Original Contribution

# Upper Extremity Venous Thrombosis in Patients With Cancer With Peripherally Inserted Central Venous Catheters: A Retrospective Analysis of Risk Factors

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## Abstract

**Purpose:** Peripherally inserted central catheters (PICCs) are often used in place of mediport catheters because of cost and lack of operating room time and to prevent delays in therapy. One common complication associated with their use is upper extremity venous thrombosis (UEVT). The purpose of this study was to ascertain risk factors associated with an increased risk of PICC-associated UEVT in patients with cancer.

**Methods:** Retrospective analysis identified 237 patients with cancer who received PICCs at the Dallas Veterans Affairs Medical Center from 2006 to 2009. We analyzed many risk factors, including PICC infection (PI), use of erythropoiesis-stimulating agents (ESAs), antiplatelet agents (APAs), treatment dose anticoagulation (TDA), and bevacizumab.

**Results:** Of 237 patients, 36 (15%) were found to have UEVT. Stepwise logistic regression analysis showed risk factors positively associated with UEVT were use of ESAs (odds ratio [OR], 10.66; 95% CI, 2.25 to 50.49), hospitalization (OR, 2.38; 95% CI, 1.05 to 5.39), PI (OR, 2.46; 95% CI, 1.03 to 5.86), and TDA (OR, 8.34; 95% CI, 2.98 to 23.33), whereas patients receiving APAs had a lower risk of UEVT (OR, 0.25; 95% CI, 0.07 to 0.92).

**Conclusion:** Specific factors significantly increase the risk of UEVT in patients with cancer with PICCs, whereas use of APAs seems to have a protective effect against UEVT. These results may aid in the development of a predictive model for identifying patients at high risk of UEVT who may benefit from APAs, as well as in determining preventive strategies for reducing the risk of PICC-associated UEVT.

## Introduction

The advent of central venous catheters (CVCs) has had a significant impact in medicine, as increased numbers of patients require long-term venous access for intravenous antibiotics, ease of blood draws, chemotherapy, nutrition, and analgesia.[1] It is estimated that in the United States, more than 5 million CVCs are inserted annually, with approximately 15% of them being in patients with cancer.[2] Frequently, central access is provided through peripherally inserted central catheters (PICCs). PICCs offer several advantages over other CVCs because they can be inserted at the bedside without the need for a surgical procedure or operating room. In addition, they are more cost effective, and their relative ease of placement prevents delays in therapy.[3-5] Unfortunately, one common complication with the use of long-term venous catheters is upper extremity venous thrombosis (UEVT). The incidence of catheter-associated asymptomatic UEVT has been reported to be as high as 66%.[1,6] Although most cases are asymptomatic and of uncertain clinical significance, UEVT can have a significant impact on a patient's health care. Catheters that have lost functioning often need to be replaced at an average cost of approximately $5,000 and can lead to serious morbidity, including recurrent UEVT, postphlebitic syndrome, and pulmonary embolism.[7-9] The incidence of UEVT in patients with cancer has been reported to be from 0.3% to 28.3%, but the data on PICC-related UEVT in patients with cancer are limited.[10] The purpose of this study was to ascertain and identify which factors are associated with PICC-associated symptomatic UEVT in patients with cancer.

## Methods

The Dallas Veteran Affairs (VA) Medical Center (DVAMC) is a 544-bed referral center for the VA North Texas Health Care System. We conducted a retrospective study identifying all patients with cancer in both the ambulatory and inpatient settings who received PICCs at the DVAMC during a 4-year span from January 1, 2006, to December 31, 2009. This study was approved by the institutional review board of the DVAMC. We acquired data by identifying patients using the VA electronic medical record database in addition to the PICC service archive. A member of the PICC nursing team inserted all PICC lines. A specific protocol was implemented by the VA for PICC insertion to minimize complications, entailing the use of ultrasound for placement and sterile barrier precaution to minimize infections, which was documented in the VA electronic medical record system. The position of the tip of the PICC in the superior vena cava was confirmed by chest x-ray by a physician in the radiology department. In the 4-year period, 237 patients with cancer received PICCs. Risk factors investigated include: age, WBC, platelet count, ethnicity, catheter size (diameter), number of lumens, use of capecitabine/fluorouracil (FU), location of the tip of the catheter, PICC-associated infection, prior CVC, use of erythropoiesis-stimulating agents (ESAs), use of antiplatelet agents (APAs), solid versus hematologic malig-

nancy, stage of cancer, chemotherapy, radiotherapy treatment, hospitalization, use of prophylactic dose versus treatment dose anticoagulation, and if the patient was receiving bevacizumab. Patients were categorized as receiving capecitabine/FU if these drugs were administered after PICC placement. Chemotherapy was defined as patients who received chemotherapy after PICC insertion, and radiotherapy as patients receiving concurrent radiation treatment. All laboratory results were obtained on the day before or the day of PICC insertion. We defined a PICC-related infection as a positive blood culture either from the catheter segment or peripheral blood in patients with clinical symptoms of bacteremia and no other apparent source of infection. Hospitalization was defined as any 23-hour stay for observation or inpatient admission for more than 23 hours. Prophylactic dose anticoagulation was defined as unfractionated heparin 5,000 units subcutaneously three times per day, dalteparin 5,000 units subcutaneously daily, or enoxaparin 40 mg subcutanously daily. Patients with symptoms concerning for UEVT underwent Doppler ultrasound of the affected extremity for evaluation. $\chi^2$ or Fisher's exact tests were conducted to examine association between UEVT and categorical risk factors. Also, *t*-tests were performed to examine association between UEVT and continuous risk factors. Stepwise logistic regression analysis was conducted to identify significant independent risk factors associated with UEVT, using risk factors with *P* values $\leq 0.2$ from univariate analyses.

## Results

During the 4-year investigative period, a total of 237 patients with cancer received PICCs. The demographic profile of the 237 patients is listed in Table 1, with baseline characteristics listed in Table 2. Overall, the patient population included 229 men and eight women, with a mean age of 64.09 years (range, 39 to 86 years). Within a month of PICC insertion, 180 patients received chemotherapy, and 64 received radiation therapy. At the time of PICC insertion, 21 patients were already receiving therapeutic dose anticoagulation (TDA) for thrombotic indications (eg, atrial fibrillation, mechanical heart valve), and all continued to receive anticoagulation after insertion. Five of these patients were receiving low–molecular weight heparin, and 16 patients were receiving warfarin. Also, 70 patients were receiving prophylactic anticoagulation at the time of PICC placement. In these cases, prophylactic anticoagulation continued until hospital discharge. The results also showed PICC-associated infection in 33 (13.9%) of 237 patients. In these individuals, the median time from PICC insertion to infection was 50 days.

The incidence of symptomatic UEVT was 15% (36 of 237 patients). Stepwise logistic regression analysis revealed four statistically significant risk factors for UEVT (Table 3): use of ESAs (odds ratio [OR], 10.66; 95% CI, 2.25 to 50.49; $P = .003$), hospitalization (OR, 2.38; 95% CI, 1.05 to 5.39; $P = .04$), infection (OR, 2.46; 95% CI, 1.03 to 5.85; $P = .04$), and TDA (OR, 8.34; 95% CI, 2.98 to 23.33; $P < .001$). The analysis also revealed that patients receiving APAs (OR, 0.25; 95% CI, 0.07 to 0.92; $P = .037$) had a 75% lower likelihood of UEVT.

**Table 1.** Patient Demographic Characteristics

| Characteristic | No. | % |
|---|---|---|
| Age by quartile, years | | |
| < 45 | 3 | 1.2 |
| > 45 to ≤ 55 | 26 | 11.0 |
| > 55 to ≤ 65 | 104 | 43.9 |
| > 65 | 104 | 43.9 |
| Mean | 64.09 | |
| Sex | | |
| Male | 229 | 96.6 |
| Female | 8 | 3.4 |
| Ethnicity | | |
| Non-Hispanic white | 157 | 65.8 |
| African American | 72 | 30.4 |
| Other | 9 | 3.8 |
| Received chemotherapy within past month | 180 | 75.9 |
| Metastatic disease present | 93 | 39.2 |
| Received radiation therapy | 64 | 27.0 |

## Discussion

UEVT is a well-recognized complication of PICCs, and in patients without cancer, asymptomatic UEVT has been detected in 37% to 66%.[1,6,10] This retrospective study is the first to our knowledge to determine the incidence of symptomatic UEVT in patients with cancer and identify the risk factors specifically associated with PICC-related UEVT in this population. Although previous studies have identified PICC-specific qualities that increase UEVT risk, this study also evaluated patient-specific risk factors. In the present study, 36 (15%) of 237 patients with cancer developed symptomatic UEVT. The incidence of 15% is somewhat higher than that in previous studies, which have reported rates of 2% to 7.8%.[8,11-15] In addition, the infection rate in this study (13.9%) is higher than the 2.46% to 13.04% reported in previous studies.[3,5,11,14] This was seen despite the fact that evidence-based infection-prevention strategies were performed with every PICC insertion, which entailed using appropriate sterile conditions and follow-up care.[3,16-18] The higher observed rate of both UEVT and infection may be related to the number of days spent with a PICC inserted, because there was no institutional standard for the duration of PICC placement. Our results showed a median time of 50 days from the day of line insertion to infection. However, we did not examine the duration of PICC placement in those without symptomatic UEVT. Further investigation would be needed to determine the association between PICC placement duration and time to infection. Additionally, we did not examine length of hospitalization or admission diagnosis to determine if either of these variables had a significant impact on the rate of UEVT.

This analysis identified three baseline risk factors (hospitalization at time of PICC placement, infection, and use of ESAs) that predicted for development of symptomatic UEVT as well

**Table 2.** Baseline Patient Characteristics

| Characteristic | Thrombosis | | | | P |
|---|---|---|---|---|---|
| | No (n = 201) | | Yes (n = 36) | | |
| | No. | % | No. | % | |
| Age, years | | | | | .829* |
| Mean | 64.1 | | 63.8 | | |
| SD | 8.5 | | 9.4 | | |
| WBC count ($\times 10^3/\mu L$) | | | | | .974* |
| Mean | 8.8 | | 8.8 | | |
| SD | 9.7 | | 4.7 | | |
| Platelet count ($\times 10^3/\mu L$) | | | | | .395* |
| Mean | 234.7 | | 258.0 | | |
| SD | 120.9 | | 154.3 | | |
| Ethnicity | | | | | .365 |
| Non-Hispanic white | 132 | 66 | 23 | 64 | |
| African American | 60 | 30 | 13 | 36 | |
| Hispanic | 9 | 4 | 0 | 0 | |
| Catheter size, French units | | | | | .967 |
| 4 | 118 | 59 | 21 | 58 | |
| 5 | 83 | 41 | 15 | 42 | |
| No. of lumens | | | | | .989 |
| 1 | 117 | 58 | 21 | 58 | |
| 2 | 84 | 42 | 15 | 42 | |
| Capecitabine/FU | 81 | 40 | 14 | 39 | .874 |
| Location | | | | | 1.000† |
| Tip of SVC | 199 | 99 | 36 | 100 | |
| Not at tip of SVC | 2 | 1 | 0 | 0 | |
| PICC-associated infection | 24 | 12 | 9 | 25 | .037 |
| Prior CVC | 73 | 36 | 16 | 44 | .354 |
| Concurrent use of ESAs | 4 | 2 | 4 | 11 | .020† |
| APAs | 45 | 22 | 3 | 8 | .053 |
| Solid‡ *v* hematologic malignancy§ | | | | | .651 |
| 1 | 161 | 80 | 30 | 83 | |
| 2 | 40 | 20 | 6 | 17 | |
| Stage of cancer | | | | | .817 |
| I | 16 of 186 | 9 | 2 of 33 | 6 | |
| II | 37 of 186 | 20 | 6 of 33 | 18 | |
| III | 53 of 186 | 28 | 12 of 33 | 36 | |
| IV | 80 of 186 | 43 | 13 of 33 | 39 | |
| Chemotherapy | 157 | 78 | 23 | 64 | .066 |
| Radiotherapy | 56 | 28 | 8 | 22 | .483 |
| Hospitalization | 98 | 49 | 25 | 69 | .022 |
| Prophylactic dose anticoagulation during hospitalization | 55 | 27 | 15 | 42 | .083 |
| TDA | | | | | < .001† |
| None | 190 | 95 | 26 | 72 | |
| Yes‖ | 11 | 5 | 10 | 28 | |
| Warfarin | 11 | 5 | 5 | 14 | |
| Enoxaparin¶/dalteparin | 0 | 0 | 5 | 14 | |
| Bevacizumab | 25 | 12 | 4 | 11 | 1.000† |

NOTE. All *P* values based on $\chi^2$ test unless otherwise noted.
Abbreviations: APA, antiplatelet agent; CVC, central venous catheter; ESA, erythropoiesis-stimulating agent; FU, fluorouracil; PICC, peripherally inserted central catheter; SD, standard deviation; SVC, superior vena cava; TDA, therapeutic dose anticoagulation.
* *t*-test.
† Fisher's exact test.
‡ All other malignancies not included in hematologic malignancy (eg, colon, breast, lung, and so on).
§ Leukemia, lymphoma, myeloma, and myelodysplastic syndrome.
‖ Warfarin and enoxaparin/dalteparin were combined and categorized as yes.
¶ Lovonex; sanofi-aventis, Bridgewater, NJ.

**Table 3.** Clinical Variables and Risk of PICC-Associated UEVT

| Parameter | Estimate | SE | OR | 95% CI | *P* |
|---|---|---|---|---|---|
| ESA | 2.366 | 0.794 | 10.66 | 2.25 to 0.49 | .003 |
| APA | −1.396 | 0.669 | 0.25 | 0.07 to 0.92 | .04 |
| Hospitalization | 0.865 | 0.418 | 2.38 | 1.05 to 5.39 | .04 |
| TDA | 2.121 | 0.525 | 8.34 | 2.98 to 23.33 | < .001 |

Abbreviations: APA, antiplatelet agent; ESA, erythropoiesis-stimulating agent; OR, odds ratio; PICC, peripherally inserted central catheter; TDA, therapeutic dose anticoagulation; UEVT, upper extremity venous thrombosis.

as one that showed a protective effect. Hospitalization and infection are well-established risk factors for thrombosis.[19,20] The present results, showing an OR of 2.38 for hospitalization and UEVT, confirm the rate of PICC-associated thrombosis from previous studies.[21-23] Of note, this study is the first to our knowledge to identify that concurrent use of ESAs significantly increased the risk for PICC-associated UEVT. This further adds to the body of literature suggesting a link between ESA use in patients with cancer and negative outcomes including thrombosis, which ultimately led the US Food and Drug Administration to restrict the use of these agents in those with cancer. Somewhat paradoxically, this analysis also demonstrated a statistically significant association between the use therapeutic anticoagulation at the time of PICC placement and UEVT. Although the precise explanation for this observation is not clear, it is possible that this group of patients is at higher risk of additional thrombotic events despite attempted therapeutic anticoagulation. A majority of these patients were receiving warfarin, and we did not attempt to ascertain whether these patients were at therapeutic dosing of anticoagulation at the time of PICC insertion or throughout the duration of placement. Results from our analysis also identified that patients receiving APAs had a lower rate of PICC-associated UEVT (OR, 0.25; 95% CI, 0.07 to 0.92; $P = .04$). APAs have been well documented to protect against arterial and venous thrombosis in specific settings, but their role as antithrombotic agents in CVCs has not.

There are several limitations with our study. This was a retrospective single-center study, so the results may not be applicable to other institutions, especially if the type of catheter used and protocol for catheter maintenance and care differ from those in our institution. The present cohort consisted of predominately white male patients who received care in the VA system. As a result, the application of these results to the general population is uncertain. Furthermore, the true incidence of UEVT is likely higher, because the diagnosis of UEVT via ultrasound is less sensitive in the upper than in the lower extremity.[24] Additionally, UEVT was only recorded in those patients who were symptomatic; early UEVT may not have detected. Last, the relationship between specific cancer type and primary site was not examined; because of our sample size, it would not have been significant. In addition, with the exceptions of capecitabine/FU and bevacizumab, we did not consider other potentially prothrombotic chemotherapy agents such as lenalidomide and thalidomide because their use was limited in our cohort of patients with PICCs.

In conclusion, our study identified several patient characteristics that may predispose those with cancer to PICC-associated UEVT. Specifically, at the time of PICC insertion, patients with active infections, hospitalized patients, patients receiving ESAs, and patients receiving TDA had a significantly increased risk of UEVT, whereas the use of APAs had a protective effect against UEVT. Future prospective studies are required to better define the significant risk factors for PICC-associated UEVT in this population and may then allow the development of risk stratification models for development of UEVT. Currently, there is a lack of consistent evidence on the efficacy of thrombosis prophylaxis in patients with cancer.[25] Our results suggest that the use of APAs is one prophylactic strategy that could be further evaluated in those patients with cancer felt to be at high risk for the development of PICC-associated UEVT.

***Authors' Disclosures of Potential Conflicts of Interest***

*The author(s) indicated no potential conflicts of interest.*

***Author Contributions***

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