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Peripherally inserted central catheter–related thrombosis rate in modern vascular access era—when insertion technique matters: A systematic review and meta-analysis

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Abstract

Background: Technical factors at the moment of catheter insertion might have a role in peripherally inserted central catheter–related thrombotic risk. We performed a systematic review and meta-analysis to define the actual rate of peripherally inserted central catheter–related symptomatic deep vein thrombosis in patients in whom catheter insertion was performed according to ultrasound guidance, appropriate catheter size choice, and proper verification of tip location.

Methods: We searched Medline, Embase, and Cochrane Library. Only prospective observational studies published in peer-reviewed journals after 2010 up to November 2018 reporting peripherally inserted central catheter–related deep vein thrombosis rate were included. All studies were of adult patients who underwent peripherally inserted central catheter insertion. Results were restricted to those studies which included in their methods ultrasound guidance for venipuncture, catheter tip location, and a catheter size selection strategy. Random-effect meta-analyses and *arcsine* transformation for binomial data were performed to pool deep vein thrombosis weighted frequencies.

Results: Of the 1441 studies identified, 15 studies involving 5420 patients and 5914 peripherally inserted central catheters fulfilled our inclusion criteria. The weighted frequency of peripherally inserted central catheter–related deep vein thrombosis was 2.4% (95% confidence interval = 1.5–3.3) and remained low in oncologic patients (2.2%, 95% confidence interval = 0.6–3.9). Thrombotic rate was higher in onco-hematologic patients (5.9%, 95% confidence interval = 1.2–10). Considerable heterogeneity ($I^2 = 74.9$) was observed and all studies were considered at high risk of attrition bias.

Conclusions: A proper technique is crucial at the moment of peripherally inserted central catheter insertion. Peripherally inserted central catheter–related deep vein thrombosis rate appears to be low when evidence-based technical factors are taken into consideration during the insertion procedure.

Keywords

Catheterization, central venous, catheterization, peripheral, peripherally inserted central catheter line catheterization, upper extremity deep vein thrombosis, venous thrombosis

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Introduction

Peripherally inserted central catheters (PICCs) represent common devices for reliable administration of intravenous therapy in different medical settings. Their use has become a routine part of the management of oncologic and non-oncologic patients, for the administration of chemotherapy, antimicrobial therapy, total parenteral nutrition, and blood sampling.[1–4]

In cancer and non-cancer patients, PICCs' use has been increasing steadily over the last 15 years thanks to some important intrinsic features: avoidance of central venous catheter–related procedural complications (pneumothorax, hemorrhage, hemothorax, etc.), ease of insertion, ease of transition from hospital to intermediate care settings and home for intermittent chemotherapy, and perceived safety and cost-effectiveness compared with other central venous access devices.[5] Furthermore, the implementation of nurse-based PICC teams has led to a proliferation of these devices in many settings.[6,7]

Despite all these advantages, in the last few years, PICCs have been criticized because of a prohibitive risk of deep vein thrombosis (DVT).[8–10] Since DVT can lead to serious consequences, resulting in catheter removal, interruptions in treatment, and acute, life-threatening events such as pulmonary embolism and post-thrombotic syndrome,[11] guidelines recommend caution in the use of PICCs in high-risk settings such as critical care or oncology.[12] However, PICC-related DVT rates are extremely variable, ranging from 0% to 71.9%, due to heterogeneity in study settings in terms of thrombosis definition, diagnostic techniques, and whether symptomatic or asymptomatic thrombotic events are used as the measured variable.[9,13–17] Furthermore, technical factors during the insertion phase might influence the incidence of PICC-related DVT. A low vein to catheter diameter ratio and smaller catheters are suggested in order to limit catheter impact on vein flow reduction and subsequent thrombosis predisposition.[18–22] Furthermore, central lines tip location seems to affect thrombotic rates, with the atrio-caval junction being the site associated with the lowest risk of thrombotic events.[23–25] Furthermore, in recent years, PICC-related complications have been reduced by the adoption of bundles of evidenced-based interventions (i.e. ultrasound-guided vein puncture, micro-introducers, novel materials, sutureless securement devices, healthcare professionals training).[17,26–28]

Therefore, we performed a systematic review and meta-analysis of the scientific literature in order to assess PICCs-related thrombotic rate in modern vascular access era. Our objective was to define the actual rate of PICC-related symptomatic DVT in patients in whom catheter insertion was performed according to state of art recommendations aimed at DVT minimization, namely ultrasound guidance, appropriate catheter size choice, and proper verification of tip location.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was performed in accordance with PRISMA guidelines.[29] The review was registered with the international prospective register of systematic reviews (PROSPERO registration number, CRD42018092996).

A systematic search of three electronic databases, Medline, Embase, and Cochrane Central Register of Controlled Trials, was performed with the assistance of a medical search librarian. Only studies between January 2010 and August 2018 were included. We opted arbitrarily for this time window, to limit results to newly published studies, in consideration of relatively recent advances in the understanding of technical factors related to PICC-associated thrombosis. We performed serial literature searches for English and non-English articles between August 2018 and November 2018, to seek for further evidences. Duplicated articles were filtered through automated functions and then manually searched. The search strategy combined MeSH terms and Boolean logic with free text terms including "PICC," "peripherally inserted central catheter," "central venous access," "thrombosis," thrombotic," "thromboembolism." The full strategy is available as Supplemental Appendix.

Only articles published in peer-reviewed journals were included. We limited results to prospective studies only. Pediatric populations were excluded (younger than 18 years). We excluded articles reporting rates of asymptomatic thrombosis, arbitrarily deciding to limit our results to clinically relevant events, namely symptomatic DVT. Results were restricted to those studies which included in their methods ultrasound guidance for venipuncture, catheter tip location strategies and catheter size selection according to either vein diameter assessment, or any multimodal strategy to reduce thrombotic risk, or the systematic use of small catheters (4FR catheters).

The primary outcome was the occurrence of PICC-related symptomatic deep venous thrombosis. Two investigators (P.B. and G. Vil.) independently screened titles and abstracts produced by the search and identified potentially relevant articles. Full-text articles identified as relevant were assessed against the eligibility criteria. In case of disagreements, these were resolved in discussion with a third author (F.P.). Two authors (P.B. and G. Vil.) independently extracted data from individual studies and entered information into a pre-designed data collection adapted from the Cochrane Collaboration. Data on study characteristics, number of patients, study population, indication for PICC insertion, PICC size, number of DVT, tip location modality, catheter size choice criteria, and pharmacologic DVT prophylaxis were independently extracted by two different authors (P.B. and G. Vil.), according to pre-specified criteria. In case of

disagreements, these were resolved in discussion with a third author (F.P.). Study authors were contacted in case of missing data. The adjusted k statistic addressed inter-rater agreement regarding eligibility. All the authors conducted independent searches to check for further evidence before the final editing of the article.

Data analysis

Since we aimed to include observational studies investigating the occurrence of DVT in patients with PICC, appropriate tools for non-comparative observational studies were adopted for appraisal. To assess the quality of reporting of the included studies, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was used.[30] We found no established tool to assess the risk of bias of non-comparative studies investigating the occurrence of rare adverse events. We followed the methodology developed by Mantarro and colleagues to conduct a meta-analysis of the risk of cardiotoxicity after trastuzumab treatment for breast cancer.[31] These authors assessed the risk of bias in the included studies according to the following key domains: representativeness of the exposed cohort (lack of generalizability bias), retrospective or prospective analysis and source of data (record bias: not used in this review since we included only prospective studies), withdrawals and dropouts (attrition bias), length of period of observation (detection bias), and relevance and definition of measured outcome (reporting bias). Each study was eligible for a maximum of two stars per evaluation criterion, up to a total of eight stars. Studies assigned 6–8 points were considered as high quality, 4–5 as medium quality, and 1–3 as low quality. The full strategy for quality assessment is available as Supplemental Appendix.

We analyzed the rate of PICC-related DVT as the number of patients with DVT events over the total number of patients with PICC in the studies. Since we expected that some studies reported on the number of DVT events per catheter rather than per patient, we extracted per-patient data when available and used per-catheter data otherwise.

We used the Freeman–Tukey *arcsine* transformation for binomial data to pool weighted frequencies in meta-analyses.[32] We performed subgroup analysis according to the type of patient population (oncologic patients, onco-hematologic patients, mixed population), patient setting (inpatients vs outpatients), and whether tip location verification was intra-procedural or post-procedural. We performed the DerSimonian and Laird random-effect model using the inverse variance weight method, which considers the within-study variation and between-study heterogeneity. The I^2 statistic was used to describe the variation across studies due to heterogeneity. We defined the level of heterogeneity as low, moderate, and high corresponding to values of 25%, 50%, and 75%, respectively. Finally, we performed leave-one-out meta-analyses to explore the effect of individual studies on the pooled estimates. All analyses were performed with STATA (version 14.0, StataCorp).

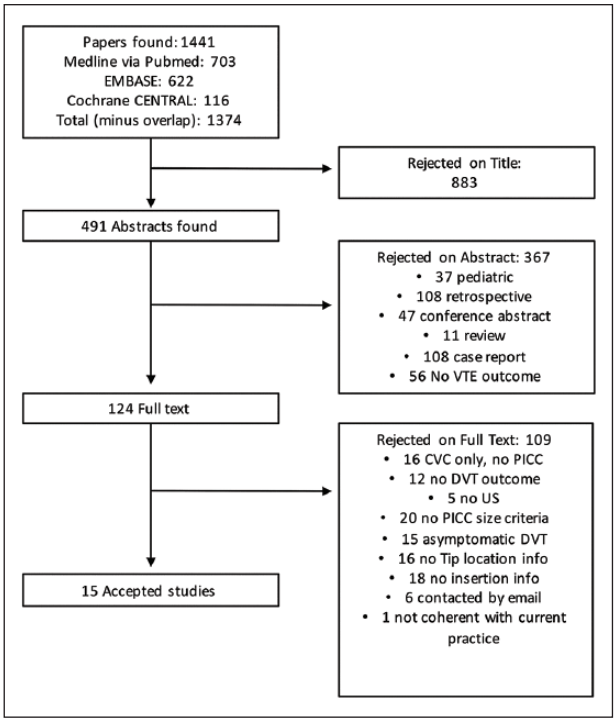

Figure 1. Flowchart and study selection.
CVC: central venous catheter; VTE: venous thromboembolism; DVT: deep venous thrombosis.

Results

The search identified 1441 articles (Figure 1). After removal of duplicates and assessment for eligibility, only 23 findings were identified as potentially relevant. All the authors conducted an independent search on Medline checking for further evidence, and two authors explored all the references of the 23 studies. Neither searches yielded further relevant findings. The authors of six studies were contacted by e-mail due to lack of information about PICCs insertion technique; none of them replied and their studies were excluded. One study[33] was excluded because its results were part of another study by the same author at the same institution performed a year later on a bigger population, which was included in the analysis.[34] One study which fulfilled eligibility criteria was excluded because the majority of PICCs (90%) had been inserted at or below the cubital fossa without ultrasound guidance, which does not represent standard practice for PICCs insertion, and in more than 50% of the cases catheter tip was not properly located.[35]

As a result, 15 studies involving 5420 patients and 5914 PICCs were included in the final analysis (Table 1).

Table 1. General characteristics of included studies.

Author	Location	Study type	Study population	Primary reasons for PICC insertion	Setting	Total patients (n)	Total PICCs (n)	DVT events (n (% of events/ total PICCs))	DVT diagnosis	DVT prophylaxis at the time of insertion (n (%))
Bellesi et al.[36]	Rome (Italy)	PC	Hematology	Chemo, hydration, ATB, other	Inpatients	57	60	3 (5)	US	NR
Bertoglio et al.[37]	Genoa (Italy)	PC	Oncology	Chemo, nutrition	Outpatients	291	291	34 (11.7)	US	NR
Cornillon et al.[38]	St-Priest-en-Jarez (France)	PC	Hematology	Chemo, hydration, ATB, other	Outpatients	37	37	3 (8.1)	US	NR
Cotogni et al.[34]	Turin (Italy)	PC	Oncology	Chemo, nutrition	Outpatients	250	269	3 (1.1)	US	NR
DeLemos et al.[39]	Sacramento (USA)	PC	Neuro-ICU	Hydration, ATB, other	Inpatients	33	33	1 (3)	US	Yes
Dupont et al.[40]	Paris (France)	PC	Cystic fibrosis, bronchiectasis	ATB	Mixed	117	174	4 (2.2)	US	NR
Evans et al.[41]	Utah (USA)	PC	In-hospital	Variable	Inpatients	1879	2014	60 (2.9)	US	966 (48)
Evans et al.[42]	Utah (USA)	PC	In-hospital	Variable	Inpatients	1758	1827	35 (1.9)	US	800 (44)
Kang et al.[43]	Beijing (China)	PC	Oncology	Chemo, ATB, nutrition	Mixed	477	477	9 (1.9)	US	NR
Mermis et al.[44]	Kansas City (USA)	PC	Cystic fibrosis	ATB	Inpatients	61	117	4 (3.4)	US	65 (56)
Pittiruti et al.[45]	Rome (Italy)	RCT	Oncology	Chemo	Outpatients	180	180	1 (0.5)	US	NR
Sharp et al.[46]	Adelaide (Australia)	PC	Oncology, variable	Chemo, ATB, others	Mixed	136	136	4 (2.9)	US	52 (38)
Tian et al.[47]	Shenzhen (China)	PC	Oncology	Chemo	Mixed	161	165	1 (0.6)	US	NR
Zerla et al.[48]	Melegnano (Italy)	PC	Oncology, variable	Variable	Mixed	30	30	0 (0)	NR	NR
Liu et al.[49]	Nanjing (China)	RCT	Oncology	Chemo	Mixed	104	104	2 (1.92)	US	9 (8.6)

PICC: peripherally inserted central catheter; PC: prospective cohort study; ICU: intensive care unit; RCT: randomized controlled trial; Chemo: chemotherapy; ATB: antibiotics; DVT: deep vein thrombosis; NR: not reported; US: ultrasound.

Eligible studies varied in size from 30 to 1758 patie nts.[34,36–49] All studies were prospective observational studies except two, which were randomized controlled trials on safety of three different types of PICCs and handgrip exercise impact on DVT rate, respectively.[45,49] One study had been carried out over a 3-year period, but a change in practice had been adopted in the last year of observation to minimize catheter size and number of lumens in order to reduce thrombotic complications; only thrombosis rates following this change of practice were included.[42] Inter-rater agreement of abstracting was almost perfect (k = 0.81).

In eight studies, PICCs were inserted in oncologic or onco-hematologic patients undergoing chemotherapy,[34,36–38,43,45,47,49] while in seven studies, indication for PICC insertion was variable, including antibiotic therapy, hydration, and parenteral nutrition.[42,39–41,44,46,48] In 14 studies, DVT was confirmed by ultrasonography,[34,36–47,49] while in one study, no thrombotic events were reported and authors did not specify any potential diagnostic modality.[48] Five studies included inpatie nts,[36,39,41,42,44] four studies included outpatients,[34,37,38,45] while the remaining studies were performed on a mixed population (Table 1).[40,43,46–48,49]

Studies greatly differed as to criteria used to choose catheter size. A vein to catheter ratio of three is suggested in order to minimize thrombotic complications.[18] Only 4 out of 14 studies adopted the aforementioned criteria for catheter size selection.[34,37,43,45] A full description of catheter size selection criteria is reported in Table 2.

Studies also differed as to timing and modality of tip location confirmation (Table 2). Post-procedural tip location control can lead to an increased number of primary misplacements, which can be easily avoided if tip location is performed during the procedure. In six (42%) studies, tip location control was intra-procedural,[37,38,40,45–47] while in seven studies, it was performed after catheter insertion by means of chest X-Rays.[36,39,41–43,48,49] In two studies, tip location was either intra-procedural or post-procedural.[33,44] Intra-procedural tip location was verified by fluoroscopy in three studies,[38,40,46] intracavitary electrocardiography (ECG) in one study,[45] and variable (either ECG or fluoroscopy) in one study.[37] In one study, immediate post-procedural chest X-Rays with catheter guidewire still in situ were performed, with the chance to reposition catheters in case of misplacement.[47]

The inclusion criteria for study selection limited the heterogeneity between studies in terms of study design. One study was judged of high quality.[37] Eight studies were of medium quality,[34,36,38,43,45–47,49] while six studies were of low quality.[42,39–41,44,48] Despite acceptable overall quality, very few studies observed a predefined follow-up[37,46,49] and loss to follow-up was reported in two studies only but it was unacceptably high.[46,49] In all the other studies, no statement on missing data was provided. As a result, we considered all studies at high risk of attrition bias. The results can be found in detail in the Supplemental Appendix (Table 1S).

Across 15 studies involving 5420 patients and 5914 PICCs, 164 PICC-related thrombotic events were reported. Since in some studies more than one PICC was inserted for a single patient, we expressed the thrombotic rate as the number of thrombotic events over the total number of PICC catheters.

Figure 2 shows the percentage of catheter-related thrombotic events observed in each study and the weighted summary proportions of thrombotic events along with 95% confidence intervals (CIs). Overall, the weighted frequency of PICC-related DVT was 2.4% (95% CI = 1.5–3.3). Heterogeneity was large ($I^2 = 74.7\%$), apparently due to two studies in onco-hematologic patients and one in oncologic patients.[36–38]

In subgroup analyses, thrombotic rate was 5.9% (95% CI = 1.2–10) in onco-hematologic patients, 2.2% (95% CI = 0.6–3.9) in oncologic patients and 2.4% (95% CI = 1.9–2.9) in patients representative of a mixed population (Figure 2). These differences across groups were not statistically significant (p = 0.34), possibly due to the small number of studies in each subgroup. Similar thrombotic event rates were also found in subgroups of studies in which tip location was either intra-procedural (3.4%, 95% CI = 1–5.8), post-procedural (2.3%, 95% CI = 1.8–2.9), or mixed (1.4, 95% CI = 0.2–2.6), p = 0.23 (Figure 1S in Supplemental Appendix). When patient setting was considered, thrombotic events occurred in 2.5% (95% CI = 1.8–3.3) of patients admitted to hospital, 4.3% (95% CI = 0.8–7.8) of outpatients and 1.5% (95% CI = 0.8–2.3) in a mixed population (Figure 2S in Supplemental Appendix). These differences did not reach statistical significance (p = 0.08).

To evaluate the robustness of the results, we performed a leave-one-out analysis by iteratively removing one study at a time and recalculating the weighted frequency of PICC-related DVT. Overall and oncological subgroup heterogeneities were reduced from 74.7% to 51.6% and from 85% to 0%, respectively, when the study by Bertoglio and colleagues was removed. Furthermore, this exclusion significantly reduced the overall PICC-related DVT rate from 2.4 (95% CI = 1.5–3.3) to 1.9 (95% CI = 1.2–2.5) (Figure 3S in Supplemental Appendix). All other exclusions did not affect results.

Discussion

Deep venous thrombosis is the most common and clinically relevant noninfectious complication associated with PICCs, as it can lead to catheter removal, treatment failure, and life-threatening events such as pulmonary embolism and post-thrombotic syndrome.[11] Furthermore, technical factors at the moment of catheter insertion might have a role in PICC-related thrombotic risk. In our meta-analysis of 15 studies, we found a low rate of symptomatic PICC-related DVT, when a criterion for catheter size selection was adopted and catheter tip location control was verified.

Table 2. Technical aspects of included studies.

Author	Tip location	Catheter size criteria	PICCs size, n (%)	Comments
Bellesi et al.[36]	Post-procedural	Only 4FR catheters inserted	4FR, 60 (100)	Study on patients undergoing autologous stem cell transplantation
Bertoglio et al.[37]	Intra-procedural	Vein to PICC ratio $\geqslant 3$	4FR, 73 (25); 5FR, 218 (75)	Mostly 5FR PICCs (75%)
Cornillon et al.[38]	Intra-procedural	60% of vein diameter	NR	Study on patients after allogenic stem cell transplantation
Cotogni et al.[34]	Variable	Vein to PICC ratio $\geqslant 3$	NR	Mostly 4FR catheters (84%)
DeLemos et al.[39]	Post-procedural	Brachial or basilic vein selected on the basis of the suitability of the site; catheter selection for each patient based on recommended guidelines for appropriate catheter gauge, vessel lumen diameter	NR	Neuro-ICU patients; non-paretic arms and use of small, single-lumen catheters in patients at high risk for upper extremity DVT
Dupont et al.[40]	Intra-procedural	4FR and 5FR catheters to best match vein diameter	4FR, 103 (59); 5FR, 71 (41)	–
Evans et al.[41]	Post-procedural	Diameter of at least 5 mm for a 6FR catheter; catheter size selection as a multidisciplinary decision; choice of the vein predefined according to site and minimum size for the intended catheter	4FR, 338 (16.8); 5FR, 1516 (75.3); 6FR, 160 (7.9)	Increasing DVT rate with increasing catheter size
Evans et al.[42]	Post-procedural	Only 4FR single catheter or 5FR double/triple catheter inserted; the study followed a change in practice aimed at minimizing catheter size and number of lumens in order to reduce thrombotic complications	4FR, 470 (25.7); 5FR, 1357 (74.2)	Only PICC data following change in practice included. No 6FR catheters inserted; more 4FR catheters inserted in respect to previous years.
Kang et al.[43]	Post-procedural	Vein to PICC ratio $\geqslant 3$	4FR, 477 (100)	Body mass index > 25 as a risk factor for complications; nearly 40% of PICCs inserted without ultrasound
Mermis et al.[44]	Variable	The study followed a quality improvement initiative to foster 4FR PICC insertion and to reduce PICCs caliper in order to reduce DVT rate	4FR, 77 (65.8); 5FR, 29 (24.8); 6FR, 8 (6.8)	Mostly 4FR catheters inserted (65%); DVT rate increasing with increasing catheter size
Pittiruti et al.[45]	Intra-procedural	Vein to PICC ratio $\geqslant 3$; only 4FR catheters	4FR, 180 (100)	ISP protocol[26] for catheter insertion; study interrupted because of three cases of catheter ruptures
Sharp et al.[46]	Intra-procedural	Largest vein chosen for PICC insertion	4FR, 100 (74); 5FR, 30 (22); 6FR, 6 (4)	Mostly 4FR catheters; 45% catheter to vein ratio as the optimal cut-off to reduce the risk of VTE
Tian et al.[47]	Intra-procedural	Only 4FR catheters inserted	4FR, 165 (100)	Education program to minimize catheter-related complications
Zerla et al.[48]	Post-procedural	Only 4FR catheters; vein diameter > 4 mm	4FR, 30 (100)	Study on PICC securement by subcutaneously anchored stabilization devices
Liu et al.[49]	Post-procedural	Only 4FR catheters	4FR, 104 (100)	RCT on handgrip exercise impact on PICC-related DVT

PICC: peripherally inserted central catheter; FR: French; DVT: deep vein thrombosis; ICU: intensive care unit; NR: not reported; ISP: safe insertion protocol; VTE: venous thromboembolism; RCT: randomized controlled trial.

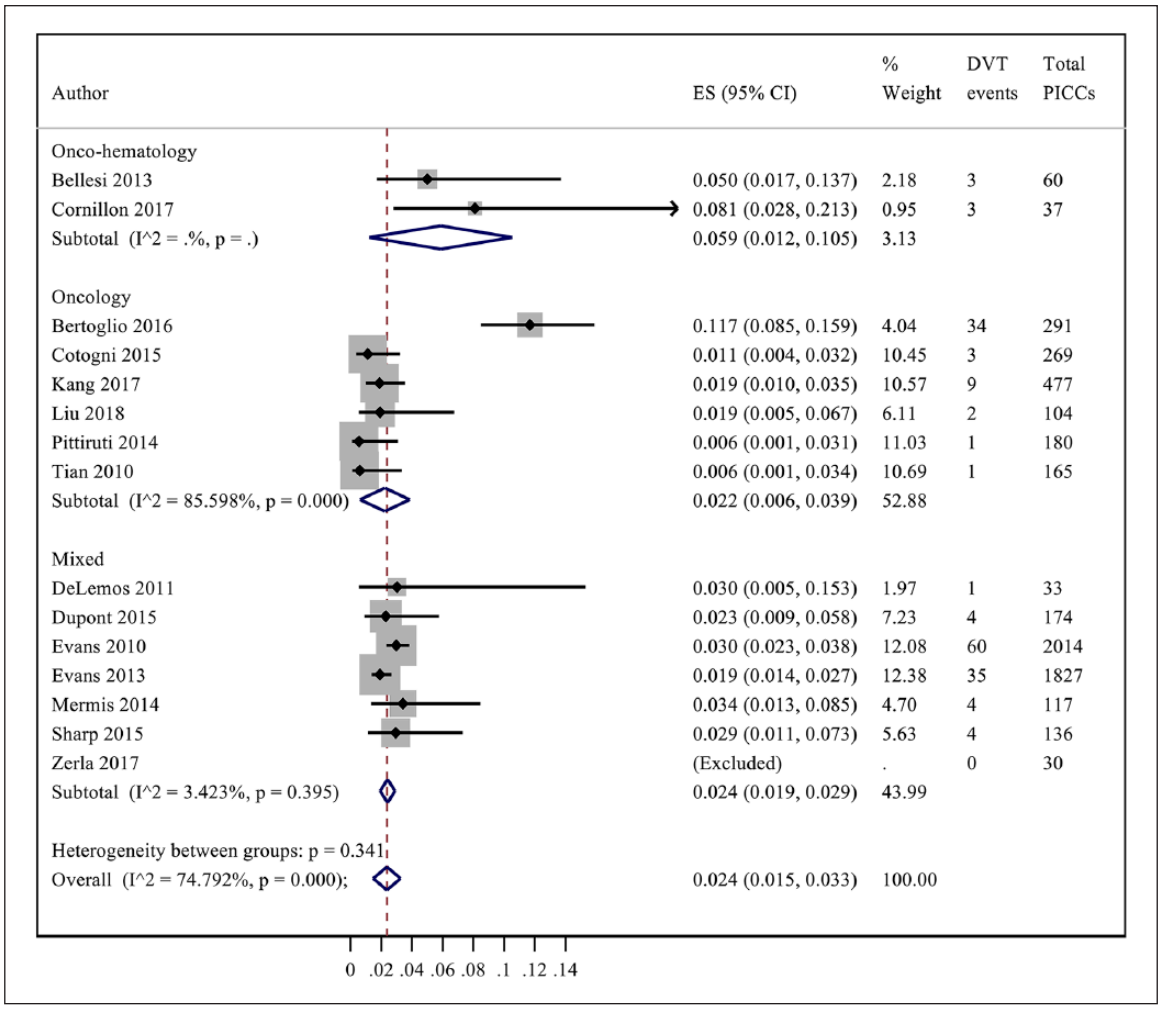

Figure 2. Forest plot showing weighted frequencies of PICC-related deep vein thrombosis rate.
Random-effect meta-analysis for PICC-related deep vein thrombosis rate and subgroup stratification by diagnosis. DVT: deep vein thrombosis; PICC: peripherally inserted central catheter.

Rates did not differ and remained low despite the setting in which PICCs had been inserted, namely inpatients, outpatients, or patients in a mixed setting, and regardless of whether tip location verification had been either intra-procedural or post-procedural. Onco-hematologic patients seemed to show the highest rates of PICC-related DVT, but this difference did not reach statistical significance, probably due to the low number of studies included in this subgroup. Furthermore, thrombotic rate was significantly reduced when the study by Bertoglio and colleagues was excluded in the analysis. In their study, the majority of PICCs were 5FR catheters, which may only partially explain the high DVT rate reported.

Thrombotic rates observed in our meta-analysis are lower than previously reported by Chopra et al.[9] In their meta-analysis a high frequency of PICC-related DVT was reported, especially in critically ill and intensive care patients. However, included studies differed according to thrombosis detection (symptomatic vs asymptomatic DVT), insertion strategies (ultrasound-guided vs blind vein puncture), and intra-procedural tip location verification (not reported in many studies), which might partially explain these differences. Furthermore, catheter size choice criteria were not reported for study selection. In view of these technical considerations, their methodologically robust results might be difficult to interpret according to the most recent recommendations.

Several elements can explain the observed differences between the two studies. First, we a priori decided to limit our research to prospective studies only. PICC thrombosis detection represents a difficult outcome to be ascertained and retrospective studies are often based on data extraction from electronic records not specifically created for this purpose. Selection bias, misclassification, and poor outcome assessment represent important issues which can impair true risk detection.[50]

Second, we focused exclusively on symptomatic thrombotic events. Despite being more frequent than symptomatic

events, the clinical relevance of asymptomatic thrombosis is not clear. The incidence of asymptomatic thrombosis may be overestimated by ultrasonography, as some images may be erroneously interpreted as DVT due to fibroblastic sleeve. It is noteworthy that in terms of clinical outcome (morbidity and mortality), PICC-related thrombosis, even if symptomatic, is less severe than centrally inserted central catheters. Furthermore, compared with lower extremity DVT, upper extremities DVT (UEDVT) has a lower risk of embolism to the pulmonary vasculature.[51] Similarly, catheter-related UEDVT seems associated with a low risk of post-thrombotic syndrome.[52]

Technical factors might play an important role in PICC-related thrombotic risk. In particular, catheter size in relation to vein diameter and tip location represent two important factors which can influence thrombotic rates. As a result, these two elements play a crucial role in strategies aimed at minimizing thrombotic risk.[17,26] In our meta-analysis, we only selected studies where criteria for catheter size choice had been followed and proper methods for tip location verification had been adopted. We observed a large heterogeneity as to size selection criteria. Despite this, the adoption of a specific criterion can be perceived as a higher effort in terms of thrombotic risk reduction. Proper catheter tip location at atrio-caval junction has been suggested in order to reduce thrombotic complications.[24,25] We selected only those articles where tip location had been verified and this aspect could have played a role in the observed thrombotic rate. Tip location can be either intra-procedural or post-procedural, with the latter potentially associated with a major number of primary misplacements and potentially leading to a higher thrombotic risk. Nevertheless, in our secondary analysis, thrombotic rates remained low whether tip location verification was intra-procedural or not.

Our results should be interpreted in the context of some limitations. First, none of our studies had a comparison group which did not allow us to estimate pooled odds ratios (ORs) of PICC-related venous thromboembolism in comparison with other devices. As a result, we were only able to estimate pooled frequencies for the desired outcome. In addition, the two randomized trials included in our analysis were not designed in order to compare different insertion techniques.

Second, we used strict criteria for study selection. We a priori decided to limit our research to prospective studies published in peer-reviewed journals. We excluded all retrospective studies, conference abstracts and gray literature. Furthermore, we limited results to studies where the insertion technique was performed according to the aforementioned criteria. Finally, we arbitrarily limited our research to studies published between January 2010 and November 2018, in an effort to reflect recent advances in terms of technical development and awareness of factors related to an increase in thrombotic risk. Therefore, our results cannot be interpreted as a generalizable estimate of PICC-related thrombotic events. However, the aim of our study was to assess actual PICC-related thrombotic rates in the modern PICC era, and strict inclusion criteria were deemed necessary in order to limit confounding factors and erroneous conclusions. Nevertheless, the adoption of strict criteria in study selection could not eliminate sources of potential confounding. In this setting omission, ascertainment and measurement bias and reliability issues cannot be completely ruled out. Furthermore, other aspects besides technical factors may influence the risk of DVT (i.e. patients thrombotic risk, types of drugs given through the catheter, use of anticoagulants), and they should be taken into consideration when interpreting our data.

Third, included studies suffered in terms of methodological rigor and were at high risk of attrition bias. The majority of studies did not have a predefined follow-up, and even when present, loss to follow-up was unacceptably high. Furthermore, many studies did not report data on catheter dwell time nor on time to thrombosis occurrence, which limit conclusions on the interaction between time and thrombosis occurrence. Finally, studies greatly differed as for sample size.

Catheter size choice and proper tip location represent important technical aspects in the modern evidence-based PICCs era. A proper insertion technique cannot be ignored when evaluating the incidence and clinical impact of PICC-related complications. In our systematic review and meta-analysis of frequencies, we have demonstrated a low rate of PICC-related DVT, when evidence-based technical factors are taken into consideration during the insertion procedure.

Author contributions

P.B. designed the study, gathered data, analyzed and interpreted data, and wrote the first draft of the report. G.Vil. helped in data gathering and writing of the report. G.Vir. designed the study and did the statistical analysis. F.P. helped with study design, data interpretation, and writing of the report. S.R. helped with writing of the report. M.P. helped with data interpretation and writing of the report. A.R.D. helped with study design and writing the report.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: F.P. received support for travel expenses, hotel accommodations, and registrations to meetings from MSD, Orion Pharma, Vygon, BBraun, Medcomp, Bard, and Teleflex, and honoraria for lectures from Bard.

Ethical statement

This study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Ethical committee.

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Supplemental material

Supplemental material for this article is available online.

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