

The Incidence of Peripherally Inserted Central Catheter Symptomatic Pulmonary Embolism after Line Removal: A Retrospective Analysis

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Abstract

Background: To date, there are no recommendations regarding the timing of removal of peripherally inserted central catheters (PICC) in the presence of confirmed upper extremity deep vein thrombosis (UEDVT).

Objective: We aimed to determine the incidence of symptomatic pulmonary embolism (PE) post line removal in patients with PICC-associated UEDVT according to treatment strategy.

Patients/Methods: We conducted a retrospective study in adult patients who received a PICC with documented UEDVT or superficial thrombosis (UESVT) by vascular ultrasound. Patients' demographic characteristics, co-morbid diseases, medications, ultrasound findings, treatment strategy for UEDVT/SVT and occurrence of symptomatic PE after PICC removal was documented.

Results: 124 patients had PICC-associated UEDVT or UESVT; 69 males and 55 females with mean age 52.2 years. Of 81 patients meeting study criteria, 57 patients had UEDVT and 24 patients UESVT. No episodes of symptomatic PE after PICC removal were documented. Regarding timing of removal, 20 patients had their PICC removed within 24 hours after UEDVT diagnosis, 15 within 1 week, 7 within 2 weeks, 11 within 1 month and 4 at more than a month after diagnosis of UEDVT. No patients had objectively confirmed PE during the follow up period.

Conclusion: This retrospective analysis revealed no symptomatic PE with removal of PICC in the presence of UEDVT or UESVT if performed within 24 hours, and an overall low rate of PE events regardless of treatment strategy and duration of PICC insertion. These findings are hypothesis generating and should be confirmed in a prospective trial.

Keywords: Anticoagulation; PICC; Pulmonary embolism; Upper extremity; Venous thrombosis

Introduction

Upper extremity deep venous thrombosis (UEDVT) accounts for 4% to 10% of all deep venous thrombosis [1]. The natural history of UEDVT is not a benign one as it increases the risk for post-thrombotic complications and pulmonary embolism (PE) [1-4]. It has been reported that PE complicates UEDVT in 2% to 36% of patients and may occur as the initial clinical presentation of this disorder [5-8]. Increased use of peripherally inserted central catheters (PICCs) is associated with an elevated risk of UEDVT, particularly in critically ill patients and those with malignancy or receiving chemotherapy [1,4,9-12]. The occurrence of symptomatic PICC-associated UEDVT is small, but due to the large number of PICCs placed each year, they account for up to 35% of all diagnosed UEDVTs [13]. Roughly 1% to 7% of hospitalized patients who undergo PICC placement will develop venous thrombosis; and, the majority of these events will occur after the 14th day post placement [10,14-20].

Prophylaxis with anticoagulation may not lower the risk of PICC-associated DVT; however, anticoagulation treatment allows an indwelling line to remain patent and with less recurrence and or extension of UEDVT [21-23]. Inconsistent use of anticoagulation treatment for UEDVT is associated with a moderate risk of PE [24]. In order to prevent thrombus progression and PE, anticoagulant treatment with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) and vitamin K antagonists (VKA) is recommended [25].

The optimal approach to managing PICC-associated UEDVT is

unclear. Few studies report outcomes after catheter removal for PICC-associated UEDVT and the safety of this approach in the setting of anticoagulation [15].

This retrospective study sought to determine the association between different treatment strategies for PICC-associated UEDVT, including catheter removal and/or anticoagulation and subsequent pulmonary embolism.

Methods

This retrospective study was performed by an electronic chart review of patients who received a PICC while hospitalized between January 1, 2011 and December 31, 2011 at OU Medical Center (OUMC), a 400 bed urban academic institution, in Oklahoma City, OK. Patients were identified through the use of a PICC database and the non-invasive diagnostic vascular laboratory. The data collected was through review

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Received September 20, 2017; **Accepted** October 06, 2017; **Published** October 17, 2017

Citation: Wasan SM, Esponda OL, Feland N, Mathew JL, Smith WJ (2017) The Incidence of Peripherally Inserted Central Catheter Symptomatic Pulmonary Embolism after Line Removal: A Retrospective Analysis. *J Vasc Med Surg* 5: 345. doi: [10.4172/2329-6925.1000345](https://doi.org/10.4172/2329-6925.1000345)

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of the medical record and included patient's demographics, the date of PICC placement, anticoagulation previous to venous thrombosis, date of venous thrombotic event associated to PICC, date of removal of PICC, pharmacologic treatment strategy previous to removal of PICC, the vein assessed and the reason for PICC placement. Data were extracted by physicians and clinical pharmacists. The institutional review board approved the study protocol prior to data extraction.

Patients older than 18 years of age who had a PICC inserted during the study period and who did not have an UEDVT or upper extremity superficial vein thrombosis (UESVT) or PE at the time of PICC insertion but developed a PICC-related UEDVT or UESVT during hospitalization were included in the study. UEDVT included thrombosis of the internal jugular, brachiocephalic, subclavian, axillary, brachial, radial or ulnar veins. UESVT included thrombosis of the cephalic or basilic veins.

Patients younger than 18 years of age were excluded from this study. Patients who had incomplete electronic medical records, not hospitalized at the time of PICC placement, had UEDVT or UESVT associated with indwelling venous catheter other than a PICC or previous PICC-related thrombosis, UEDVT or UESVT that was not associated with PICC line, or removal of PICC line prior to UEDVT or UESVT of more than 24 hours were excluded from this study.

PICCs were placed as per institutional protocol using a modified Seldinger technique at the bedside with a portable ultrasound. Confirmation of catheter tip placement was done with chest X-ray prior to use the PICC as per institutional protocol. The PICC manufacturer was Bard Access Systems, Inc.

An upper extremity deep vein thrombosis/superficial vein thrombosis (UEDVT/UESVT) was defined as a symptomatic event in the ipsilateral extremity of PICC placement leading to the performance of duplex ultrasound, confirming the diagnosis of UEDVT/UESVT. Sonographic diagnosis of venous thrombosis was based on non-compressibility of a venous segment of the upper arm or the internal jugular, or the presence of echogenic material compatible with thrombosis in the arm or central venous vasculature with disruption in real-time imaging with the use of color Doppler flow.

Pulmonary embolism (PE) was defined as a symptomatic event that prompted the performance of an imaging study confirming the diagnosis of pulmonary embolism. Radiological diagnosis of PE was based on intraluminal and filling defect of a lobar artery or more proximal pulmonary arterial vasculature on computed tomography angiography or an abnormal ventilation perfusion scan with a high clinical suspicion for pulmonary embolism according to report. Deaths were adjudicated by a physician not related to care of the patient by review of medical record and death certificate if available. Pulmonary embolism and related death was confirmed if objective imaging evidence confirming PE was available. The primary outcome measure was objectively confirmed PE at the predetermined endpoints: within 24 hours, and within 1 week, 2 weeks and 1 month of PICC-related UEDVT/UESVT diagnosis. Anticoagulation regimens administered after confirmed diagnosis of PICC-related UEDVT or UESVT included: prophylactic anticoagulation=enoxaparin 30 mg daily, enoxaparin 40 mg daily, heparin 500 units bid or tid and therapeutic anticoagulation=enoxaparin 1 mg/kg twice daily or 1.5 mg/kg daily, fondaparinux 7.5 mg daily, heparin intravenous infusion adjusted to therapeutic PTT, warfarin INR 2 to 3. The exact 95% confidence intervals for the true incidence of PE occurring during the follow-up period were calculated from the binomial distribution.

Results

From January 1, 2011 to December 31, 2011, 2261 PICCs were inserted; of those 124 had associated venous thrombosis. After exclusion criteria, these totaled 81 patients who had removal of PICC with the documented primary outcome of interest: 57 with upper extremity deep venous thrombosis and 24 with upper extremity superficial venous thrombosis events associated with PICC. Demographics and baseline characteristics of the 81 patients are given in Table 1. The patient flow diagram is given in Figure 1.

Twenty-six percent of patients had active cancer and/or were being treated for malignancy. A history of cancer was present in 32.1% of patients. A history of deep vein thrombosis was present in 27.2% of patients. The most common indication for PICC insertion was poor peripheral intravenous access in 38.3% of PICCs placed. The basilic vein

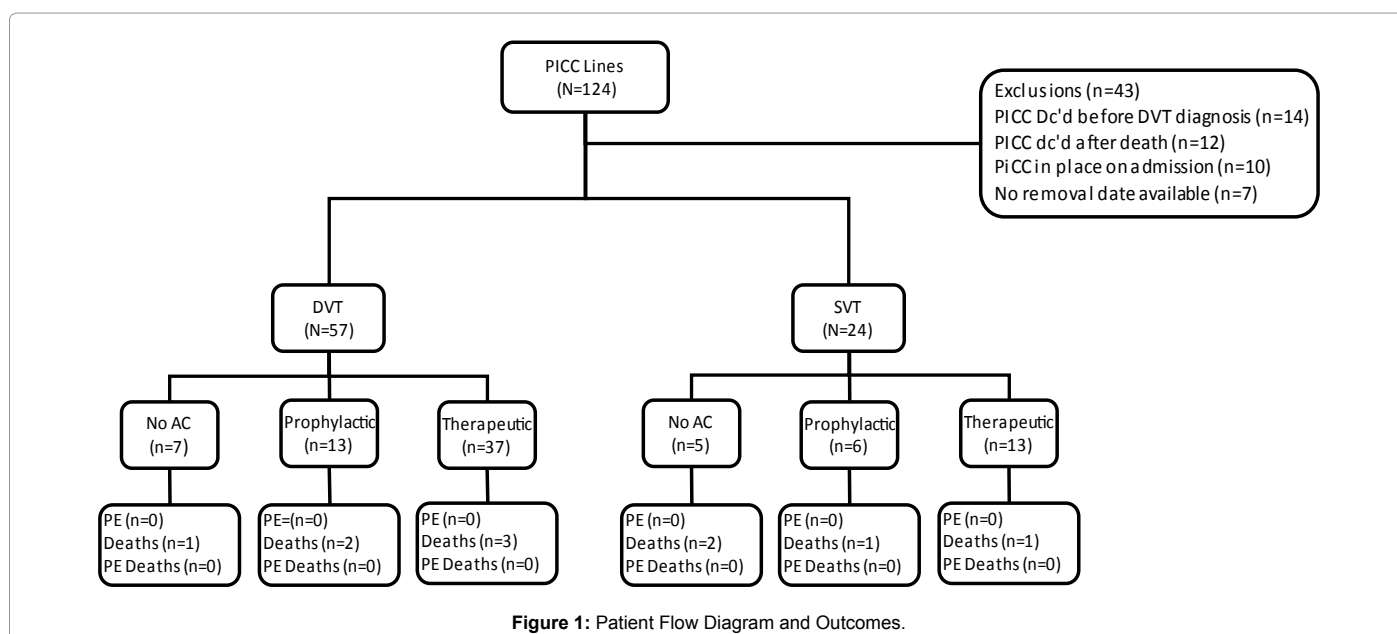


Figure 1: Patient Flow Diagram and Outcomes.

| | | n=81 | Percent |
|--|----------------------------|------------|--------------|
| Age, mean (range) | | 53 (18-83) | |
| Gender | Female | 36 | 44.4% |
| | Male | 45 | 55.6% |
| Race | African American | 10 | 12.4% |
| | Asian | 3 | 3.7% |
| | Caucasian | 64 | 79.0% |
| | Native American | 3 | 3.7% |
| | Other | 1 | 1.2% |
| Ethnicity | Hispanic/Latino | 3 | 3.7% |
| | Not Hispanic or Latino | 78 | 96.2% |
| Weight (kg), mean | | 84 | |
| History Cancer | | 26 | 32.1% |
| Active Cancer | | 21 | 25.9% |
| History DVT | | 22 | 27.2% |
| PICC location | Left basilic | 19 | 23.5% |
| | Left brachial | 6 | 7.4% |
| | Left cephalic | 2 | 2.5% |
| | Right basilic | 34 | 42.0% |
| | Right brachial | 16 | 19.8% |
| | Right cephalic Unknown | 1 3 | 1.2% 3.7% |
| Reason for PICC | Antibiotics | 20 | 24.7% |
| | Access | 31 | 38.3% |
| | Chemotherapy | 13 | 16.0% |
| | Total Parenteral Nutrition | 9 | 11.1% |
| | Other | 8 | 9.9% |
| Days with PICC line, mean (range) | | 32 (0-269) | |
| Treatment Strategy Previous to UE Thrombosis | No anticoagulation | 40 | 49.4% |
| | Prophylactic | 31 | 38.3% |
| | Therapeutic | 10 | 14.3% |

Table 1: Baseline Characteristics of Patients after Exclusion Criteria.

| | Management Strategy Post UE Venous Thrombosis (DVT) | | | Symptomatic Pulmonary Embolism after PICC line removal | Deaths | | |
|--|---|--------------|-------------|--|--------|--------------|-------------|
| | No AC | Prophylactic | Therapeutic | n (95% CI) | No AC | Prophylactic | Therapeutic |
| PICC line removed within 24 h | 0 | 6 | 14 | 0/20 (0, 16.8) | 0 | 1 | 2 |
| PICC line removed within 1 week | 4 | 3 | 8 | 0/15 (0, 21.8) | 0 | 1 | 0 |
| PICC line removed within 2 weeks | 0 | 2 | 5 | 0/7 (0, 40.9) | 0 | 0 | 1 |
| PICC line removed within 1 month | 2 | 2 | 7 | 0/11 (0, 28.5) | 1 | 0 | 1 |
| PICC line removed after 1 month | 1 | 0 | 3 | 0/4 (0, 60.2) | 0 | 0 | 0 |
| Symptomatic PE after PICC line removed | 0/7 | 0/13 | 0/37 | 0/57 (0, 6.2) | 0/1 | 0/2 | 0/3 |

Prophylactic anticoagulation: enoxaparin 30mg daily, enoxaparin 40 mg daily, heparin 500 units bid or tid. Therapeutic anticoagulation: enoxaparin 1mg/kg twice daily or 1.5 mg/kg daily, fondaparinux 7.5 mg daily, heparin intravenous infusion adjusted to therapeutic PTT, warfarin INR 2 to 3.

No AC: No anticoagulation given

Table 2: Management Strategy Post UE Deep Vein Thrombosis and Symptomatic PE.

was accessed 65.5% of the time. The average dwell time of PICCs was 32 days. Forty-nine percent did not receive anticoagulation prophylaxis prior to the diagnosis of PICC line related venous thrombosis.

The most common location for upper extremity deep vein thrombosis was the right axillary vein and the most common location for upper extremity superficial vein thrombosis was the right basilic vein with 19.2% and 75.0%, respectively.

After diagnosis of UEDVT/UESVT associated with PICCs, the mean dwell time of catheter before removal was 10.38 days. The most common treatment strategy was administration of therapeutic anticoagulation followed by pharmacological prophylaxis and PICC removal. PE after catheter removal was evaluated within 24 h, one week, two weeks, one month and after one month. No symptomatic

pulmonary embolism was identified at any of the time points or after any of the treatment strategies following diagnosis of UEDVT/UESVT associated with PICCs (Tables 2 and 3). Six patients diagnosed with UEDVT and 4 patients with UESVT died during the follow-up period (Tables 4 and 5). Medical record review excluded pulmonary embolism related to the cause of death.

Discussion

To our knowledge, our study is the first to examine the association between PICC associated UEDVT/UESVT and different treatment strategies to prevent adverse venous thromboembolic events. No symptomatic pulmonary embolism was reported regardless of timing of removal of the PICC line and duration of anticoagulation treatment.

| | Management Strategy Post UE Venous Thrombosis (DVT) | | | Symptomatic Pulmonary Embolism after PICC line removal n (95% CI) | Deaths | | |
|--|---|--------------|-------------|--|--------|--------------|-------------|
| | No AC | Prophylactic | Therapeutic | | No AC | Prophylactic | Therapeutic |
| PICC line removed within 24 h | 3 | 3 | 4 | 0/10 (0, 30.8) | 1 | 1 | 1 |
| PICC line removed within 1 week | 1 | 1 | 2 | 0/4 (0, 60.2) | 1 | 0 | 0 |
| PICC line removed within 2 weeks | 1 | 0 | 0 | 0/1 (0, 97.5) | 0 | 0 | 0 |
| PICC line removed within 1 month | 0 | 1 | 5 | 0/6 (0, 45.9) | 0 | 0 | 0 |
| PICC line removed after 1 month | 0 | 1 | 2 | 0/3 (0, 70.8) | 0 | 0 | 0 |
| Symptomatic PE after PICC line removed | 0/5 | 0/6 | 0/13 | 0/24 (0, 14.2) | 0/2 | 0/1 | 0/1 |

Table 3: Management Strategy Post UE Superficial Vein Thrombosis & Symptomatic PE.

| PICC Removed | Days treated | Anticoagulation | Cause of death |
|--------------|--------------|-----------------|---|
| 24 h | 11 | Prophylactic | Nasopharyngeal carcinoma of head and neck with extensive intracranial extension |
| | 22 | Therapeutic | MRSA bacteremia |
| | 137 | Therapeutic | Pneumonia, stroke |
| 1 week | 9 | Prophylactic | Lymphoma, sepsis, |
| 2 weeks | 9 | Therapeutic | Acute myeloid leukemia |
| 1 month | no treatment | no treatment | Septicemia |

Table 4: Adjudication of Deaths in patients with PICC-related UEDVT.

| PICC Removed | Days treated | Anticoagulation | Cause of death |
|--------------|--------------|-----------------|--|
| 24 hours | 11 | Prophylactic | Subarachnoid hemorrhage |
| 24 hours | 3 | Therapeutic | Full cardiac arrest |
| 1 week | no treatment | no treatment | Acute myeloid leukemia, septic shock, GI bleed, |
| | no treatment | no treatment | End stage liver disease/cirrhosis, GI bleed, sepsis, acidosis, |

Table 5: Adjudication of Deaths in patients with PICC-related SVT.

Removal of the PICC line within 24 hours of diagnosis of UEDVT or UESVT appeared safe.

The incidence of symptomatic PE as a complication of UEDVT is approximately 9 to 12%, of which less than one percent results in fatal PE [26-28]. The overall incidence of PICC associated UEDV has been reported to be from 0 to 56% due to the heterogeneity of study conditions [26]. However, the overall incidence of PICC associated symptomatic venous thrombosis is most commonly reported at 2 to 7% [24].

The 2012 (without changes from the 2016 update) American College of Chest Physicians guidelines suggest that for patients with UEDVT associated with an indwelling central venous catheter, the catheter should not be removed if it is functional and there is an ongoing need for the catheter [25]. In this case, anticoagulation is recommended as long as the catheter remains in place [25]. If the catheter is removed, the recommended duration of anticoagulation treatment after removal is 3 months over a shorter period [25].

Another common strategy is to prescribe anticoagulation to patients prior to catheter removal after the diagnosis of PICC-associated UEDVT. However, the common recommendation for removal of central catheters with confirmed thrombosis after 3 to 5 days of anticoagulation treatment is based on observational data in the neonatal population due to high incidence of patent foramen ovale [29,30].

It is important to note that the recommendations by the American College of Chest Physicians are based on moderate to low quality of evidence and further research is likely to have an important impact on the confidence of recommendations.

Our study has several limitations. First, the low incidence of PE after PICC line removal might be explained by the low incidence of patients with active cancer, 25.9% in our study group; as the

estimated incidence of symptomatic PE is likely between 15 to 25% in this population. Another interesting finding is that more than half of the patients within our study had either prophylactic therapy or treatment with anticoagulants before the diagnosis of PICC associated venous thrombosis, however, in this study we did not account for the duration of pharmacologic prophylaxis or treatment previous to PICC placement. Our primary outcome was limited to symptomatic PE after PICC diagnosis and removal.

Unfortunately, the sample size of this single institutional retrospective study provides inadequate power for definitive conclusions. No attempt to control for confounding variables using multivariable analysis was possible. The small sample size raises the possibility of study patient and treatment selection biases. However, through recent search of the literature, we have found no previously published studies that address this very common and important clinical dilemma. Our preliminary study may inform larger more definitive trials going forward.

In summary, because no symptomatic pulmonary embolism event was identified regardless of timing of line removal or treatment strategy following diagnosis of PICC-associated DVT; this finding is hypothesis generating for immediate PICC line removal following diagnosis without specific prescription of anticoagulation. The optimal approach to timing of the removal of the line in the setting of PICC associated venous thrombosis should be evaluated in a prospective study.

Acknowledgement

We acknowledge the contribution of Matthew Bird in the collection of data and Donald Harrison for database management.

Author Contribution

SM Wasan participated in the design of the study, analyzed the data, wrote the manuscript and guided the project. N Feland participated in the analysis of data, adjudication of events and deaths and review of manuscript. OL Esponda participated in the design of the study, collected and analyzed the data and wrote

the manuscript. JL Mathew participated in the design of the study, collected and analyzed the data and reviewed the manuscript. WJ Smith participated in the design of the study collected the data and reviewed the manuscript.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

References

1. Margey R, Schainfeld RM (2011) Upper Extremity Deep Vein Thrombosis: The Oft-forgotten Cousin of Venous Thromboembolic Disease. *Current Treatment Options in Cardiovascular Medicine* 13: 146-158.
2. Rathbun SW, Stoner JA, Whitsett TL (2011) Treatment of upper-extremity deep vein thrombosis. *Journal of Thrombosis and Haemostasis: JTH* 9: 1924-1930.
3. Marshall PS, Cain H (2010) Upper extremity deep vein thrombosis. *Clinics in Chest Medicine* 31: 783-797.
4. Grant JD, Stevens SM, Woller SC, Lee EW, Kee ST, et al. (2012) Diagnosis and management of upper extremity deep-vein thrombosis in adults. *Thrombosis and Haemostasis* 108: 1097-1108.
5. Prandoni P, Bernardi E (1999) Upper extremity deep vein thrombosis. *Current Opinion in Pulmonary Medicine* 5: 222-226.
6. Levy MM, Albuquerque F, Pfeifer JD (2012) Low incidence of pulmonary embolism associated with upper-extremity deep venous thrombosis. *Annals of Vascular Surgery* 26: 964-972.
7. Lee JA, Zierler BK, Zierler RE (2012) The risk factors and clinical outcomes of upper extremity deep vein thrombosis. *Vascular and Endovascular Surgery* 46: 139-144.
8. Hyman GS, Cardenas DD (2002) Upper-extremity deep vein thrombosis associated with peripherally inserted central catheters in acute spinal cord injury: a report of 2 cases. *Archives of Physical Medicine and Rehabilitation* 83: 1313-1316.
9. Aw A, Carrier M, Kocerginski J, McDiarmid S, Tay J (2012) Incidence and predictive factors of symptomatic thrombosis related to peripherally inserted central catheters in chemotherapy patients. *Thrombosis Research* 130: 323-326.
10. Ong B, Gibbs H, Catchpole I, Hetherington R, Harper J (2006) Peripherally inserted central catheters and upper extremity deep vein thrombosis. *Australasian Radiology* 50: 451-454.
11. Fletcher JJ, Stetler W, Wilson TJ (2011) The clinical significance of peripherally inserted central venous catheter-related deep vein thrombosis. *Neurocritical Care* 15: 454-460.
12. Chopra V, Anand S, Hickner A, Buist M, Rogers MA, et al. (2013) Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. *Lancet* 382: 311-325.
13. Liem TK, Yanit KE, Moseley SE, Landry GJ, DeLoughery TG, et al. (2012) Peripherally inserted central catheter usage patterns and associated symptomatic upper extremity venous thrombosis. *Journal of Vascular Surgery* 55: 761-767.
14. Schimp VL, Munkarah AR, Morris RT, Deppe G, Malone J (2003) Upper extremity deep vein thrombosis associated with indwelling peripheral venous catheters in gynecology oncology patients. *Gynecologic Oncology* 89: 301-305.
15. Lobo BL, Vaidean G, Broyles J, Reaves AB, Shorr RI (2009) Risk of venous thromboembolism in hospitalized patients with peripherally inserted central catheters. *Journal of Hospital Medicine*. 4: 417-422.
16. Grove JR, Pevec WC (2000) Venous thrombosis related to peripherally inserted central catheters. *Journal of Vascular and Interventional Radiology* 11: 837-840.
17. Allen AW, Megargell JL, Brown DB, Lynch FC, Singh H, et al. (2000) Venous thrombosis associated with the placement of peripherally inserted central catheters. *Journal of Vascular and Interventional Radiology* 11: 1309-1314.
18. Yi XL, Chen J, Li J, Feng L, Wang Y, et al. (2013) Risk factors associated with PICC-related upper extremity venous thrombosis in cancer patients. *Journal of Clinical Nursing* 23: 837-843.
19. Martin C, Viviand X, Saux P, Gouin F (1999) Upper-extremity deep vein thrombosis after central venous catheterization via the axillary vein. *Critical Care Medicine* 27: 2626-2629.
20. Abdullah BJ, Mohammad N, Sangkar JV, Abd Aziz YF, Gan GG, et al. (2005) Incidence of upper limb venous thrombosis associated with peripherally inserted central catheters (PICC). *The British Journal of Radiology* 78: 596-600.
21. Marnejon T, Angelo D, Abu Abdou A, Gemmel D (2012) Risk factors for upper extremity venous thrombosis associated with peripherally inserted central venous catheters. *The Journal of Vascular Access* 13: 231-238.
22. Kovacs MJ, Kahn SR, Rodger M, Anderson DR, Andreou R, et al. (2007) A pilot study of central venous catheter survival in cancer patients using low-molecular-weight heparin (dalteparin) and warfarin without catheter removal for the treatment of upper extremity deep vein thrombosis (The Catheter Study). *Journal of Thrombosis and Haemostasis* 5: 1650-1653.
23. King MM, Rasnake MS, Rodriguez RG, Riley NJ, Stamm JA (2006) Peripherally inserted central venous catheter-associated thrombosis: retrospective analysis of clinical risk factors in adult patients. *Southern Medical Journal* 99: 1073-1077.
24. Major KM, Bulic S, Rowe VL, Patel K, Weaver FA (2008) Internal jugular, subclavian, and axillary deep venous thrombosis and the risk of pulmonary embolism. *Vascular* 16: 73-79.
25. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, et al. (2012) Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, (9th edn.), American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141: 419-494.
26. Paauw JD, Borders H, Ingalls N, Boomstra S, Lambke S, et al. (2008) The incidence of PICC line-associated thrombosis with and without the use of prophylactic anticoagulants. *Journal of Parenteral and Enteral Nutrition* 32: 443-447.
27. Marschang P (2012) Deep Vein Thrombosis of the Arms. In: Cheng G, editor. *Deep Vein Thrombosis*. InTech; pp: 129-142.
28. Murray J, Precious E, Alikhan R (2013) Catheter-related thrombosis in cancer patients. *British Journal of Haematology* 162: 748-757.
29. Monagle P, Chan AK, Goldenberg NA, Ichord RN, Journeycake JM, et al. (2012) Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, (9th edn.), American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141: 737-801.
30. Filippi L, Palermo L, Pezzati M, Dani C, Matteini M, et al. (2004) Paradoxical embolism in a preterm infant. *Developmental Medicine and Child Neurology* 46: 713-716.