The incidence of catheter-related bloodstream infections in different central venous access devices: a network meta-analysis of randomized controlled trials

Keywords
central venous catheters, central venous access devices, network meta-analysis, catheter-related bloodstream infections, peripheral-ly inserted central venous catheters, totally implantable venous access ports

Abstract

Introduction
Direct paired meta-analyses and network meta-analysis were conducted to compare the incidence of Catheter-associated bloodstream infections (CRBSIs) in different types of central venous access devices (CVADs).

Material and methods
The PubMed, EMBASE, Web of Science, Cochrane databases, CNKI and CBM were systematically searched from inception to May 31, 2024 for randomized controlled trials (RCTs) comparing the incidence of CRBSIs across various types of CVADs. Literature screening, data extraction, and risk bias evaluation were all independently conducted by two individuals. Direct paired meta-analyses and network me-ta-analysis were performed using RevMan5.3 and Stata14.0 software, respectively.

Results
A total of five literatures were included. Paired meta-analyses revealed that the incidence of CRBSIs was lower in the peripherally inserted central catheters (PICCs) group compared to the central venous catheters(CVCs) group(RR=0.23, 95%CI(0.13-0.43), P<0.00001). The incidence of CRBSIs in PICCs group was observed to be lower compared to that in totally implantable venous access ports(TIVAPs) group (RR=0.45, 95%CI(0.23-0.87), P=0.02). Descriptive analysis revealed a higher incidence of CRBSIs in CVCs group compared to the TIVAP group (RR=2.97, 95%CI(1.65-5.17), P=0.0002). The network meta-analysis revealed a significantly lower incidence of CRBSIs in the PICCs group compared to the CVCs group. However, no statistically significant differences were observed in other comparisons. Based on the cumulative ranking curve test, the incidence of CRBSIs in various CVADs was ranked as follows: PICCs(97.20%)> TIVAPs(50.00%)>CVCs(2.80%).

Conclusions
The available evidence suggests that PICCs exhibit the lowest incidence of CVADs, followed by TIVAPs. Therefore, PICCs should be prioritized when selecting CVADs.

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Keywords catheter-related bloodstream infections; central venous access devices; network meta-analysis; peripherally inserted central venous catheters; totally implantable venous access ports; central venous catheters.

1. Introduction

Central vein access devices (CVADs) are catheters equipped with catheter tips positioned in the central vein [1]. Currently, the commonly employed CVADs in clinical practice encompass central venous catheters (CVCs), peripherally inserted central catheters (PICCs) and totally implantable venous access ports (TIVAPs) [2]. CVADs are extensively utilized in critically ill patients and cancer patients necessitating multiple chemotherapy regimens [3]. The clinical application of CVADs has led to an increasing prominence of complications,

including catheter thrombosis, puncture site bleeding, catheter slippage, and catheter related bloodstream infections (CRBSIs) [4]. The occurrence of CRBSIs represents a significant and consequential complication [5]. CRBSIs are defined as the occurrence of bacteremia or fungemia within 48 hours of intravascular catheter insertion or withdrawal, accompanied by infection manifestations such as fever (greater than 38℃), chill or hypotension, and absence of any other identifiable source of infection apart from vascular catheter-associated infection [6,7]. The occurrence of CRBSIs not only impacts patient prognosis but also significantly elevates mortality rates and hospitalization costs [8]. Treatment expenses for CRBSIs range from $32,000 to $69,332 [9-11]. Furthermore, patients with CRBSIs face a 2.71-fold higher risk of mortality compared to those without this condition [12].

The incidence of CRBSIs varied among different types of CVADs. In patients with PICCs, the reported incidence ranged from 0.46% to 13.4% [13-15], while in patients with CVCs, the reported incidence ranged from 1.88% to 23.53% [16-18], and the incidence of CRBSIs in TIVAPs patients ranged from 1.32% to 13.02% [13,17,19]. The incidence of CRBSIs was found to be higher in patients with TIVAPs compared to those with PICCs, as demonstrated by a meta-analysis [20]. A meta-analysis conducted by Chopra et al. revealed that PICCs had a lower risk of CRBSIs compared to CVCs [21]. Another meta-analysis conducted by Capozzi et al .[22] reported no statistically significant difference in the incidence of CRBSIs between TIVAPs and PICCs patients. The literature included in these meta-analyses primarily consisted of retrospective studies, which are associated with numerous confounding factors. Consequently, there may be limitations regarding the reliability and accuracy of the data derived from these studies. Existing randomized controlled trials (RCTs) [23-26] or meta-analyses [20-22] have solely compared the incidence of CRBSIs between two types of these CVADs, failing to provide a comprehensive and clear comparison among various CVADs, thereby hindering optimal clinical decision-making.

While traditional paired meta-analyses are limited to comparing only two interventions, network meta-analysis enables simultaneous comparison of multiple interventions and provides a quantitative ranking of different outcome measures based on the likelihood of advantages and disadvantages [27,28]. In this study, a systematic review and network meta-analysis of RCTs were conducted on the incidence of CRBSIs in various types of CVADs, with the objective of providing an evidence-based foundation for selecting the most optimal CVADs (Supplementary material Figure S1).

2. Materials and methods

This network meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement extension for network meta-analysis[29].

2.1.Inclusion and exclusion criteria

2.1.1.Inclusion criteria

2.1.1.1. Type of study

Comparing the incidence of CRBSIs among different types of CVADs in RCTs.

2.1.1.2. Types of participants

Adult patients aged 18 years or older who were undergoing implantation of CVADs, including CVCs, PICCs, and TIVAPs.

2.1.1.3. Types of outcomes

Incidence of CRBSIs.

2.1.2. Exclusion criteria

(1) Studies with unextractable or incomplete data;
(2) Animal experiments;
(3) Duplicate publications.

2.2. Searching strategy

The incidence of CRBSIs in different types of CVADs was investigated through a comprehensive search of RCTs from PubMed, EMBASE, Web of Science, Cochrane databases, CNKI and CBM. MeSH terms were combined with free words to optimize the search strategy. Additionally, manual tracing of references in the included literature was conducted. The search period extended until May 31, 2024. The search terms included

catheter-related bloodstream infection, central venous access device, central venous catheter, peripherally inserted central catheter, totally implantable venous access port, random*,etc.

2.3. Literature screening and data extraction

The literature was imported into the Endnote software for deduplication purposes. Two researchers independently screened the literature, and any disagreements were resolved through discussion with a third researcher. Initially, the titles of the literature were read to exclude obviously irrelevant studies. Subsequently, both abstracts and full texts were reviewed for further filtering. Relevant data including first author, publication date, study design type, study start time, sample size, catheter type, and number of CRBSI cases were extracted from the selected literature.

2.4. Risk of bias assessment

The quality of the literature was assessed by two researchers in accordance with the RCT bias risk assessment tool recommended by the Cochrane reviewers'handbook. The evaluation primarily encompassed seven aspects: random sequence generation, allocation concealment, blinding of both researchers and subjects, blind evaluation of outcomes, integrity of outcome data, selective reporting and other potential biases.

2.6. Statistical analysis

Direct pairwise meta-analyses was performed using RevMan 5.3 software, and heterogeneity was tested. Risk ratio (RR) was employed as the effect size for the count data, with each effect size presented along with 95% confidence interval (CIs). Stata 14.0 software was utilized to perform network meta-analysis based on the frequency framework. Network evidence plots were drawn for comparison between each outcome measure intervention. In case of a closed loop in the network evidence plots, node analysis was applied to test the inconsistency. If $P > 0.05$, consistency model was used for analysis. The Surface Under the Cumulative Ranking Curve (SUCRA) was used to rank outcome indicators accordingly. A " comparison-adjusted " funnel plot was employed to assess potential publication bias.

3. Results

3.1. Study selection, characteristics and risk of bias assessment

A preliminary search yielded 9626 relevant literatures sources, and after a gradual screening process (Figure 1), five studies [23-26,30] were ultimately included. The included studies were published between 2014 and 2021 and all of them were RCTs. Two studies were conducted in China, while the remaining three originated from Sweden, Italy and the UK. The number of catheters involved ranged from 23 to 303. Table 1 presents the essential characteristics of the included literature sources. Four studies employed appropriate randomization methods, while one study had an unclear randomization approach. Three studies concealed their allocation scheme effectively, while it remained unclear in two other studies. Regarding blinding method, although results were not explicitly stated, however, due to challenges in achieving double or triple blinding for CVAD placement evaluation purposes, this aspect was excluded from the scope of literature quality reference to enhance risk control within the articles. Other aspects exhibited low risk bias levels. The risk of bias in included studies is shown in Figure 2.

3.2. Pairwise Meta-Analyses

3.2.1.PICCs versus CVCs

Two studies compared the incidence of CRBSIs between the PICCs group and the CVCs group. The heterogeneity test result was: I^2=0%, P=0.74, therefore a fixed-effect model was adopted. Meta-analysis demonstrated a statistically significant lower incidence of CRBSIs in PICCs group compared to the CVCs group (RR=0.23, 95%CI(0.13-0.43), P<0.00001) (Figure 3).

3.2.2. PICCs versus TIVAPs

Four studies compared the incidence of CRBSIs between the PICCs group and the TIVAPs group. The heterogeneity test result was: I^2=0%, P=0.45, therefore a fixed-effect model was adopted. Meta-analysis demonstrated a statistically significant lower incidence of CRBSIs in PICCs group compared to the TIVAPs group (RR=0.45, 95%CI(0.23-0.87), P=0.02) (Figure 4).

3.2.3. CVCs versus TIVAPs

One study compared the incidence of CRBSIs between patients with CVCs and those with TIVAPs.

Descriptive analysis revealed a significantly higher incidence of CRBSIs in the CVCs group compared to the TIVAPs group (RR=2.97, 95%CI(1.65-5.17), P = 0.0002).

3.3. Network Meta-Analysis

3.3.1. Evidence Network Diagram

The occurrence of CRBSIs was reported in five RCTs involving three types of CVADs. In the figure, each dot represents a specific CVAD, while the thickness of the line connecting two points indicates the corresponding sample size. A thicker solid line signifies a greater amount of direct comparative evidence, whereas a thinner line suggests less evidence in that regard. Notably, it can be observed that PICCs exhibit both the largest number of relevant literature and sample size (Figure 5).

3.3.2. Inconsistency test

The inconsistency test was performed using node analysis, and the result indicated the absence of any significant inconsistencies (P>0.05). This indicated that the the findings from direct comparison align with those obtained through indirect comparison.

3.3.3. Network Meta-Analysis results of CRBSIs

The incidence of CRBSIs was significantly lower in PICCs group compared to the CVCs group. No significant differences were observed in other comparisons (Figure 6). Based on SUCRA values, the ranking of three CVADs was as follows: PICCs(97.20%)> TIVAPs(50.00%)>CVCs(2.80%)(Figure 7).

3.4. Publication bias analysis

The findings revealed a non-uniform distribution of all study sites across both sides of the median line, indicating a lack of symmetry and suggesting potential publication bias (Figure 8).

4. Discussion

As an invasive procedure, CVADs are susceptible to complications [31]. CRBSIs represent a significant complication [32]. The presence of a venous indwelling catheter compromises the integrity of the skin, allowing pathogens to invade and proliferate along the catheter, leading to bloodstream infection or even systemic infection. This poses a serious threat to patient health, resulting in prolonged hospital stays, increased mortality rates, and escalated healthcare costs [31,33-35]. Therefore, CRBSIs serve as a crucial indicator for nosocomial infection prevention and control and have garnered considerable attention in clinical practice. The incidence of CRBSIs varies depending on different infusion tools; thus, selecting appropriate CVADs is paramount when considering CRBSI occurrence.

The present study conducted a systematic analysis comparing the incidence of CRBSIs among PICCs, CVCs, and TIVAPs. Both direct pairwise meta-analyses and network meta-analysis results consistently demonstrated that the PICCs group had a lower incidence of CRBSIs compared to the CVCs group. From the perspective of SUCRA probability ranking, PICCs group ranks first. Previous meta-analyses have found a reduced risk of CRBSIs in PICCs compared to CVCs [21]. Another meta-analysis showed the same results [36]. This difference in incidence of CRBSIs between PICCs group and CVCs group may be attributed to variations in puncture locations; predominantly upper limb for PICCs versus neck and subclavicle for CVCs. The skin on the upper limb is less prone to bacterial colonization, sweat accumulation, and oily secretions than that on the neck and subclavicle region, thereby contributing to higher incidence of CRBSIs observed in the CVCs group [14].

TIVAPs group also exhibited a significantly lower incidence of CRBSIs than the CVCs group, with a more pronounced disparity observed when compared to the PICCs group. TIVAPs offer durable venous access and employ a closed intravenous infusion system, thereby mitigating complications, particularly those related to infection [37]. TIVAPs represent an entirely implanted closed intravenous infusion device that remains subcutaneously placed within the human body [38]. This technology boasts advantages such as minimal risk of infection, enhanced quality of life convenience, simplified maintenance requirements, and prolonged service life [39]. Since TIVAPs is an intravenous infusion device that is completely implanted under the skin and has no exposed part, the entire device has less direct contact with the external environment, reducing the incidence of CRBSIs [40,41]. However, the PICCs catheter is exposed at the elbow, which requires regular dressing change

and tube flushing, and the skin colonizing bacteria are easy to migrate into the blood vessels, resulting in the occurrence of CRBSIs [20,23]. When using PICCs for infusion, blood drawing, tube flushing and other operations, there is a potential risk of introducing microorganisms into the catheter lumen. Notably, the manipulation of the catheter hub represents the most prevalent source of infection [20]. In direct comparison based on meta-analytical findings, the incidence of CRBSIs was observed to be lower in the PICCs group compared to the TIVAPs group, which is consistent with the findings of another meta-analysis [20]. The results of the network meta-analysis comparison showed no difference between the two. From the perspective of SUCRA probability ranking, PICCs group ranks ahead of TIVAPs group. In RCTs involving a large sample of solid tumors, the incidence of CRBSIs in TIVAPs was lower than in PICCs [30]. Conversely, in RCTs with a large sample size of blood tumors, the incidence of CRBSIs was higher in TIVAPs compared to PICCs [26]. Additionally, in RCTs focusing on long-term parenteral nutrition, the incidence of CRBSIs was higher in TIVAPs compared to PICCs [23,24]. Infusion of parenteral nutrition with TIVAPs increases the risk of catheter-associated infections. This may be due to the fact that parenteral nutrition itself, both lipids and amino acids, are conducive to bacterial colonization and biofilm formation, or that the procedure required for parenteral nutrition infusion is more frequent [42-44]. For patients with solid tumors, TIVAPs may represent a preferable option.

Although the incidence of CRBSIs varies among different types of CVADs, it is crucial to consider other risk factors that contribute to the high risk of CRBSIs. Previous studies have demonstrated that diabetes, the use of antibiotics, Long-term indwelling urinary catheter (>7 days), the use of antibiotics, advanced age (>55 years old), a higher Acute Physiology and Chronic Health Evaluation (APACHE) score are high-risk factors for the development of CRBSIs [45]. Therefore, we recommend constructing relevant risk prediction models to identify high-risk groups for CRBSIs and implementing targeted interventions promptly, which will effectively reduce the incidence of CRBSI. In order to better control the occurrence of CRBSIs, we recommend the use of some effective measures, such as the use of antibacterial coating restraint tubes, and strict cleaning, disinfection and puncture procedures. When intravenous therapy teams or nurses perform standardized and standardized nursing work, the infection rate will be greatly reduced, from 25% to 33% to 4% on average, or even lower [46,47]. The guidelines state that all healthcare workers inserting catheters should receive formal insertion training and strictly adhere to aseptic procedures [48].

4.1. Advantages

The present network meta-analysis represents the first attempt to compare the incidence of CRBSIs among three types of CVADs, yielding a relatively robust conclusion. First of all, in terms of incidence of CRBSIs, PICCs outperformed both CVCs and TIVAPs, thus demonstrating their potential clinical value and guiding significance. This study provides a scientific basis for the selection of PICCs, CVCs and TIVAPs catheters for CVADs. Furthermore, these findings offer valuable guidance for clinicians when making decisions regarding treatment options. Secondly, this study included five high-quality RCTs, ensuring its representativeness and credibility. Lastly, by employing network meta-analysis and SUCRA probability ranking techniques, this study enhances objectivity and comprehensiveness in its results while providing more accurate references for clinical practice.

4.2. Limitations

First of all, there are variations in the number of included studies across different CVADs. Some literature exhibits a limited number of CVADs and a small sample sizes. Therefore, to ensure the reliability and objectivity of the conclusions, it is imperative to confirm their scientific nature through multi-center RCTs with large samples and high-quality collaboration. Secondly, although all included subjects were adult patients with CVADs placement, differences in regional medical expertise and hospital capabilities as well as variations in intervention programs' intensity may contribute to result heterogeneity. Third, the included studies were published in both Chinese and English literature; however, some publications might be incomplete. Fourth, CRBSIs are related to the ycatheter type, and other factors such as total parenteral nutrition, chemotherapy, and use of immunosuppression are also related, which may lead to certain bias in this meta-analysis.

4.3. Conclusions

In summary, the limited evidence suggests that the incidence of CRBSIs with PICCs is lowest, followed

by TIVAPs. Therefore, when selecting CVADs, PICCs should be prioritized based on these findings, which offer valuable clinical guidance. However, it is important to interpret these results cautiously due to the limitations in the number and quality of included studies and literature. Further high-quality direct comparative randomized controlled trials are needed to provide more reliable references for clinical applications.

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Ethical approval

Ethical approval was not sought for the present study because this article did not involve any patients.

Conflict of interest

None of the authors have any financial and personal relationships with other people or organizations that could inappropriately influence their work.

Data availability statement

All data generated or analysed during this study are included in this article.

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Figure Legends

Figure 1. Flow diagram of study inclusion.

Figure 2. Risk of bias graph.

Figure 3. Forest plot of meta-analysis(peripherally inserted central catheters versus central venous catheters); PICC, peripherally inserted central catheter; CVC, central venous catheter.

Figure 4. Forest plots showing the catheter-related bloodstream infections of meta-analysis(peripherally inserted central catheters versus totally implantable venous access ports); PICC, peripherally inserted central catheter; TIVAP, totally implantable venous access port.

Figure 5. Evidence network plot; PICC, peripherally inserted central catheter; CVC, central venous catheter; TIVAP, totally implantable venous access port.

Figure 6. Network Meta analysis results; PICC, peripherally inserted central catheter; CVC, central venous catheter; TIVAP, totally implantable venous access port.

Figure 7. Surface under the cumulative ranking of catheter-related bloodstream infections; PICC, peripherally inserted central catheter; CVC, central venous catheter; TIVAP, totally implantable venous access port.

Figure 8. Publication bias.

Supplementary material

Figure S1. Study flow chart; PICC, peripherally inserted central catheter; CVC, central venous catheter; TIVAP, totally implantable venous access port.

Table 1. Characteristics of interventions of included studies

Study, year	Design	Region	Duration	PICCs		CVCs		TIVAPs	
				Sample	Event	Sample	Event	Sample	Event
Taxbro 2019	RCTs	Sweden	March 2013 until February 2017	198	4			201	16
Picardi 2019	RCTs	Italy	April 2015 until October 2017	46	2	47	11		
Moss 2021	RCTs	UK	November 2013 until February 2018	212	10	212	41		
						303	49	253	14
				199	7			147	8
Chen 2014	RCTs	China	March 2008 until June 2013	30	2			23	1
Lian 2016	RCTs	China	August 2012 until August 2015	80	2			80	0

Abbreviation:PICCs, peripherally inserted central catheters; CVCs, central venous catheters; TIVAPs, totally implantable venous access ports;RCTs, randomised controlled trials.

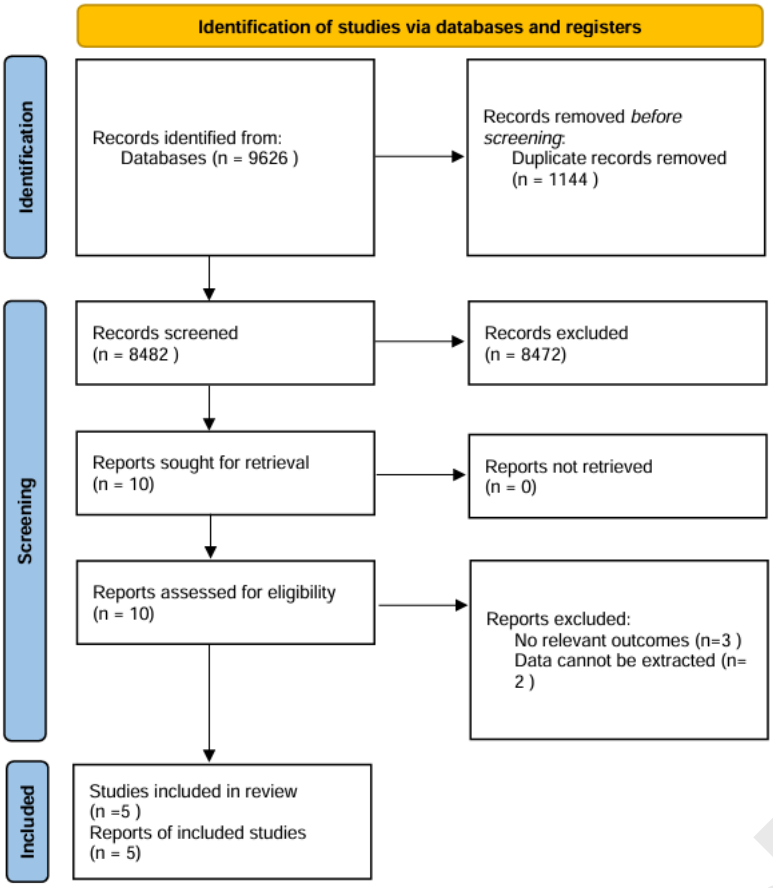

Figure 1

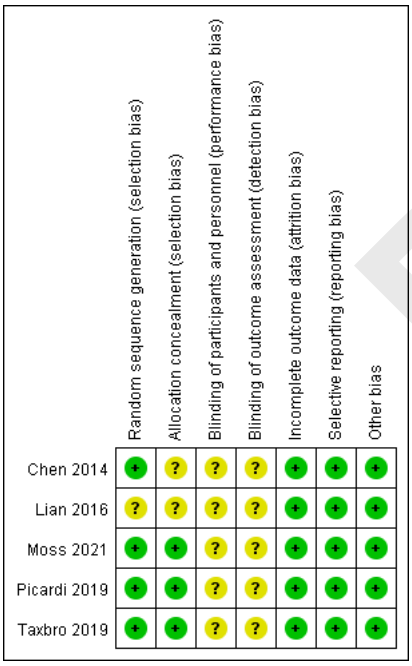

Figure 2

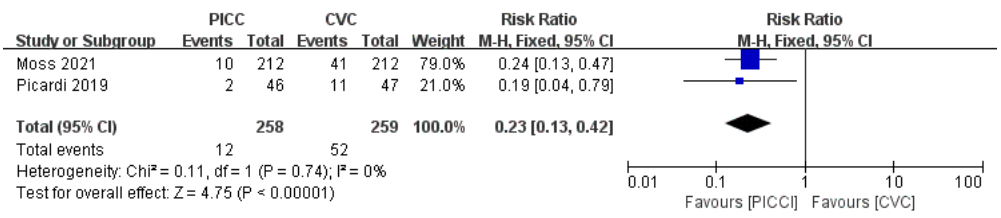

Figure 3

Figure 4

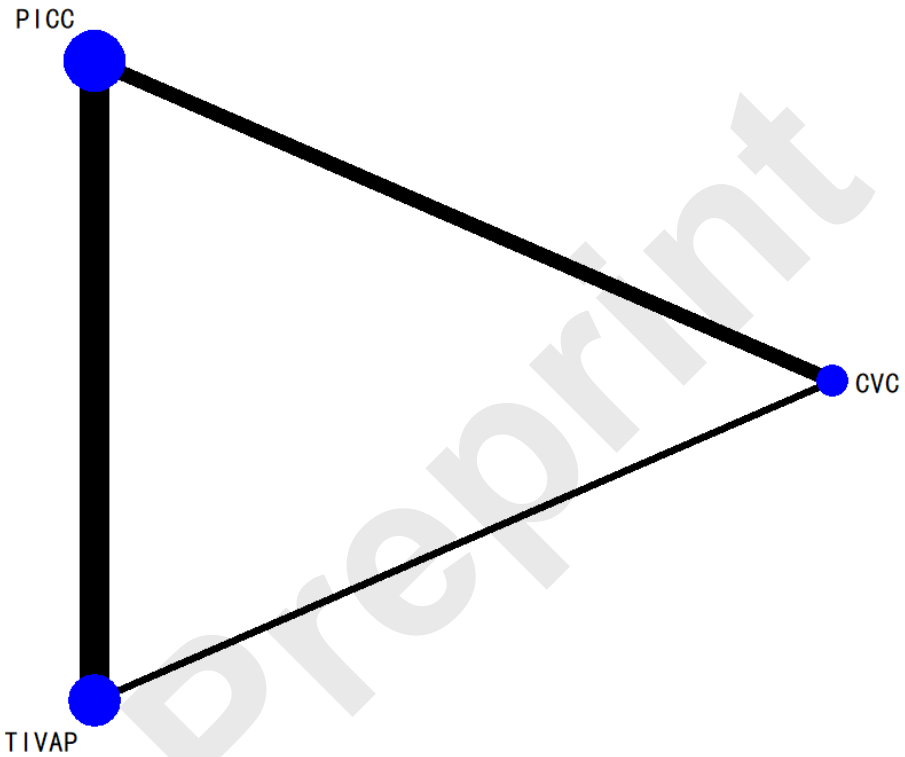

Figure 5

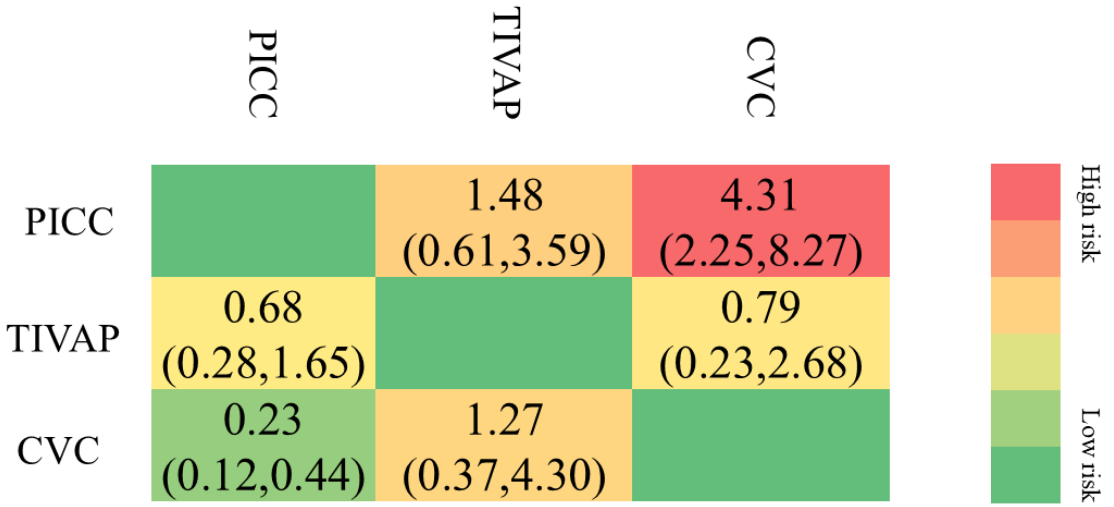

Figure 6

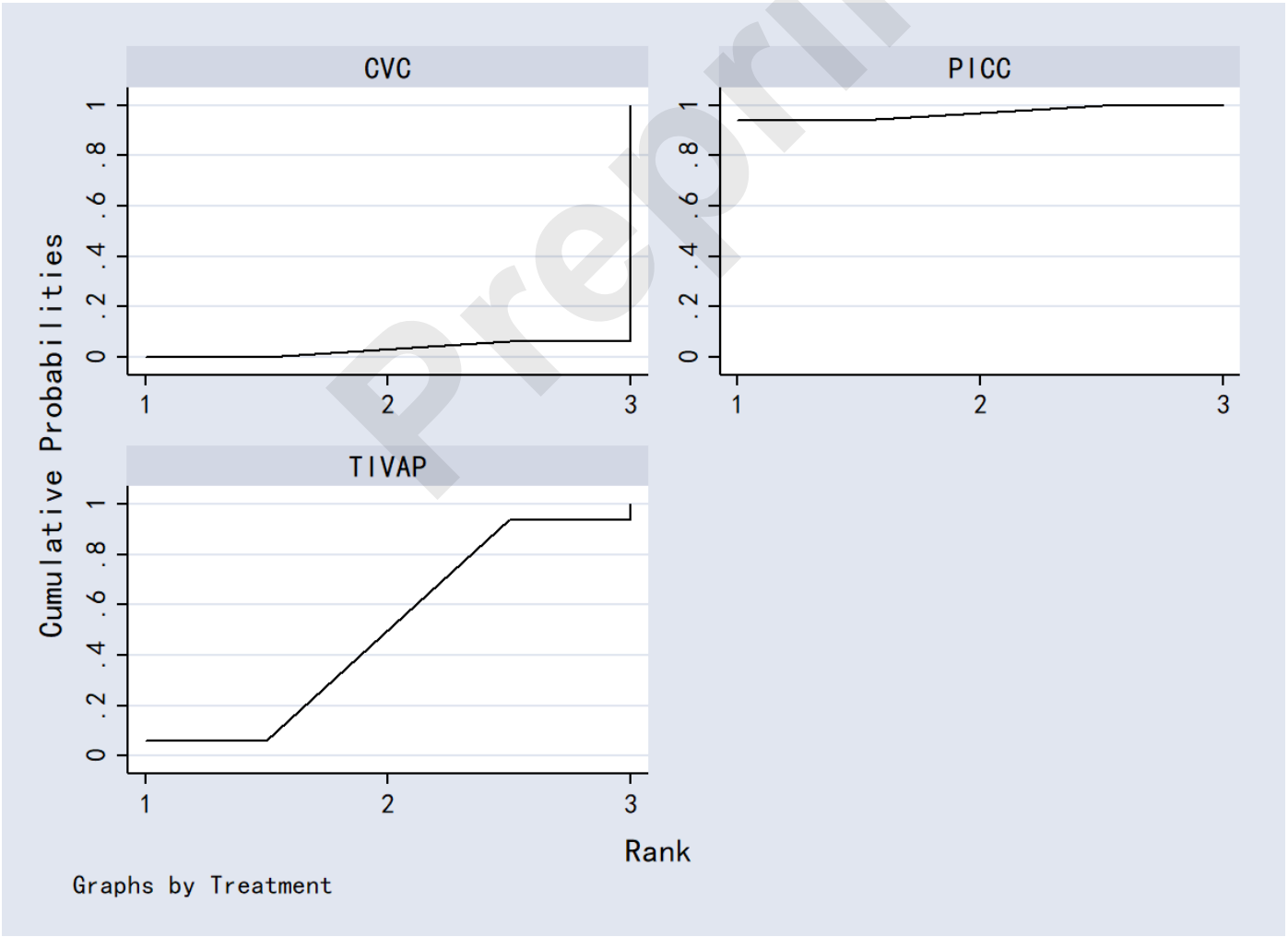

Figure 7

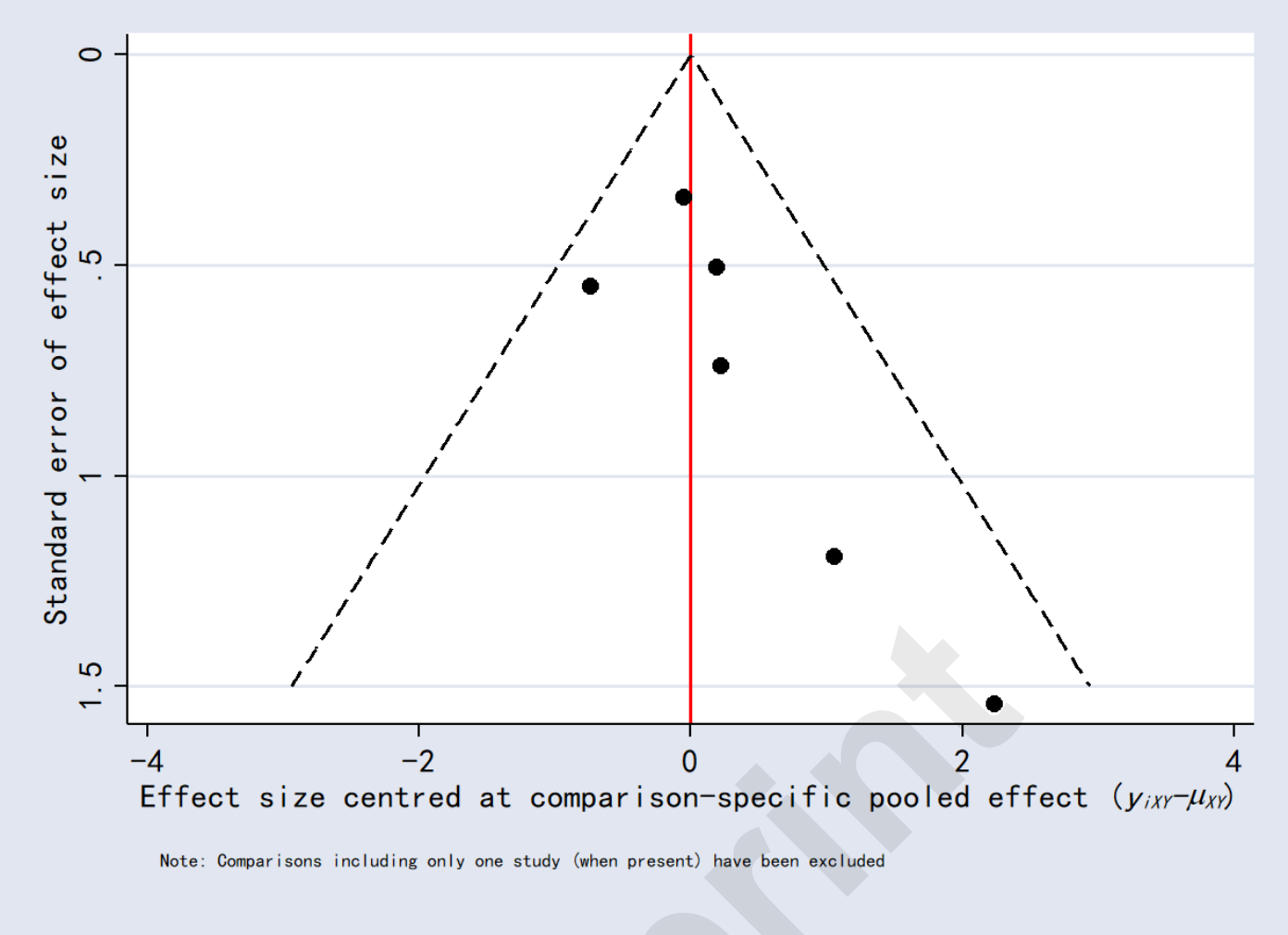

Figure 8

The incidence of catheter-related bloodstream infections in different central venous access devices: a network meta-analysis of randomized controlled trials

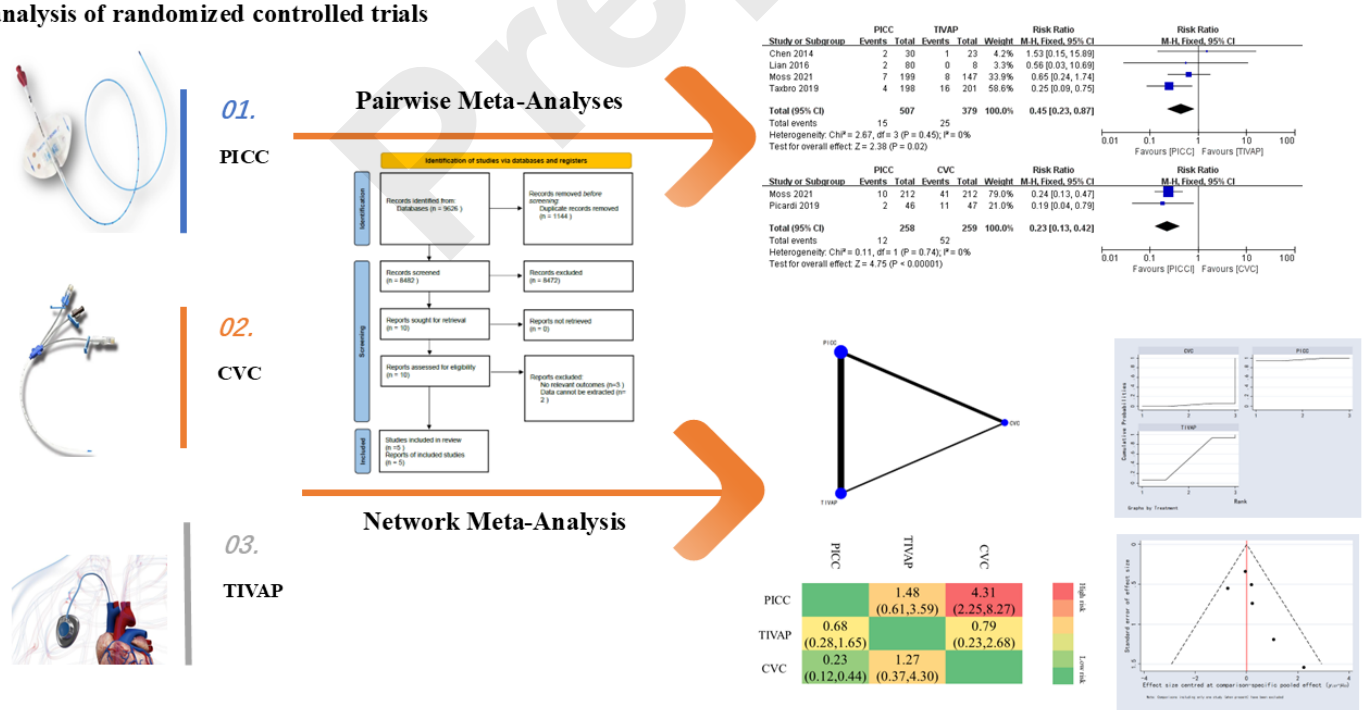

Figure S1.

The incidence of catheter-related bloodstream infections in different central venous access devices: a network meta-analysis of randomized controlled trials