

REVIEW ARTICLE

The incidence of asymptomatic thrombosis related to peripherally inserted central catheter in adults: A systematic review and meta-analysis People's

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Abstract

Aim: To examine the incidence and risk factors for asymptomatic peripherally inserted central catheter-related thrombosis (PICC-RT).

Design: We performed a systematic review and meta-analysis following the PRISMA guidelines.

Methods: The review was registered in PROSPERO (CRD42020186732). A systematic search of EMBASE, CINAHL, PubMed, Web of Science and Cochrane was performed from inception to 4 June 2020. Meta-analysis was performed to determine the pooled incidence of asymptomatic PICC-RT.

Results: Ten studies comprising 1591 participants with 1592 PICCs were included in this meta-analysis. The pooled incidence of asymptomatic PICC-RT in adults was 22% (95% CI, 0.17–0.29). The pooled incidence of PICC-RT in cancer patients was 19% (95% CI, 0.13–0.26). Asymptomatic PICC-RT mainly occurred in superficial veins. Most asymptomatic thrombosis occurred 3–12 days after the PICC insertion. A higher Eastern Cooperative Oncology Group score (ECOG), slower blood flow velocity and left basilic vein were independent risk factors of asymptomatic thrombosis.

KEYWORDS

asymptomatic, incidence, peripherally inserted central catheter, thrombosis

1 | INTRODUCTION

The peripherally inserted central catheter (PICC) has been widely used for various indications, such as delivering chemotherapy drugs and parenteral nutrition support (Al Hadidi, 2018; Chopra et al., 2017). PICC is cost-effective and could facilitate the management of patients and improve their quality of life (Campagna et al., 2019; Xie et al., 2017). Nonetheless, PICC could cause a series of complications including peripherally inserted central catheter-related

thrombosis (PICC-RT), catheter-related bloodstream infection and medical adhesive-related skin injury (Scrivens et al., 2020). Of these, PICC-RT is the most detrimental complication which could result in pulmonary embolism and even death (Hua et al., 2019). PICC-RT could also interrupt the intravenous treatment and increase the cost of care, bringing huge psychological burdens to the patients and economic burdens to the society (Burns & McLaren, 2009). Thus, early detection and prevention of PICC-RT have clinical and societal significance.

Pei Chen and Bingqian Zhu contributed equally to the preparation of this manuscript and should be considered as joint first authors.

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Asymptomatic PICC-RT has been a focus of current research. Asymptomatic PICC-RT refers to the appearance of PICC-RT indicated by ultrasound, without clinical symptoms such as upper limb swelling, tenderness of the catheterization site or adjacent site, elevation of skin temperature, skin cyanosis, limb sensation and dysfunction, or shoulder discomfort (Wang et al., 2020). Asymptomatic PICC-RT could develop into symptomatic thrombosis, eventually leading to complications such as infection, pulmonary embolism, post-thrombotic syndrome even death (Chopra et al., 2014). Asymptomatic PICC-RT is often ignored in clinical practice (Fallouh et al., 2015), which undoubtedly increases the risk of patients' death. Thus, more attention should be paid to asymptomatic PICC-RT.

2 | BACKGROUND

Current evidence suggests a higher incidence of asymptomatic PICC-RT than symptomatic PICC-RT. Specifically, the incidence of asymptomatic and symptomatic PICC-RT was 2.2%-58% (Pittiruti et al., 2014; Trerotola et al., 2010; Yuxiu et al., 2015) and 2%-15%, respectively (Fallouh et al., 2015). Reported risk factors of asymptomatic PICC-RT included BMI ≥ 25 , less activity, obesity and chemotherapy history (Wang et al., 2020; Yi et al., 2014; Yuxiu et al., 2015). While these studies offered important information about the incidence and risk factors of asymptomatic PICC-RT, there remains a need to synthesize findings from each study. Such an effort will provide us a holistic view of asymptomatic PICC-RT, which may enable us to provide better care for patients undergoing PICC treatment.

Prior reviews have been focused on symptomatic thrombosis (Chopra et al., 2013; Fallouh et al., 2015). For instance, Chopra et al., (2013) did a systematic and meta-analysis to compare the risk of venous thromboembolism associated with PICC versus that associated with other CVC (central venous catheter). In that review, seven studies screened for asymptomatic CVC-RT (CVC-related thrombosis); however, the incidence of asymptomatic PICC-RT was not reported. Similarly, another review only mentioned that the majority of PICC-RT was asymptomatic (Fallouh et al., 2015). Collectively, the research question remains to be answered: what is the pooled incidence and risk factors for asymptomatic PICC-RT in adults? Thus, the aim of this systematic review was to identify and analyse the incidence and risk factors for asymptomatic PICC-RT. Findings from this review will advance the understanding of asymptomatic PICC-RT and provide important evidence for the management of PICC-RT.

3 | METHODS

3.1 | Design

The protocol for this systematic review was registered in PROSPERO (CRD42020186732). This systematic review followed the guidelines

of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al., 2009).

3.2 | Search strategy

Five databases (EMBASE, CINAHL, PubMed, Web of Science and Cochrane) were searched from inception to 4 June 2020. Search terms were pilot tested so that they could capture relevant studies. The following search terms were used in each database: (a) PICC or "peripheral Catheter*" or "Peripherally Inserted Central Catheter" or "central venous catheter" or "central venous access device" or "central venous line" or CVC; (b) thromb* or "Blood Clot"; and (c) asymptomatic. The combinations of the above search terms were applied to the title/abstract/keywords. No language restriction was applied during the searching process.

3.3 | Study selection

The studies were included if the incidence or risk factors of asymptomatic PICC-RT were reported and they were conducted in adults (age ≥ 18 years old). The exclusion criteria included: (a) animal studies; (b) studies reporting symptomatic PICC-RT; (c) non-English papers; (d) conference abstracts, commentary, review and case reports. There was no restriction on study design such as case-control, cross-sectional, longitudinal cohort and randomized controlled trials (RCT).

Two reviewers independently screened the title and abstract of the articles for eligibility, followed by full-text review. Disagreements were discussed to reach a consensus. A third reviewer was consulted if there were any unresolved discrepancies between the two reviewers at any stage during the study selection process.

3.4 | Data extraction

Data extraction was performed by two reviewers independently using an electronic form. We extracted study- and participant-related characteristics including first author, year of publication, country, study design, population, sample size, total PICCs, follow-up time, age, male, BMI and diagnostic tool. We also extracted main findings including asymptomatic PICC-RT events, time of PICC-RT formation, PICC-RT characteristics and risk factors.

3.5 | Quality appraisal

Two reviewers independently assessed the quality of each study. The Joanna Briggs Institute's (JBI) critical appraisal checklist for studies reporting prevalence data was adapted for prevalence studies (Munn et al., 2015). The JBI includes 9 items, and the overall

quality of the study is evaluated from the sampling frame, study objectives, data collection and analysis method. A sample item is "Was the sample size adequate?" Each item is rated as yes, no, unclear and inapplicable.

The Cochrane Risk of Bias 2 Tool was used to assess the quality of RCTs (Sterne et al., 2019). This tool covers five domains of bias: "risk of bias arising from the randomization process," "risk of bias due to deviations from the intended interventions," "missing outcome data," "risk of bias in measurement of the outcome," "risk of bias in selection of the reported result" and "overall bias." Within each domain, assessments are conducted for one or more items, which covers different aspects of the domain or different outcomes. The risk of bias can be "Low," "High" or "Some concerns." If all domains for this result were assessed as "Low" risk, the overall bias is "Low". If at least one domain for this result was assessed as "Some concerns" but none were assessed as "High" risk, the overall bias is "Some concerns". If at least one domain was assessed as "High" risk, or if we had "Some concerns" about several domains, the overall bias is "High" risk. A third reviewer was consulted if a consensus could not be reached between the two reviewers.

3.6 | Statistical analysis

Data analysis was performed using Stata SE version 15 (StataCorp LP) and RevMan 5.3 (The Cochrane Collaboration). Mean and SD (standard deviation) or SE (standard error) were extracted for continuous variables. The incidence of asymptomatic PICC-RT from each study was extracted and presented as percentage. Logarithmic transformation was applied to the incidence estimate extracted from each study to achieve normal distribution (Barendregt et al., 2013). To obtain the pooled effect size (Odds Ratio, OR), a meta-analysis was performed by using the double arcsine transformation of proportions. The pooled incidence of PICC-RT was calculated as $OR/(1 + OR)$. Risk factors for asymptomatic PICC-RT were presented as OR with 95% confidence interval (CI). Separate subgroup analyses were performed based on the type of disease (cancer VS. non-cancer) and study design (prospective VS. RCT). Between-study heterogeneity was assessed using the I^2 index. When significant heterogeneity was detected ($I^2 > 50\%$) (Higgins et al., 2003), the random-effects model was used. Publication bias was assessed using funnel plots and the Egger test with a significance level set at $p < .10$ (Begg & Mazumdar, 1994). If publication bias was detected, the trim and fill method developed by Duval and Tweedie was used to account for publication bias (Duval & Tweedie, 2000).

3.7 | Ethics

As this study was a systematic review and meta-analysis, ethical approval was not required.

4 | RESULTS

4.1 | Study selection

The results of the literature search are shown in Figure 1. The initial search resulted in 650 articles. After excluding duplicates, the titles and abstracts of 333 articles were screened for eligibility. Of these, the full text of 94 articles was screened for inclusion. A total of 10 studies were included in this review.

4.2 | Quality assessment

Five RCTs were assessed using the Cochrane Risk of Bias 2 tool, and five prospective studies were assessed using the JBI tool. All of the RCTs were rated a low risk of bias on the four domains: randomization process, deviations from intended interventions, measurement of the outcome and selection of the reported results. More details are shown in Table 1.

All of the prospective studies were unclear on the adequacy of sample size. Similarly, it was not clear if the data analysis was conducted with sufficient coverage of the identified sample. The studies were rated a low risk on the remaining of the criteria. The details are shown in Table 2.

4.3 | Characteristics of studies and participants

Study characteristics are presented in Table 3. In total, the 10 studies comprised 1575 participants with 1576 PICCs (Bonizzoli et al., 2011; Itkin et al., 2014; Liu et al., 2018; Luo et al., 2016; Periard et al., 2008; Pittiruti et al., 2014; Trerotola et al., 2010; Wang et al., 2020; Yi et al., 2014; Yuxiu et al., 2015). The individual sample size ranged from 31–332. Five studies used a prospective design, consisting of 878 patients (Bonizzoli et al., 2011; Luo et al., 2016; Wang et al., 2020; Yi et al., 2014; Yuxiu et al., 2015). Five studies were RCTs, consisting of 697 patients (Itkin et al., 2014; Liu et al., 2018; Periard et al., 2008; Pittiruti et al., 2014; Trerotola et al., 2010). The studies were conducted in China ($n = 5$), Italy ($n = 2$), the United States ($n = 2$) and Switzerland ($n = 1$). The incidence of asymptomatic PICC-RT in the individual study varied from 2.2%–58%.

Participant characteristics are presented in Table 3. Among the patients, 45.5% (726/1591) were males. The patients had solid tumour, cancer, or fibrosis and were receiving chemotherapy or intensive care. Nine studies reported the follow-up length, ranging from 21 days to 3 months (Bonizzoli et al., 2011; Itkin et al., 2014; Liu et al., 2018; Luo et al., 2016; Periard et al., 2008; Trerotola et al., 2010; Wang et al., 2020; Yi et al., 2014; Yuxiu et al., 2015). One study reported days with PICC, ranging from 2780 to 3699 days (Pittiruti et al., 2014). All of the studies detected PICC-RT using an ultrasound.

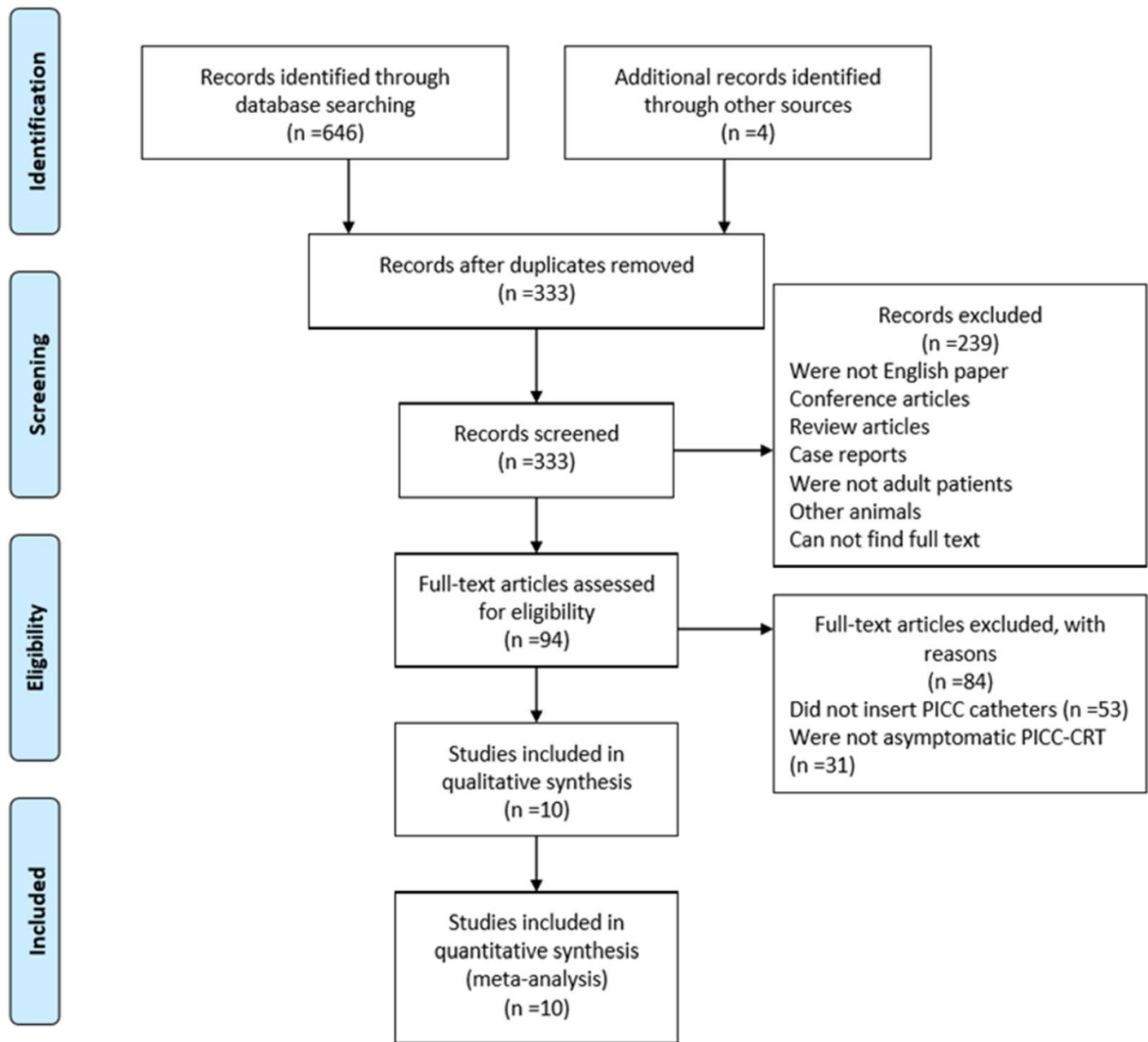


FIGURE 1 PRISMA flowchart for study selection

4.4 | Characteristics of PICC-RT and related risk factors

Characteristics of the PICC-RT are presented in Table 4. Seven studies reported the time that PICC-RT occurred (Bonizzoli et al., 2011; Liu et al., 2018; Luo et al., 2016; Periard et al., 2008; Wang et al., 2020; Yi et al., 2014; Yuxiu et al., 2015). Four of these seven studies focused on asymptomatic PICC-RT (Bonizzoli et al., 2011; Luo et al., 2016; Periard et al., 2008; Wang et al., 2020), and three of them included both asymptomatic and symptomatic PICC-RT (Liu et al., 2018; Yi et al., 2014; Yuxiu et al., 2015).

The thrombosis occurred at different times after the PICC placement. Based on the four studies (Bonizzoli et al., 2011; Luo et al., 2016; Periard et al., 2008; Wang et al., 2020) that reported asymptomatic PICC-RT, the thrombosis occurred 3 to 11.7 days after the placement.

Based on the three studies that reported asymptomatic and symptomatic PICC-RT, the thrombosis occurred 11.0 days to 12.5 days after the placement (Liu et al., 2018; Yi et al., 2014; Yuxiu et al., 2015).

Five studies further differentiated where the PICC-RT occurred (Bonizzoli et al., 2011; Luo et al., 2016; Periard et al., 2008; Wang et al., 2020; Yi et al., 2014). Four of them reported the site of asymptomatic PICC-RT (Bonizzoli et al., 2011; Luo et al., 2016; Periard et al., 2008; Wang et al., 2020). We classified PICC-RT as “superficial” if it involved the cephalic, basilic, median antebrachial, median antecubital, and accessory cephalic veins and as “deep” if the PICC-RT extended into the axillary, subclavian and internal jugular veins or was located more centrally (Chin et al., 2005; Kleinjan et al., 2014). Overall, asymptomatic PICC-RT occurred more often in the superficial vein (45.2%-98.8%) than in the deep vein (1.2%-54.8%). More details are showed in Table 4.

TABLE 1 The Cochrane Risk of Bias 2 Tool for assessing risk of bias

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Liu et al. (2018)						
Reviewer1	Low	Low	Low	Low	Low	Low
Reviewer2	Low	Low	Low	Low	Low	Low
Itkin et al. (2014)						
Reviewer1	Low	Low	Some concerns	Low	Low	Some concerns
Reviewer2	Low	Low	Some concerns	Low	Low	Some concerns
Pittiruti et al. (2014)						
Reviewer1	Low	Low	Some concerns	Low	Low	Some concerns
Reviewer2	Low	Low	Some concerns	Low	Low	Some concerns
Trerotola et al. (2010)						
Reviewer1	Low	Low	Some concerns	Low	Low	Some concerns
Reviewer2	Low	Low	Some concerns	Low	Low	Some concerns
Periard et al. (2008)						
Reviewer1	Low	Low	Low	Low	Low	Low
Reviewer2	Low	Low	Low	Low	Low	Low

Four studies (Bonizzoli et al., 2011; Wang et al., 2020; Yi et al., 2014; Yuxiu et al., 2015) examined the risk factors of asymptomatic PICC-RT. Wang et al. found that activity status measured by patient's Eastern Cooperative Oncology Group score (ECOG, OR = 2.79, $p = .000$) and slower blood flow velocity (OR 0.25, $p = .014$) were risk factors of asymptomatic PICC-RT (Wang et al., 2020). Bonizzoli et al. found that left basilic vein (OR = 1.42, $p = .019$) was a risk factor of asymptomatic PICC-RT (Bonizzoli et al., 2011). Two studies reported less activity (OR = 1.476, $p = .006$; OR = 2.11, $p = .009$) was a significant risk factor of PICC-RT (Yi et al., 2014; Yuxiu et al., 2015). In Yi et al. study, chemotherapy history was a risk factor for PICC-RT (OR = 3.19, $p = .017$) (Yi et al., 2014); however, it was not a risk factor (OR = 2.11, $p = .249$) in another study (Yuxiu et al., 2015). Yi et al. also showed that diabetes was a risk factor of asymptomatic PICC-RT (OR = 1.12, $p = .006$). Similarly, Liu et al. showed that obesity was a risk factor for PICC-RT (OR = 3.47, $p = .014$) (Yi et al., 2014; Yuxiu et al., 2015). An RCT suggested that daily hand-grip exercise for 3 weeks decreased the incidence of PICC-RT (Liu et al., 2018).

4.5 | Incidence of asymptomatic PICC-RT

Based on the random-effects model, the pooled incidence of asymptomatic PICC-RT was 22% (95% CI, 0.17%–0.29%). Subgroup analysis (Figure 2) showed that the incidence of asymptomatic PICC-RT in cancer and non-cancer patients was 19% (95% CI, 0.13–0.26) and 28% (95% CI, 0.2–0.39), respectively. The incidence of asymptomatic PICC-RT in prospective studies and RCTs was 23% (95% CI, 0.19–0.29) and 19% (95% CI, 0.11–0.33), respectively (Figure 3).

4.6 | Publication bias

Visual inspection of the forest plot suggested slight asymmetry (Figure 4). Egger's test revealed no apparent publication bias, $p = .073$, 95% CI (–8.61 to 0.47) (Figure 5).

5 | DISCUSSION

To the best of our knowledge, this current systematic review and meta-analysis were the first to quantitatively synthesize the incidence of asymptomatic PICC-RT and summarized the occurrent time, the occurrent site and risk factors of asymptomatic PICC-RT, which further expanding our knowledge in this topic area. We found that the pooled incidence of asymptomatic PICC-RT was 22%. We also found that a higher ECOG score, slower blood flow velocity and left basilic vein were risk factors of asymptomatic PICC-RT. Findings from this review provided further evidence for the prevention and management of asymptomatic PICC-RT.

In this review, the incidence of asymptomatic PICC-RT was 22%, higher than that of symptomatic PICC-RT (2%–15%) (Fallouh et al., 2015). This finding is consistent with a previous study of children in which PICC-RT was usually asymptomatic (Menendez et al., 2016). The reason for the higher incidence of asymptomatic PICC-RT may be related to the frequency of ultrasound examination. In this review, for studies reporting asymptomatic PICC-RT, weekly or monthly ultrasound examinations were performed after PICC insertion. In contrast, for studies reporting symptomatic PICC-RT, ultrasound examinations were performed only when the patients had clinical symptoms. Thus, the incidence of PICC-RT may be underestimated. Collectively, the above evidence suggests that ultrasound examination should be performed regularly. In order to save medical

TABLE 2 The Joanna Briggs Institute's critical appraisal checklist for studies reporting prevalence data

	1. Was the sample frame appropriate to address the target population?	2. Were study participants sampled in an appropriate way?	3. Was the sample size adequate?	4. Were the study patients and the setting described in detail?	5. Was the data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way for all participants?	8. Was there appropriate statistical analysis?	9. Was the response rate adequate, and if not, was the low response rate managed appropriately?
Wang et al. (2020)									
Reviewer1	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Reviewer2	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Luo et al. (2016)									
Reviewer1	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Reviewer2	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Liu et al. (2015)									
Reviewer1	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Reviewer2	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Yi et al. (2014)									
Reviewer1	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Reviewer2	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Bonizzoli et al. (2011)									
Reviewer1	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Reviewer2	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes

TABLE 3 study and participants characteristics

Author, year	Country	Study Design	Population	Sample Size, n	Total PICCs, n	Follow-up time	Age, year n (%)/mean (SD), range	Male, n (%)	BMI, kg/m ² n (%)/mean (SD)	Diagnostic Tool
Wang et al. (2020)	China	Prospective Study	Patients with cancer	127	127	6 weeks	52.7 (SD312.0)	68 (53.5)	≤25:93 (73.2%)	Colour Doppler ultrasonography
Liu et al. (2018)	China	Randomized Controlled Trial	Patients with solid cancers	104	104	3 weeks	Control group 59.3 (SD8.3) Exercisegroup1 55.8 (SD9.8) Exercisegroup2 57.7 (SD9.2)	42 (35)	NA	Colour Doppler ultrasonography
Luo et al. (2016)	China	Prospective Study	Patients with cancer	245	246	6 weeks	≤60:179 (72.8%)	135 (55.1)	≤25:184 (74.8%)	Doppler ultrasonography
Liu, (2015)	China	Double-centre Prospective Investigation	Patients with cancer	311	311	30–35 days	18–45:67 (21.5%) 46–65:183 (58.8%) >65:61 (19.7%)	111 (35.7)	<25:179 (57.6%)	Doppler ultrasonography
Yi et al. (2014)	China	Prospective Study	Patients with cancer	81	81	1 month	54.4 (SD NA) Range 22–81 years	32 (39.5)	NA	Doppler ultrasonography
Pittiruti et al. (2014)	Italy	Randomized Controlled Trial	Patients with cancer	180	180	NA PICC days: Solo valve: 56 (SD23) days PASV: 64 (SD31) days No valve: 65 (SD27) days	Solo valve: 64 (SD12.1) PASV: 61 (SD10.1) No valve: 62 (SD14.5)	65 (36.1)	NA	Doppler ultrasonography
Itkin et al. (2014)	U.S.A	Randomized Controlled Study	Adult patients	332	332	4 weeks	Nontapered PICC 53.9 (SD15.1) Reverse Tapered PICC: 53.9 (SD14.3) Range 18–90 years	154 (46.4)	NA	Doppler ultrasonography
Bonizzoli et al. (2011)	Italy	Prospective Study	patients discharged from the intensive care unit (ICU)	239 (114 for PICCs)	114	30 days	54.3 (SD1.8)	65 (57.0)	25.6 (SD0.5)	Doppler ultrasonography
Trerotola et al. (2010)	U.S.A	Randomized Controlled Trial	Patients in the Critical Care Unit	50	50	4 weeks	51.6 (SD NA) Range 18–83 years	32 (64.0)	NA	Doppler ultrasonography
Periard et al. (2008)	Switzerland	Randomized Controlled Trial	Hospitalized patients	60 (31 for PICCs)	31	3 months	66 (SD NA) Range 57–77 years	22 (71.0)	NA	Compression ultrasonography (CUS)

TABLE 4 Main research findings

Author, year	Asymptomatic PICC-RT events (n[%] of events/total PICCs)	The time of PICC-RT formation, M (SD), range	PICC-RT characteristics	Risk factor OR (95% CI) P value
Wang et al. (2020)	62 (48.8%)	Asymptomatic PICC-RT, 3 (SD NA) days, 1–33 days	80 (98.8%) were superficial, and 1 (1.2%) were deep	ECOG, 2.791 (0.08–0.76), $p = .000$ Blood flow velocity (cluster 2 versus cluster 1), 0.250 (2.01–3.87), $p = .014$
Liu et al. (2018)	30 (25.0%)	PICC-RT, 18 (56.3%) cases occurred during the second day, 5 (15.6%) cases occurred during the third day, 9 (28.1%) cases occurred during the 21 day	NA	NA
Luo et al. (2016)	62 (25.2%)	Asymptomatic PICC-RT, 3 (SD NA) days, 2–26 days	35 (56.5%) were superficial 27 (43.6%) were deep	NA
Liu, (2015)	73 (23.5%)	PICC-RT, 11.0 (SD 5.5) days, 2–35 days	85 (53.1%) were Class I thrombosis 23 (14.4%) were Class II thrombosis 52 (32.5%) were Class III thrombosis	less activity, 9.58 (3.17–28.96), $p = .000$ Obesity, 3.47 (1.29–9.31), $p = .014$ Chemotherapy history, 2.11 (0.59–7.48), $p = .249$
Yi et al. (2014)	28 (34.6%)	PICC-RT, 12.5 (SD 6.2) days, 2–27 days	37 (88.1%) were superficial 5 (11.9%) were deep	Diabetes, 1.12 (0.89–4.57), $p = .006$ Less activity, 2.11 (0.77–3.97), $p = .009$ Chemotherapy history, 3.19 (1.07–9.77), $p = .017$
Pittiruti et al. (2014)	4 (2.2%)	NA	NA	NA
Itkin et al. (2014)	184 (55.4%)	NA	NA	NA
Bonizzoli et al. (2011)	31 (27.2%)	Asymptomatic PICC-RT, 9 (29.0%) cases occurred during the first week, 17 (54.8%) cases occurred during the second week, 5 (16.1%) cases occurred during the third week	14 (45.2%) were superficial 17 (54.8%) were deep	Female sex, 1.42 (0.18–1.33), $p = .2917$ Left basilic vein, 2.18 (1.12–4.24), $p = .0199$
Trerotola et al. (2010)	29 (58.0%)	NA	NA	NA
Periard et al. (2008)	6 (19.4%)	Asymptomatic PICC-RT, 11.7 (SD 11.0) days, 5–34 days	9 (60%) were superficial 6 (40%) were deep	NA

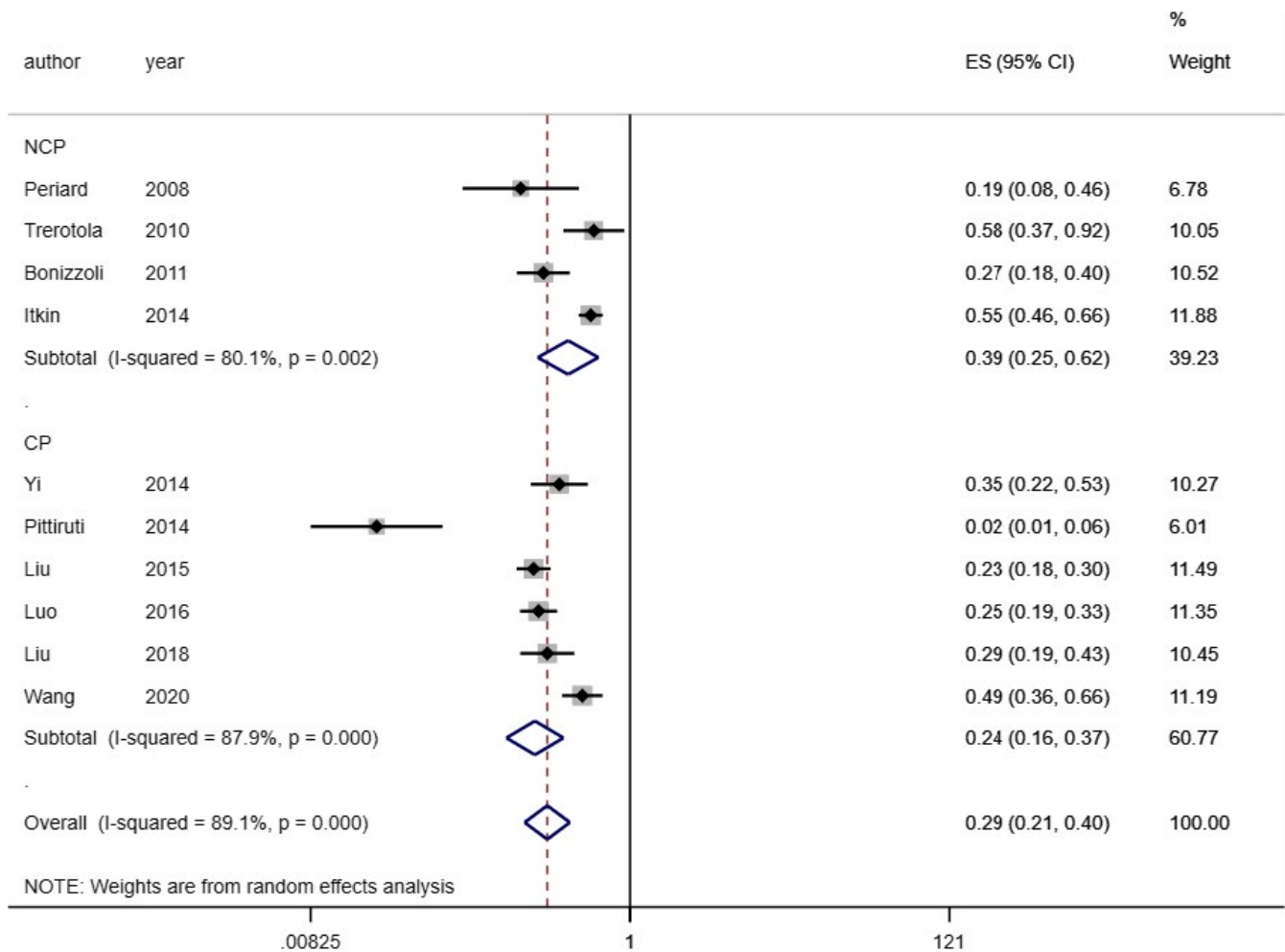


FIGURE 2 Forest plots for 10 studies assessing the incidence of asymptomatic PICC-RT: subgroup analysis based on whether cancer patients or not. Notes. NCP, non-cancer patients: OR = 0.39, $p = .002$; CP, cancer patients: OR = 0.24, $p = .000$; Overall: OR = 0.29, $p = .000$

costs, an ultrasound examination should be conducted according to the occurrence time of the asymptomatic PICC-RT, which will be discussed below.

Additionally, the subgroup analysis showed that the incidence of asymptomatic PICC-RT was 19% in cancer patients, higher than that of symptomatic PICC-RT (5%-15%) (Fallouh et al., 2015). The hypercoagulable state caused by cancer may be an important cause of venous thrombosis (Farge et al., 2019; Mukai & Oka, 2018). Cancer patients who undergo chemotherapy usually experience nausea, vomiting, anorexia and fatigue, leading to reduced activity and prolonged bedtime, which could ultimately reduce blood flow and stagnation (Cuiping et al., 2020). Findings from this review suggest that cancer patients with PICC should be monitored closely so that early screening for asymptomatic PICC-RT could be initiated.

The subgroup analysis also showed that the incidence of asymptomatic PICC-RT in prospective studies and RCTs was 23% and 19%, respectively. The reason for the higher incidence of prospective studies is that these studies have more ultrasound examinations than the RCTs. In these prospective studies, patients were investigated for PICC-RT by ultrasound three times a day or weekly within

1 month after catheter insertion (Luo et al., 2016; Yi et al., 2014; Yuxiu et al., 2015). However, for RCTs, ultrasound examinations were usually performed on day 28 or before catheters were removed (Itkin et al., 2014; Trerotola et al., 2010). So, the incidence of asymptomatic PICC-RT may be underestimated. Regular ultrasound examinations are necessary to determine the true incidence of asymptomatic PICC-RT (Luo et al., 2016).

In this review, we found that asymptomatic PICC-RT mainly occurred in the superficial veins and was accompanied by deep vein thrombosis. Asymptomatic thrombosis is an adaptation process and a result of PICC insertion. It has been argued that PICC-related deep vein thrombosis is a concomitant or progressive outcome of superficial venous thrombosis (Chopra et al., 2014). Asymptomatic thrombosis eventually develops into symptomatic thrombosis (Luo et al., 2016). Chopra et al., (2014) also suggested that the risk of PICC-RT could be reduced by preventing superficial venous thrombosis. Based on the above findings, when conducting vascular ultrasound examinations on patients with PICC, the superficial vein should be a primary focus.

In this review, two studies (Bonizzoli et al., 2011; Wang et al., 2020) found that a higher ECOG score, slower blood flow

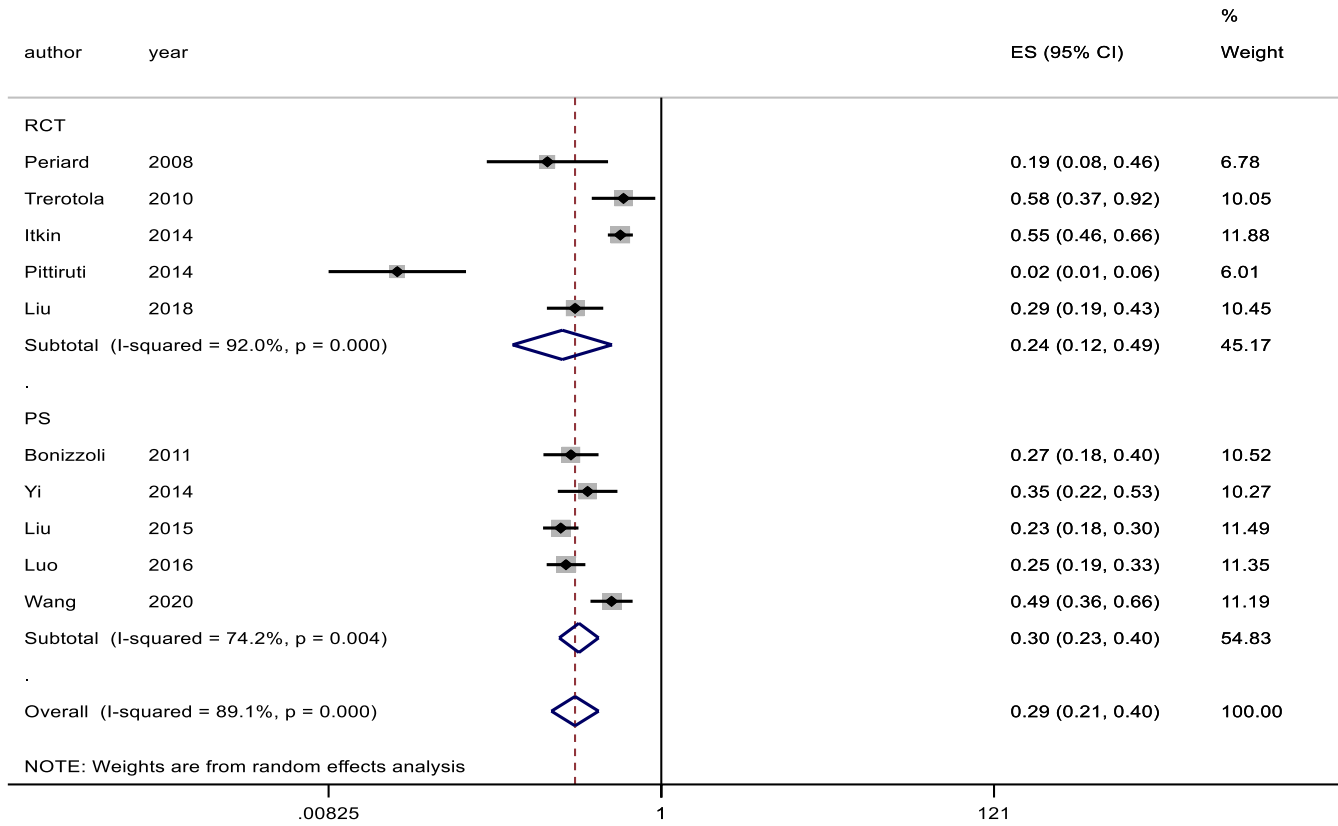


FIGURE 3 Forest plots for 10 studies assessing the incidence of asymptomatic PICC-RT: subgroup analysis based on study design. Notes. RCT, randomized controlled trial: OR = 0.24, $p = .000$; PS, prospective study: OR = 0.30, $p = .004$; Overall: OR = 0.29, $p = .000$

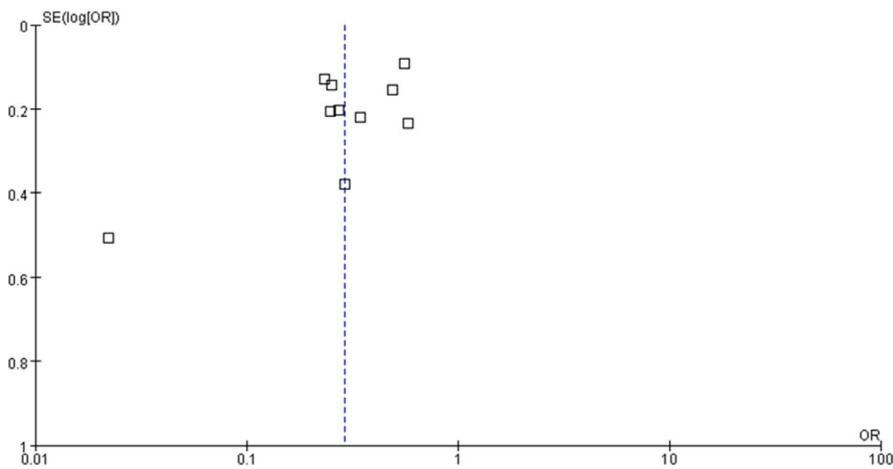


FIGURE 4 Funnel plot assessing the heterogeneity of the 10 studies on incidence of asymptomatic PICC-RT

velocity and left basilic vein were independent risk factors of asymptomatic thrombosis. The ECOG score reflects the patient's activity status (Greipp et al., 1998). A higher ECOG score indicates poorer activity status (Liang et al., 2018). Previous studies found that lower patient activity was a risk factor of PICC-RT (Yi et al., 2014; Yuxiu et al., 2015). Reduced activity could lead to slow blood flow velocity and even blood stasis, which leads to thrombosis (Yi et al., 2014). Therefore, the patient's activity status should be assessed before catheterization. In parallel, the limbs with the catheter should start exercises as soon as possible to prevent asymptomatic PICC-RT (Liu et al., 2018).

Slower blood flow velocity was one of the risk factors of asymptomatic PICC-RT. According to Virchow's triad, slower blood flow is one of the causes of thrombosis (Brotman et al., 2004). The placement of PICC can lead to intimal injury, which affects normal blood flow and blood flow velocity, thus increasing the risk of PICC-RT (Bajd et al., 2012; Wilson et al., 2013). Therefore, maintaining normal blood flow is beneficial to prevent the occurrence of PICC-RT. Some studies suggest when conditions permit, ultrasound examination can be used to evaluate the blood flow velocity before and after insertion, changes in blood flow may give us some clues of PICC-RT formation (Wang et al., 2020).

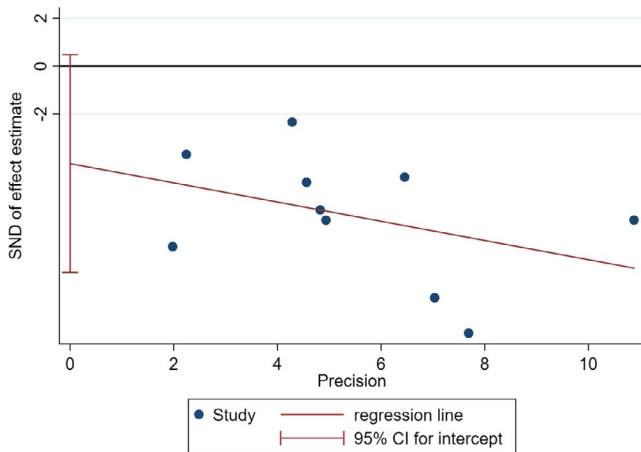


FIGURE 5 Egger assessing the heterogeneity of the 10 studies on incidence of asymptomatic PICC-RT. $p = .073$, 95% CI (-8.61 to 0.47)

In this review, we also found that the asymptomatic PICC-RT was more likely to occur in the left basilic vein than the right basilic vein (Bonizzoli et al., 2011). This finding might be explained by the fact that activity of the left arm is lower than that of the right arm for most people whose dominant hands are right hands (Ardon et al., 2014) and activity promotes blood circulation (Lee et al., 2020; Liu et al., 2018). When PICC is inserted on the left hand, the catheterization arm cannot get enough exercise. The blood will become sticky, resulting in an increased risk of PICC-RT (Liu et al., 2018). Therefore, for patients whose left arm was inserted with PICC, nurses should pay more attention to supervise patients' functional exercise (Liu et al., 2018). Besides, future studies need to further prove the relationship between catheterization arms and PICC-RT.

This study has implications for clinical practice. We found that most asymptomatic PICC-RT occurred 3–12 days after PICC insertion. This finding suggests that the first two weeks after PICC catheterization is a critical period, warranting a routine ultrasound examination. Relatedly, thrombosis prevention should be initiated. Previous evidence supports the use of low molecular weight heparin (Huang et al., 2020; Lv et al., 2019) and daily handgrip exercise by an elastic ball (Liu et al., 2018) for those at risk of PICC-RT. These methods may be used in clinical practice to facilitate blood circulation after PICC insertion. Additionally, before PICC catheterization, extra attention should be paid to those with a high risk for PICC-RT (e.g. higher ECOG score or left basilic vein). Ultrasound dynamics should be used to monitor the blood flow velocity before insertion whenever possible.

6 | LIMITATIONS

Including only prospective studies and RCTs was a strength of this systematic review. In addition, the diagnosis of thrombosis was based on objective measurements, which may increase the validity of the diagnose. However, there are some limitations to this review.

First, half of the included studies were conducted in China. Regions such as Africa or Oceania were not represented. Therefore, the results may not be generalizable to these regions. Second, there were variations in the frequency of PICC-RT screening, which might result in heterogeneity between studies. Lastly, only two studies examined the risk factors of asymptomatic PICC-RT. We thus could not conduct quantitative meta-analyses. More research is needed to further investigate the risk factors for asymptomatic PICC-RT. As such, future studies with a multicentre, prospective design may provide more evidence for the prevention and management of asymptomatic PICC-RT.

7 | CONCLUSIONS

In conclusion, the incidence of asymptomatic PICC-RT among adult patients is high. It usually occurs in the superficial veins within two weeks after the PICC placement. Additionally, the higher ECOG score, slower blood flow velocity and left basilic vein were independent risk factors of asymptomatic PICC-RT.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

PC, BZ, LQ and GW: Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, drafting the manuscript or revising it critically for important intellectual content, final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content, accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

PATIENT CONSENT FORM

As this study was a systematic review and meta-analysis, patient consent was not required.

DATA AVAILABILITY STATEMENT

Author elects to not share data.

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