The development of upper extremity deep vein thrombosis (UEDVT) related to central venous catheters (CVCs) has been studied extensively in the literature with several studies focusing exclusively on peripherally inserted central catheter (PICC)-related thrombosis. Studies can be divided into 2 major categories: those that focus on UEDVT related to all CVCs and those that focus specifically on UEDVT related to PICCs. Because studies overlap in their exploration of selected risk factors, it is necessary to discuss both categories of studies as they relate to various risk factors.

Many studies exploring the issue of CVCs and PICCs and UEDVTs review a limited set of researcher-selected risk factors. When these studies are combined, however, they reveal a large number of possible risk factors, including infection; comorbidities (cancer, diabetes, hypertension [HTN], and osteomyelitis); history of deep vein thrombosis (DVT); anticoagulant use; insertion variables (number of insertion attempts, catheter size, type of catheter, vein selection, depth of insertion, and whether inserted by a registered nurse or a radiologist); obesity, smoking history, surgery, and presence of pain or edema were examined in a limited number of studies and lacked consistent evidence of their impact on UEDVT development. The subsequent study that evolved from the review of the literature investigates the relationship between identified risk factors and UEDVT development.

Key words: catheter-related thrombosis, peripherally inserted central venous catheter, PICC, risk factors, upper extremity deep vein thrombosis

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types of intravenous fluids infused; patient symptoms (pain and edema); surgery; pregnancy; demographic variables (age, sex, and race); smoking history; and immobility. In all, 28 risk factors have been discussed in the literature and will be reviewed here.

### INFECTION

Crowley et al, in a prospective observational cohort study, examined 48 patients with catheter-associated *Staphylococcus aureus* (*S. aureus*) who had CVCs placed in either the internal jugular, brachial, or subclavian veins. *S. aureus* bacteremia was defined as clinically significant if the patient had more than 1 blood culture that was positive for *S. aureus* or a single blood culture with *S. aureus* and the patient had clinical evidence for infection. All patients in the study had more than 1 blood culture positive for *S. aureus*. Thirty-four of 48 (71%) patients with catheter-associated *S. aureus* bacteremia presented with thrombosis. The authors concluded that thrombosis is a common complication of CVCs when *S. aureus* bacteremia is present.

van Rooden et al studied 105 patients with CVCs who were undergoing chemotherapy to assess the incidence of CVC-related infection and to determine whether infection increased the risk of clinically symptomatic thrombosis. Surveillance cultures of CVC lock fluids were used to assess the presence of infection. CVC-related infection occurred in 24% of patients, and symptomatic thrombosis occurred in 12%. Forty-four percent of patients with CVC-related infection developed thrombosis compared with 3% of patients without infection (RR 17.6; 95% confidence interval [CI], 4.1-74.1; *P* < .05). In addition, the absolute risk of thrombosis increased with the severity of infection. Patients with systemic infections had an absolute risk of 57.1% compared with 27.3% for patients with local infection. Infection increased the risk for thrombosis development in patients receiving chemotherapy. The authors suggest that routine CVC lock fluid cultures may be beneficial in assessing risk of thrombosis development.

In a prospective study of 43 patients with hematological cancer, Lordick et al examined the relationship between CVC-related thrombosis and infection. The patients had the CVC placed in jugular veins. Patients were screened for jugular vein thrombosis every 4 days using bedside ultrasound. Infection was determined by use of blood cultures, catheter tip cultures, and visual inspection of the insertion site. Twelve patients were found to have both infection and thrombosis. Using the Fisher exact test, catheter-related thrombosis (CRT) and catheter-related infection were significantly correlated (*P* < .0001). Among patients diagnosed with catheter-related infection, 93% were neutropenic (13/14), suggesting that neutropenia may increase the risk for catheter-related infection.

Timsit et al studied the relationship between CVC-related thrombosis and CVC-related septicemia in 208 intensive care patients with internal jugular or subclavian catheters. Thrombosis was diagnosed using ultrasound either just before removal of the catheter or within 24 hours of removal. Using multivariate analysis, 3 statistically significant risk factors were found to be associated with the development of CVC-related thrombosis: age (≥ 65; *P* = .001), jugular vein CVC (P = .005), and absence of anticoagulation therapy (*P* = .04). Using logistical regression, CRT was associated with catheter-related infection (odds ratio [OR] 2.97; 95% CI, 1.17-7.53; *P* = .02). The incidence of catheter-related infection in patients with CRT was 18.8% (13 of 69), compared with 7.2% (10 of 139) in patients without CRT, resulting in a 2.6-fold increase in the risk of infection when CRT is present. The researchers acknowledged that it is unclear whether catheter-related infection promotes thrombosis formation or whether the presence of thrombosis encourages infection.

### COMORBIDITIES

#### Cancer

Several studies have suggested the presence of cancer as a risk factor for UEDVT in patients with CVCs. Mustafa et al, in a retrospective descriptive study, examined 65 patients with symptomatic UEDVT and found that CVCs were present in 60% of cases (39/65), and cancer was diagnosed in 46% of cases (30/65). Of the 30 cancer patients with UEDVT, 23 also had a CVC. The authors conclude that cancer, CVCs, or the combination of the 2 seemed to be associated with UEDVT. Similarly, Hingorani et al, in their study of 546 patients with UEDVT, found that the presence of a CVC or pacemaker (60% of patients) and a history of cancer (22% of patients) were positive risk factors for UEDVT. A major weakness of both studies was the reliance on descriptive statistics with no statistical procedures used to determine the statistical significance of the findings relative to risk factors.

Lee et al studied the incidence and risk factors for CRT in 444 patients with cancer. The incidence of symptomatic thrombosis was 4.3%. Using multivariate logistic regression, 3 statistically significant risk factors were identified. These included 2 or more insertion attempts (*P* = .01), ovarian cancer (*P* = .01), and previous history of CVC (*P* = .01).

Blom et al explored the relationship between cancer diagnosis, CVCs, and risk for developing UEDVT in a population-based case-control study. The sample included 179 patients with UEDVT and 2299 control subjects. They found that cancer increased the risk of upper extremity venous thrombosis 8-fold (OR 7.7; 95% CI, 4.6-13.0), but the risk increased to 18-fold
(OR 17.9; 95% CI, 12.0-26.7) when a CVC was also present.

**Osteomyelitis**

Osteomyelitis has been suggested as a risk factor for UEDVT in 1 study. Osteomyelitis as a reason for PICC insertion was found to be a statistically significant variable in the development of UEDVT ($P = .012$) in a study conducted by Seeley et al.\(^9\) Using backward elimination logistic regression, a prediction model for UEDVT was developed that included osteomyelitis as 1 of the 5 variables ($P < .001$). Other variables included recent bedrest, localized tenderness along the venous system, smoking, and anticoagulant use.

**Obesity**

Obesity as a risk factor is discussed in several studies. Most suggest that obesity may be a risk factor for development of UEDVT, but none explored this risk factor in detail.

Seeley et al\(^9\) found that patients who were obese and had other risk factors were more likely to develop a UEDVT during their hospital stay. However, obesity as an independent risk factor was not statistically significant ($P = .081$).

Cadman et al\(^10\) examined body mass index (BMI) in a retrospective review of 332 patients and found that obesity was not a significant independent predictor of UEDVT. Blom et al\(^8\) found no increase in risk related to BMI alone. However, for patients whose BMI was greater than 25 and who had undergone surgery within the previous 3 months, the risk of UEDVT was found to be higher than that of patients who underwent surgery but whose BMI was less than 25. Additionally, patients with a BMI greater than 30 who had also undergone surgery had a 23-fold increase in risk for developing an UEDVT, when compared with nonobese patients who underwent surgery.

Spencer et al\(^11\) examined 69 patients with UEDVT and compared BMI measurements of those with CVCs and those without CVCs. There was no significant difference between the BMIs of patients with CVCs when compared with patients without CVCs. When comparing BMIs of patients with upper versus lower extremity DVTs, patients with UEDVTs were found to have significantly lower BMI than those with lower extremity DVTs ($P = .02$).

**HTN and Diabetes**

HTN has been mentioned in several studies as a risk factor and/or comorbidity in the development of UEDVT. Joffe et al\(^12\) found that the most frequent comorbidities in patients with UEDVTs were HTN, diabetes mellitus, neurological disease, and nonpulmonary infection within 30 days of UEDVT diagnosis. However, the study did not identify HTN as an independent risk factor for UEDVT. Seeley et al\(^9\) found a significant difference ($P = .049$) between rates of UEDVT when comparing patients with HTN and patients without HTN, with more than 70% of patients who developed UEDVT having a history of HTN.

### HISTORY OF DVT AND USE OF ANTICOAGULANTS

The research suggests that having a history of DVT is an important risk factor in the development of UEDVT. Chemaly et al\(^13\) completed a retrospective case-controlled study that included 50 patients diagnosed with UEDVT and 107 control patients. All patients had PICCs inserted in an outpatient setting for long-term antibiotic therapy. The study found that patients with a history of DVT were more likely to develop UEDVT (OR 4.53; 95% CI, 1.22-16.84; $P = .02$).

In a large prospective study that followed 738 patients with symptomatic DVT for 3.7 to 8.8 years, Hansson et al\(^14\) found the “cumulative incidence of a recurrent venous thromboembolism” was 7.0% (95% CI, 4.8%-9.1%) after 1 year; 12.1% (95% CI, 9.3%-14.9%) after 2 years; 15.0% (95% CI, 11.8%-18.1%) after 3 years; 17.9% (95% CI, 14.5%-21.3%) after 4 years; and 21.5% (95% CI, 17.7%-25.4%) after 5 years of followup.\(^{17,11}\) The authors concluded that the rate of recurrent venous thromboembolisms after a DVT is high.

Seeley et al\(^9\) also found that a history of UEDVT was associated with an increased risk of developing a UEDVT ($P = .047$).

Using a retrospective design, Lobo et al\(^15\) examined the rate of UEDVT in 777 patients who were admitted to an acute care hospital during a 3-month period. Univariate analysis revealed that a history of venous thrombosis was the strongest risk factor for developing a PICC-related thrombosis (OR 10.33; 95% CI, 4.81-22.34).

In a study of 57 patients with PICC-related UEDVT, Evans et al\(^16\) found previous DVT to be the most significant risk factor ($P < .001$), followed by PICC size and use of anticoagulants. A multivariate predictive model was developed. The variables that produced the best predictive model included previous DVT (OR 9.92; $P < .001$), surgery lasting more than 1 hour (OR 1.66; $P < .1$), or use of double-lumen 5Fr (OR 7.54; $P < .05$) or triple-lumen 6Fr (OR 19.50; $P < .01$) PICCs. Although the use of anticoagulants was a statistically significant risk factor with univariate analysis, once it was introduced in the predictive model, it was no longer statistically significant.

The results of studies looking at the effect of anticoagulants on UEDVT development are confounding.
Anticoagulant use has been associated with both an increased and decreased risk of UEDVT. King et al,\textsuperscript{17} in a retrospective case-controlled study of 896 patients with PICCs, found prophylactic warfarin at 1 mg/d to be a significant risk factor (\(P = .014\)). However, the authors note that this finding was most likely attributable to the practice of providing prophylactic anticoagulant therapy to cancer patients with PICC devices. Seeley et al\textsuperscript{15} found use of anticoagulants significant for the development of UEDVT, with 76.5\% of patients with UEDVT taking anticoagulants at home or in the hospital (\(P = .005\)). However, in a study that examined the effect of prophylactic anticoagulants on the incidence of nonsymptomatic UEDVT in patients with PICCs, Paauw et al\textsuperscript{18} concluded that anticoagulants significantly decreased the risk of UEDVT development. Patients who had received anticoagulant therapy had a 22.9\% event rate, whereas those who did not receive anticoagulants had an event rate of 61.9\% (\(P < .05\)). The authors concluded that the use of prophylactic anticoagulant to reduce the risk of UEDVT outweighs the risks of anticoagulant use.

### INSERTION AND USE-RELATED VARIABLES

Numerous studies or articles cite mechanical injury to the intima of the vein, typically caused by multiple venipunctures, as a potential cause of thrombosis. Shah et al\textsuperscript{19} hypothesized that catheter-related UEDVT results from the disruption of the vein intima due to the mechanical disruption that occurs when the catheter is inserted.

#### Insertion Attempts

In a study of 444 cancer patients with CVCs, 19 of whom developed UEDVT, Lee\textsuperscript{7} found that more than 1 insertion attempt increased the risk for developing a UEDVT (OR 5.5; 95\% CI, 1.2-24.6; \(P = .03\)), as did a history of previous CVC insertion (OR 3.8; 95\% CI, 1.4-10.4; \(P = .01\)).

#### Catheter Tip Location

Catheter tip location is a well-studied risk factor. A position statement issued by the National Association of Vascular Access Networks\textsuperscript{20} calls for the catheter tip of a PICC to be placed in the lower one-third of the superior vena cava (SVC), close to the junction of the SVC and right atrium. The Infusion Nurses Society specifies “the CVAD should have the distal tip dwelling in the superior vena cava near the junction of the right atrium.”\textsuperscript{21} If the tip is located in the proximal one-third to the lower SVC, there is an increased risk of the development of a UEDVT.\textsuperscript{14}

Caers et al\textsuperscript{22} completed a retrospective study of 437 cancer patients with placement of subcutaneous infusion ports and found that catheter tip position in the brachiocephalic vein (OR 8.07; 95\% CI, 2.97-21.89; \(P < .001\)) and in the cranial third of the SVC (OR 1.62; 95\% CI, 1.62-10.19; \(P = .002\)) was the most significant risk factor related to the development of CRT. Luciani et al\textsuperscript{23} studied 113 chest x-rays of patients with surgically implanted CVCs, 17 of whom developed CRT. Their analysis revealed that correct positioning of the CVC significantly (\(P < .001\)) lowers the risk of CRT but does not totally eliminate it, because 6\% of the patients who had correctly positioned CVCs developed CRT. Cadman et al\textsuperscript{10} found that the proximal-placed CVCs were 16 times more likely to develop thrombosis than those in the distal position (95\% CI, 9.23-76.47; \(P < .0005\)). None of the patients (58) with the CVC in the right atrium developed thrombosis or other complications.

Lobo et al\textsuperscript{25} studied 777 patients with PICCs, 38 of whom developed CRT. Noncentral PICC tip location was associated with a 2.34-fold higher risk of thrombosis development (95\% CI, 1.05-1.33; \(P < .05\)) when compared with superior vena cava or right atrium tip location. Conversely, Grove and Pevec\textsuperscript{24} found that PICC tip location did not increase the risk for CRT. The rate of thrombosis for the PICCs in the SVC/right atrium was 3.6\%, whereas the rate for other locations was 9.3\%. The higher rate was not statistically significant (\(P = .15\)).

#### Size of the Catheter

Size of the catheter used for PICC insertion has been linked as a risk factor in some studies. Grove and Pevec\textsuperscript{24} found that catheter diameters greater than 3Fr increased the risk for CRT. There was a 1\% rate of venous thrombosis with 4Fr catheters. However, the rate increased significantly with 5Fr (6.6\%; \(P = .0001\)) and 6Fr (9.8\%; \(P = .0006\)) catheters. Evans et al\textsuperscript{16} studied 57 patients with PICCs who developed UEDVTs. PICC size was determined to be a significant risk factor for CRT, with double- and triple-lumen catheters increasing risk when compared with single-lumen catheters (OR 7.54; \(P < .05\); OR 19.50; \(P < .01\), respectively). Single-lumen catheters in the study measured 4Fr, double-lumen catheters were 5Fr, and triple-lumen catheters were 6Fr.

Trerotola et al\textsuperscript{25} studied complication (thrombosis and infection) rates with the use of 6Fr, triple-lumen PICCs (TL-PICCs) in the adult intensive care setting. The trial was halted prematurely because of higher-than-expected rates of venous thrombosis compared with rates found in other studies. The rate of symptomatic thrombosis was 20\% (10/50), and the combined rate of symptomatic and asymptomatic thrombosis was 58\% (6/45). It is unclear whether the high CRT rate was a sole function of catheter size or whether the additional lumen may have played some role. Regardless,
the 6Fr TL-PICC demonstrated high thrombosis rates for both symptomatic and asymptomatic thrombosis.

**Vein Selected**

There is evidence to support that the vein selected for PICC insertion is a risk factor for development of UEDVT. Allen et al.\(^{26}\) in a retrospective review of 119 patients and 32 UEDVTs, identified the rate of thrombosis associated with each vein. The cephalic (57%) had the highest rate of thrombosis, followed by the basilic (14%) and brachial (10%). The cephalic vein was 10.1 times more likely to develop thrombosis than the basilic vein \(P < .0001\). The authors hypothesized that the increased percentage of thrombosis in the cephalic vein was possibly due to its smaller diameter.

In a prospective review of 56 patients with PICCs by Paauw et al.\(^{18}\) 26 patients developed nonsymptomatic UEDVT. All patients in the study had their PICC lines inserted into the basilic vein. Of those who developed UEDVT, the thrombosis began at or immediately adjacent to the vessel insertion site and propagated centrally.

Bonizzoli et al.\(^{27}\) compared the thrombosis rate in patients with PICCs. The PICC group consisted of 114 patients who developed 31 UEDVTs. In comparison, the CVC group consisted of 125 patients who developed 12 UEDVTs. The rate of UEDVT per 1000 catheter-days was 4.4 for CVCs and 7.7 for PICCs. There was a significantly higher risk of UEDVT if the left basilic vein was used \(\text{OR} 2.402; 95\% \text{ CI}, 1.259-8.544; P = .013\).

**Catheter Tip Position**

Cadman et al.\(^{10}\) studied 334 cancer patients with CVCs to determine the relationship between tip position and thrombosis formation. Nine percent \(30/334\) of patients developed venous thrombosis. Venous thrombosis occurred most frequently, 41.7% \(20/48\), in the proximal position, while the rate of thrombosis in the distal position was 2.6% \(5/191\), resulting in a statistically significant risk of thrombosis based on catheter location \(P < .0005\). CVCs located in the proximal position were 16 times more likely to develop thrombosis than those in a distal position.

**Type of Solution Infused**

The relationship between type of solution infused into a CVC or PICC and CRT is not clear, because in some studies the type of infusate had no impact on the development of UEDVT, whereas in others the type of solution was significant.

Grove and Pevec\(^{24}\) identified type of solution infused through the PICC line as a factor in the development of UEDVT. The solutions infused were chemotherapy in 120 (15%), antibiotics in 386 (47%), total parenteral nutrition (TPN) in 118 (15%), and other in 189 (23%). The rate of thrombosis by solution infused was 8.3% for chemotherapy, 1.6% for antibiotics, 4.2% for TPN, and 5.8% for other. The thrombosis rate for chemotherapy was higher than for the other solutions \((P = .051)\). Stepwise logistic regression determined that solution infused was a significant risk factor for thrombosis \((P = .006)\).

Chemaly et al.\(^{13}\) found amphotericin B to be an independent risk factor of UEDVT \((P = .005)\). The authors concluded that the irritant effect of amphotericin B on the vein was the likely cause. In their retrospective review of 896 patients with PICCs, 27 of whom developed UEDVT, King et al.\(^{17}\) did not find that the infusion of chemotherapy or other solutions through the PICC increased the risk of development of UEDVT; rather, the risk of UEDVT was highly associated with active cancer treatment. They state that “this elevation in risk may be more attributed to inherent hypercoagulable state, rather than the toxic nature of the chemotherapy solution, as has been previously published.”\(^{27}(p1075)\)

**Provider Who Places the PICC**

Who places the PICC—a radiologist or a specialized infusion nurse—has been studied as a possible risk factor in 2 studies.

Grove and Pevec\(^{24}\) examined the incident rates of UEDVT when the PICC was inserted by a radiologist or by a nurse. In the study, nurses placed 269 PICC lines with 12 patients developing CRT for a thrombosis rate of 4.5%; radiologists placed 544 PICC lines with 20 patients developing CRT for a thrombosis rate of 3.7%. There was no significant difference between the rates. However, after adjusting for catheter diameter and using stepwise logistical regression, the type of provider approached significance \((P = .07)\). Their explanation for this finding was that nurses are only able to palpate the vein segment in the antecubital fossa, whereas the radiologist is able to access the vein more proximally and direct the placement of the sheath with use of a guide wire.

Cadman et al.\(^{13}\) found that the rate of thrombosis based on the operator (nurse versus physician) was a significant predictor of CRT \((P = .006)\). Nurses had a 4.1% rate of thrombosis \((6/145)\), whereas physicians had a 12.8% rate \((24/188)\). They also found that clinicians (physicians) inserting central lines had 3 times the odds of the patients developing CRT compared with those inserted by clinical nurse specialists.

**SYMPTOMS**

A number of studies discuss the occurrence of pain and/or swelling of the affected arm. Paauw et al.\(^{18}\) found that
when symptoms of UEDVT were present they included localized redness, swelling, and pain. Major et al26 completed a retrospective study on all patients who underwent venous duplex scanning of the upper arm veins to identify internal jugular, subclavian, and axillary DVT. Of the 189 patients scanned, 63 (33%) had developed an acute UEDVT. Scans were ordered because of arm swelling (56%), to rule out pulmonary embolism (36%), and because of fever (15.8%). Schmittling et al29 studied 234 patients who underwent color duplex scanning; 40 (23%) of the patients were diagnosed with UEDVT in the internal jugular, subclavian, axillary, or brachial veins. Using univariate analysis, edema ($P = .007$) and tenderness of the arm ($P = .033$) were identified as 2 of the 4 variables significantly associated with UEDVT. “Signs and symptoms of arm pain or swelling in the presence of a recent central venous catheterization warrant a high index of suspicion of UEDVT.”29

In a study of 90 patients with UEDVT, Marinella et al30 found that the most common predisposing factor for UEDVT was the presence of a CVC (72%) and that for all patients with UEDVT, edema was the most common symptom (84%), followed by pain (34%), erythema (17%), tenderness (10%), and a palpable cord (3%).

### MAJOR SURGERY

Major surgery has been identified as a possible risk factor for development of UEDVT. Joffe et al12 found that major surgery within the previous 30 days was a significant risk factor for thrombosis in patients with CVCs ($P < .0001$). Blom et al8 also found that patients undergoing surgery had an increased risk of developing UEDVT. Constands et al31 in a retrospective study, analyzed the records of 50 patients who developed UEDVT. They found that 14% of subjects had undergone surgery within 4 weeks of PICC insertion. Evans et al16 found that surgery lasting more than 1 hour was an independent risk factor for UEDVT in patients with CVCs ($P < .05$).

### PREGNANCY, CONTRACEPTION, AND HORMONE REPLACEMENT THERAPY

Flinterman et al32 and Seeley et al9 discuss the possible relationship between pregnancy and the risk of development of UEDVT. However, there has been little empirical study of the possible link. Using multivariate analysis, Gbaguidi et al33 found that patients with ovarian hyperstimulation syndrome (OHSS) had a significant risk of internal jugular DVT (OR 3.4; 95% CI, 1.3-5.9; $P = .0093$). Two case studies were reviewed for the possible link between UEDVT and pregnancy. Casele et al34 describe the case of a 41-year-old pregnant woman with triplets who developed upper arm swelling after in vitro fertilization. At 6 weeks’ gestation, she had difficulty lifting her arm and noted swelling of the neck and left upper extremity. A duplex ultrasound of the left upper extremity revealed a thrombosis of the left brachial, axillary, and subclavian veins, and occlusive thrombosis of the internal jugular vein. The patient was treated with low-molecular-weight heparin.

Casele et al34 go on to discuss the development of UEDVT in the pregnant population that has had either ovulation induction or in vitro fertilization. The development of UEDVT is not thoroughly understood in the pregnant population, but it is felt that the thrombophilic state that occurs with increased levels of estrogen may play a role in its development. Additionally, these patients are at risk for the development of OHSS, which may increase the risk of the development of UEDVT. Women with OHSS develop enlarged multicystic ovaries and produce vasoactive substances that increase capillary permeability. The patient then develops a massive shift of fluid out of the intravascular spaces, which results in hemoconcentration and increases hypercoagulability.

Chan and Ginsberg35 reviewed 35 cases of pregnancy-associated UEDVT. The objectives were to estimate the incidence of UEDVT associated with assisted reproductive techniques (ART) to examine the risk factors and presentation of UEDVT in pregnancy and to determine whether differences exist between this cohort and the general population. Although CVC was not the focus of the study, at least 2 of the patients from this review had CVCs, and both of the patients had a catheter placed for treatment of OHSS. The researchers found that almost all of the cases of UEDVT in their review were associated with ART, with 2 cases associated with CVC and a third case associated with malignancy.

Few articles have investigated the link between hormone replacement therapy and oral contraceptives to the development of UEDVT. In their population case-control study involving 179 patients, Blom et al8 found that hormone replacement therapy did not increase risk, but hormone users did have an increased risk of the development of UEDVT when they also had prothrombotic mutations or surgery. Flinterman et al32 found that the use of oral contraceptives did not increase the risk of UEDVT in most studies.

### DEMOGRAPHIC VARIABLES

The association between age and UEDVT is not clearly understood. Seeley et al9 in their retrospective review of 233 patients, found no statistical difference in rates of UEDVT based on age, but a large number of subjects...
were older than 50 years of age. Spencer et al,11 in their study of a community-based perspective of 483 patients from Worcester, Massachusetts, who had validated acute DVT, 69 were diagnosed with UEDVT. The patients from this study were younger.

Gender as a risk factor for UEDVT has not been clearly demonstrated. Constans et al31 found a predominance of males with UEDVT, but the effect of gender on UEDVT was not significant (P = .16). Caers et al32 found, by multivariate analysis, female and lung cancer as significant variables (OR 3.16 and 6.03; P = .03 and P = .008, respectively). Cadman et al30 found that chi-square analysis indicated that females were twice as likely to develop a thrombosis as men (OR 2.53; 95% CI, 1.12-5.69; P = .025). They hypothesized that the CVC may be displaced in females because of the size of their breasts. They divided females into groups by breast size: small, average, and large. Breast size was not a significantly independent predictor of DVT (P > .05). In study of 479 patients in a neurological intensive care unit with PICCs who developed 39 symptomatic thrombosis, Fletcher et al36 found that males more often developed UEDVT (P = .02).

The role of race or ethnicity in the development of UEDVT has been explored in a limited number of studies. Joffe et al12 identified ethnicity in their study, but it was not considered a statistically significant factor. On the other hand, Spencer et al11 identified that the patients who developed UEDVT in their community-based study were most likely to be non-Caucasian (P = .02). Fletcher et al,36 in their study of patients in a neurological intensive care unit, found that 82% (32/39) of patients were Caucasian.

### SMOKING AND IMMOBILITY

Smoking is considered a risk factor in the development of lower extremity DVT, but it is inconclusive regarding any impact on the development of UEDVT. Three studies have identified smoking as a variable of interest; 2 found that smoking was not significant. Seeley et al9 found a history of smoking to be a statistically significant independent variable (P = .018).

Like smoking, immobility is a known risk factor for development of lower extremity DVT, but its importance in UEDVT is unclear. Seeley et al9 found immobility to be a statistically significant independent variable (P < .001). However, Constans et al31 included paralysis or immobilization in their characteristics of patients with UEDVT and did not find either of these variables statistically significant; in addition, they did not include mobility in their prediction tool. Although not statistically significant, Spencer et al11 found that 46.5% of the patients who had a CVC and were positive for UEDVT had more than 48 hours of bedrest in the previous month compared with 26.9% of patients with CVCs and no UEDVT (P = .23).

### PREDICTION TOOLS

Although many studies have attempted to identify risk factors for UEDVT, few developed prediction tools for preventing UEDVT. Only 2 studies were identified that developed prediction tools for UEDVT; one focused on the development of UEDVTs in patients with CVCs, and the other focused on UEDVT development in patients with PICCs.

Constans et al31 examined UEDVT development in patients with CVCs and developed a prediction tool that includes 4 items: venous material, defined as a catheter or venous access device in a subclavian or jugular vein or a pacemaker; localized pain; unilateral pitting edema; and other diagnosis at least as plausible, defined as hematoma, erysipelas, cellulites, and lymphangitis.

They tested their probability table by using 3 groups of patients. The derivation and internal validation groups were made up of hospitalized patients who were referred to the vascular exploration unit for suspicion of UEDVT. The third group of patients who made up the external validation group was from a multicenter prospective study (OPTIMEV sample). The score was developed from the derivation sample using logistic regression with the 4 items by giving 1 point to venous material, edema, or pain and by subtracting 1 point when another diagnosis was at least plausible. Scoring was as follows: -1 to 0 = 12% probability; 1 = 20% probability; and a score of 2 to 3 = 70% probability. According to the authors, “Low probability score identified a prevalence of UEDVT of 12%, 9%, and 13%, respectively, in the derivation, validation, and OPTIMEV samples. High probability score identified a prevalence of UEDVT of 70%, 64%, and 69%, retrospectively.” A major weakness of the tool lies in the small number of risk factors addressed, and this may explain why both the positive and negative predictive value of the model were limited.

Seeley et al7 examined 23 variables to determine statistically significant risk factors for UEDVT in patients with PICCs. Backward elimination logistic regression using 23 variables produced a prediction model. Variables identified as statistically significant were recent bedrest status, smoking, local tenderness along the distribution of the venous system, osteomyelitis, and the use of anticoagulants at home. A prediction tool was developed that produces a score of 0 to 66. A total of 20 or more is considered predictive for the development of a UEDVT. The prediction tool was tested by applying it to the 233 patients in the study, with the result that 82% of cases were classified correctly. The authors report high sensitivity, specificity, and negative predictive values. However, the positive predictive value
### TABLE 1
Most Frequently Cited Risk Factors for UEDVT

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Author(s)</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Results</th>
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<tr>
<td>History of deep vein thrombosis</td>
<td>Chemaly et al</td>
<td>Retrospective case-control</td>
<td>157</td>
<td>Patients with a history of DVT were more likely to develop UEDVT (OR 4.53; 95% CI, 1.22-16.84; ( P = .02 )).</td>
</tr>
<tr>
<td></td>
<td>Hansson et al</td>
<td>Prospective</td>
<td>738</td>
<td>Rate of recurrence of DVT is high. Incidence of 21.5% (95% CI, 17.7%-25.4%) after 5 years of follow-up.</td>
</tr>
<tr>
<td></td>
<td>Lobo et al</td>
<td>Retrospective</td>
<td>777</td>
<td>History of venous thrombosis was the strongest risk factor for developing a PICC-related thrombosis (OR 10.33; 95% CI, 4.81-22.34).</td>
</tr>
<tr>
<td></td>
<td>Seeley et al</td>
<td>Retrospective</td>
<td>233</td>
<td>History of UEDVT was associated with an increased risk of developing a UEDVT (( P = .047 )).</td>
</tr>
<tr>
<td></td>
<td>Evans et al</td>
<td>Prospective</td>
<td>57</td>
<td>Previous DVT was the most significant risk factor (( P &lt; .001 )) for PICC-associated UEDVT.</td>
</tr>
<tr>
<td>Catheter tip placement</td>
<td>Caers et al</td>
<td>Retrospective</td>
<td>437</td>
<td>Tip position in the brachiocephalic vein (OR 8.07; CI 95%, 2.97-21.89; ( P &lt; .001 )) and in the cranial third of the SVC (OR 1.62-10.19; ( P = .002 )) was the most significant risk factor related to the development of catheter-related thrombosis.</td>
</tr>
<tr>
<td></td>
<td>Luciani et al</td>
<td>Retrospective</td>
<td>113</td>
<td>Correct positioning of the CVC significantly (( P &lt; .001 )) lowered the risk of catheter-related thrombosis.</td>
</tr>
<tr>
<td></td>
<td>Cadman et al</td>
<td>Retrospective</td>
<td>332</td>
<td>Proximal placed CVCs were 16 times more likely to develop thrombosis than those in the distal position (95% CI, 9.23-76.47; ( P &lt; .0005 )).</td>
</tr>
<tr>
<td></td>
<td>Lobo et al</td>
<td>Retrospective</td>
<td>777</td>
<td>Noncentral PICC tip location was associated with a 2.34-fold higher risk of thrombosis development (95% CI, 1.05-1.33; ( P &lt; .05 )) compared with superior vena cava or right atrium tip location.</td>
</tr>
<tr>
<td></td>
<td>Grove et al</td>
<td>Retrospective</td>
<td>678</td>
<td>The rate of thrombosis for PICCs in the SVC/right atrium was 3.0%, while the rate for other locations was 9.3%. Although the rate was higher, it was not statistically significant (( P = .15 )).</td>
</tr>
<tr>
<td>Infection</td>
<td>Crowley et al</td>
<td>Prospective</td>
<td>48</td>
<td>Thirty-four of 48 (71%) patients with catheter-associated ( S. ) aureus bacteremia presented with thrombosis.</td>
</tr>
<tr>
<td></td>
<td>van Rooden et al</td>
<td>Prospective</td>
<td>105</td>
<td>Forty-four percent of patients with CVC-related infection developed thrombosis compared with 3% in patients without infection (( P &lt; .05 )).</td>
</tr>
<tr>
<td></td>
<td>Lordick et al</td>
<td>Prospective</td>
<td>43</td>
<td>CRT and catheter-related infection were significantly correlated (( P &lt; .0001 )).</td>
</tr>
<tr>
<td></td>
<td>Timsit et al</td>
<td>Prospective</td>
<td>265</td>
<td>CRT was associated with catheter-related infection (OR = 2.97; 95% CI, 1.17-7.53; ( P = .02 )).</td>
</tr>
<tr>
<td>Cancer</td>
<td>Blom et al</td>
<td>Case-control</td>
<td>179</td>
<td>The presence of both cancer and a central venous catheter (CVC) increased the risk of UEDVT 18-fold (OR 17.9; 95% CI, 12.0-26.7).</td>
</tr>
<tr>
<td></td>
<td>Lee et al</td>
<td>Prospective</td>
<td>444</td>
<td>Incidence rate of catheter-related thrombosis was 4.3% in patients with cancer.</td>
</tr>
<tr>
<td></td>
<td>Hingorani et al</td>
<td>Retrospective</td>
<td>546</td>
<td>Twenty-two percent of patients with a history of cancer developed a DVT.</td>
</tr>
<tr>
<td></td>
<td>Mustafa et al</td>
<td>Retrospective</td>
<td>65</td>
<td>Of the 65 patients with symptomatic UEDVT, 66% had a CVC and 46% had a cancer diagnosis. Of the 30 cancer patients with UEDVT, 23 also had a CVC.</td>
</tr>
<tr>
<td>Cancer</td>
<td>Joffe et al</td>
<td>Retrospective</td>
<td>324</td>
<td>HTN was one of the most frequent comorbidities in patients with UEDVTs.</td>
</tr>
<tr>
<td>HTN</td>
<td>Seeley et al</td>
<td>Retrospective</td>
<td>233</td>
<td>A significant difference (( P = .049 )) in rates of UEDVT between patients with HTN and patients without HTN. Seventy percent of patients who developed UEDVT had a history of HTN.</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; CRT, catheter-related thrombosis; CVC, central venous catheter; DVT, deep vein thrombosis; HTN, hypertension; OR, odds ratio; PICC, peripherally inserted central catheter; SVC, superior vena cava; UEDVT, upper extremity deep vein thrombosis.
of the tool was low at 27.3%, indicating that the tool will likely tell the user who will not experience an UEDVT, not who will. This may be a result of the small sample size or of the fact that other, unidentified variables significantly raise the risk of UEDVT.

CONCLUSION

The review of the literature identified 28 suspected risk factors for the development of UEDVT. A history of DVT, comorbidities such as cancer, infection, and HTN, and tip placement were identified most frequently in the literature as being associated with UEDVT development (Table 1). Other risk factors were examined in a limited number of studies and lacked consistent evidence of the impact of the risk factor on UEDVT development. In addition, many of the articles that were reviewed used a retrospective design to identify factors that may lead to UEDVT development in patients with PICCs and CVCs. Although retrospective designs provide quality data, there are some limitations because they are dependent on the accuracy of the database and can only capture data on variables for which there are accurate records. This does limit the number of variables that can be studied and may exclude other relevant variables because a particular data set is not captured. For these reasons, a prospective cohort study was undertaken to examine the many risk factors identified in the review and to provide the researchers with an opportunity to explore a wide variety of variables and collect data with greater confidence in their reliability and accuracy. As the literature review clearly demonstrates, there is a need for a study that engages in a comprehensive examination of known and suspected risk factors. Part 2 of this series will present the results of the study.

REFERENCES


