## Title
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# Symptomatic Catheter-Associated Thrombosis in Pediatric Trauma Patients: Choose Your Access Wisely

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## Abstract

**Background:** Traumatic injury and the presence of a central venous catheter are two of the strongest risk factors for venous thromboembolism in children. The purpose of this study was to determine the incidence of symptomatic catheter-associated thrombosis in critically-injured children. We hypothesized that femoral venous catheters are associated with a higher rate of thrombotic complications when compared to all other central venous access points.

**Methods:** We reviewed a retrospective cohort (2006–2016) of injured children (≤18 years) admitted to a pediatric intensive care unit with central access placed ≤ 7 days from admission. Symptomatic catheter-associated thrombosis was determined by radiographic evidence. Poisson regression was used to compare the incidence of catheter-associated thrombosis per 1000 catheter days between femoral and non-femoral catheters. All comparisons were two-tailed with alpha = 0.05.

**Results:** We examined 209 pediatric trauma patients with central access (65% femoral, 19% subclavian, 11% arm vein, and 5% internal jugular). Femoral catheters were removed earlier (median [IQR] 4 [2–7] vs 8 [3–12] days, p<0.001), and were larger in diameter (5 Fr [4,7] vs 4 Fr [4,4], p<0.001), when compared to all other catheters. Catheter-associated thrombosis was more frequent in femoral versus non-femoral catheters (18.4 vs 3.5 per 1000 catheter days, p=0.01).

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**Conclusions:** Femoral venous catheters are associated with higher incidence of symptomatic catheter-associated thrombosis in pediatric trauma patients. When central venous access is indicated for injured children, the femoral site should be avoided. If a femoral venous catheter is necessary, use of a smaller catheter should be considered.

### Keywords

catheter-associated thrombosis; pediatric trauma; venous thromboembolism; deep vein thrombosis; children; injury

## INTRODUCTION

Venous thromboembolism (VTE) has been increasingly recognized as a major public health problem and source of morbidity and mortality in hospitalized adults, especially in trauma patients.[1–4] While the incidence of VTE is lower in children, their risk also increases after traumatic injury.[5] Higher injury severity, immobility, major surgery, older age, and a low Glasgow Coma Score (GCS) are known risk factors for VTE in pediatric trauma patients. However, the majority of clots in children occur in those with an existing or previous central venous catheter (CVC).[6–12]

Avoiding use of CVCs unless absolutely indicated is considered standard of care to minimize risk for catheter-associated complications such as infection and thrombosis.[13] When a CVC is needed, however, the location of the catheter may impact a child's risk profile. Femoral and subclavian CVCs have been reported to have a higher incidence of catheter-associated thrombosis in mixed-population pediatric and leukemia patients,[14,15] but this has not been reported in pediatric trauma patients. The purpose of this study was to determine the association between CVC location and incidence of catheter-associated thrombosis in pediatric trauma patients.

## METHODS

### Study design and cohort selection

Institutional Review Board approval was obtained from the Children's Hospital of Los Angeles and University of Southern California. A retrospective cohort (2006–2016) was obtained from two American College of Surgeons (ACS) verified level one trauma centers that care for pediatric patients. We included all patients ≤18 years old in the trauma registry at each institution that were admitted to the pediatric intensive care unit and underwent CVC placement. Patients were excluded if the CVC was placed >7 days from injury or if they had a pre-existing indwelling CVC or history of CVCs prior to admission.

Demographic and clinical data abstracted from chart review included: patient age, weight, height, race, ethnicity, primary language, insurance status, comorbidities, mechanism of injury, GCS, and serum coagulation markers at admission, presence of traumatic brain injury, spine fracture, pelvic fracture, femur fracture, tibia fracture, venous injury, and blood stream infection. We followed the international standard[16] to classify obesity by age and gender; calculating (with PediTools.org)[17] weight-for-height percentile for infants 0–24 months using the World Health Organization (WHO) growth standards, and body mass index (BMI) percentile for children >2 years old using the Centers for Disease Control and Prevention (CDC) growth chart. Use of pharmacologic thromboprophylaxis and date of initiation was recorded.

The presence of a central venous catheter was determined via nursing/provider documentation or radiographic evidence. Specific CVC characteristics were recorded including insertion site (femoral, subclavian, internal jugular, or arm vein), side of insertion, type of CVC (peripherally-inserted central catheter (PICC), non-tunneled, tunneled, or port), catheter size, date of placement, and date of removal. Catheter days were calculated by subtracting date of placement from removal. If date of removal could not be accurately determined in chart review, catheter days were considered missing.

### Definition of Catheter-Associated Thrombosis

The primary outcome was the incidence of symptomatic catheter-associated thrombosis. A thrombosis event was determined by radiographic evidence. We reviewed all diagnostic studies and recorded the type of diagnostic modality (ultrasound, computed tomography, magnetic resonance imaging, or venography) and first date in which a VTE was present. The VTE vein location and laterality were also recorded. The incidence of catheter-associated thrombosis was calculated per 1,000 catheter days. Routine screening for asymptomatic DVT was not utilized at either of the participating centers. The decision to obtain an imaging study to diagnose a DVT was at the discretion of the treating physician and not determined by protocol.

### Statistical Analysis

The primary comparison groups in this study were patients with femoral versus upper extremity (subclavian, internal jugular, and arm vein) CVCs. Categorical data was compared using Chi-square or Fisher exact test (for cell counts <5). Continuous, non-parametric data was compared using Mann-Whitney U. Poisson regression was used to compare the incidence of catheter-associated thrombosis, using catheter days as an offset. Statistical analyses were conducted with SAS® software, Version 9.4 (Copyright © 2013, SAS Institute Inc). SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. All comparisons were two-tailed with alpha = 0.05.

## RESULTS

A total of 209 pediatric trauma patients met criteria to be included in the study. The distribution of CVC location in descending frequency was femoral (65%), subclavian (19%), arm vein (11%), and internal jugular (5%)., There was no significant difference between patients with femoral versus upper extremity catheters with respect to age, gender, race, ethnicity, primary language, insurance, weight-for-length or BMI, comorbidities, mechanism of injury, admission coagulation profile, admission GCS, spine fracture, pelvic fracture, tibia fracture, venous injury, or acquired blood stream infection per bivariate comparison.(Table 1). More frequent use of upper extremity CVCs was seen in patients with non-accidental trauma (35% vs 18%, p=0.01) and femur fractures (21% vs 5%, p<0.01). Femoral CVCs were used more frequently in patients with traumatic brain injury (85% vs 64%, p<0.01), more commonly placed on the right side (70% vs 53%, p=0.03), more likely to be larger in diameter (median, IQR 5 Fr [4,7] vs 4 Fr [4,4], p<0.001), and were removed earlier (4 [2–7] vs 8 [3–12] days, p<0.001). Thromboprophylaxis was rarely used (5%) and not significantly associated with CVC location.

The overall incidence of symptomatic thrombosis was 6% in this cohort (Table 2). Patients developing DVT were younger, less often of Hispanic ethnicity, and more frequently thrombocytopenic on admission when compared to patients not developing DVT (Supplemental Table 1). Nearly all (92%) VTE events were diagnosed via ultrasound, and only one via computed tomography (Table 3). All imaging studies potentially diagnostic of VTE were reviewed regardless of the indication for the study (e.g., CT scan or duplex ultrasound for fever of unknown etiology), and no asymptomatic thrombosis events were seen. The median time to diagnosis was nine days (IQR 4,13 days) overall, and there was no significant difference between the two groups. The total number of catheter days was 598 and 580 days for femoral and upper extremity CVCs, respectively. The incidence of VTE when normalized for catheter days was significantly higher in children with femoral catheters (18.4 vs 3.5 VTE/1,000 catheter days, p=0.01). There was no significant difference in hospital stay, ICU stay, or mortality among children with femoral or upper extremity catheters.

## DISCUSSION

This retrospective study found that femoral catheters were associated with a higher incidence of catheter-associated VTE in pediatric trauma patients. Femoral CVCs were placed more frequently in patients with traumatic brain injury and tended to be larger catheters. Despite being removed earlier, femoral CVCs still had a higher rate of VTE. There was no significant difference in hospital or PICU length of stay. These findings suggest that, when a CVC is absolutely indicated, an upper extremity catheter may be the best choice. If a lower extremity catheter is necessary, the use of the smallest functional catheter to meet resuscitation needs should be considered.

There are number of factors which have been associated with VTE in pediatric trauma patients including critical illness, increased ISS, lower GCS, surgery, and immobility.[6,9,11,12] Older children have been associated with higher risk for VTE,[7,9,11] but our data suggests that younger children are still quite susceptible – potentially related to injury burden from non-accidental injury or related to small vessel size. For example, the group with the highest frequency of VTE events was children <1 year (10%). The risk for thrombosis may be so disproportionally increased by the presence of a CVC,[6,9,12] however, that the effect of age on thrombosis is marginalized. The decision to place a CVC requires careful consideration. The population of children in which a CVC is typically needed are patients who already have an increased risk for VTE based on their clinical state. Such would include hemodynamically unstable, polytrauma patients with poor vascular access, and those who need parenteral nutrition.

The main finding of this study – that femoral CVCs are associated with a higher rate of thrombosis – is consistent with two previous studies from general pediatric populations. Shah *et al* examined 3,733 CVCs over 3 years, finding that femoral CVCs had an odds ratio of 11.1 for thrombosis.[14] Male et al used a multicenter cohort of 158 children with CVCs, finding that 32% of VTE events occurred in children with femoral catheters.[18] In contrast, other studies have reported that internal jugular[19] and subclavian[15] lines confer a higher risk for thrombosis. Our hypothesis was based on the reports that the incidence of thrombosis is higher in the lower extremity in adult patients[20], and that younger and smaller children have proportionally smaller femoral veins in comparison to their internal jugular veins.[21] In our cohort, 8 of 11 children (73%) with femoral-associated thrombosis were under 3 years old. Ultrasound data suggests that the femoral vein does not double in diameter until 5–7 years old,[22] suggesting that younger age and size may have played in role in the increased incidence of femoral thrombosis in our cohort.

Despite the increased incidence of femoral catheter-associated VTE, there was no significant difference in hospital days, ICU days, or mortality between upper extremity and femoral CVC groups. These outcomes, however, may not be an appropriate measure of the clinical importance of VTE in pediatric trauma. The benefit of preventing VTE may reside in reducing the need for therapeutic anticoagulation. Many children who develop thrombosis will be placed on therapeutic anticoagulation, but patients with traumatic brain injury (TBI, 78% of our cohort) or gastrointestinal bleeding pose a bleeding risk. Prophylactic anticoagulation may be considered for VTE prevention, but current Eastern Association for the Surgery of Trauma (EAST) guidelines only recommend pharmacologic prophylaxis for postpubertal patients[23] – which represented a minority of patients with VTE in our cohort. Perhaps there may be a role for prophylaxis in younger pediatric trauma patients with CVCs, but future study will be needed to support this measure, as there has been no benefit of chemoprophylaxis demonstrated for young children. Decreasing the use of femoral CVCs, and thereby lowering the risk for VTE, may obviate the need to make this challenging decision.

Studying an outcome as infrequent as VTE in children presents several challenges from a research design standpoint. The main limitation is often sample size, as a large study cohort is frequently needed to detect a difference in VTE incidence. While we did find a significant association between femoral CVCs and thrombosis, the low number of VTE events excluded the possibility of performing a robust multivariate analysis. Another notable limitation is that this study aimed to detect clinically evident VTE - thrombosis events that were diagnosed because clinical suspicion warranted further investigation. We did not intend to capture asymptomatic VTEs, which are relatively common,[19] and therefore the effect of catheter location on overall thrombosis events (symptomatic + asymptomatic) is not known. It is possible that asymptomatic VTE may have a different relationship with catheter location – particularly in the upper extremity location – which could have led to Type 1 error. This study was also limited by its retrospective design which resulted in missing data due to inadequate documentation, and inability to randomize groups to control for confounding. Provider-level factors at the time of CVC placement (such as trainee vs attending, use of ultrasound-guidance, reason for site selection, and number of attempts) are a significant source of unmeasured confounding that may affect the incidence of VTE. Despite these limitations, this study was the first to our knowledge to report an association between femoral CVCs and catheter-associated thrombosis in critically injured pediatric trauma patients.

## CONCLUSIONS

In summary, femoral venous catheters are associated with higher rate of catheter-associated thrombosis in pediatric trauma patients. While CVCs are commonly needed in injured children for resuscitation, inotropic support, and delivery of parenteral nutrition, they should be inserted when indicated and femoral catheters should be avoided. If a lower extremity line is necessary, perhaps the use of a smaller diameter catheter should be considered.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1:**

Baseline characteristics of pediatric trauma patients with central venous catheters, comparing femoral to upper extremity catheter location.

| Category | Upper N = 72 | Femoral N = 136 | P-value* |
|---|---|---|---|
| Age, years | 7.6 (1.4, 12.9) | 5.6 (1.8, 11.4) | 0.58 |
| Male gender | 82 (60%) | 47 (65%) | 0.55 |
| Weight-for-length/BMI percentile | 69 (37, 93) | 63 (33, 92) | 0.50 |
| Race | | | 0.20 |
| White | 15 (21%) | 26 (19%) | |
| Black | 5 (7%) | 13 (10%) | |
| Asian | 2 (3%) | 14 (10%) | |
| Other/Unknown | 50 (69%) | 83 (61%) | |
| Hispanic/Latino ethnicity | 51 (73%) | 77 (60%) | 0.17 |
| Admission GCS | 7 (3, 9) | 6 (3, 9) | 0.39 |
| Mechanism of injury | | | 0.84 |
| Blunt | 67 (93%) | 129 (95%) | |
| Penetrating | 4 (5.6%) | 6 (4.4%) | |
| Combined | 1 (1.4 %) | 1 (0.7%) | |
| Non-accidental trauma | 25 (35%) | 25 (18%) | 0.01 |
| Type of Injury | | | |
| TBI | 46 (64%) | 116 (85%) | <0.001 |
| Spine Fracture | 7 (10%) | 25 (18%) | 0.11 |
| Pelvic Fracture | 8 (11%) | 17 (13%) | 0.83 |
| Femur Fracture | 15 (21%) | 7 (5%) | <0.001 |
| Tibia Fracture | 11 (15%) | 11 (8.1%) | 0.15 |
| Venous Injury | 1 (1.4%) | 3 (2.2%) | 1.0 |
| Blood stream infection | 5 (7.3%) | 9 (7.0%) | 1.0 |
| Platelets | | | 0.17 |
| Normal | 50 (70%) | 103 (76%) | |
| Low | 20 (28%) | 26 (19%) | |
| High | 1 (1.4%) | 7 (5.2%) | |
| INR | | | 0.77 |
| Normal | 28 (44%) | 58 (45%) | |
| Low | - | 1 (0.8%) | |
| High | 36 (56%) | 71 (55%) | |
| PTT | | | 0.46 |
| Normal | 40 (63%) | 67 (53%) | |
| Low | 7 (11%) | 19 (15%) | |
| High | 17 (27%) | 40 (32%) | |

| Category | Upper N = 72 | Femoral N = 136 | P-value* |
|---|---|---|---|
| CVC Location | | | - |
| Femoral | - | 136 (100%) | |
| Subclavian | 39 (54%) | - | |
| Internal Jugular | 10 (14%) | - | |
| Arm vein | 23 (32%) | - | |
| CVC on right side | 38 (53%) | 90 (70%) | 0.03 |
| CVC size, Fr | 4 (4, 4) | 5 (4, 7) | <0.001 |
| DVT prophylaxis | 5 (6.9%) | 5 (3.7%) | 0.32 |
| | | | |

Continuous data presented as median (IQR), categorical data as N (%).

*Chi-square or Fisher exact test (for counts <5) for categorical data; Mann-Whitney U for continuous data. Missing data: CVC location (n=1), ethnicity (n=9), platelets (n=1), INR (n=14), PTT (n=18), bacteremia (n=10), CVC side (n=7).

**Table 2:**

Incidence of catheter-associated thrombosis and outcomes by catheter location.

| Outcome | Upper N = 72 | Femoral N = 136 | P-value* |
|---|---|---|---|
| Thrombosis, total | 2 (2.8%) | 11 (8.2%) | 0.23 |
| Days to diagnosis | 8 (6, 9) | 11 (3, 13) | 0.85 |
| CVC days | 8 (3, 12) | 4 (2, 7) | <0.001 |
| Thrombosis per 1000 catheter days | 3.5 | 18.4 | 0.01 |
| Hospital LOS, days | 16 (7, 28) | 13 (6, 25) | 0.26 |
| ICU LOS, days | 5 (3, 10) | 7 (3, 13) | 0.22 |
| Mortality | 13 (18%) | 24 (18%) | 1.0 |

Continuous data presented as median (IQR), categorical data as N (%).

* Chi-square or Fisher exact test (for counts <5) for categorical data; Mann-Whitney U for continuous data. Poisson regression for events per 1000 catheter days. Missing data: CVC days (n=35).

**Table 3:**

Characteristics of children with catheter-associated thrombosis.

| # | Age | Gender | BMI ± | AssociatedInjuries | Non-AccidentalTrauma | CVC Location | CVC size (F) | PICC | CVC days | Days to Diagnosis | DVT prophylaxis | Diagnostic Study | Hospital LOS | ICU LOS | Mortality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 17 y | F | 2 | TBI | No | Femoral | 7 | No | 5 | 13 | No | CT | 18 | 8 | No |
| 2 | 10 y | F | 0 | Spine Injury<br>Tib/Fib Fracture | No | Femoral | - | No | 3 | 13 | No | US | 31 | 3 | No |
| 3 | 14 y | F | 64 | TBI<br>Tib/Fib Fracture<br>Femur Fracture | No | Subclavian | - | No | 2 | 6 | Yes | US | 60 | 5 | No |
| 4 | 9 y | F | 99 | TBI | No | Femoral | 4 | No | 6 | 18 | No | US | 24 | 13 | No |
| 5 | 22 m | M | 48 | TBI | No | Femoral | 4 | No | 8 | 6 | No | US | 27 | 14 | No |
| 6 | 15 m | F | 95 | TBI | No | Femoral | 4 | No | 8 | 13 | No | US | 30 | 16 | No |
| 7 | 5 m | M | 100 | TBI | Yes | Arm | 4 | Yes | 6 | 9 | No | US | 34 | 4 | No |
| 8 | 23 m | M | 1 | TBI<br>Tib/Fib Fracture | Yes | Femoral | 4 | No | 3 | 3 | No | US | 44 | 14 | Yes |
| 9 | 3 m | F | 17 | TBI | No | Femoral | 4 | No | 4 | 4 | No | US | 45 | 16 | No |
| 10 | 1 m | F | 72 | TBI | Yes | Femoral | - | No | 2 | 3 | No | US | 8 | 8 | No |
| 11 | 3 y | M | 6 | TBI | Yes | Femoral | - | No | 15 | 11 | No | US | 25 | 15 | No |
| 12 | 5 m | M | 1 | TBI | No | Femoral | - | No | 10 | 2 | No | US | 26 | 13 | No |
| 13 | 13 m | M | 87 | TBI<br>Spine Injury | No | Femoral | - | No | 5 | 110 | No | US | 160 | 62 | No |

±Weight-for-length percentile for infants <2 years, BMI percentile for children ≥2 years. Missing data: CVC size (n=6). PICC = peripherally-inserted central catheter.