Heart & Lung 000 (2020) 1–12

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

Peripherally Inserted Central Catheter lines for Intensive Care Unit and onco-hematologic patients: A systematic review and meta-analysis

Georgios Mavrovounis, MD[a,*], Maria Mermiri, MD[a], Dimitrios G Chatzis, MD, PhD[b], Ioannis Pantazopoulos, MD, MSc, PhD[a]

[a] Department of Emergency Medicine, Faculty of Medicine, School of Health Sciences, University of Thesstaly, General University Hospital of Larissa, Mezourlo 41110, Larissa, Greece
[b] School of Medicine, European University of Cyprus, Nicosia, Cyprus, Diogenous Str 2404, Nicosia, Cyprus

ARTICLE INFO

Article History:
Received 2 April 2020
Revised 12 June 2020
Accepted 13 July 2020
Available online xxx

Keywords:
Peripherally Inserted Central Catheter
Thrombosis
Central Line Associated Bloodstream Infection
Intensive Care Unit

ABSTRACT

Background: It is unclear whether Peripherally Inserted Central Catheter (PICC) lines are associated with lower complication rates as compared to conventional Central Venous Catheters (CVCs), especially in high risk patients.
Objective: To compare Central Line Associated Bloodstream Infection (CLABSI) and catheter-related thrombosis rates in Intensive Care Unit (ICU) and onco-hematologic patients with PICC lines and CVCs.
Methods: We systematically reviewed the PubMed, Cochrane and Google Scholar databases to identify relevant studies. Study quality was evaluated using appropriate assessment tools and the pooled odds ratio (OR) and confidence interval (CI) were calculated. Sensitivity analyses were performed based on meta-analysis method, type of study and prophylaxis implementation.
Results: Thirteen studies were included in our meta-analysis. PICC lines were associated with a significantly higher rate of thrombosis in ICU [OR (95%CI): 2.58(1.80,3.70); $P_z<0.00001$] and onco-hematologic [OR (95%CI): 2.91(2.11,4.02); $P_z<0.00001$] patients. CLABSI rates with PICC lines were not significantly different in ICU patients [OR (95%CI): 1.65(0.91,2.99); $P_z= 0.1$], but significantly lower CLABSI rates were observed in onco-hematologic patients [OR (95%CI): 0.38(0.16,0.91); $P_z=0.03$]. Sensitivity analyses verified the robustness of our results.
Conclusions: PICC lines are associated with higher rates of thrombotic events. However, they might be suitable for onco-hematologic patients due to lower CLABSI rates.

CVC: Central Venous Catheter,
CLABSI: Central Line Associated Blood Stream Infection,
PICC: Peripherally Inserted Central Catheter,
ICU: Intensive Care Unit,
RCT: Randomized Controlled Trial,
NOS: Newcastle-Ottawa Scale,
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Introduction

The use of Central Venous Catheters (CVCs) is common in the everyday medical practice, as a means of vascular access, especially in the setting of critically ill patients.[1] All types of CVCs are associated with a number of important complications,[2,3] while Central Line Associated Blood Stream Infections (CLABSIs) and catheter-related thrombosis constitute the most feared of them.[4,5]

Central line thrombosis, resulting in complete or partial catheter occlusion, occurs in 14-36% of patients with long-term use of CVCs and it may be linked to an increased risk of pulmonary embolism.[6,7] Thrombotic complications are associated with longer hospital stay and increased mortality.[8] Prolonged use of CVCs is also associated with blood stream infections, even when the clinical practice guidelines of the Infectious Diseases Society of America are properly followed.[9] In line with thrombotic events, CLABSIs have also been shown to increase the length of hospital stay, cost of hospitalization and mortality.[10]

Peripherally Inserted Central Catheter (PICC) lines typically have a length of 50-60 cm and they are placed in a peripheral arm vein through palpation or under ultrasound guidance and terminate in the lower 1/3 of the superior vena cava.[11] They can be left in place for up to six months, compared to conventional CVCs which are typically used for a few days.[11] They have been increasingly utilized in recent

* Corresponding author.
E-mail address: mavrovou@uth.gr (G. Mavrovounis).

https://doi.org/10.1016/j.hrtlng.2020.07.008
0147-9563/

years due to a variety of reasons, namely easier and safer insertion and cost-effectiveness,[12] as well as decreased incidence of CLABSIs.[13]

Despite the potential benefits of PICC use, previous studies have revealed that their application entails a higher risk of thrombotic events compared to conventional CVCs, especially in critically ill patients or those suffering from hematologic malignancies.[14–16] The risk of CLABSI in hospitalized patients with PICC lines compared to those with CVCs has been reported to be similar.[17] Despite the insights provided by the aforementioned studies, the included patient populations were rather heterogenous, thus their conclusions cannot be generalized and utilized to establish evidence-based practices. In order to guide clinical decision-making and optimize patient care, it is imperative to ascertain the effects of PICC line application in patient populations with inherently high risk of thrombotic events and systematic infections, such as those hospitalized in the Intensive Care Unit (ICU) and onco-hematologic wards.[18–21]

The aim of our study is to systematically review the current literature with respect to CLABSI and catheter-related thrombosis and compare their incidence in ICU and onco-hematologic patients with PICC lines versus CVCs.

Methods

The protocol for this systematic review and meta-analysis was registered on the International Platform of Registered Systematic Review and Meta-Analysis Protocols, INPLASY (ID number: INPLASY202050043) and is available in full on https://inplasy.com/inplasy-2020-5-0043/.

Literature search

Two of the authors (M.G. and M.M.) individually performed an electronic database search of the PubMed (MEDLINE), Cochrane Library and Google Scholar databases. The search algorithm included the following terms combined with the Boolean operators “AND” and “OR”, as appropriate: “CVC”, “central venous catheter”, “central venous line”, “PICC”, “peripherally inserted central catheter”, “thrombosis”, “CLABSI”, “BSI”. Two filters were applied when available: English language and Human species. The exact search algorithms for all three databases are provided in Appendix A. To identify additional original studies, we reviewed the reference lists of the retrieved articles and any identified review articles. The last literature search was on May 12th, 2020.

Inclusion and exclusion criteria

We included: (1) Randomized Controlled Trials (RCTs) and observational studies, (2) comparing the complications (thrombosis and CLABSI) of PICC lines with those of conventional CVCs in (3) adult populations (4) hospitalized in the ICU/ Acute Care or (5) treated for hematological malignancies. We excluded studies which: (1) were performed in diverse patient populations (outpatient, pediatric/neonatal, parenteral nutrition) (2) were performed in different types of catheters and (3) explored non-relevant outcomes. (4) Abstracts, reviews and case report studies were also excluded.

Data extraction

Using a standardized data form, two independent investigators (M.G. and M.M.) performed the data extraction. We extracted the following data: First Author’s Name, Year of Publication, Type of Study, Clinical Setting in which the central line was used, Prophylactic Measures implemented, Male/Female Ratio, Age, Total/Mean/Median Days with central line in place, Number of Patients in the PICC and CVC groups and Number of CLABSI and Thrombosis Events in each group. Finally, when available, the exact Definition used for CLABSI and catheter-related thrombosis was extracted from each study. Any discrepancy between the reviewers was resolved by a third investigator (P.I.).

Definitions

PICC lines were defined as devices inserted via the brachial/basilic/cephalic vein and terminated in the superior vena cava or the right atrium. A CVC was defined as any device inserted via the internal jugular or subclavian vein and terminated in the superior vena cava or the right atrium or via the femoral vein terminating in the inferior vena cava. CLABSI and thrombosis definitions varied amongst the studies; we excluded from our analysis thrombosis cases identified by the presence of pulmonary embolism.

Quality scoring

The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Jadad Scale for RCTs.[22,23] The NOS scale is a tool for the assessment of non-randomized studies, taking into consideration the selection of study groups, their comparability and the ascertainment of the outcome of interest. Quality scoring utilizing the Jadad Scale, evaluates the method of randomization and the blinding conditions.

Statistical analysis

The comparison of CLABSI and thrombosis occurrence between the PICC and the CVC groups was done by calculating the 95% confidence interval (95% CI) and the pooled odds ratio (OR). The significance was set at $P<0.05$. The statistical significance of the OR was determined by the use of the Z test.

To estimate the statistical heterogeneity of the studies, Cochran’s Q and I^2 indices were calculated. Random effects model was applied when $I^2>50\%$ and/or $P_Q<0.10$.[24] Otherwise, the fixed effects model was used. In order to visualize and evaluate heterogeneity, L’ Abbe Plots were used.[25]

Publication bias was assessed using funnel plots and the Egger’s and Begg’s tests;[26–28] P values less than 0.05 indicate significant publication bias.

All statistical analyses were performed in Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.[29]

Subgroup and meta-regression analyses were not performed, because the number of studies included in our meta-analysis was limited. As the Cochrane handbook suggests, subgroup and meta-regression analyses with less than 10 studies rarely provide useful insight into the data.[30] Moreover, Borenstein and colleagues recommend that each covariate should at least contain ten studies.[31]

Sensitivity analyses were performed to assess the robustness of our results.[30] We looked into 3 different parameters: study type, prophylactic measures and meta-analysis models. For the study type sensitivity analysis, we removed all retrospective studies in order to only analyze high quality data from prospective cohort studies and RCTs. For the prophylactic measures sensitivity analysis, we removed studies using prophylaxis against thrombosis or CLABSI to assess whether their inclusion might have obscured our results. Finally, both random and fixed effects meta-analysis models were used to assess whether model choice affected our results.

PRISMA guidelines for reporting reviews and meta-analyses were applied (Appendix B).[32]

Results

Selection and characteristics of the included studies

Our electronic database search resulted in 779 unique articles, after removal of the duplicates. 745 of those were excluded based on their titles and/or abstracts. The full texts of the remaining 34 articles were reviewed resulting in 13 articles that fulfilled our predetermined criteria and were included in our systematic review and meta-analyses.[15,33–44] Out of those, 2 were RCTs, 5 were Observational Prospective Cohort studies and 6 were Observational Retrospective Cohort studies. The flow chart for study selection according to PRISMA guidelines is shown in Fig. 1.

ICU population

Out of 34 possibly relevant articles, 8 were identified with an ICU-derived study population. Seven of those studies compared the occurrence of catheter related thrombosis and 5 compared the occurrence of CLABSI, in patients with PICC lines versus patients with CVCs. The male to female ratio was 1.55 (1384/895). Four studies reported the total number of days with a central line, ranging from 665 to 4024 in the PICC group and 637 to 2747 in the conventional CVC group. One of the studies did not report any CLABSI events for the PICC and CVC arms and it was not included in our statistical analysis.[34] A total of 955 patients with PICC lines were included in the ICU-thrombosis analysis, with the corresponding number for CVCs being 899. For the ICU-CLABSI analysis, 811 patients with PICC lines and 800 with CVCs were included. Three studies implemented prophylactic measures against thrombosis and two studies implemented prophylactic measures against CLABSI. Appendix Table C.1 summarizes the prophylactic measures used by our included studies. Further details for each study are shown in Appendix Table C.2.

Onco-hematological population

Out of 34 possibly relevant articles, 5 were identified with an onco-hematological study population. Four studies compared the occurrence of catheter related thrombosis and 4 compared the occurrence of CLABSI, in patients with PICC lines versus patients with CVCs. The male to female ratio was 1.38 (594/430), however raw numbers were not available in one study.[40] Three studies reported the total number of days with a central line, ranging from 5920 to 48293 in the PICC group and 699-9471 in the conventional CVC group. A total of 947 patients with PICC lines were included in the onco-hematologic thrombosis analysis with the corresponding number for CVCs being 934. For the onco-hematologic CLABSI analysis, 978 patients with PICC lines and 945 with CVCs were included. Two studies implemented prophylactic measures against thrombosis and

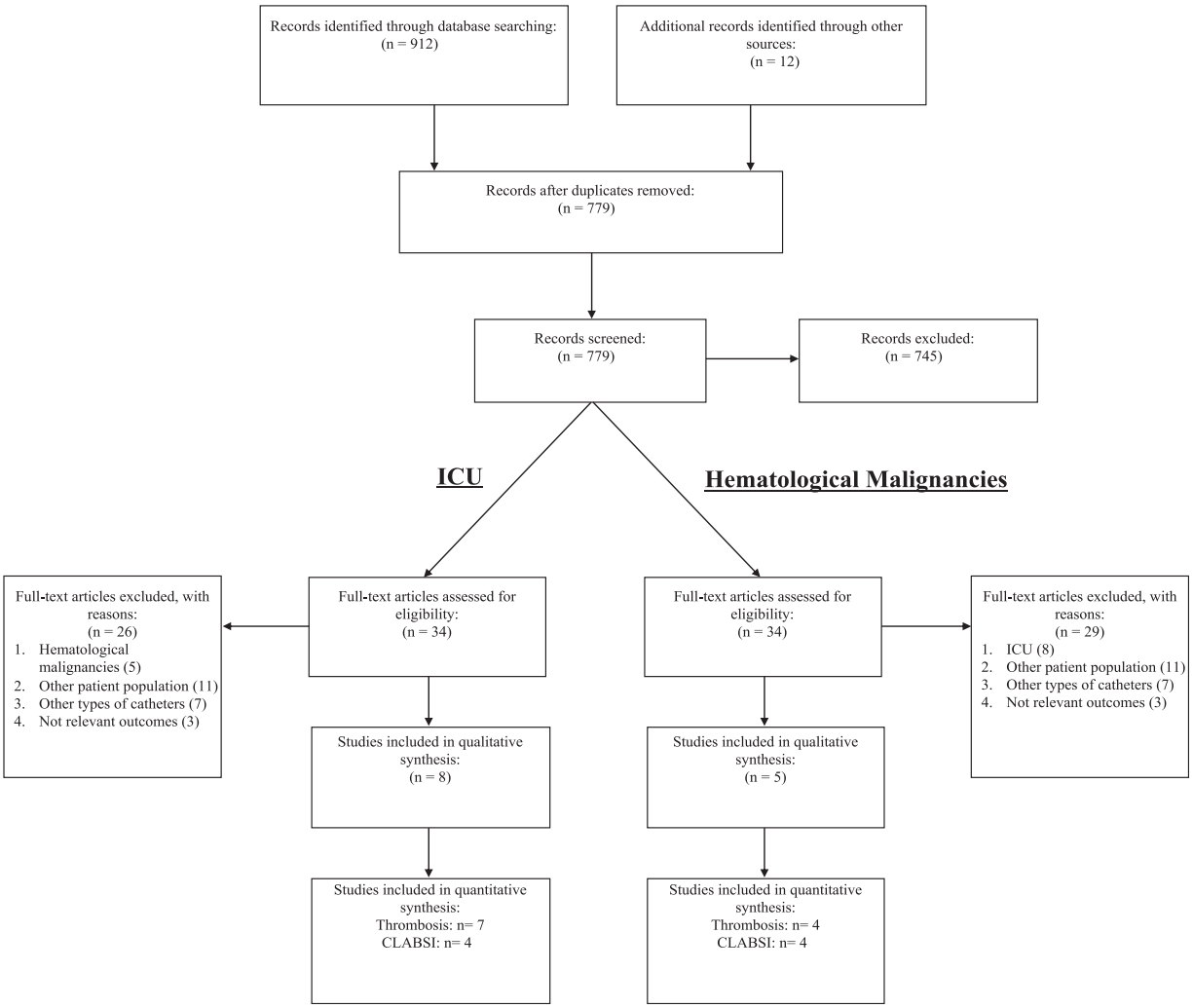

Fig. 1. Flow diagram of literature search. Flow diagram describing the process of the literature search according to the PRISMA guidelines, including the reasons for exclusion of articles.

one study implemented prophylactic measures against CLABSI. Further details for each study are shown in AppendixTable C.2.

Definitions

The included studies used a variety of definitions for CLABSI and thrombosis. Most studies defined CLABSI as positive blood culture and thrombosis as either thrombi identification on ultrasonography or thrombi identification on the catheters' tip. The exact definition provided by each study is shown in Table 1.

Publication bias and study quality

Regarding the presence of publication bias, funnel plots for all the comparisons didn't reveal significant asymmetry, as shown in Fig. 2. This was verified with the use of the Egger's and Begg's tests for each of the comparisons (AppendixTable C.3).

Study quality for both RCTs was estimated to be 3/5 (Jadad Scale); for the rest of the studies (cohort) the quality scores ranged from 6/9 to 8/9 (NOS). The exact score for each study is shown in Table 1.

ICU patients

Risk of thrombosis in ICU patients

Due to low heterogeneity indicated by the L'Abbe plot (Appendix Fig. D.1) and verified by Cochran's Q and I^2 index (I^2=40%, P_Q=0.12), the fixed effects model was used. Our analysis revealed a statistically significant difference [OR (95% CI): 2.58 (1.80, 3.70); P_z<0.00001] in the occurrence of thrombosis in ICU patients who had a PICC line placed versus those with a CVC line. The results of this analysis are presented in Fig. 3A.

Table 1
General Characteristics and Quality of the Included Studies. Table presenting type of study, patient population, CLABSI and thrombosis definitions and quality of each study included in our meta-analysis. The Newcastle-Ottawa Scale is used to assess the quality of non-randomized studies based on the selection of study groups, the comparability of the groups and the identification of the outcome of interest. The Jadad Scale is used to assess the quality of randomized controlled trials based on randomization, blinding and follow-up.

First Author - YOP	Type of study	Patient population	CLABSI definition	Catheter Related Thrombosis definition	Quality of study – Test used
Bonizzoli - 2011[14]	Prospective	ICU	Not studied	Thrombi in ultrasound	7/9 - NOS
Brandmeir - 2019[32]	RCT	Neuro-ICU	Positive blood culture/clinical and laboratory evaluation	Positive venous Doppler ultrasound	3/5 – Jadad Scale
Fletcher - 2016[33]	RCT	Neuro-ICU	Not studied	Thrombosis adherent to the catheter and involving the deep veins of the neck, upper extremity or cephalic/basilic	3/5 – Jadad Scale
Griffiths - 2002[37]	Prospective	ICU	N/A	N/A	7/9 - NOS
Malinoski - 2013[34]	Prospective	Surgical ICU (2 Centers)	Not studied	Positive flow sonography: routine screening (Centre 1)/factors and symptoms (Centre 2)	7/9 - NOS
Nolan - 2016[35]	Retrospective	ICU	Standard Center for Disease Control/National Healthcare Safety Network reporting definitions	New acute thrombus in a deep vein where a catheter was present or removed within the previous 5 days for which a venous Doppler ultrasound was obtained	8/9 - NOS
Ryu - 2019[31]	Retrospective	Acute Care -ICU *	National Healthcare Safety Network recommendations	Not studied	7/9 - NOS
Wilson - 2013[36]	Retrospective	Neuro-ICU	Identification of the same bacteria cultured from the line as well as from one or more blood cultures not drawn from the line	Event that prompted duplex ultrasonography of the ipsilateral extremity/neck in which an acute, proximal large vein thrombosis was confirmed	8/9 - NOS
Cortelezzia - 2003[39]	Prospective	Hematological malignancies	Not studied	Ultrasound or spiral CT scan visualization of an intravascular thrombus	7/9 - NOS
Fracchiola - 2017[38]	Retrospective	Hematological malignancies	N/A	N/A	6/9 - NOS
Refaei - 2016[40]	Retrospective	Hematological malignancies (leukemia)	Positive blood culture with evidence of colonized catheter tip	Formation of thrombus in the vein or connected vein of the inserted catheter as confirmed by imaging/as well as non-catheter-related VTE such as pulmonary embolism, lower extremity DVT, or thrombosis in other venous systems **	7/9 - NOS
Sakai – 2014[42]	Retrospective	Hematological malignancies	Infectious Disease Society of America (IDSA) Clinical Practice Guidelines	Not studied	8/9 - NOS
Worth - 2008[41]	Prospective	Hematological malignancies	CLABSI was defined as removal of a CVC because CLABSI was suspected by the treating clinician	Thrombosis was defined as clinically identified occlusion of ≥1 lumen of CVC	7/9 - NOS

Abbreviations. YOP: Year of Publication, CLABSI: Central Line Associated Bloodstream Infection, ICU: Intensive Care Unit, NOS: Newcastle – Ottawa Scale RCT: Randomized Controlled Trial, CT: Computed Tomography, N/A: Not Available, VTE: Venous Thromboembolism, DVT: Deep Vein Thrombosis, CVC: Central Venous Catheter
* A small percentage of catheters (4.5%), not enough to alter the results of the meta-analysis, were placed in General Wards.
**Patients diagnosed with thrombosis due to an event of non-catheter related VTE (Pulmonary Embolism, lower extremity DVT, thrombosis in other venous systems) were excluded from further analysis.

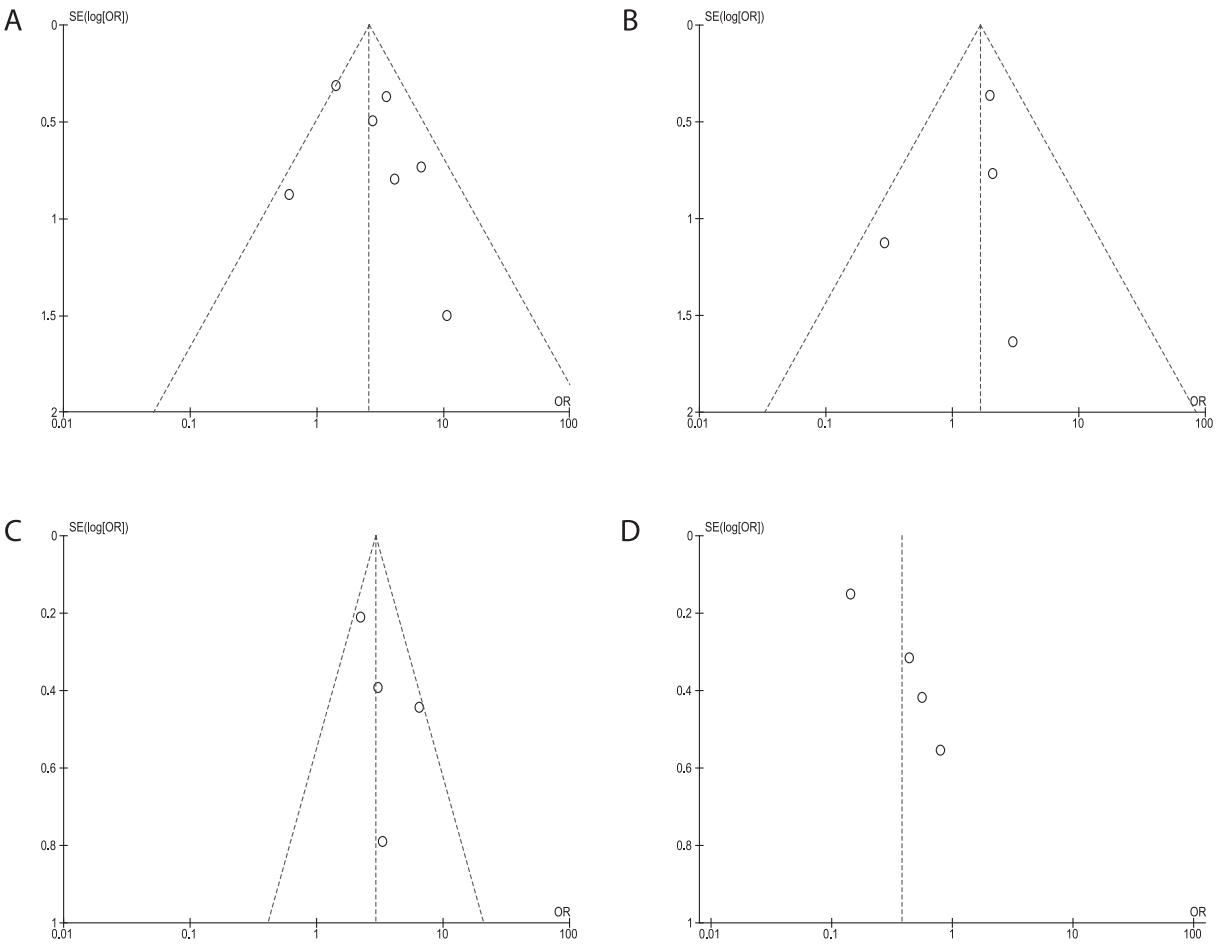

Fig. 2. Funnel plots assessing for publication bias. A. Catheter-related thrombosis in the ICU group, B. CLABSI in the ICU group, C. Catheter-related thrombosis in the Onco-hematological group, D. CLABSI in the Onco-hematological group

Risk of CLABSI in ICU patients

Due to low heterogeneity indicated by the L'Abbe plot (Appendix D.2) and verified by Cochran's Q and I^2 index (I^2=0%, P_Q=0.41), the fixed effects model was used. Our analysis didn't reveal a statistically significant difference [OR (95% CI): 1.65 (0.91, 2.99); P_z=0.1] in the occurrence of CLABSI in ICU patients who had a PICC line placed versus those with a CVC line. The results of this analysis are presented in Fig. 3B.

Onco-hematologic patients

Risk of thrombosis in onco-hematologic patients

Due to low heterogeneity indicated by the L'Abbe plot (Appendix D.3) and verified by Cochran's Q and I^2 index (I^2=39%, P_Q=0.18), the fixed effects model was used. Our analysis revealed a statistically significant difference [OR (95% CI): 2.91 (2.11, 4.02); P_z<0.00001] in the occurrence of thrombosis in onco-hematologic patients who had a PICC line placed versus those with a CVC line. The results of this analysis are presented in Fig. 3C.

Risk of CLABSI in onco-hematologic patients

Due to high heterogeneity indicated by the L'Abbe plot (Appendix D.4) and verified by Cochran's Q and I^2 index (I^2=87%, P_Q<0.0001), the random effects model was used. Based on the L'Abbe plot, the high heterogeneity value can be attributed to one individual study.[40] We were not able to further investigate the source of high heterogeneity, due to the fact that subgroup analysis was not feasible, owing to the limited number of studies. Our analysis revealed a statistically significant difference [OR (95% CI): 0.38 (0.16, 0.91); P_z=0.03] in the occurrence of CLABSI in onco-hematologic patients who had a PICC line placed versus those with a CVC line. The results of this analysis are presented in Fig. 3D.

Sensitivity analysis

Sensitivity analyses based on meta-analysis model choice, study type and prophylactic measures did not reveal considerable differences, proving the robustness of our results. Table 2 summarizes the results of the sensitivity analyses.

Discussion

Study overview

The aim of the current meta-analysis was to assess the incidence of catheter-related thrombosis and CLABSI in ICU and onco-hematologic patients with PICC lines compared to those with conventional CVCs.

Our study demonstrates that the use of PICC lines is associated with a statistically significant augmented risk of catheter-related thrombosis in both ICU and onco-hematologic patients. Moreover, the use of PICC lines is linked to a statistically significant lower risk of CLABSI in onco-hematologic patients, although no statistically significant difference was found in ICU patients.

Sensitivity analysis further proved the consistency of our results, however subgroup and meta-regression analyses could not have been performed, due to the limited number of studies included.

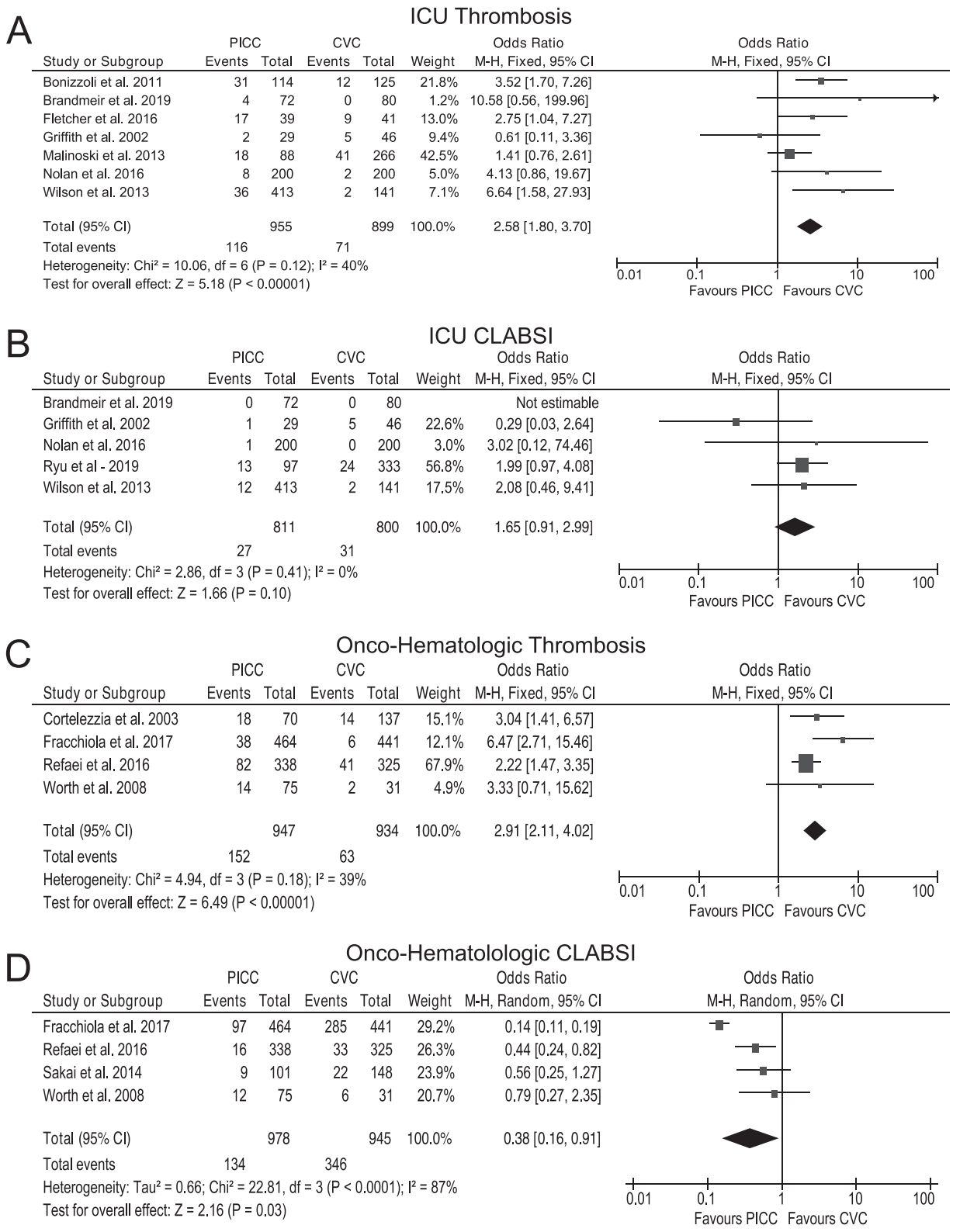

Fig. 3. Forest plots, Forest plots showing the odds ratio for catheter related thrombosis and CLABSI with PICCs versus CVCs. A. Catheter-related thrombosis in the ICU group, B. CLABSI in the ICU group, C. Catheter-related thrombosis in the Onco-hematological group, D. CLABSI in the Onco-hematological group

Population-specific Central Catheter Complications

Patients at high risk of developing thrombotic events and systematic infections are more prone to developing catheter-related complications.[14]

There are several risk factors associated with thrombotic events which seem to be more prevalent in ICU patients, including vasopressors administration, mechanical ventilation, pharmacologic sedation and end-stage renal failure.[18,45] Similarly, patients suffering from hematological malignancies have an increased susceptibility to

Table 2
Sensitivity analysis. Table presenting the results of sensitivity analyses regarding the utilized meta-analysis model, the study type and the implementation of prophylactic measures.

	Meta-analysis Model Used (Fixed-Effects/Random-Effects)		Study Type (Only RCTs and Prospective)	Absence of Prophylactic Measures
	Fixed-Effects Model	Random-Effects Model		
ICU Thrombosis	**OR: 2.58 (CI: 1.80, 3.70), P<0.00001**	OR: 2.57 (CI: 1.48, 4.48), P=0.0009	OR: 2.17 (CI: 1.47, 3.20), P<0.0001	OR: 2.60 (CI: 1.33, 5.11), P=0.005
	I2 = 40% *	I2 = 40%	I2 = 43% (Fixed-Effects Model)	I2 = 25% (Fixed-Effects Model)
ICU CLABSI	**OR: 1.65 (CI: 0.91, 2.99), P=0.10**	OR: 1.76 (CI: 0.96, 3.23), P=0.07	Not applicable**	OR: 0.92 (CI: 0.14, 6.14), P=0.94
	I2 = 0% *	I2 = 0%		I2 = 52% (Random-Effects Model)
Onco-hematologic Thrombosis	**OR: 2.91 (CI: 2.11, 4.02), P<0.00001**	OR: 3.13 (CI: 1.91, 5.14), P<0.00001	OR: 3.11 (CI: 1.55, 6.23), P=0.001	OR: 3.53 (CI: 1.24, 10.09), P=0.02
	I2 = 39% *	I2 = 39%	I2 = 0% (Fixed-Effects Model)	I2 = 79% (Random-Effects Model)
Onco-hematologic CLABSI	OR: 0.22 (CI: 0.17, 0.28), P<0.00001	**OR: 0.38 (CI: 0.16, 0.91), P=0.03**	Not applicable**	OR: 0.31 (CI: 0.12, 0.80), P=0.02
	I2 = 87%	**I2 = 87% ***		I2 = 88% (Random-Effects Model)

Abbreviations. RCT: Randomized Controlled Trial, ICU: Intensive Care Unit, OR: Odds Ratio, CLABSI: Central Line Associated Bloodstream Infection
*The models used in the primary analysis are indicated with bold.
**Only 1 study available.

thrombotic events, since any type of cancer has been shown to induce a hypercoagulable state.[16,19] The susceptibility of ICU and oncologic patients to PICC line associated thrombosis has been shown in a meta-analysis by Chopra et al.,[14] however their results only concerned non-comparative studies.

ICU patients are at an increased risk of developing CLABSIs, with high incidence of infections caused by multi-drug resistant bacteria.[21] Likewise, patients with hematological malignancies are prone to systematic infections, not only because the disease itself carries an inherent risk,[20] but also due to chemotherapy-induced neutropenia.[46] In a meta-analysis by Chopra et al.,[17] CLABSI occurrence in hospitalized patients did not seem to be affected by the type of catheter used, though no subgroup analysis was conducted based on the study population.

The selection of our study population was based on the established knowledge that ICU and onco-hematologic patients have a higher risk of catheter-related thrombosis and CLABSI. Moreover, there is a lack of published data concerning the development of catheter-related thrombosis and CLABSI in those patient groups.

Clinical implications

Central catheter-related thrombosis

The connection between PICC lines use and catheter-related thrombosis has been established in several studies. However, the precise incidence of thrombosis related to PICC lines varies amongst studies, ranging between 0.3 and 28.3%. Risk factors associated with thrombosis are narrow catheter lumens and malignant diseases.[47] The smaller diameter of the veins in which PICC lines are inserted has been hypothesized to contribute to the higher incidence of thrombosis, however, the whole concept needs to be further elucidated.[48]

RCTs have shown that the occurrence of catheter-related thrombosis in ICU patients with PICC lines is significantly higher than in patients with conventional CVCs.[34,35] Various prospective cohort studies demonstrated similar results in onco-hematologic patients.[41,43]

The aforementioned findings are confirmed by our meta-analysis; patients with PICC lines in both selected patient populations (ICU, onco-hematological units) were more likely to develop thrombotic events. As a consequence, conventional CVCs may constitute a safer choice in patients highly susceptible to thrombosis.[49,50] Alternatively, these patients might benefit from more intense antithrombotic prophylaxis or the use of anti-thrombogenic PICC lines.[51]

Central Line Associated Bloodstream Infections

Previous studies have shown conflicting results concerning the association between PICC lines and the development of CLABSI, with evidence suggesting both lower and higher incidence of bloodstream infections when compared with conventional CVCs.[40,52] When first introduced into clinical practice, it was hypothesized that PICC lines would lower CLABSI incidence since their longer lumen would not allow for microbe migration to the tip of the catheter through the skin entry site.[17] However, migration of bacteria from the hub to the tip of the catheter due to personnel handling, remains an important route of infection in long-term catheters such as long-dwelling PICC lines. This is considered to be the cause of the apparent data discrepancy observed in the literature.[53]

According to our results, PICC lines are associated with a lower risk of CLABSI in hospitalized patients with hematological malignancies. Therefore, PICC lines are a sensible choice when the need for central venous access arises in these patients.

On the other hand, our analysis suggests that the use of PICC lines is not associated with a statistically significant incidence as compared to conventional CVCs in the ICU, in terms of CLABSI occurrence. This, as mentioned above, may be attributed to the fact that ICU patients are often colonized with multidrug resistant bacteria and fungi.

Limitations

Our study has some limitations, mainly derived from the design of the included studies, that must be taken into consideration when interpreting our results. Most importantly, the studies in our meta-analysis did not use universal definitions for catheter related thrombosis and CLABSI. As a result, some events that could have been included were possibly overlooked. In addition to that, our meta-analysis only included specific patient populations (ICU, onco-hematologic) with certain clinical and pathophysiological characteristics such as immobility, hypercoagulability, immunosuppression, hospitalization etc. As a consequence, our results only concern those patients and should not be generalized to other patient populations. Another important limitation is that a variety of preventing methods against CLABSI and thrombosis were used in the studies included. Moreover, we only included studies written in English. As a result, we may have excluded possibly relevant studies written in other languages. Finally, it is important to mention that the number of studies on onco-hematologic patients included were limited and concrete conclusions cannot be drawn.

Conclusion

Our study supports the use of PICC lines in onco-hematologic patients under antithrombotic prophylaxis, since they are associated with less risk of CLABSI but higher risk of thrombosis compared to CVCs. Their use in the ICU is limited due to the significantly higher risk of thrombosis without decreasing the CLABSI rate compared to conventional CVCs.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of Competing Interest

None

Appendix A. Algorithms used for database search

Algorithms used for database search:

PubMed	((CVC) OR (Central Venous Catheter) OR (Central Venous Line)) AND (PICC OR (Peripherally inserted central catheter)) AND (thrombosis OR CLABSI OR BSI))	Filters Used: Studies in humans, English language
Google Scholar	With all of the words: "CVC" OR "Central Venous Catheter|Line" OR "PICC" OR "Peripherally inserted central catheter" With at least one of the words: "thrombosis" "CLABSI" "BSI"	Filters Used: Search in title, English language, No patents/citations
Cochrane	(CVC OR "Central Venous Catheter" OR "central venous line") AND (PICC OR "Peripherally inserted central catheter") AND (thrombosis OR CLABSI OR BSI)	Filters Used: Search in title, abstract, keywords

Appendix B. PRISMA checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	-
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions	7

(*continued*)

		at each stage, ideally with a flow diagram.	
Study characteristics	18		
For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8		
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

Appendix C

Tables C.1–C.3

Table C.1
Prophylactic measures against Thrombosis and CLABSI. Table presenting the prophylactic measures implemented in each study.

First Author - YOP	Thrombosis Prophylaxis	CLABSI Prophylaxis
Bonizzoli - 2011[14]	Dalteparin, 5000 IU/day	NS
Brandmeir - 2019[32]	None	None
Fletcher - 2016[33]	None	None
Griffiths - 2002[37]	None	None
Malinoski - 2013[34]	SCDs Enoxaparin, 30 mg/12 hours Dalteparin, 5000 IU/day	NS
Nolan - 2016[35]	None	Antimicrobial patch
Ryu - 2019[31]	NS	Disinfected once every 7 days
Wilson - 2013[36]	SCDs Dalteparin, 5000 IU/day	None
Cortellezia - 2003[39]	Unfractionated heparin, 2500 IU/day Bolus LMWH, 3800 IU	NS
Fracchiola - 2017[38]	None	None
Refaei - 2016[40]	None	None
Sakai - 2014[42]	NS	None
Worth - 2008[41]	Heparinized saline, continuous infusion	Sterile occlusive film dressing

Abbreviations. YOP: Year of Publication, CLABSI: Central Line Associated Blood Stream Infection, IU: International Unit, NS: Not Studied, SCD: Sequential Compression Device, LMWH: Low Molecular Weight Heparin

Table C.2
Demographics and Central Line-related Characteristics of the Included Studies. Table presenting male/female ratios, age of participants, days with the line and the numbers for the studied complications for each study.

First Author - YOP	Male/Female	Age (Years)		Days with the line		Complications							
						Catheter Related Thrombosis				CLABSI			
		PICC	CVC	PICC	CVC	PICC		CVC		PICC		CVC	
						Events	Total	Events	Total	Events	Total	Events	Total
Bonizzoli - 2011[14]	144/95	54.3	58.8	Total: 4024,Mean: 35.3	Total: 2747,Mean: 22.5	31	114	12	125	Not studied	Not studied		
Brandmeir - 2019[32]	80/72	61.4	61.4	Mean: 6	Mean: 7.2	4	72	0	80	0	72	4	80
Fletcher - 2016[33]	49/31	Mean: 61	Mean: 59	Mean: 12	Mean: 11	17	39	9	41	Not studied	Not studied		
Griffiths - 2002[37]	28/24	Mean: 69	Mean: 60	Mean: 15.14	Mean: 6.38	2	29	5	46	1	29	5	46
Malinoski - 2013[34]	242/112	Mean:C1:55.78,C2:56.62	Mean:C1:55.78,C2:56.62	Total: 665	Total: 2128	18	88	41	266	Not studied	Not studied		
Nolan - 2016[35]	228/172	Mean: 63.8	Mean: 65.3	Total: 1730,Median: 5.9	Total: 637,Median: 2.4	8	200	2	200	1	200	0	200
Ryu - 2019[31]	330/100	Mean: 55.64	Mean: 55.3	Total: 2227,Median: 20, Mean: 23	Total: 2626,Median: 7, Mean: 7.9	Not studied	Not studied	13	97	24	333		
Wilson - 2013[36]	283/289	Mean: 55	Mean: 55	Median: 16	Median: 5	36	413	2	141	12	413	2	141
Total		116	955	71	899	27	811	31	800				
Cortelezzia - 2003[39]	63/63	Median: 54	Median: 54	Total: 5920	Total: 699	18	70	14	137	Not studied	Not studied		
Fracchiola - 2017[38]	1.5(PICC), 1(CVC) *	Median: 57	Median: 52	Total: 48293, Median: 76, Mean: 104	Total: 9471, Median: 19, Mean:20	38	464	6	441	97	464	285	441
Refaei - 2016[40]	386/277	Median: 55	Median: 50	Mean: 38	Mean: 98	82	338	41	325	16	338	33	325
Sakai - 2014[42]	107/62	Mean: 61	Mean: 61.5	Total: 7321Median: 53Mean: 72.4	Total: 4148Median: 25.5Mean: 28	Not studied	Not studied	9	101	22	148		
Worth - 2008[41]	38/28	Median: 56.2	Median: 56.2	Mean: 24.2	Mean: 18.8	14	75	2	31	12	75	6	31
Total		152	947	63	934	134	978	346	945				

Abbreviations. YOP: Year of Publication, CLABSI: Central Line-Associated Blood Stream Infection, PICC: Peripherally Inserted Central Catheter, CVC: Central Venous Catheter C1: Centre 1, C2: Centre 2
*Male to female ratio for the PICC and the CVC groups.

Table C.3
Egger's and Begg's test . Table presenting the results of the Egger's and Begg's test assessing for publication bias.

Analysis	Egger (P value)	Begg (P value)
ICU Thrombosis	0.424	0.881
ICU CLABSI	0.492	0.142
Onco-Hematologic Thrombosis	0.324	0.497
Onco-Hematologic CLABSI	0.09	1

Abbreviations. ICU: Intensive Care Unit, CLABSI: Central Line Associated Blood Stream Infection

Appendix D

Fig. D.1

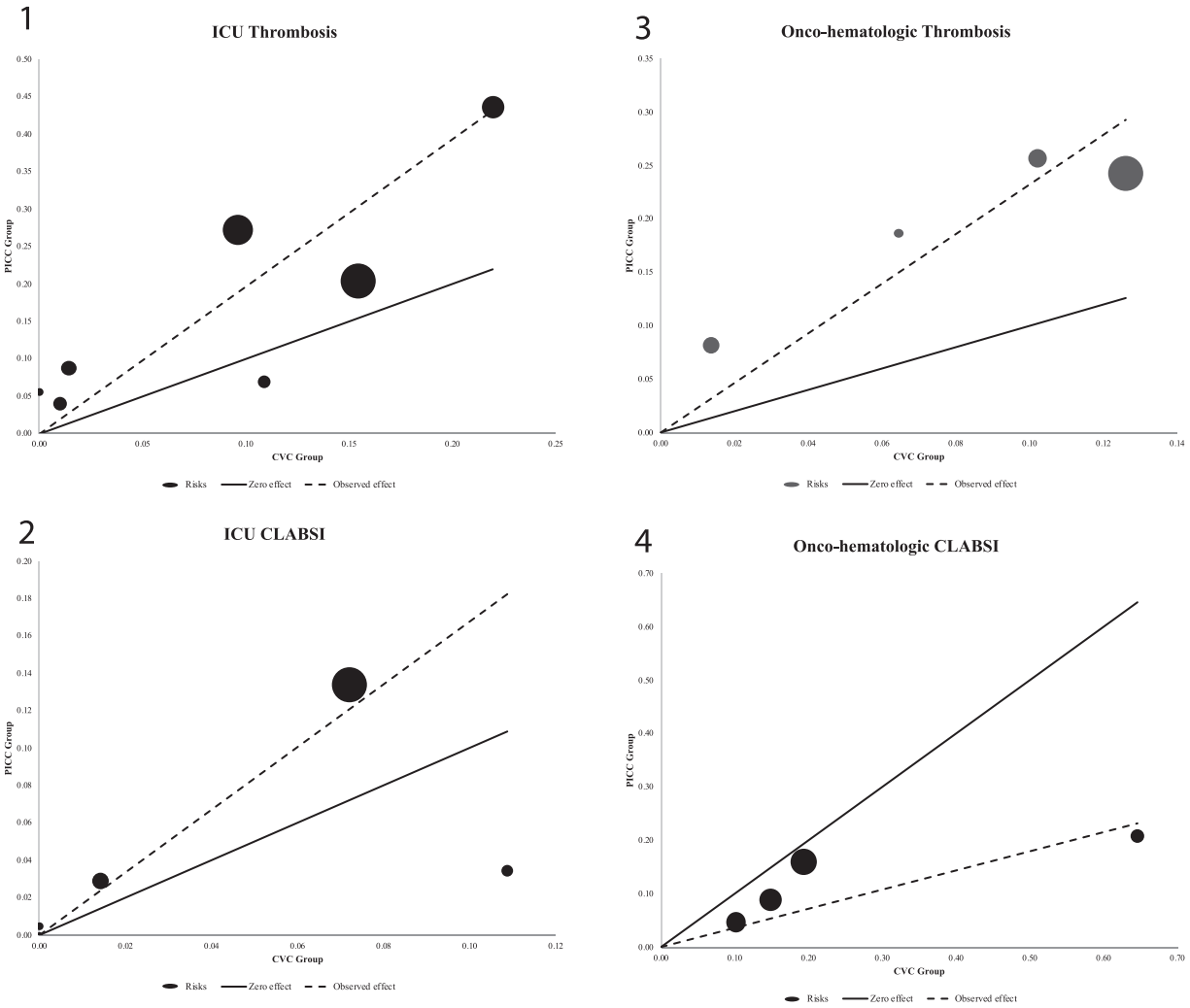

Fig. D.1. L'Abbe plots for the visualization of heterogeneity. 1. Catheter-related thrombosis in the ICU group, 2. CLABSI in the ICU group, 3. Catheter-related thrombosis in the Onco-hematologic group, 4. CLABSI in the Onco-hematologic group

References

1 Johansson E, Hammarskjöld F, Lundberg D, Arnlind MH. Advantages and disadvantages of peripherally inserted central venous catheters (PICC) compared to other central venous lines: a systematic review of the literature. *Acta Oncol Stockh Swed*. 2013;52(5):886–892. https://doi.org/10.3109/0284186X.2013.773072.

2 Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA*. 2001;286(6):700–707. https://doi.org/10.1001/jama.286.6.700.

3 O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control*. 2011;39(4 Suppl 1):S1–34. https://doi.org/10.1016/j.ajic.2011.01.003.

4 Bishop L, Dougherty L, Bodenham A, et al. Guidelines on the insertion and management of central venous access devices in adults. *Int J Lab Hematol*. 2007;29(4):261–278. https://doi.org/10.1111/j.1751-553X.2007.00931.x.

5 Kornbau C, Lee KC, Hughes GD, Firstenberg MS. Central line complications. *Int J Crit Illn Inj Sci*. 2015;5(3):170–178. https://doi.org/10.4103/2229-5151.164940.

6 Lokich JJ, Bothe A, Benotti P, Moore C. Complications and management of implanted venous access catheters. *J Clin Oncol Off J Am Soc Clin Oncol*. 1985;3(5):710–717. https://doi.org/10.1200/JCO.1985.3.5.710.

7 Monreal M, Raventos A, Lerma R, et al. Pulmonary embolism in patients with upper extremity DVT associated to venous central lines - a prospective study. *Thromb Haemost*. 1994;72(10):548–550. https://doi.org/10.1055/s-0038-1648912.

8 Polderman KH, Girbes AJ. Central venous catheter use. Part 1: mechanical complications. *Intensive Care Med*. 2002;28(1):1–17. https://doi.org/10.1007/s00134-001-1154-9.

9 Safdar N, Maki DG. Risk of catheter-related bloodstream infection with peripherally inserted central venous catheters used in hospitalized patients. *Chest*. 2005;128 (2):489–495. https://doi.org/10.1378/chest.128.2.489.

10 Haddadin Y, Regunath H. Central line associated blood stream infections (CLABSI). *StatPearls*. StatPearls Publishing; 2020. Accessed March 13, 2020; http://www.ncbi.nlm.nih.gov/books/NBK430891/.

11 Gonzalez R, Cassaro S. Percutaneous central catheter (PICC). *StatPearls*. StatPearls Publishing; 2020. Accessed February 26, 2020; http://www.ncbi.nlm.nih.gov/books/NBK459338/.

12 Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2001;32 (9):1249–1272. https://doi.org/10.1086/320001.

13 Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc*. 2006;81(9):1159–1171. https://doi.org/10.4065/81.9.1159.

14. Chopra V, Anand S, Hickner A, et al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. *Lancet*. 2013;382(9889):311–325. https://doi.org/10.1016/S0140-6736(13)60592-9.

15 Bonizzoli M, Batacchi S, Cianchi G, et al. Peripherally inserted central venous catheters and central venous catheters related thrombosis in post-critical patients. *Intensive Care Med*. 2011;37(2):284–289. https://doi.org/10.1007/s00134-010-2043-x.

16 Mosquera Orgueira A, Antelo Rodríguez B, Díaz Arias JÁ, Díaz Varela N, Bello López JL. A three-gene expression signature identifies a cluster of patients with short survival in chronic lymphocytic leukemia. *J Oncol*. 2019;2019: 9453539. https://doi.org/10.1155/2019/9453539.

17 Chopra V, O'Horo JC, Rogers MAM, Maki DG, Safdar N. The risk of bloodstream infection associated with peripherally inserted central catheters compared with central venous catheters in adults: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2013;34(9):908–918. https://doi.org/10.1086/671737.

18 Cook D, Attia J, Weaver B, McDonald E, Meade M, Crowther M. Venous thromboembolic disease: an observational study in medical-surgical intensive care unit patients. *J Crit Care*. 2000;15(4):127–132. https://doi.org/10.1053/jcrc.2000.19224.

19 Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111(10):4902–4907. https://doi.org/10.1182/blood-2007-10-116327.

20 Gedik H, Şimşek F, Kantürk A, et al. Bloodstream infections in patients with hematological malignancies: which is more fatal – cancer or resistant pathogens? *Ther Clin Risk Manag*. 2014;10:743–752. https://doi.org/10.2147/TCRM.S68450.

21 Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *JAMA*. 1995;274(8):639–644.

22 Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed March 6, 2020. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

23. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1–12. https://doi.org/10.1016/0197-2456(95)00134-4.

24 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558. https://doi.org/10.1002/sim.1186.

25 L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Ann Intern Med*. 1987;107(2):224–233. https://doi.org/10.7326/0003-4819-107-2-224.

26 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088–1101. https://doi.org/10.2307/2533446.

27 Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634. https://doi.org/10.1136/bmj.315.7109.629.

28 Mavridis D, Salanti G. How to assess publication bias: funnel plot, trim-and-fill method and selection models. *Evid Based Ment Health*. 2014;17(1):30. https://doi.org/10.1136/eb-2013-101699.

29 Review Manager (RevMan). *Copenhagen: the Nordic Cochrane Center*. The Cochrane Collaboration; 2014.

30 Higgins JPT, Thomas J. *Cochrane Handbook for Systematic Reviews of Interventions Version 6 [Updated 2019]*. The Cochrane Collaboration; 2019. Accessed May 15, 2020. Available from; www.handbook.cochrane.org.

31 Michael Borenstein. *Introduction to Meta-Analysis*. Wiley; 2009. Accessed June 9, 2020; https://www.wiley.com/en-us/Introduction+to+Meta+Analysis-p-9780470057247.

32. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLOS Med*. 2009;6: (7) e1000097. https://doi.org/10.1371/journal.pmed.1000097.

33 Ryu DY, Lee SB, Kim GW, Kim JH. A peripherally inserted central catheter is a safe and reliable alternative to short-term central venous catheter for the treatment of trauma patients. *J Trauma Inj*. 2019;32(3):150–156. https://doi.org/10.20408/jti.2019.015.

34 Brandmeir NJ, Davanzo JR, Payne R, et al. A randomized trial of complications of peripherally and centrally inserted central lines in the neuro-intensive care unit: results of the NSPVC trial. *Neurocrit Care*. 2019. https://doi.org/10.1007/s12028-019-00843-z. Published online September 25.

35 Fletcher JJ, Wilson TJ, Rajajee V, et al. A randomized trial of central venous catheter type and thrombosis in critically ill neurologic patients. *Neurocrit Care*. 2016;25 (1):20–28. https://doi.org/10.1007/s12028-016-0247-9.

36. Malinoski D, Ewing T, Bhakta A, et al. Which central venous catheters have the highest rate of catheter-associated deep venous thrombosis: a prospective analysis of 2128 catheter days in the surgical intensive care unit. *J Trauma Acute Care Surg*. 2013;74(2):454–460. https://doi.org/10.1097/TA.0b013e31827a0b2f. discussion 461-462.

37 Nolan JP, Soar J, Zideman DA, et al. European resuscitation council guidelines for resuscitation 2010 section 1. Executive summary. *Resuscitation*. 2010;81 (10):1219–1276. https://doi.org/10.1016/j.resuscitation.2010.08.021.

38 Wilson TJ, Stetler WR, Fletcher JJ. Comparison of catheter-related large vein thrombosis in centrally inserted versus peripherally inserted central venous lines in the neurological intensive care unit. *Clin Neurol Neurosurg*. 2013;115(7):879–882. https://doi.org/10.1016/j.clineuro.2012.08.025.

39. Griffiths VR, Philpot P. Peripherally inserted central catheters (PICCs): do they have a role in the care of the critically ill patient? *Intensive Crit Care Nurs*. 2002;18 (1):37–47. https://doi.org/10.1054/iccn.2002.1615.

40. Fracchiolla NS, Todisco E, Bilancia A, et al. Clinical management of peripherally inserted central catheters compared to conventional central venous catheters in patients with hematological malignancies: a large multicenter study of the REL GROUP (Rete Ematologica Lombarda - Lombardy Hematologic Network, Italy). *Am J Hematol*. 2017;92(12):E656–E659. https://doi.org/10.1002/ajh.24903.

41 Cortelezzia A, Fracchiolla NS, Maisonneuve P, et al. Central venous catheter-related complications in patients with hematological malignancies: a retrospective analysis of risk factors and prophylactic measures. *Leuk Lymphoma*. 2003;44(9):1495–1501. https://doi.org/10.3109/10428190309178770.

42 Refaei M, Fernandes B, Brandwein J, Goodyear MD, Pokhrel A, Wu C. Incidence of catheter-related thrombosis in acute leukemia patients: a comparative, retrospective study of the safety of peripherally inserted vs. centrally inserted central venous catheters. *Ann Hematol*. 2016;95(12):2057–2064. https://doi.org/10.1007/s00277-016-2798-4.

43 Worth LJ, Seymour JF, Slavin MA. Infective and thrombotic complications of central venous catheters in patients with hematological malignancy: prospective evaluation of nontunneled devices. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer*. 2009;17(7):811–818. https://doi.org/10.1007/s00520-008-0561-7.

44 Sakai T, Kohda K, Konuma Y, et al. A role for peripherally inserted central venous catheters in the prevention of catheter-related blood stream infections in patients with hematological malignancies. *Int J Hematol*. 2014;100(6):592–598. https://doi.org/10.1007/s12185-014-1677-9.

45 Shorr AF, Williams MD. Venous thromboembolism in critically ill patients. Observations from a randomized trial in sepsis. *Thromb Haemost*. 2009;101(1):139–144.

46 Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. *Cancer*. 2004;100(2):228–237. https://doi.org/10.1002/cncr.11882.

47 Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. *J Clin Oncol Off J Am Soc Clin Oncol*. 2003;21(19):3665–3675. https://doi.org/10.1200/JCO.2003.08.008.

48 Liem TK, Yanit KE, Moseley SE, et al. Peripherally inserted central catheter usage patterns and associated symptomatic upper extremity venous thrombosis. *J Vasc Surg*. 2012;55(3):761–767. https://doi.org/10.1016/j.jvs.2011.10.005.

49 Grant PJ, Greene MT, Chopra V, Bernstein SJ, Hofer TP, Flanders SA. Assessing the caprini score for risk assessment of venous thromboembolism in hospitalized medical patients. *Am J Med*. 2016;129(5):528–535. https://doi.org/10.1016/j.amjmed.2015.10.027.

50 Mulder FI, Candeloro M, Kamphuisen PW, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. *Haematologica*. 2019;104(6):1277–1287. https://doi.org/10.3324/haematol.2018.209114.

51 Ullman AJ, Bulmer AC, Dargaville TR, Rickard CM, Chopra V. Antithrombogenic peripherally inserted central catheters: overview of efficacy and safety. *Expert Rev Med Devices*. 2019;16(1):25–33. https://doi.org/10.1080/17434440.2019.1555466.

52. Al Raiy B, Fakih MG, Bryan-Nomides N, et al. Peripherally inserted central venous catheters in the acute care setting: a safe alternative to high-risk short-term central venous catheters. *Am J Infect Control*. 2010;38(2):149–153. https://doi.org/10.1016/j.ajic.2009.06.008.

53 Chopra V, Anand S, Krein SL, Chenoweth C, Saint S. Bloodstream infection, venous thrombosis, and peripherally inserted central catheters: reappraising the evidence. *Am J Med*. 2012;125(8):733–741. https://doi.org/10.1016/j.amjmed.2012.04.010.