0 (0)	0 (0)	18 (2.0)
Insertion arm			
Right	22 (66.7)	8 (88.9)	644 (69.7)
Left	11 (33.3)	1 (11.1)	280 (30.3)
Time to DVT (days)	16.5 ± 17.1	10.7 ± 10.2	NA

PICC, peripherally inserted central catheter; DVT, deep vein thrombosis; LE DVT, lower extremity DVT; LOS, length of stay; ICU, intensive care unit; CLABSI, central line-associated bloodstream infection; IR, interventional radiology; ABX, antibiotics; Chemo, chemotherapy; TPN, total parenteral nutrition; NH, nursing home; NA, not applicable.

inserted in the basilic vein (77%, $n = 742$) and in the right arm (70%, $n = 674$).

Among the 966 included PICCs, 33 (3.4%) were associated with PICC-DVT and 9 (1%) were associated with lower extremity DVT, accounting for a total of 42 symptomatic thrombotic events (4.3%). The mean time to PICC-DVT was 16.5 days vs. 10.7 days for lower-extremity DVT with a PICC *in situ*. Most patients who experienced PICC-DVT did so in the context of prolonged hospitalization (average length of stay 12 days), including a significant number of ICU days (6.5 days). Exactly half ($n = 21$) of PICC-DVT patients had a recent cancer diagnosis when thrombosis occurred, and many were receiving chemotherapy at the time (Table 2). Despite reports of an association between thrombosis and infection [19], no patient with PICC-DVT experienced a preceding central line-associated bloodstream infection in our study. With respect to location of thrombosis, PICC-DVT more commonly involved the axillary and subclavian veins, though many were associated with thrombosis at ≥ 1 site.

On bivariate analysis, a number of patient-, provider- and device-related characteristics, including recent cancer (OR 2.30 [95% CI 1.12–4.41]), interventional radiology placement (OR 2.42 [1.24–4.73]), chemotherapy infusion (4.11 [1.78–9.47]), number of lumens (OR 2.51 [1.22–5.15] and OR 3.32 [1.24–8.84] for double- and triple-lumen PICCs, respectively) and PICC gauge (OR 2.28 [1.11–4.68] and OR 2.74 [1.03–7.29] for 5Fr and 6Fr PICCs, respectively) were associated with PICC-DVT. We did not observe an association between vein (cephalic vs. all others) or arm (right vs. left) of insertion with PICC-DVT. POWER-PICCs did not confer a greater risk of thrombosis compared with non-POWER devices in bivariate analysis (Table 3).

In our multivariable logistic regression and Cox proportional hazards regression models, only a diagnosis of recent cancer (cancer diagnosis in the 6-months prior to PICC placement) (OR 1.95 [1.01–3.76]) and PICC gauge (HR 2.21 [95% CI 1.04–4.70] and HR 3.56 [95% CI 1.31–9.66] for 5-Fr and 6-Fr PICCs, respectively) remained associated with PICC- DVT (Table 4). Importantly, the influence of gauge on thrombosis was noted to be time dependent, with an ear-

Table 2 Types of cancers among patients with PICC-DVT

Type of malignancy*	Number of cases
None	21
Gastrointestinal malignancies	
Esophagus	4
Stomach	2
Colon	1
Respiratory/upper airway	
Larynx	2
Hypopharyngeal/tracheal	3
Genitourinary	
Prostate	1
Testicular	1
Hematologic	
Leukemia	5
Lymphoma	3

PICC, peripherally inserted central catheter; DVT, deep vein thrombosis. *As identified by ICD-9 Code.

lier time-to-event in patients with 5-Fr and 6-Fr PICCs compared with 4-Fr PICCs.

Discussion

In this retrospective cohort study of a representative group of consecutively hospitalized Veterans who underwent PICC placement, we found that a cancer diagnosis in the past 6 months and catheter gauge were the strongest predictors of PICC-DVT after adjustment for other patient-, provider- and device-specific factors. The relationship between cancer and thrombosis persisted despite inclusion of characteristics often cited as being associated with DVT (e.g. prior surgery or prior VTE) and receipt of pharmacologic DVT prophylaxis by most patients. Additionally, 5-Fr and 6-Fr PICCs showed an earlier time to DVT, suggesting an accelerated course towards thrombosis in patients who received these larger devices. These findings question the wisdom of the use of PICCs in patients with cancer and the use of devices of greater gauge, as their thrombogenicity may outweigh presumed benefits, especially among patients with malignancies.

The link between cancer and thrombosis was established centuries ago [20]. Venous thromboembolism is a common, costly and often morbid development in patients with cancer. In fact, the development of thrombosis among patients with cancer is often an ominous finding, as studies suggest that cancer patients who experience thrombosis have a higher mortality rate than those who do not [21–23]. Indeed, many of these deaths may be due to fatal VTE, including pulmonary embolism. However, some of these events may also reflect underlying tumor biology, as activation of the coagulation cascade and thrombin generation are often cited as mechanisms by which tumor propagation may occur [24,25]. It is thus not uncommon for malignancies to declare themselves first with thromboses; in fact, up to 10% of patients with so-called idiopathic or unprovoked thromboses ultimately develop cancer on long-term follow-up [26].

Table 3 Bivariable (unadjusted) analysis of risk factors associated with PICC-DVT

Variable	Odds ratio	95% Confidence interval		*P* -value
Age	0.988	0.967	1.009	0.27
Acute LOS	1.019	0.999	1.040	0.07
ICU LOS	1.000	0.987	1.013	0.95
Cancer	2.300	1.120	4.410	0.01
Prior surgery (> 1 h)	0.984	0.489	1.982	0.97
Prior PICCs	1.181	0.780	1.789	0.43
No. of insertion attempts	1.126	0.804	1.578	0.49
Adjustments during insertion				
Yes	0.619	0.255	1.502	0.29
Number of adjustments	0.588	0.304	1.136	0.11
Duration of PICC use (days)	1.007	0.998	1.016	0.15
Operator				
IR	**2.421**	**1.240**	**4.727**	**0.01**
PICC nurse	1	Ref		Ref
Therapy				
ABX	1	Ref		Ref
Access	2.066	0.910	4.688	0.08
Chemo	**4.109**	**1.784**	**9.468**	**0.001**
TPN	0.642	0.180	2.288	0.49
Lumens				
1	1	Ref		Ref
2	**2.506**	**1.220**	**5.149**	**0.01**
3	**3.315**	**1.243**	**8.840**	**0.02**
Power-PICC				
Yes	1.716	0.901	3.269	0.10
French (gauge)				
4	1	Ref		Ref
5	**2.279**	**1.109**	**4.682**	**0.03**
6	**2.740**	**1.030**	**7.291**	**0.04**
Admitting bed section				
ICU	0.750	0.256	2.198	0.60
Surgery	0.963	0.410	2.265	0.93
Other	1	Ref		Ref
Vein of insertion				
Cephalic	2.221	0.839	5.877	0.11
Other	1	Ref		Ref
Arm of insertion				
Right	1	Ref		Ref
Left	0.920	0.478	1.772	0.80

PICC, peripherally inserted central catheter; LOS, length of stay; ICU, intensive care unit; DVT, deep vein thrombosis; IR, interventional radiology; ABX, antibiotics; Chemo, chemotherapy; TPN, total parenteral nutrition; Ref, reference group. Bold indicates statistically significant result.

Thrombotic events in cancer patients are often also related to, or triggered by vascular access devices [13,27–29]. With the growing use of PICCs among patients with cancer, the burden of PICC-DVT is becoming more apparent, as some studies report thrombosis rates as high as 30% with these devices [3]. Often, many of these events remain clinically silent. In a recent randomized controlled clinical trial that used screening ultrasound to detect PICC-DVT, up to 75% of patients with catheters were

Table 4 Multivariable (adjusted) analysis of risk factors associated with PICC-DVT

	Logistic regression				Cox proportional hazards			
Variable	Odds ratio	Confidence interval		*P* -value	Hazard ratio	Confidence interval		*P* -value
Cancer	**1.953**	**1.014**	**3.761**	**0.05**	1.896	0.980	3.667	0.06
Prior surgery (> 1 h)	0.883	0.421	1.851	0.74	0.959	0.467	1.967	0.91
Prior VTE	1.427	0.305	6.682	0.65	1.050	0.217	5.074	0.95
French (gauge)								
4	1	Ref		Ref	1	Ref		Ref
5	1.890	0.889	4.018	0.10	**2.211**	**1.040**	**4.699**	**0.04**
6	2.454	0.880	6.842	0.09	**3.555**	**1.309**	**9.659**	**0.01**

PICC, peripherally inserted central catheter; DVT, deep vein thrombosis; VTE, venous thromboembolism; IR, interventional radiology; ABX, antibiotics; Chemo, chemotherapy; TPN, total parenteral nutrition; Ref, reference group. Bold indicates statistically significant result.

found to have thrombosis, with the majority of events occurring in patients with cancer. Despite this high event rate, only 4% of patients with image-confirmed thrombosis developed clinical symptoms [30]. This finding is important because some suggest that long-term pharmacological DVT prophylaxis be routinely implemented in patients with cancer to offset thrombosis. To date, however, several systematic reviews and meta-analyses of the literature have found no benefit associated with this approach [31–33]. A recent Cochrane update echoed these findings, noting no benefit even for asymptomatic thrombosis in this subset [34]. Indeed, in our study, PICC-DVT occurred despite high rates of DVT prophylaxis given the largely hospitalized cohort.

Uniquely, we also found that some thrombotic events occurred in the lower, not just the upper, extremities. This finding echoes early results of our larger, ongoing study of 52 989 hospitalized patients, where we found that PICC presence by hospital day 2 was associated with a significantly increased risk of not only upper- but also lower-extremity DVT in patients with and without cancer (OR=3.1 [95% CI 1.3–7.5]) [35]. Although we are not able to mechanistically explain this observation, it is possible that the insertion or presence of a PICC can result in endothelial damage, vascular reactivity and up-regulated coagulation. These changes may predispose towards a greater overall risk of thrombosis that extends beyond the vascular bed of the PICC itself. Studies that measure systemic markers of coagulation (e.g. D-dimer) in the presence of PICCs may shed more light on this association.

Our findings regarding the association between PICC gauge and greater risk of PICC-DVT are in accord with the published evidence [14,15]. Uniquely, however, we observed that patients with 5-Fr and 6-Fr devices are not only at greater risk, but also develop thrombosis earlier compared with those with 4-Fr devices. This finding is novel and important because many multi-lumen PICCs are available only in larger sizes and clinicians typically only consider the number of lumens, not catheter size, when ordering PICCs. The interaction between number of lumens and thrombosis is thus likely to be confounded by PICC gauge, suggesting that better delineation of this relationship for front-line providers is necessary. Given what is known, dual-lumen 4-Fr PICCs may offer the best option for venous access and therapies from a complication perspective when feasible [12,36].

As many patients with cancer require multi-lumen (e.g. greater gauge) PICCs and no effective strategies to offset thrombosis risk exist, what can providers do to prevent PICC-DVT in this population? One approach is to simply consider alternative vascular access devices for this subset. Patients with malignancies often require longer-term venous access for parenteral hydration, nutrition, blood products and antimicrobials, in addition to chemotherapy and laboratory draws [37,38]. While PICCs are appealing because they can be safely placed in those with thrombocytopenia or bleeding diathesis [39], these benefits may be outweighed by the associated thrombosis and infection burden [19,40]. Because other, potentially less thrombogenic, options (e.g. infusion ports and tunneled catheters) are available for venous access and some patients may not require central venous access for delivery of irritants or vesicants, the 'reflexive' use of PICCs should be reconsidered in this population. The use of midlines (devices that terminate in arm veins as opposed to central chest veins) may also prove useful in this subset if short-term administration of non-vesicant or irritant substances is being considered [41]. At the very least, this study and the available evidence call for a mindful approach when selecting PICCs as the vascular device of choice in patients with malignancies [42].

Our study has important limitations. First, our analysis was conducted in an almost exclusively male population at a single academic VA medical center, limiting generalizability to dissimilar populations. Second, although enhanced by combining medical record review and administrative data, our ability to draw inferences is limited by available covariates owing to the retrospective design of this study and the specific inclusion of populations who had complete data. It is therefore important to note that information or selection biases may have influenced our findings. Third, we included both upper and lower-extremity thromboses when defining PICC-DVT;

although some may consider this inappropriate, this approach has been used extensively in the VTE literature to define thrombotic risk and is more reflective of the problems associated with these devices [8,9,17]. Fourth, we are unable to separate the incremental thrombotic burden posed by a PICC from that of an underlying cancer when these coexisted. However, as our symptomatic PICC-DVT rates parallel those of the published literature, our results appear to accurately reflect the interplay between these two factors and thus carry the same clinical implications.

These limitations notwithstanding, our study has important strengths, including a large sample size and the ability to track outcomes over time given the integrated nature of the VA healthcare system. Furthermore, our results clearly have important clinical care and policy implications and suggest that a recent diagnosis of cancer should prompt consideration of non-PICC-based modalities for venous access. Additionally, whenever considered absolutely necessary, devices with the least number of lumens and smallest gauge should be considered [36]. Finally, our study is strengthened by the fact that we scientifically selected covariates for inclusion in our multivariable models known to influence PICC-DVT, increasing the applicability and relevance of our results to clinical practice.

In conclusion, we found that patients with a recent diagnosis of cancer and those who receive greater gauge PICCs are at significant risk of PICC-DVT. Policies and procedural oversights that restrict the use of this device for vascular access and encourage mindfulness when it comes to insertion of PICCs in this population are warranted.

Addendum

V. Chopra: concept, design, analysis, interpretation, critical writing, revision and final approval. D. Ratz and L. Kuhn: design, analysis, interpretation, revision and final approval. T. Lopus: design, interpretation, revision and final approval. A. Lee: design, interpretation, critical revision and final approval. S. Krein: concept, design, analysis, interpretation, revision and final approval.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interests.

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