SYSTEMATIC REVIEW OPEN

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Risk factors and incidence of central venous access devicerelated thrombosis in hospitalized children: a systematic review and meta-analysis

Maoling Fu^{1,2}, Quan Yuan², Qiaoyue Yang^{1,2}, Yaqi Yu^{1,2}, Wenshuai Song^{1,2}, Xiuli Qin¹, Ying Luo¹, Xiaoju Xiong¹ and Genzhen Yu¹

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BACKGROUND: The risk factors for central venous access device-related thrombosis (CRT) in children are not fully understood. We used evidence-based medicine to find the risk factors for CRT by pooling current studies reporting risk factors of CRT, aiming to guide clinical diagnosis and treatment.

METHODS: A systematic search of PubMed, Web of Science, Embase, Cochrane Library, Scopus, CNKI, Sinomed, and Wanfang databases was conducted. RevMan 5.4 was employed for data analysis.

RESULTS: The review included 47 studies evaluating 262,587 children with CVAD placement. Qualitative synthesis and quantitative meta-analysis identified D-dimer, location of insertion, type of catheter, number of lumens, catheter indwelling time, and central line-associated bloodstream infection as the most critical risk factors for CRT. Primarily due to observational design, the quality of evidence was regarded as low certainty for these risk factors according to the GRADE approach.

CONCLUSION: Because fewer high-quality studies are available, larger sample sizes and well-designed prospective studies are still needed to clarify the risk factors affecting CRT. In the future, developing pediatric-specific CRT risk assessment tools is important. Appropriate stratified preventive strategies for CRT according to risk assessment level will help improve clinical efficiency, avoid the occurrence of CRT, and alleviate unnecessary suffering of children.

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IMPACT:

- This is the latest systematic review of risk factors and incidence of CRT in children.
- A total of 47 studies involving 262,587 patients were included in our meta-analysis, according to which the pooled prevalence of CRT was 9.1%.
- This study identified several of the most critical risk factors affecting CRT in children, including D-dimer, insertion location, type of catheter, number of lumens, catheter indwelling time, and central line-associated bloodstream infection (CLABSI).

INTRODUCTION

Central venous access device (CVAD) is an infusion device inserted through different parts to make the tip of the catheter to the vena cava. In the clinic, CVAD is mainly divided into the following four categories: tunneled central venous catheter (CVC), nontunneled CVC, peripherally inserted central catheter (PICC), and totally implantable venous access port (TIVAP).¹ Pediatric patients often require stable, multifunctional, and comfortable long-term vascular access due to factors such as poor puncture cooperation, small vessel diameter, poor peripheral venous visibility and tolerance, high water content in the body leading to easy dehydration, and easy changes in condition after diseases.² The application of CVAD can significantly reduce the frequency of venipuncture, relieve the stimulation of drugs on the venous blood vessels, alleviate the pain and fear of the children, improve their medication compliance, ensure the effectiveness of intravenous

infusion, and improve the quality of disease treatment.^{3–5} Therefore, CVAD is widely used in pediatric clinics and has become an indispensable aspect of complex medical care for children with severe and chronic diseases.

Although CVAD has become an important tool in the pediatric treatment and nursing process, there are also risks of complications related to it, including CVAD-related thrombosis (CRT), phlebitis, fluid and blood leakage at the puncture point, catheter displacement, catheter obstruction, central line-associated blood-stream infection (CLABSI) and so on.^{6,7} Among these, CRT is one of the most common and serious complications. The prevalence of CRT in children varies significantly by country, age, disease, and medical institution, ranging from 2 to 81%,^{4,8–10} while in Chinese children without prophylactic treatment ranges from 20 to 66%.^{11,12} CRT has no obvious clinical symptoms in the early stage, but it may still cause serious side effects, not only increasing the

¹Department of Nursing, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. ²School of Nursing, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. ^{Elemail:} 691007@tjh.tjmu.edu.cn

patient pain and medical costs but also delaying treatment timing, affecting prognosis and quality of life, and in severe cases, may even lead to thromboembolism, endangering life.^{13–15}

Identifying risk factors and incidence of CRT facilitates clinical practitioners in the early identification of high-risk patients, designing specific preventive strategies, treatment regimens, and management plans, thereby effectively reducing the incidence of CRT in hospitalized children and alleviating unnecessary patient suffering. However, most current research on CRT involves only small-scale groups in isolated nursing units or specific disease types. To date, no up-to-date systematic review provides pooled estimates of the risk factors and prevalence of CRT in children. Therefore, this study had a dual purpose: 1. to explore potential risk factors for CRT in children and to determine a pooled level of CRT prevalence; and 2. to provide evidence-based recommendations to improve the recognition, control, and treatment of CRT in children, as well as better nursing management for CRT.

METHODS

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁶ The detailed research protocol can be accessed on the PROSPERO website (registration number: CRD42023421353).

Search strategy

Eight electronic databases were utilized to conduct a thorough literature search: PubMed, Web of Science, Embase, Cochrane Library, Scopus, China National Knowledge Infrastructure (CNKI), Sinomed, and Wanfang. The search in these databases was conducted from the earliest records available up to January 31st, 2024. The search strategy used a combination of Mesh terms and free words. The following Mesh terms and free words were mainly used: "child," "children," "adolescent," "infant," "pediatrics," "central venous access device-related thrombosis," "CRT," "catheter-related thrombosis," "risk factors," "protective factors," "predictors," "causality," "influencing factors". The full search strategy for each database is available in the Supplementary Materials. In addition, we screened the reference lists of all included studies for relevant studies that met the criteria. Grey literature was searched as well. Some authors were contacted through email to gather more information or clarify any uncertainties.

Inclusion criteria

- The study population was hospitalized children aged ≤18 years.
- The primary research objective was to explore the risk factors for CRT.
- The study results have at least one statistically significant predictor.
- Case-control studies or cohort studies.
- Published in English or Chinese.

Exclusion criteria

- Catheter-related infection, catheter dysfunction, or other catheter complications as the primary outcome indicators.
- Repeated published research.
- Case reports, study designs, or clinical trials.
- Reviews, editorials, letters, and conference abstracts.
- In vitro or animal research.
- Data were incomplete and could not be extracted.
- Unable to find the original article.

Data extraction

Data from each eligible study were independently extracted by two reviewers using a pre-designed data collection form. Any disagreements were resolved by discussions among all authors. Data on the following characteristics were obtained from all included studies (see Supplementary Table S1 for details):

- (1) Basic information: first author, country, year of publication, study duration, and study design.
- Demographic characteristics: study population, sample size, number of CRT, and CRT rate.
- (3) Catheter-related features: catheter type, CRT type, and diagnostic method.
- (4) Potential risk factors for CRT: odds ratios (OR) or relative risks (RR) values and 95% confidence interval (CI) were extracted for each risk factor. If the study did not provide specific values, it was calculated by constructing a 2 × 2 contingency table.

Quality assessment

Two reviewers evaluated the quality of each study independently using the Risk of Bias Assessment for Nonrandomized Studies tool,¹⁷ with any differences settled via group discussion. The tool assessed six domains of risk of bias: participant selection, confounding variables, exposure measurement, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. If all six domains were rated as low risk, the overall risk of bias for the study was low. The overall risk of bias was moderate if at least one domain was rated as unclear risk, and no domain was rated as high risk, and high if one or more domains were rated as high risk.

To ensure the accuracy of the assessment results, a third reviewer randomly selected five studies to check the data extraction and quality assessment.

Qualitative synthesis and quantitative meta-analysis

Qualitatively classify each risk factor as definite, likely, unclear, or not a risk factor based on the total number of studies with low and moderate bias risks and the proportion of studies demonstrating positive association (Box 1 in the supplementary material). If a risk factor was reported by more than two studies with low or moderate risk of bias, and the definition and reference range were sufficiently consistent, a quantitative meta-analysis was performed to estimate the combined OR.

Data were analyzed using Revman 5.4 software. In the metaanalysis of risk factors and CRT rate, the generic inverse variance method was applied, which only required effect estimate and standard error (SE).¹⁸ The SE was obtained by inverse transforming the 95% CI applying the standard normal distribution. Heterogeneity tests were performed on the studies included in the Metaanalysis to examine for the combinability of the results of each independent study. $P \ge 0.05$ and I-squared (I^2) < 50% considered less heterogeneity between studies and therefore a fixed-effects model was chosen for the analysis, conversely, P < 0.05 or $I^2 \ge 50\%$ considered greater heterogeneity, and a random-effects model was chosen.

Certainty of the evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method was used to assess the certainty of the evidence. In this method, observational studies were initially classified as low-quality evidence and then downgraded and upgraded according to five downgrading and three upgrading principles. The 5 downgrading factors included risk of bias, inconsistency, indirectness, imprecision, and publication bias, and the 3 upgrading factors included the magnitude of an effect, doseresponse gradient, and effect of plausible residual confounding. Based on these considerations, the overall certainty of each piece of evidence was rated as one of four levels: high, moderate, low, or very low.

RESULTS

The initial search of the databases extracted a total of 4193 articles, of which 1656 were duplicates and removed. The titles and abstracts of the remaining 2537 articles were screened according to the inclusion criteria and 142 were selected for full-text search. After a rigorous eligibility review, 45 articles met the inclusion criteria. In addition, two articles were found to meet the eligibility criteria in a search of the reference lists of the selected articles and grey literature. In the end, a total of 47 articles were included in this review, of which 43 contributed to the qualitative synthesis and quantitative meta-analysis (Fig. 1).

synthesis and quantitative meta-analysis (Fig. 1). Of the 47 studies, 19 were prospective^{4,13,19–35} and the rest were retrospective,^{9,12,36–61} of which 10 were multicenter^{4,9,13,21,23,26–28,49,59} and 37 were single-center.^{12,19,20,22,24,25,29–48,50–58,60,61} The sample sizes ranged from 47 to 158,299, with the two largest being 71,782¹³ and 158,299,⁵⁹ respectively. In addition, three studies constructed clinical prediction models.^{22,28,47} Table 1 lists the summary characteristics of the included studies.

Study populations and CRT rates in included studies

These studies investigated a series of hospitalized children of different ages and departments, of which 12 studies with all hospitalized children as the study population, 12 studies with PICU hospitalized children as the study population, six studies with NICU hospitalized children as the study population, one study with all ICU hospitalized children as the study population, four studies with leukemia children as the study population, two studies with infants under 1-year-old as the study population, and the other ten studies with children with a specific disease as the study population.

The combined CRT rate was 9.1% (95% *Cl*: 5.7–14.5%) with a high degree of heterogeneity ($l^2 = 100\%$). The combined CRT rate was 11.5% (95% *Cl*: 5.7–23.1%; $l^2 = 99\%$) in both male and female children. The frequency of CRT in PICU and NICU was available from 13 articles with 234,464 children and 7 articles with 6093 infants, which combined CRT rates were 10.7% (95% *Cl*: 3.8–23.7%; $l^2 = 100\%$), 2.9% (95% *Cl*: 1.0–6.5%; $l^2 = 96\%$), respectively. The combined CRT rate of children with leukemia was 13.0% (95% *Cl*: 2.9–38.3%; $l^2 = 98\%$) (Supplementary Material Figs. S1–6)

Quality of the CRT studies

The methodological quality of the included studies varied (Fig. 2 and Supplementary Material Fig. S7). Nine studies had a low overall risk of bias, as all six domains were categorized as low risk. Four studies had a high overall risk of bias, three of which were associated with confounding variables and one to participant selection. The remaining 34 studies had a moderate overall risk of bias, with at least one of the six domains having an unclear risk.

Risk factors of CRT in included studies

The 47 included studies reported 61 statistically significant risk factors for CRT (Table 1). These factors were classified into three categories: patient-related risk factors (37.7%, 23/61); CVAD-related risk factors (34.4%, 21/61), and treatment-related risk factors (27.9%, 17/61).



Fig. 1 Flow chart of the systematic literature search. Demonstrate the screening and inclusion process for systematic literature search.

	Potential risk factors	The line tip in IVC, history of thrombosis, history of catheterization, cardiac surgery	Cancer, age	Type of catheter	ALL	Asphyxia, infection, catheter indwelling time	Type of catheter, D-dimer	Location of insertion	Anticoagulant thromboprophylaxis	Thrombophilia	Age	Thrombophilia	Repetitive PICC insertions in the same arm, PICC material, number of lumens	Location of insertion, type of catheter, number of lumens	Birth weight <1000 g, <28 weeks gestation	Type of catheter, history of thrombosis, number of lumens, cancer, CLABSL/catheter dysfunction	Catheter indwelling time, D-dimer, fibrinogen, days of sedation, vasoactive drugs, pediatric critical illness score,	Cardiac arrest, location of insertion, hypotension	Difficult insertion, anesthesia time, blood products, length of hospital admission	Catheter size, location of insertion, cholestasis
	Diagnostic methods	Ultrasonography	Doppler ultrasound	Doppler ultrasound	Echocardiography	Ultrasonography	Doppler ultrasound	Doppler ultrasound	Ultrasonography	Doppler ultrasound, Venography	Doppler ultrasound	Ultrasonography	Ultrasonography	Ultrasonography	Doppler ultrasound	Doppler ultrasound	Doppler ultrasound	Ultrasonography	Ultrasonography	Ultrasonography
	CRT type	Not mention	DVT	Not mention	Not mention	Not mention	Not mention	VTE	VTE	DVT	DVT	DVT	DVT, SVT	DVT	Not mention	ИТЕ	DVT	Not mention	internal jugular vein thrombosis	Not mention
	CRT rate	64 (10.4%)	17 (18.3%)	18 (9.4%)	18 (17.3%)	16 (2.2%)	19 (14.0%)	40 (1.5%)	5 (10.6%)	20 (9.3%)	16 (15.8%)	37 (43.5%)	92 (4.2%)	60 (18.0%)	69 (10.7%)	94 (5.4%)	53 (22.6%)	32 (21.9%)	31 (38.8%)	17 (2.2%)
	Catheter type	CVC, PICC	CVC	tunneled CVC, PICC	CVC	CVC	PICC	CVC	CVC	PICC	nontunneled CVC	nontunneled CVC	PICC	CVC	CVC	РІСС, ТІ.	CVC	CVC	CVC	PICC,UVC,UAC,tunneled long-term catheter
	sample size	613	93	192	104	729	136	2714	47	214	101	85	2180	333	645	1742	234	146	80	766
	Study population	Infants younger than 1 year	PICU	Children with Ieukemia	Hospitalized children	NICU	PICU	PICU	Children with active IBD	Hospitalized children	PICU	PICU	Hospitalized children	Infants younger than 1 year	NICU	Hospitalized children	Children with congenital heart disease	PICU	Pediatric surgical patients	NICU
led in this review	Sample sources	Single-center	Single-center	Single-center	Single-center	Single-center	Single-center	Single-center	Single-center	Single-center	Multicenter	Multicenter	Single-center	Single-center	Single-center	Multicenter	Single-center	Single-center	Single-center	Single-center
17 studies includ	Study design	Retrospective cohort	Prospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort	Prospective cohort	Prospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort	Prospective cohort	Prospective cohort	Prospective cohort	Retrospective cohort
eristics of the 4	Year of publication (data)	2021 (2015–2018)	1998 (1996–1997)	2018 (2008–2014)	2016 (2008–2013)	2022 (2013–2016)	2020 (2013–2018)	2019 (2013–2016)	2018 (2015–2017)	2007 (2004–2005)	2013 (2009–2011)	2015 (2012–2013)	2018 (2010–2015)	2012 (2005–2009)	2014 (2003–2009)	2020 (2013–2018)	2022 (2021–2022)	2019 (NA)	2022 (2018–2020)	2019 (2013–2015)
ımmary charact	Country of study	America	Canada	France	Canada	Poland	China	America	America	Canada	America	America	Canada	America	Canada	America	China	Australia	Korea	America
Table 1. Su	Author	Badheka	Beck	Charny	Chen	Chojnacka	Deng	Derderian	Diamond	Dubois	Faustino	Faustino	Gnannt	Gray	Haddad	Jaffray	Jiang	Jones	Кï	Lambert

	Potential risk factors	Sex, age, ICU admission, catheter size, catheter duwelling time, surgery, infection, cardiac disease	Age, hypertonic liquid, catheter placing personnel, insertion length, D- dimer, limb exercises	Cardiovascular surgery, NON-PICC	Mechanical ventilation duration	Tissue plasminogen activator	Side of insertion, location of insertion, insertion technique	Location of insertion	Age, blood products, surgery, location of insertion, risk of mortality (PIM2 score)	Location of insertion	Catheter to vein ratio,procedure time, location of insertion, SVT, catheter indwelling time,non- optimal tip location	Type of catheter, side of insertion	Age, type of catheter, sepsis, tissue plasminogen activator	Location of insertion, number of lumens, sex	Type of catheter, line presence at admission geographic location of line placement, freestanding freestanding	TPN, hypertonic liquid	CLABSI
	Diagnostic methods	Doppler ultrasound, computed tomography	Doppler ultrasound	Doppler ultrasound, phlebography, echocardiogram	Ultrasonography	Radiological imaging	Bilateral venography, ultrasound, MRI, echocardiography	Venography, ultrasonography	Ultrasonography	Ultrasonography, computed tomography, MRI, venography	Doppler ultrasound	Radiographic imaging	Doppler ultrasound, MRV, computed tomography	Doppler ultrasound	Not mention	Ultrasonography	Doppler ultrasound or venography
	CRT type	DVT	Not mention	DVT	DVT	VTE	VTE	VTE	DVT	DVT	DVT, SVT	VTE	VTE	Not mention	VTE	DVT	Not mention
	CRT rate	282 (15.4%)	158 (26.6%)	22 (8.3%)	23 (29.9%)	28 (5.1%)	29 (34.1%)	21 (13.3%)	53 (30.3%)	13 (6.2%)	88 (41.5%)	70 (2.6%)	18 (9.1%)	64 (30.3%)	(%) (0.6%)	7 (6.7%)	13 (12.4%)
	Catheter type	CVC	CVC	CVC, PICC, UVC	CVC, PICC	CVC	CVL	CVL	nontunneled CVC	CVC	PICC	PICC, CVC	CVC	nontunneled CVC	CVAD	CVC	CVC
	sample size	1830	594	264	77	546	85	158	175	209	212	2709	198	211	71782	105	105
	Study population	Ū	Hospitalized children	NICU	Children with sTBI	Pediatric oncology patients	Children with leukemia	Hospitalized children	PICU	Pediatric trauma patients	Hospitalized children	Hospitalized children	Children with hematologic malignancies	Hospitalized children	D	PICU	Children in hematology
	Sample sources	Single-center	Single-center	Single-center	Single-center	Multicenter	Multicenter	Multicenter	Multicenter	Multicenter	Single-center	Single-center	Single-center	Single-center	Multicenter	Single-center	Single-center
	Study design	Retrospective cohort	Retrospective cohort	Prospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort	Prospective cohort	Prospective cohort	Retrospective cohort	Prospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort	Prospective cohort	Retrospective cohort	Prospective cohort
	Year of publication (data)	2021 (2015–2018)	2022 (2019–2020)	2021 (2015–2016)	2023 (2015–2021)	2018 (2000–2015)	2003 (1997–1999)	2005 (1998–1999)	2016 (2009–2013)	2019 (2006–2016)	2016 (2012–2015)	2018 (2012–2016)	2018 (2012–2016)	2019 (2015–2016)	2020 (2010–2015)	2016 (2011–2015)	2005 (2000–2002)
htinued	Country of study	China	China	Argentina	America	Canada	Austria	Austria	America	America	Spain	America	America	Sweden	America	China	Netherlands
Table 1. co	Author	Э		Longo	Lovett	MacLean	Male	Male	Marquez	McLaughlin	Menêndez	Noonan	Onyeama	Östlund	Patel	Pei	Rooden

	Potential risk factors	Type of catheter, location of insertion, geographic location of line placement	History of catheterization	Age, dialysis, diagnosis of IBD or SBS	CLABSI	Number of catheters, age, LCOS, sepsis, CLABSI, cardiac catheterization, cardiac surgery	Age, mechanical ventilation, surgery, acraiac cardiac, type achteter, ECMO, neurological disease, autoimmune disease, ancer	Type of catheter	D-dimer	Side of insertion, D-dimer	Congenital heart defect, TPN	Type of catheter, glucocorticoid, TPN	Mothers' use of anticoagulants, cardiac insufficiency, TTTS-donor	vein thrombosis, us thrombosis, 7L es, MRI magnetic syndrome, ECMO
	Diagnostic methods	Doppler ultrasound, echocardiography	Doppler ultrasounds, contrast venograms, MRA	Doppler ultrasound, venogram, MRV, echocardiogram	Ultrasonography	Ultrasonography	Not mention	Doppler ultrasound	Doppler ultrasound	Ultrasonography	Ultrasonography	Doppler ultrasound	Ultrasonography	ive care unit, DVT deep 2, SVT superficial veno CVL central venous lin 5 low cardiac output
	CRT type	Not mention	Not mention	DVT, SVT	Not mention	DVT	VTE	Not mention	VTE	Not mention	VTE	DVT	Not mention	pediatric intens ex of mortality ic brain injury, syndrome, <i>LCO</i>
	CRT rate	62 (1.7%)	292 (26.3%)	36 (4.4%)	13 (9.7%)	57 (7.6%)	1602 (1.0%)	14 (2.5%)	19 (2.1%)	33 (28.4%)	125 (5.2%)	87 (25.7%)	7 (0.23%)	ena cava, <i>PICU</i> 2: pediatric ind severe traumat short bowel s
	Catheter type	cvL	PICC	PICC, tunneled, nontunneled, and port	femoral CVC	nontunneled CVC,UVC	CVC	FVC, UVC, PICC	PICC	PICC	CVL	CVC	PICC	ral catheter, I/VC inferior vi natory bowel disease, PIM al arterial catheters, <i>sTBI</i> nance angiograms, <i>SBS</i>
	sample size	3733	1100	815	134	747	158299	552	806	116	2388	338	3043	Ily inserted centu sm, <i>IBD</i> inflamm ter, <i>UAC</i> umbilic. A magnetic reso ion syndrome.
	Study population	Hospitalized children	Hospitalized children	Noncritically ill Children	PICU	CICU	PC	NICU	Children with Ieukemia	Children with Ieukemia	Hospitalized children	PICU	NICU	PICC peripheral thromboembolii I venous cathet I nutrition, <i>MR</i> o-twin transfusi
	Sample sources	Single-center	Single-center	Single-center	Single-center	Single-center	Multicenter	Single-center	Single-center	Single-center	Single-center	Single-center	Single-center	ral venous catheter, e unit, <i>VTE</i> venous t ction, <i>UVC</i> umbilica <i>PN</i> total parentera atheter, <i>TTT</i> twin-t
	Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort	Retrospective cohort	Prospective cohort	Retrospective cohort	ombosis, CVC centu natal intensive car bloodstream infe- ce venography, 7 femoral venous c
	Year of publication (data)	2015 (2010–2012)	2017 (2010–2013)	2015 (2009–2012)	2015 (2007–2009)	2019 (2017)	2018 (2009–2014)	2018 (2006–2013)	2021 (2015–2019)	2017 (2014)	2015 (2007–2012)	2020 (2016)	2022 (2014–2021)	wice-related thro temia, <i>NICU</i> neor line-associated agnetic resonanc tygenation, <i>FVC</i> i
ntinued	Country of study	America	America	America	Netherlands	America	America	Netherlands	China	China	America	China	China	enous access de nphoblastic leuk e, <i>CLABSI</i> central naging, <i>MRV</i> mé al membrane ox
Table 1. co.	Author	Shah	Shin	Smitherman	Sol	Steen	Tran	Verheij	Wang	Wei	Wisecup	Zeng	Zhu	<i>CRT</i> central v <i>ALL</i> acute lyn tunneled lint resonance in extracorpore.

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6

SPRINGER NATURE

Based on the qualitative synthesis, six variables were considered to be definite risk factors for CRT, including D-dimer, location of insertion, type of catheter, number of lumens, catheter indwelling time, and CLABSI. Eleven variables were considered likely associated with CRT, including gastrointestinal diseases, history of catheterization, thrombophilia, geographic location of line placement, catheter dysfunction, number of catheters, insertion length (cm), catheter to vein ratio, dialysis,



Fig. 2 Summary of risk of bias in the included studies. A summary presentation of the assessment results of risk of bias for the 47 studies.

hypertonic liquid, and cardiac catheterization. For 42 variables, the relationship with CRT was deemed unclear due to conflicting results from studies assessed as having low and moderate risk of bias, or because they were positively associated in only one study. Additionally, birth weight and gestational age were considered non-risk factors (Table 2).

Meta-analyses were implemented for risk factors that were reported by at least two low or moderate risk of bias studies with a consistent definition and reference range (Table 3 and Figs. 3–6).

GRADE assessment of evidence

Supplementary Table S2 shows GRADE assessments for the certainty of evidence. Due to the design of the observational studies, all evidence was initially rated as low certainty. Based on five downgrading and three upgrading principles, 17 pieces of evidence were still rated as low certainty, and the remaining 44 pieces of evidence were downgraded to very low certainty for serious inconsistency and imprecision.

DISCUSSION

Our study is the latest systematic review of risk factors and the incidence of CRT in hospitalized children. Based on 47 studies included in the current meta-analysis, which involved a total

Table 2. Summary of CRT risk factors										
Categories	Risk factors									
Definite factors (6)	D-dimer, location of insertion, type of catheter, number of lumens, catheter indwelling time and CLABSI									
Likely factors (11)	Gastrointestinal diseases, history of catheterization, thrombophilia, geographic location of line placement, catheter dysfunction, number of catheters, insertion length (cm), catheter to vein ratio, dialysis, hypertonic liquid, and cardiac catheterization									
Unclear factors (42)	Sex, age, history of thrombosis, infection, sepsis, cancer, cardiovascular disease, neurological disease, autoimmune disease, asphyxia, ECMO, catheter size, side of insertion, non-optimal tip location, difficult insertion, TPN, surgery, mechanical ventilation, mechanical ventilation duration, mechanicalthromboprophylaxis / limb exercises, tissue plasminogen activator, glucocorticoid, vasoactive drugs, blood products, length of hospital admission, fibrinogen, PICC material, catheter placing personnel, insertion technique, the line tip in IVC, repetitive insertions in the same arm, procedure time, line presence at admission, anesthesia time, SVT, ICU admission, days of sedation, pediatric critical illness score, risk of mortality (PIM2 score), mothers' use of anticoagulants, TTTS-donor, freestanding children's hospital									
Not a risk factor (2)	Birth weight and gestational age									

CLABSI central line-associated bloodstream infection, ECMO extracorporeal membrane oxygenation, TPN total parenteral nutrition, PICC peripherally inserted central catheter, IVC inferior vena cava, SVT superficial venous thrombosis, ICU intensive care unit, PIM2 pediatric index of mortality 2, TTTS twin-to-twin transfusion syndrome.

Table 3. The effect size of risk factors for CRT in children

Categories	Potential risk factors	n	Effect siz	e		Hetero	ogeneity	Analyzed model	
			odds ratio	95% CI	P-Value	l ² (%)	P-Value	model	
Patient-related risk	Sex (Male vs Female)	23	1.03	0.95–1.12	0.43	24	0.15	Fixed	
factors	Age: <1 year old	10	1.27	1.00-1.62	0.05	79	<0.00001	Random	
	Age: >5 year old	2	1.30	0.86–1.96	0.21	0	0.50	Fixed	
	Age: >13 year old	3	1.57	0.43-5.70	0.50	72	0.03	Random	
	Age: continuous variable	5	1.01	1.00-1.02	0.21	73	0.005	Random	
	History of thrombosis	9	2.78	1.90-4.07	<0.00001	0	0.95	Fixed	
	History of catheterization	3	1.90	1.23–2.92	0.003	28	0.25	Fixed	
	Thrombophilia	4	2.28	1.32-3.95	0.003	0	0.60	Fixed	
	Infection	11	1.37	0.91-2.06	0.13	64	0.002	Random	
	Sepsis	8	1.20	0.62-2.31	0.58	75	0.0002	Random	
	Cancer	13	1.38	0.97-1.95	0.07	49	0.02	Random	
	Cardiovascular disease	18	1.01	0.70-1.44	0.97	76	< 0.00001	Random	
	Gastrointestinal diseases	4	2.09	0.95-4.60	0.07	76	0.006	Random	
	Neurological disease	3	1.05	0.67–1.63	0.84	58	0.09	Random	
	Autoimmune disease	2	3.82	1.42-10.31	0.008	0	0.38	Fixed	
	Asphyxia	2	3.70	0.26-51.97	0.33	71	0.06	Random	
	ECMO	3	1.52	1.32–1.75	< 0.00001	0	0.57	Fixed	

Tab	e	3.	continued

Categories	Potential risk factors	n	Effect size	2		Hetero	ogeneity	Analyzed
			odds ratio	95% CI	P-Value	l ² (%)	P-Value	model
CVAD-related risk	Geographic location of line placement	3	0.27	0.21-0.34	<0.00001	0	1.00	Fixed
factors	Location of insertion 1 (Femoral VS Jugular)	15	1.69	0.98-2.91	0.06	88	<0.00001	Random
	Location of insertion 2 (Femoral VS Subclavian)	12	2.68	2.08-3.46	<0.00001	37	0.09	Fixed
	Location of insertion 3 (Subclavian VS Jugular)	13	0.81	0.42-1.54	0.51	74	<0.00001	Random
	Location of insertion 4 (Femoral VS Upper extremity)	4	4.81	1.08–21.29	0.04	74	0.009	Random
	Location of insertion 5 (Jugular VS Upper extremity)	3	2.30	1.18–4.48	0.01	0	0.62	Fixed
	Location of insertion 6 (Subclavian VS Upper extremity)	2	0.68	0.32–1.48	0.33	37	0.21	Fixed
	Location of insertion 7 (Brachial VS Basilic)	3	0.71	0.47-1.08	0.11	0	0.73	Fixed
	Location of insertion 8 (Brachial VS Cephalic)	3	0.89	0.49–1.64	0.72	35	0.21	Fixed
	Location of insertion 9 (Cephalic VS Basilic)	4	0.84	0.52–1.36	0.48	0	0.82	Fixed
	Location of insertion 10 (Basilic VS Median vein)	2	0.95	0.38–2.36	0.91	0	0.76	Fixed
	Location of insertion 11 (Upper extremity VS Lower extremity)	3	0.63	0.12–3.39	0.59	82	0.003	Random
	Catheter size (<5 F VS \geq 5 F)	6	0.68	0.47-1.00	0.05	0	0.53	Fixed
	Catheter dysfunction	4	1.74	1.29–2.35	0.0003	0	0.98	Fixed
	Side of insertion (right VS left)	15	0.97	0.77-1.22	0.81	46	0.02	Random
	Type of catheter 1 (PICC VS tunnedlled CVC)	6	1.34	0.73–2.46	0.34	64	0.02	Random
	Type of catheter 2 (PICC VS nontunneled CVC)	6	1.00	0.52–1.93	0.99	91	<0.00001	Random
	Type of catheter 3 (PICC VS Tunneled lines)	6	1.81	1.02-3.21	0.04	76	0.0008	Random
	Type of catheter 4 (PICC VS TIVAP)	4	2.17	0.84–5.60	0.11	72	0.01	Random
	Type of catheter 5 (PICC VS Hemodialysis catheters)	3	1.00	0.84–1.19	1.00	45	0.16	Fixed
	Type of catheter 6 (NON-PICC)	5	0.70	0.31–1.56	0.38	82	0.0002	Random
	Type of catheter 7 (tunnedlled CVC VS nontunneled CVC)	5	0.62	0.35–1.10	0.10	54	0.07	Random
	Type of catheter 8 (TIVAP VS tunnedlled CVC)	4	0.68	0.30-1.54	0.36	58	0.07	Random
	Type of catheter 9 (TIVAP VS nontunneled CVC)	3	0.39	0.09–1.64	0.20	65	0.06	Random
	Non-optimal tip location	4	2.75	1.36–5.56	0.005	0	0.82	Fixed
	Number of lumens (Multiple VS Singer)	10	1.82	1.13–2.93	0.01	87	<0.00001	Random
	Number of catheters (Multiple VS Singer)	3	2.97	2.16-4.08	<0.00001	33	0.23	Fixed
	Catheter indwelling time	6	1.01	1.00-1.02	0.008	47	0.09	Fixed
	CLABSI	9	4.93	3.02-8.05	<0.00001	41	0.10	Fixed
	Difficult insertion	7	1.57	0.90-2.73	0.11	67	0.006	Random
Treatment-related	TPN	14	1.37	1.10–1.71	0.004	26	0.18	Fixed
risk factors	Surgery	13	0.90	0.62–1.32	0.59	86	<0.00001	Random
	Dialysis	4	1.85	1.56–2.19	<0.00001	6	0.36	Fixed
	Mechanical ventilation	8	1.50	1.01-2.22	0.04	66	0.005	Random
	Mechanical thromboprophylaxis/limb exercises	4	1.27	0.44–3.67	0.65	81	0.001	Random
	Tissue plasminogen activator	2	0.32	0.01-14.82	0.56	92	0.0003	Random
	Glucocorticoid	2	2.17	1.36-3.48	0.001	0	0.73	Fixed
	Vasoactive drugs	7	1.70	1.22-2.37	0.002	37	0.15	Fixed
	Hypertonic liquid	3	3.42	0.76-15.46	0.11	55	0.11	Random
	Blood products	7	1.36	0.91-2.03	0.14	0	0.57	Fixed
	Cardiac catheterization	2	3.15	1.27-7.83	0.01	88	0.004	Random
	Length of hospital admission	2	1.51	0.54-4.22	0.43	73	0.05	Random

CRT central venous access device-related thrombosis, *CI* confidence interval, *I*² tested for heterogeneity, *ECMO* extracorporeal membrane oxygenation, *PICC* peripherally inserted central catheter, *CVC* central venous catheter, *TIVAP* totally implantable venous access port, *CLABSI* central line-associated bloodstream infection, *TPN* total parenteral nutrition.



Fig. 3 Meta-analysis of patient-related risk factors. Forest plots of odds ratios (OR) that were included in the quantitative meta-analysis and the associated overall OR. For each OR, the size of the red square region is proportional to the corresponding study weight. Diamond shape intervals represent the overall OR. I² represents the fraction of variability among the individual OR that cannot be explained by sampling variability.

0.1

0.01

Heterogeneity: $Chi^2 = 1.87$, df = 3 (P = 0.60); $I^2 = 0\%$ Test for overall effect: Z = 2.96 (P = 0.003)

100

Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Odds F IV, Ramdon	Ratio n, 95% Cl	
1.4 >13 year old							
Faustino 2013	2.6462	1.0226	22.3%	14.10 [1.90, 104.6]			
Faustino 2015	-0.4343	0.7281	30.2%	0.65 [0.16, 2.70]			
Tran 2018	-0.0202	0.0786	47.5%	0.98 [0.84, 1.14]	-		
Total (95%CI)			100%	1.57 [0.43, 5.70]			
Heterogeneity: Tau ²	² = 0.91; Chi ² = 7.10, df	= 1 (P = 0	0.03); l ² = 72	%			
Test for overall effect	ct: Z = 0.68 (P = 0.50)			H			—
				0.01	0.1 1	10	100
				Odds Ratio	Odds F	Ratio	
Study	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random	n, 95% Cl	
1.5 age (continuou	s variable)						
Badheka 2021	0.002	0.0023	49.4%	1.00 [1.00, 1.01]	-		
Kim 2022	1.0986	0.652	0.0%	3.00 [0.84, 10.77]	+		
Marquez 2016	0.009	0.003	47.2%	1.01 [1.00, 1.01]	-		
Onyeama 2018	0.0862	0.0339	3.3%	1.09 [1.02, 1.16]			
Pei 2016	-0.4095	0.2522	0.1%	0.66 [0.41, 1.09]			
Total (95%CI)			100%	1.01 [1.00, 1.02]			
Heterogeneity: Tau ²	² = 0.00; Chi ² = 14.72, o	df = 4 (P =	0.005); l ² =	73%			
Test for overall effect	ot: Z = 1.25 (P = 0.21)			F			

				Odds Ratio	Odds Ratio	
Study	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI	
1.6 history of thror	mbosis					
Badheka 2021	0.8738	0.3725	27.3%	2.40 [1.15, 4.97]		
Beck 1988	0.6144	1.2003	2.6%	1.85 [0.18, 19.43]		
Dubois 2007	0.6302	1.5665	1.5%	1.88 [0.09, 40.47]		
Faustino 2013	0.6122	1.1883	2.7%	1.84 [0.18, 18.94]		
Faustino 2015	1.7394	1.652	1.4%	5.69 [0.22, 145.1]		
Jaffray 2020	1.2821	0.2733	50.7%	3.60 [2.11, 6.16]		
Marquez 2016	0.8502	1.0151	3.7%	2.34 [0.32, 17.11]		
Onyeama 2018	0.0583	1.5106	1.7%	1.06 [0.05, 20.47]		
Wisecup 2015	0.434	0.6673	8.5%	1.54 [0.42, 5.71]		
Total (95%CI)			100%	2.78 [1.90, 4.07]	-	
Heterogeneity: Chi ²	= 2.76, df = 8 (P = 0.9	5); l ² = 0%				
Test for overall effect	ct: Z = 5.26 (P < 0.0000	001)				
				0.01	0.1 1	10 100

				Odds Ratio	Odds Ratio	
Study	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
1.7 history of cathe	terization					
Badheka 2021	1.0303	0.4193	27.3%	2.80 [1.23, 6.37]		
Kim 2022	-0.1061	0.543	16.3%	0.90 [0.31, 2.61]		
Shin 2017	0.6678	0.2921	56.3%	1.95 [1.10, 3.46]		
Total (95%CI)			100%	1.90 [1.23, 2.92]	-	
Heterogeneity: Chi ² :	= 2.76, df = 8 (P = 0.25	5); l ² = 28%	6			
Test for overall effect	t: Z = 2.92 (P = 0.003)			L		
				0.01	0.1 1 1	0 100

Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% Cl	IV	Odds Ratio , Fixed, 95% Cl	
1.8 thrombophilia							
Dubois 2007	1.9564	0.9456	8.7%	7.07 [1.11, 45.14]			
Faustino 2013	1.6452	2.018	1.9%	5.18 [0.10, 270.5]			
Faustino 2015	0.6831	0.2999	86.5%	1.98 [1.10, 3.56]			
Onyeama 2018	1.1738	1.6511	2.9%	3.23 [0.13, 82.26]			
Total (95%CI)			100%	2.28 [1.32, 3.95]		-	
Heterogeneity: Chi ²	= 1.87, df = 3 (P = 0.60	0); $l^2 = 0\%$					
Test for overall effect	ct: Z = 2.96 (P = 0.003)						
				0.01	0.1	1 1	0 10

Fig. 3 Continued

log[Oddo Potio]	ee.	Woight	Odds Ratio	Odds Ratio	
	35	weight			
1.5339	0.695	5.7%	4.64 [1.19, 18.10]		
0.4134	0.5049	8.2%	1.51 [0.56, 4.07]		
0.5365	0.4935	8.4%	1.71 [0.65, 4.50]		
0.0729	0.5353	7.8%	1.08 [0.38, 3.07]		
0.7002	0.1522	14.7%	2.01 [1.49, 2.71]		
0.0862	0.349	11.0%	1.09 [0.55, 2.16]		
0.3669	0.5111	8.1%	1.44 [0.53, 3.93]		
-0.0202	0.4203	9.7%	0.98 [0.43, 2.23]		
-1.0542	0.3404	11.2%	0.35 [0.18, 0.68]		
0.9544	0.6517	6.2%	2.60 [0.72, 9.32]		
0.6633	0.4586	9.0%	1.94 [0.79, 4.77]		
		100%	1.37 [0.91, 2.06]	►	
27; Chi ² = 28.12, df =	= 10 (P = 0.	002); $l^2 = 649$	%		
= 1.51 (P = 0.13)			1	1	, i
			0.01	0.1 1 10	100
log[Oddo Potio]	ee.	Woight	Odds Ratio	Odds Ratio	
	log[Odds Ratio] 1.5339 0.4134 0.5365 0.0729 0.7002 0.0862 0.3669 -0.0202 -1.0542 0.9544 0.6633 27; Chi ² = 28.12, df = = 1.51 (P = 0.13)	log[Odds Ratio] SE 1.5339 0.695 0.4134 0.5049 0.5365 0.4935 0.0729 0.5353 0.7002 0.1522 0.0862 0.349 0.3669 0.5111 -0.0202 0.4203 -1.0542 0.3404 0.9544 0.6517 0.6633 0.4586 27; Chi ² = 28.12, df = 10 (P = 0. = 1.51 (P = 0.13) SE	log[Odds Ratio]SEWeight 1.5339 0.695 5.7% 0.4134 0.5049 8.2% 0.5365 0.4935 8.4% 0.0729 0.5353 7.8% 0.7002 0.1522 14.7% 0.0862 0.349 11.0% 0.3669 0.5111 8.1% -0.0202 0.4203 9.7% -1.0542 0.3404 11.2% 0.9544 0.6517 6.2% 0.6633 0.4586 9.0% 27 ; Chi ² = 28.12, df = 10 (P = 0.002); l ² = 645= 1.51 (P = 0.13)SE	Iog[Odds Ratio] SE Weight IV, Random, 95% CI 1.5339 0.695 5.7% 4.64 [1.19, 18.10] 0.4134 0.5049 8.2% 1.51 [0.56, 4.07] 0.5365 0.4935 8.4% 1.71 [0.65, 4.50] 0.0729 0.5353 7.8% 1.08 [0.38, 3.07] 0.7002 0.1522 14.7% 2.01 [1.49, 2.71] 0.0862 0.349 11.0% 1.09 [0.55, 2.16] 0.3669 0.5111 8.1% 1.44 [0.53, 3.93] -0.0202 0.4203 9.7% 0.98 [0.43, 2.23] -1.0542 0.3404 11.2% 0.35 [0.18, 0.68] 0.9544 0.6517 6.2% 2.60 [0.72, 9.32] 0.6633 0.4586 9.0% 1.94 [0.79, 4.77] 100% 1.37 [0.91, 2.06] 27; Chi ² = 28.12, df = 10 (P = 0.002); l ² = 64% = 1.51 (P = 0.13) Image: Paid on Paid 0.01	Odds Ratio Odds Ratio Odds Ratio $log[Odds Ratio]$ SE Weight IV, Random, 95% CI IV, Ramdom, 95% CI 1.5339 0.695 5.7% 4.64 [1.19, 18.10] IV, Ramdom, 95% CI 0.4134 0.5049 8.2% 1.51 [0.56, 4.07] IV, Ramdom, 95% CI 0.5365 0.4935 8.4% 1.71 [0.65, 4.50] IV 0.7002 0.1522 14.7% 2.01 [1.49, 2.71] IV 0.8662 0.349 11.0% 1.09 [0.55, 2.16] IV 0.3669 0.5111 8.1% 1.44 [0.53, 3.93] IV -0.0202 0.4203 9.7% 0.98 [0.43, 2.23] IV -1.0542 0.3404 11.2% 0.35 [0.18, 0.68] IV 0.9544 0.6517 6.2% 2.60 [0.72, 9.32] IV 0.6633 0.4586 9.0% 1.94 [0.79, 4.77] IV 100% 1.37 [0.91, 2.06] IV Odds Ratio 27; Chi ² = 28.12, df = 10 (P = 0.002); l ² = 64% IV Dodds Ratio Odds Ratio <

-			-		
1.10 sepsis					
Chen 2016	0.8772	0.5514	12.6%	2.4 [0.82, 7.08]	
Chojnacka 2022	0.6931	0.7906	9.3%	2.00 [0.42, 9.42]	
Dubois 2007	-0.755	1.0502	6.6%	0.47 [0.06, 3.68]	
Faustino 2013	0.2538	0.5665	12.4%	1.29 [0.42, 3.91]	
Onyeama 2018	-2.0402	0.6014	11.8%	0.13 [0.04, 0.42]	
Ostlund 2019	-0.1744	0.1717	18.3%	0.84 [0.60, 1.18]	
Steen 2019	1.6864	0.5605	12.5%	5.40 [1.80, 16.20]	
Zeng 2020	0.5461	0.3108	16.5%	1.73 [0.94, 3.17]	
Total (95%CI)			100%	1.20 [0.62, 2.31]	
Heterogeneity: Tau ² = 0.58;	Chi ² = 28.48, df	= 7 (P = 0.0	0002); l ² = 75	5%	
	(

Test for overall effect: Z = 0.55 (P = 0.58)

l est for overall effect:	Z = 0.55 (P = 0.58)			↓ 0.01	0.1 1 10	
Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Odds Ratio IV, Ramdom, 95% Cl	
1.11 cancer						
Beck 1988	1.9136	0.8912	3.4%	6.78 [1.18, 38.87]		-
Chen 2016	1.9196	0.5714	6.7%	6.82 [2.22, 20.90]		
Dubois 2007	0.47	0.5177	7.6%	1.60 [0.58, 4.41]		
Faustino 2013	-0.3365	1.5357	1.3%	0.71 [0.04, 14.49]		
Faustino 2015	-0.5196	1.6516	1.1%	0.59 [0.02, 15.14] -		
Jaffray 2020	0.303	0.2118	16.4%	1.35 [0.89, 2.05]	+	
Kim 2022	0.2652	0.714	4.8%	1.30 [0.32, 5.28]		
Menendez 2016	-0.2723	0.31	13.0%	0.76 [0.41, 1.40]		
Ostlund 2019	-0.462	0.3299	12.3%	0.63 [0.33, 1.20]		
Smitherman 2015	0.3365	0.5253	7.5%	1.40 [0.50, 3.92]		
Sol 2015	-1.5282	1.4661	1.4%	0.22 [0.01, 3.84]		
Tran 2018	0.392	0.1514	18.5%	1.48 [1.10, 1.99]		
Zeng 2020	0.9122	0.6188	6.0%	2.49 [0.74, 8.37]		
Total (95%CI)			100%	1.38 [0.97, 1.95]	•	
Heterogeneity: Tau ² =	0.15; Chi ² = 23.48, df =	= 12 (P = 0	.02); l ² = 49%	5	•	

⊢ 0.01

0.1

Test for overall effect: Z = 1.80 (P = 0.07)

Fig. 3 Continued

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1	2
т	2

Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Odds Ratio IV, Ramdom, 95% Cl
1.12 cardiovascular diseas	e				
Badheka 2021	-0.7809	0.6047	4.7%	0.46 [0.14, 1.50]	
Chen 2016	0.4187	0.7164	3.9%	1.52 [0.37, 6.19]	
Chojnacka 2022	0.1744	0.972	2.6%	1.19 [0.18, 8.00]	
Faustino 2013	-0.5596	0.8031	3.4%	0.57 [0.12, 2.76]	
Faustino 2015	-0.6821	0.5356	5.3%	0.51 [0.18, 1.44]	
Jones 2019	1.2	0.4823	5.8%	3.32 [1.29, 8.54]	
Lambert 2019	0.0014	1.0424	2.3%	1.00 [0.13, 7.73]	
Li 2021	-0.8712	0.1625	9.0%	0.42 [0.30, 0.58]	
Marquez 2016	-0 462	0.3958	6.7%	0.63 [0.29, 1.37]	
Menendez 2016	0.0556	0.3827	6.8%	1 06 [0 50 2 24]	
Noonan 2018	-0 6543	0 2956	7.7%	0.52 [0.29, 0.93]	_
Shin 2017	-0.0543	0.2330	7.1%	0.52 [0.29, 0.95]	_ _
Sol 0015	-0.3021	0.0270	0.70/	0.07 [0.00, 1.00]	
SUI 2015 Steen 2010	0.9923	0.7378	3.1% 7.4%	2.70 [0.04, 11.45]	
Sieen 2019	1.1032	0.3227	7.4%	3.20 [1.70, 0.02]	-
Iran 2018	-0.0513	0.0941	9.5%	0.95 [0.79, 1.14]	
wisecup 2015	1.12/3	0.4067	6.5%	3.09 [1.39, 6.85]	
∠eng 2020	-0.4007	0.4408	6.2%	0.67 [0.28, 1.59]	
Znu 2022	3.3831	1.6046	1.1%	29.46 [1.27, 684]	•
Total (95%CI)	0		100%	1.01 [0.70, 1.44]	Ť
Heterogeneity: Tau ² = 0.34; (Chi ² = 71.12, df = 1	7 (P < 0.0	0001); l ² = 7	6%	
Test for overall effect: Z = 0.0	04 (P = 0.97)				
				0.01	0.1 1 10
Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Odds Ratio IV, Ramdom, 95% Cl
1.13 gastrointestinal diseas	ses				
Lambert 2019	1.0113	0.517	22.1%	2.75 [1.00, 7.57]	
Smitherrman 2015	1.5476	0.4334	24.8%	4.70 [2.01, 10.99]	
Tran 2018	0.077	0 1468	33.2%	1 08 [0 81 1 44]	-
Wisecup 2015	0.5138	0.5952	19.8%	1.67 [0.52, 5.37]	
Total (95%CI)			100%	2 09 [0 95 4 60]	
Laterageneity $T_{au}^2 = 0.47$	0.5 ² 10.61 df 0		c), 12 700/		
Heterogeneity: $1 au^2 = 0.47$; 0	oni ⁻ = 12.61, at = 3	(P = 0.00)	b); I [−] = 76%	L	
Test for overall effect: $Z = 1.8$	32 (P = 0.07)			0.01	0.1 1 10
Study	log[Odds Batio]	SF	Weight	Odds Ratio	Odds Ratio
4.4.4 m a suma la mina la dia a a a a	log[oudo hallo]		noight		
1.14 neurological disease					
Tran 2018	0.2927	0.1054	52.5%	1.34 [1.09, 1.65]	
114112010			1/ 0%	0 46 [0 16 1 20]	
Wisecup 2015	-0.7841	0.5295	14.078	0.40 [0.10, 1.29]	
Wisecup 2015 Zeng 2020	-0.7841 0.0055	0.5295 0.2581	33.5%	1.01 [0.61, 1.67]	
Wisecup 2015 Zeng 2020 Total (95%Cl)	-0.7841 0.0055	0.5295 0.2581	33.5% 100%	1.01 [0.61, 1.67] 1.05 [0.67, 1.63]	•
Wisecup 2015 Zeng 2020 Total (95%CI) Heterogeneity: Tau ² = 0.09; (-0.7841 0.0055 Chi ² = 4.76, df = 2 (0.5295 0.2581 P = 0.09);	33.5% 100% I ² = 58%	1.01 [0.61, 1.67] 1.05 [0.67, 1.63]	•
Wisecup 2015 Zeng 2020 Total (95%CI) Heterogeneity: Tau ² = 0.09; (Test for overall effect: Z = 0.2	-0.7841 0.0055 Chi ² = 4.76, df = 2 (20 (P = 0.84)	0.5295 0.2581 P = 0.09);	33.5% 100% 1 ² = 58%	1.01 [0.61, 1.67] 1.05 [0.67, 1.63]	
Wisecup 2015 Zeng 2020 Total (95%CI) Heterogeneity: Tau ² = 0.09; C Test for overall effect: Z = 0.2	-0.7841 0.0055 Chi ² = 4.76, df = 2 (20 (P = 0.84)	0.5295 0.2581 P = 0.09);	33.5% 100% ² = 58%	1.01 [0.61, 1.67] 1.05 [0.67, 1.63]	0.1 1 10
Wisecup 2015 Zeng 2020 Total (95%CI) Heterogeneity: Tau ² = 0.09; (Test for overall effect: Z = 0.2	-0.7841 0.0055 Chi ² = 4.76, df = 2 (20 (P = 0.84)	0.5295 0.2581 P = 0.09);	33.5% 100% $l^2 = 58\%$	0.40 [0.10, 1.29] 1.01 [0.61, 1.67] 1.05 [0.67, 1.63] ↓ 0.01 Odds Ratio	0.1 1 10 Odds Ratio
Wisecup 2015 Zeng 2020 Total (95%CI) Heterogeneity: Tau ² = 0.09; (Test for overall effect: Z = 0.2 Study	-0.7841 0.0055 Chi ² = 4.76, df = 2 (20 (P = 0.84) log[Odds Ratio]	0.5295 0.2581 P = 0.09); SE	14.0% 33.5% 100% $1^2 = 58\%$ Weight	0.40 [0.10, 1.29] 1.01 [0.61, 1.67] 1.05 [0.67, 1.63] ↓ 0.01 Odds Ratio IV, Fixed, 95% CI	0.1 1 10 Odds Ratio IV, Fixed, 95% Cl
Wisecup 2015 Zeng 2020 Total (95%CI) Heterogeneity: Tau ² = 0.09; (Test for overall effect: Z = 0.2 Study I.15 autoimmune disease	-0.7841 0.0055 Chi ² = 4.76, df = 2 (20 (P = 0.84) log[Odds Ratio]	0.5295 0.2581 P = 0.09); SE	33.5% 100% ² = 58% Weight	0.40 [0.10, 1.29] 1.01 [0.61, 1.67] 1.05 [0.67, 1.63] ↓ 0.01 Odds Ratio IV, Fixed, 95% CI	0.1 1 10 Odds Ratio IV, Fixed, 95% Cl
Wisecup 2015 Zeng 2020 Total (95%CI) Heterogeneity: Tau ² = 0.09; (Test for overall effect: Z = 0.2 Study 1.15 autoimmune disease Tran 2018	-0.7841 0.0055 Chi ² = 4.76, df = 2 (20 (P = 0.84) log[Odds Ratio] 1.1878	0.5295 0.2581 P = 0.09); SE 0.5347	$\frac{14.0}{33.5\%}$ $\frac{100\%}{l^2 = 58\%}$ Weight 89.6%	0.40 [0.10, 1.29] 1.01 [0.61, 1.67] 1.05 [0.67, 1.63] 0.01 Odds Ratio IV, Fixed, 95% Cl 3.28 [1.15, 9.35]	0.1 1 10 Odds Ratio IV, Fixed, 95% Cl
Wisecup 2015 Zeng 2020 Total (95%CI) Heterogeneity: Tau ² = 0.09; (Test for overall effect: Z = 0.2 Study 1.15 autoimmune disease Tran 2018 Zhu 2022	-0.7841 0.0055 Chi ² = 4.76, df = 2 (20 (P = 0.84) log[Odds Ratio] 1.1878 2.656	0.5295 0.2581 P = 0.09); SE 0.5347 1.5666	$\frac{14.0\%}{33.5\%}$ $\frac{100\%}{l^2 = 58\%}$ $\frac{Weight}{10.4\%}$	0.40 [0.10, 1.29] 1.01 [0.61, 1.67] 1.05 [0.67, 1.63] 0.01 Odds Ratio IV, Fixed, 95% Cl 3.28 [1.15, 9.35] 14.24 [0.66, 306.9]	0.1 1 10 Odds Ratio IV, Fixed, 95% Cl
Wisecup 2015 Zeng 2020 Total (95%CI) Heterogeneity: Tau ² = 0.09; (Test for overall effect: Z = 0.2 Study 1.15 autoimmune disease Tran 2018 Zhu 2022 Total (95%CI)	-0.7841 0.0055 Chi ² = 4.76, df = 2 (20 (P = 0.84) log[Odds Ratio] 1.1878 2.656	0.5295 0.2581 P = 0.09); SE 0.5347 1.5666	14:078 33.5% 100% I ² = 58% Weight 89.6% 10.4% 100%	0.40 [0.10, 1.29] 1.01 [0.61, 1.67] 1.05 [0.67, 1.63] ↓ 0.01 Odds Ratio IV, Fixed, 95% Cl 3.28 [1.15, 9.35] 14.24 [0.66, 306.9] 3.82 [1.42, 10.31]	0.1 1 10 Odds Ratio IV, Fixed, 95% Cl
Wisecup 2015 Zeng 2020 Total (95%CI) Heterogeneity: Tau ² = 0.09; (Test for overall effect: Z = 0.2 Study 1.15 autoimmune disease Tran 2018 Zhu 2022 Total (95%CI) Heterogeneity: Chi ² = 0.79, d	-0.7841 0.0055 Chi ² = 4.76, df = 2 (20 (P = 0.84) log[Odds Ratio] 1.1878 2.656 f = 1 (P = 0.38); l ² :	0.5295 0.2581 P = 0.09); SE 0.5347 1.5666 = 0%	14:078 33.5% 100% I ² = 58% Weight 89.6% 10.4% 100%	0.40 [0.10, 1.29] 1.01 [0.61, 1.67] 1.05 [0.67, 1.63] ↓ 0.01 Odds Ratio IV, Fixed, 95% Cl 3.28 [1.15, 9.35] 14.24 [0.66, 306.9] 3.82 [1.42, 10.31]	0.1 1 10 Odds Ratio IV, Fixed, 95% Cl
Wisecup 2015 Zeng 2020 Total (95%CI) Heterogeneity: Tau ² = 0.09; (Test for overall effect: Z = 0.2 Study 1.15 autoimmune disease Tran 2018 Zhu 2022 Total (95%CI) Heterogeneity: Chi ² = 0.79, d Test for overall effect: Z = 2.6	-0.7841 0.0055 $Chi^2 = 4.76, df = 2 (20)$ (P = 0.84) log[Odds Ratio] 1.1878 2.656 $f = 1 (P = 0.38); l^2 = 20$ (S (P = 0.008)	0.5295 0.2581 P = 0.09); SE 0.5347 1.5666 = 0%	14:0 % 33.5% 100% I ² = 58% Weight 89.6% 10.4% 100%	0.40 [0.10, 1.29] 1.01 [0.61, 1.67] 1.05 [0.67, 1.63] ↓ 0.01 Odds Ratio IV, Fixed, 95% Cl 3.28 [1.15, 9.35] 14.24 [0.66, 306.9] 3.82 [1.42, 10.31]	0.1 1 10 Odds Ratio IV, Fixed, 95% Cl
Wisecup 2015 Zeng 2020 Total (95%CI) Heterogeneity: Tau ² = 0.09; (Test for overall effect: Z = 0.2 Study 1.15 autoimmune disease Tran 2018 Zhu 2022 Total (95%CI) Heterogeneity: Chi ² = 0.79, d Test for overall effect: Z = 2.6	-0.7841 0.0055 Chi ² = 4.76, df = 2 (20 (P = 0.84) log[Odds Ratio] 1.1878 2.656 f = 1 (P = 0.38); l ² = 35 (P = 0.008)	0.5295 0.2581 P = 0.09); SE 0.5347 1.5666 = 0%	Weight 89.6% 100%	0.40 [0.10, 1.29] 1.01 [0.61, 1.67] 1.05 [0.67, 1.63] 0.01 Odds Ratio IV, Fixed, 95% Cl 3.28 [1.15, 9.35] 14.24 [0.66, 306.9] 3.82 [1.42, 10.31]	0.1 1 10 Odds Ratio IV, Fixed, 95% Cl



Fig. 3 Continued

of 262,587 patients, the pooled prevalence of CRT is 9.1%. We conducted a qualitative synthesis analysis of 61 predictive factors and a quantitative meta-analysis of 38 factors, identifying six definite factors, 11 likely factors, and 42 unclear factors associated with CRT. Definite predictors included being of D-dimer, location of insertion, type of catheter, number of lumens, catheter indwelling time and CLABSI. The findings of our systematic review provide the latest comprehensive evidence summary that can inform the early identification of children at risk for CRT and the development of intervention measures to prevent and reduce CRT.

Implantable and temporary medical devices such as CVAD are exposed to blood for weeks to years depending on the type of CVAD in place. Since CVAD is an artificial surface and lacks an endothelial layer that inhibits platelet coagulation and adhesion, it is thought to potentially activate the contact pathways, ultimately leading to thrombosis. Assembly of artificial surface contact systems might be part of the host defense mechanism against foreign substances, but it can lead to kinin and thrombin generation, and complement activation.⁶² This eventually promotes thrombosis and inflammation. The presence of CVAD is the most common risk factor for venous thrombosis (DVT) in adults and 50–80% in children.^{10,55,63} The incidence of CRT in hospitalized children has increased significantly by 30–70% over the past 20 years,^{64,65} which may cause serious medical complications besides increasing healthcare expenditures and length of stay.

We discover that a higher level of D-dimer is an independent risk factor for CRT in hospitalized children, consistent with the results of adult studies.⁶⁶ D-dimer is a soluble fibrin degradation product deriving from the plasmin-mediated degradation of crosslinked fibrin that is increased or positive in secondary hyperfibrinolysis, such as hypercoagulable states, disseminated intravascular coagulation, and thrombolytic therapy.^{67,68} Increased D-dimer suggests an association with thrombotic disorders in the body of various origins and an increase in fibrinolytic activity. D-dimer has been extensively investigated for excluding the diagnosis of VTE and is used routinely for this indication.^{67,69} Therefore, for early recognition and to reduce the incidence of CRT, D-dimer levels should be closely monitored before and after catheterization. However, the elevated D-dimer test results cannot fully explain the cause and location of CRT formation and must be analyzed in conjunction with clinical and other test results.

Inherited thrombophilia, caused by genetic defects leading to a deficiency or abnormality in associated proteins, including protein C, protein S, antithrombin, the coagulation factor V Leiden mutation, and factor II mutation G20210A, 70 is considered a potential risk factor for CRT. The prevalence of thrombophilia varies widely among different populations, with a reported prevalence of 10% to 59% in pediatric VTE patients.⁷¹ Children with gastrointestinal diseases like short bowel syndrome (SBS) and inflammatory bowel disease (IBD) have an increased risk of developing CRT during hospitalization. The precise mechanism behind this association is still uncertain according to current research. It may be attributed to the heightened inflammation levels during catheterization, particularly in patients with active IBD episodes or admissions during surgery, which leads to a period of increased inactivity.⁵⁵ This suggests that delaying placement during the most active period of inflammation may reduce the rate of thrombosis.

A narrative review pointed out that age is one of the most significant risk factors for VTE. In children, CRT shows a bimodal distribution, with the highest incidence rate in infancy and adolescence.¹⁰ The higher incidence in infancy may be due in part to the smaller diameter of the vein, making insertion difficult and requiring multiple attempts. However, whether age is a risk factor for CRT is still highly controversial. The study by Chojnacka et al. did not find a statistically significant difference,³⁹ although a trend toward a similar bimodal distribution was found in the study population. Cancer, cardiovascular disease, sepsis, asphyxia, and neurological diseases are also considered unclear factors for CRT. Pediatric patients diagnosed with leukemia have multiple risk factors for VTE formation, such as the presence of hypercoagulable blast cells, the pro-thrombotic nature of the cancer itself, and treatment with steroids and L-asparaginase. Chen et al.38 and Jaffray et al.⁴ concluded that children with leukemia are more likely to develop CRT. Sepsis causes the coagulation mechanism to become fragile, which in turn activates the coagulation system and creates thrombosis.⁷² However, a study by Onyeama et al.⁵² showed that sepsis was significantly associated with a reduced incidence of CRT, and the exact mechanism is currently unknown.

The location of insertion and type of catheter are critical risk factors for CRT. The incidence of CRT is higher in femoral vein catheterizations compared to subclavian and jugular vein catheterizations in children, which is contrary to findings in adult patients.⁷³ The femoral location is a larger vessel and allows placement of a larger size catheter. Femoral CVAD is prioritized in

urgent and emergency situations. In such cases, the patients tend to be more critically ill and often immobilized, further exacerbating the low-flow state. In addition, there may be vein compression and kinking beneath the inguinal ligament with leg movement, which may increase the risk of CRT.²⁷ PICC catheters provide a reliable medium to long-term route to intravenous therapy for

children, but compared with other types of catheters, the risk of CRT is higher. We speculate that the long tunnel length and relatively large lumen size of the PICC, compared to the diameter of the vessel at the insertion site, may lead to increased blood flow obstruction.⁵² Additionally, patients with PICC may be more likely to be diagnosed with symptomatic VTE than tunneled lines (TLs)

Study	log[Odds Ration	o] SE	Weight	Odds Ratio IV, Fixed, 95% Cl	Odds Ratio IV, Fixed, 95% Cl
2.1 geographic location o	of line placement				
Beck 1988	-1.3398	0.6665	3.1%	0.26 [0.07, 0.97]	
Patel 2020	-1.3214	0.1338	77.0%	0.27 [0.21, 0.35]	
Shah 2015	-1.3137	0.2632	19.9%	0.27 [0.16, 0.45]	
Total (95%CI)			100%	0.27 [0.21, 0.34]	•
Heterogeneity: Chi ² = 0.00,	, df = 2 (P = 1.00); l ²	= 0%			
Test for overall effect: Z = 1	11.25 (P < 0.00001)			L	
				0.01	0.1 1 10 100
Study	log[Odds Rati	o] SE	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% Cl
2.2 location of insertion 1	(Femoral VS Jugu	lar)			
Beck 1988	1.204	0.7853	5.1%	3.33 [0.72, 15.54]	
Derderian 2019	1.9329	0.6214	6.0%	6.91 [2.04, 23.36]	
Faustino 2013	-1.0761	0.6368	5.9%	0.34 [0.10, 1.19]	
Faustino 2015	-0.383	0.5546	6.3%	0.68 [0.23, 2.02]	
Gray 2012	1.1205	0.3551	7.5%	3.07 [1.53, 6.15]	
Jiang 2022	0.3785	0.2924	7.8%	1.46 [0.82, 2.59]	
Jones 2019	1.6327	0.566	6.3%	5.12 [1.69, 15.52]	
Li 2022	0.6648	0.2257	8.1%	1.94 [1.25, 3.03]	
Noonan 2018	0.9358	0.5028	6.6%	2.55 [0.95, 6.83]	
Ostlund 2019	-0.9211	0.3229	7.6%	0.40 [0.21, 0.75]	
Patel 2020	1.7558	0.154	8.3%	5.79 [4.28, 7.83]	
Shah 2015	1.7919	0.4174	7.1%	6.00 [2.65, 13.60]	
Smitherman 2015	-1.1666	1.0826	3.7%	0.31 [0.04, 2.60]	
Wisecup 2015	-1.0233	0.6264	5.9%	0.36 [0.11, 1.23]	
Zeng 2020	0.0744	0.2729	7.9%	1.08 [0.63, 1.84]	

Total (95%CI) 1.69 [0.98, 2.91] Heterogeneity: $Tau^2 = 0.91$; $Chi^2 = 113.39$, df = 14 (P < 0.00001); l² = 88%

Test for overall effect: Z = 1.89 (P = 0.06)



100%

Fig. 4 Meta-analysis of CVAD-related risk factors (1). Forest plots of odds ratios (OR) that were included in the quantitative meta-analysis and the associated overall OR. For each OR, the size of the red square region is proportional to the corresponding study weight. Diamond shape intervals represent the overall OR. I² represents the fraction of variability among the individual OR that cannot be explained by sampling variability.

Sludy	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random,	95% CI
2.4 location of insertion	on 3 (Subclavian VS J	lugular)				
Beck 1988	1.7918	0.928	6.1%	6.00 [0.97, 36.99]		•
Derderian 2019	0.325	0.9173	6.2%	1.38 [0.23, 8.36]		
Faustino 2013	-2.1322	1.0806	5.2%	0.12 [0.01, 0.99]	•	
Faustino 2015	-0.7014	0.706	7.6%	0.50 [0.12, 1.98]		_
Gray 2012	-0.1585	0.5266	9.1%	0.85 [0.30, 2.40]		
Li 2022	0.2396	0.6014	8.5%	1.27 [0.39, 4.13]		
Male 2003	1.1451	0.5096	9.2%	3.14 [1.16, 8.53]	-	
Noonan 2018	0.8683	0.581	8.6%	2.38 [0.76, 7.44]	+	-
Ostlund 2019	-2.5649	1.4637	3.5%	0.08 [0.00, 1.36]		
Patel 2020	0.7475	0.2139	11.2%	2.11 [1.39, 3.21]	-	
Shah 2015	-0.9628	0.5882	8.6%	0.38 [0.12, 1.21]		
Smitherman 2015	-1.2679	0.5672	8.7%	0.28 [0.09, 0.86]		
Wisecup 2015	-2 2091	0.72	7.5%	0.11 [0.03, 0.45]		
Total (95%CI)	2.200	0.72	100%	0.81 [0.42, 1.54]		
Hotorogonoity: $T_{0}u^2 = 0$	0.00 , $Chi^2 = 46.20$, df =	10 (P < 0.0	0001):12	749/		
Test for overall effect: 7	7 – 0 66 (P – 0 51)	12 (P < 0.0	(0001); 1 = 1	/4%		
	L = 0.00 (1 = 0.01)			0.01	01 1	10
				0.01	0.1 1	10
				Odds Ratio	Odds R	atio
Study	log[Odds Rat	io] SE	Weight	IV, Random, 95% Cl	IV, Random,	95% CI
2.5 location of insertion	on 4 (Femoral VS Upp	er extremit	(y)			
Badheka 2021	1.0578	0.7414	25.9%	2.88 [0.67, 12.32]	+	-
Lambert 2019	2.1279	0.7963	24.9%	8.40 [1.76, 39.99]		
Shah 2015	3.1549	0.6032	28.2%	23.45 [7.19, 76.49]		
Smitherman 2015	-0.5929	1.033	21.0%	0.55 [0.07, 4.19]		
Total (95%CI)			100%	4.81 [1.08, 21.29]	-	
Heterogeneity: Tau ² = 1 Test for overall effect: 2	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04)	3 (P = 0.00	9),1 = 74%	0.01 Odds Ratio	0.1 1 Odds R	10 atio
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat	3 (P = 0.00 io] SE	9),1 = 74%	⊢ 0.01 Odds Ratio IV, Fixed, 95% Cl	0.1 1 Odds Ri IV, Fixed, 5	 10 95% CI
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertio	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat	3 (P = 0.00 io] SE er extremity	9), 1 = 74% Weight	⊢ 0.01 Odds Ratio IV, Fixed, 95% Cl	0.1 1 Odds Ra IV, Fixed, S	 10 15% CI
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578	3 (P = 0.00 io] SE er extremity 0.8145	Weight y) 17.5%	Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86]	0.1 1 Odds Ri IV, Fixed, S	10 atio 95% CI
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021 Shah 2015	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363	3 (P = 0.00 io] SE er extremity 0.8145 0.6924	Weight W ight () 17.5% 24.2%	← 0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18]	0.1 1 Odds Ri IV, Fixed, S	10 10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021 Shah 2015 Smitherman 2015	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462	Weight /) 17.5% 24.2% 58.3%	← 0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26]	0.1 1 Odds Ra IV, Fixed, S	10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI)	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462	Weight W ight () 17.5% 24.2% 58.3% 100%		0.1 1 Odds Ra IV, Fixed, S	10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 ² = 0%	Weight /) 17.5% 24.2% 58.3% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48]	0.1 1 Odds Ri IV, Fixed, S	10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Uppr 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); f Z = 2.44 (P = 0.01)	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $r^2 = 0\%$	Weight /) 17.5% 24.2% 58.3% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48]	0.1 1 Odds Ri IV, Fixed, S	10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); f Z = 2.44 (P = 0.01)	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $r^2 = 0\%$	Weight /) 17.5% 24.2% 58.3% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48]	0.1 1 Odds Ri IV, Fixed, S	10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); 1 Z = 2.44 (P = 0.01)	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $r^2 = 0\%$	Weight /) 17.5% 24.2% 58.3% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio	0.1 1 Odds R IV, Fixed, S 0.1 1	10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) Iog[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); l Z = 2.44 (P = 0.01) Iog[Odds Ratio]	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $r^2 = 0\%$ SE	(y), 1 = 74% (y) 17.5% 24.2% 58.3% 100% Weight	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl	0.1 1 Odds R IV, Fixed, 9 0.1 1 0.1 1 Odds R IV, Fixed, 9	10 10 10 10 10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chl ² = 0 Test for overall effect: 2 Study 2.7 location of insertion	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) Iog[Odds Rat on 5 (Jugular VS Uppr 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); l Z = 2.44 (P = 0.01) Iog[Odds Ratio] on 6 (Subclavian VS L	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $l^2 = 0\%$ SE Upper extre	Weight y) 17.5% 24.2% 58.3% 100% Weight mity)	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl	0.1 1 Odds R IV, Fixed, 9 0.1 1 0.1 1 0.1 1 Odds R IV, Fixed, 9	10 10 10 10 10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertion Shah 2015	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) Iog[Odds Rat on 5 (Jugular VS Uppr 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); l Z = 2.44 (P = 0.01) Iog[Odds Ratio] on 6 (Subclavian VS L 0.4002	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $l^2 = 0\%$ SE Ipper extre 0.7319	Weight y) 17.5% 24.2% 58.3% 100% Weight mity) 28.8%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26]	0.1 1 Odds R IV, Fixed, 9 0.1 1 0.1 1 0.1 1 Odds R IV, Fixed, 9	10 10 10 10 10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chl ² = 0 Test for overall effect: 2 Study 2.7 location of insertion Shah 2015 Smitherman 2015	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) Iog[Odds Rat on 5 (Jugular VS Uppr 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); l Z = 2.44 (P = 0.01) Iog[Odds Ratio] on 6 (Subclavian VS L 0.4002 -0.6942	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $l^2 = 0\%$ SE Dpper extre 0.7319 0.4656	Weight y) 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24]	0.1 1 Odds R IV, Fixed, 9 0.1 1 0.1 1 0.1 1 Odds R IV, Fixed, 9	10 10 10 10 10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertion Shah 2015 Smitherman 2015 Total (95%CI)	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Uppr 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); l Z = 2.44 (P = 0.01) log[Odds Ratio] on 6 (Subclavian VS L 0.4002 -0.6942	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $l^2 = 0\%$ SE Dyper extre 0.7319 0.4656	Weight y) 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48]	0.1 1 Odds R IV, Fixed, S 0.1 1 0.1 1 Odds Ra IV, Fixed, S	10 10 10 10 10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertion Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Ration 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); 1 Z = 2.44 (P = 0.01) log[Odds Ration 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); 1 0.95, df = 2 (P = 0.	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $i^2 = 0\%$ SE Dpper extre 0.7319 0.4656 $i^2 = 37\%$	Weight y) 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48]	0.1 1 Odds R IV, Fixed, S 0.1 1 0.1 1 Odds Ra IV, Fixed, S	10 10 10 10 10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertion Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1 Test for overall effect: 2	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Ration 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); l Z = 2.44 (P = 0.01) log[Odds Ration 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); l 0.95, df = 2 (P = 0.62); l 1.363 0.5737 0.95, df = 1 (P = 0.21); l 2.59, df = 1 (P = 0.21); l 2.59, df = 1 (P = 0.23)	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $i^2 = 0\%$ SE Dpper extre 0.7319 0.4656 $i^2 = 37\%$	Weight y) 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48]	0.1 1 Odds R IV, Fixed, S 0.1 1 0.1 1 Odds Ra IV, Fixed, S	10 10 10 10 10 10 10 10 10 10
Heterogeneity: $Tau^2 = 1$ Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertio Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1 Test for overall effect: 2	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); I Z = 2.44 (P = 0.01) log[Odds Ratio] on 6 (Subclavian VS L 0.4002 -0.6942 .59, df = 1 (P = 0.21); I Z = 0.96 (P = 0.33)	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $i^2 = 0\%$ SE Dpper extre 0.7319 0.4656 $i^2 = 37\%$	Weight y) 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48]	0.1 1 Odds R IV, Fixed, S 0.1 1 0.1 1 Odds Ra IV, Fixed, S	10 10 10 10 10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertion Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1 Test for overall effect: 2	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); I Z = 2.44 (P = 0.01) log[Odds Ratio] on 6 (Subclavian VS L 0.4002 -0.6942 .59, df = 1 (P = 0.21); I Z = 0.96 (P = 0.33)	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $i^2 = 0\%$ SE Dpper extre 0.7319 0.4656 $i^2 = 37\%$	Weight y) 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48]	0.1 1 Odds R IV, Fixed, 9 0.1 1 0.1 1 Odds Ra IV, Fixed, 9	10 10 10 10 10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertion Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1 Test for overall effect: 2	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); I Z = 2.44 (P = 0.01) log[Odds Ratio] on 6 (Subclavian VS U 0.4002 -0.6942 .59, df = 1 (P = 0.21); I Z = 0.96 (P = 0.33)	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $i^2 = 0\%$ SE Dpper extre 0.7319 0.4656 $i^2 = 37\%$	(9), 1 = 74% Weight (7) 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48] 0.01 Odds Ratio	0.1 1 Odds R IV, Fixed, S 0.1 1 0.1 1 Odds Ra IV, Fixed, S	10 10 10 10 10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertion Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1 Test for overall effect: 2 Study	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); 1 Z = 2.44 (P = 0.01) log[Odds Ratio] on 6 (Subclavian VS U 0.4002 -0.6942 .59, df = 1 (P = 0.21); 1 Z = 0.96 (P = 0.33)	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $2^{2} = 0\%$ SE pper extre 0.7319 0.4656 $2^{2} = 37\%$	(9), 1 = 74% Weight (7) 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100% Weight	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48] 0.01 Odds Ratio IV, Fixed, 95% Cl	0.1 1 Odds R IV, Fixed, 9 0.1 1 0.1 1 Odds R IV, Fixed, 9 0.1 1 0.1 1 Odds R IV, Fixed, 9	10 10 10 10 10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertion Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1 Test for overall effect: 2 Study 2.8 location of insertion	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); I Z = 2.44 (P = 0.01) log[Odds Ratio] on 6 (Subclavian VS U 0.4002 -0.6942 .59, df = 1 (P = 0.21); I Z = 0.96 (P = 0.33) log[Odds Ratio] on 7 (Brachial VS Bas	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $2^{2} = 0\%$ SE 1000 - 2 = 37% SE 1100 - 2 = 0.00	(9), 1 = 74% Weight 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100% Weight	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48] 0.01 Odds Ratio IV, Fixed, 95% Cl	0.1 1 Odds R: IV, Fixed, S 0.1 1 0.1 1 Odds R: IV, Fixed, S 0.1 1 0.1 1	10 10 10 10 10 10 10 10 10 10
Heterogeneity: $Tau^2 = 1$ Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertion Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1 Test for overall effect: 2 Study 2.8 location of insertion Gnannt 2018	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); 1 Z = 2.44 (P = 0.01) log[Odds Ratio] on 6 (Subclavian VS U 0.4002 -0.6942 .59, df = 1 (P = 0.21); 1 Z = 0.96 (P = 0.33) log[Odds Ratio] on 7 (Brachial VS Bas -0.4839	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $2^{2} = 0\%$ SE pper extre 0.7319 0.4656 $2^{2} = 37\%$ SE ilic) 0.332	(9), 1 = 74% Weight 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100% Weight 40.5%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48] 0.01	0.1 1 Odds R IV, Fixed, S 0.1 1 0.1 1 Odds R IV, Fixed, S 0.1 1 0.1 1 Odds R IV, Fixed, S	10 10 10 10 10 10 10 10 10 10
Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study 2.6 location of insertion Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertion Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1 Test for overall effect: 2 Study 2.8 location of insertion Gnannt 2018 Menendez 2016	1.68; Chi ² = 11.52, df = Z = 2.07 (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737 0.95, df = 2 (P = 0.62); 1 Z = 2.44 (P = 0.01) log[Odds Ratio] on 6 (Subclavian VS U 0.4002 -0.6942 .59, df = 1 (P = 0.21); 1 Z = 0.96 (P = 0.33) log[Odds Ratio] on 7 (Brachial VS Bas -0.4839 -0.4889	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $i^2 = 0\%$ SE 0.7319 0.4656 $i^2 = 37\%$ SE ilic) 0.332 0.5304	(9), 1 = 74% Weight (7) 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100% Weight 40.5% 15.9%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 0.62 [0.32, 1.18] 0.61 [0.22, 1.73]	0.1 1 Odds R IV, Fixed, S 0.1 1 0.1 1 Odds Ra IV, Fixed, S 0.1 1 0.1 1 Odds Ra IV, Fixed, S	10 10 10 10 10 10 10 10 10 10
Heterogeneity: $Tau^2 = 1$ Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertio Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1 Test for overall effect: 2 Study 2.8 location of insertio Gnannt 2018 Menendez 2016 Shin 2017	1.68; $Chi^2 = 11.52$, $df = Z = 2.07$ (P = 0.04) log[Odds Rat on 5 (Jugular VS Uppr 0.9578 1.363 0.5737 0.95, $df = 2$ (P = 0.62); I Z = 2.44 (P = 0.01) log[Odds Ratio] on 6 (Subclavian VS U 0.4002 -0.6942 .59, $df = 1$ (P = 0.21); I Z = 0.96 (P = 0.33) log[Odds Ratio] on 7 (Brachial VS Bas -0.4839 -0.4889 -0.4889 -0.1472	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $i^2 = 0\%$ SE 1000 0.7319 0.4656 $i^2 = 37\%$ SE ilic) 0.332 0.5304 0.3198	(9), 1 = 74% Weight (7) 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100% Weight 40.5% 15.9% 43.6%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 0.62 [0.32, 1.18] 0.61 [0.22, 1.73] 0.86 [0.46, 1.62]	0.1 1 Odds R IV, Fixed, S 0.1 1 0.1 1 Odds Ra IV, Fixed, S 0.1 1 0.1 1 Odds Ra IV, Fixed, S	10 10 10 10 10 10 10 10 10 10
Heterogeneity: $Tau^2 = 1$ Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertio Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1 Test for overall effect: 2 Study 2.8 location of insertio Gnannt 2018 Menendez 2016 Shin 2017 Total (95%CI)	1.68; $Chi^2 = 11.52$, $df = Z = 2.07$ (P = 0.04) log[Odds Rate on 5 (Jugular VS Uppr 0.9578 1.363 0.5737 0.95, $df = 2$ (P = 0.62); 1 2 = 2.44 (P = 0.62); 1 log[Odds Ratio] on 6 (Subclavian VS U 0.4002 -0.6942 .59, $df = 1$ (P = 0.21); 1 Z = 0.96 (P = 0.33) log[Odds Ratio] on 7 (Brachial VS Bas -0.4839 -0.4889 -0.1472	3 (P = 0.00) io] SE er extremity 0.8145 0.6924 0.4462 $i^2 = 0\%$ SE 1000 0.7319 0.4656 $i^2 = 37\%$ SE ilic) 0.332 0.5304 0.3198	(9), 1 = 74% Weight (7) 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100% Weight 40.5% 15.9% 43.6% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 0.62 [0.32, 1.18] 0.61 [0.22, 1.73] 0.86 [0.46, 1.62] 0.71 [0.47, 1.08]	0.1 1 Odds R IV, Fixed, S 0.1 1 0.1 1 Odds Ra IV, Fixed, S 0.1 1 0.1 1 Odds Ra IV, Fixed, S	10 10 10 10 10 10 10 10 10 10
Heterogeneity: $Tau^2 = 1$ Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 2 Study 2.7 location of insertio Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1 Test for overall effect: 2 Study 2.8 location of insertio Gnannt 2018 Menendez 2016 Shin 2017 Total (95%CI) Heterogeneity: Chi ² = 0	1.68; $Chi^2 = 11.52$, $df = Z = 2.07$ (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737 0.95, $df = 2$ (P = 0.62); I log[Odds Ratio] on 6 (Subclavian VS U 0.4002 -0.6942 .59, $df = 1$ (P = 0.21); I Z = 0.96 (P = 0.33) log[Odds Ratio] on 7 (Brachial VS Bas -0.4839 -0.4889 -0.1472 0.63, $df = 2$ (P = 0.72); I	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $l^2 = 0\%$ SE 1000 10	(9), 1 = 74% Weight (7) 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100% Weight 40.5% 15.9% 43.6% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 0.62 [0.32, 1.18] 0.61 [0.22, 1.73] 0.86 [0.46, 1.62] 0.71 [0.47, 1.08]	0.1 1 Odds R: IV, Fixed, S 0.1 1 0.1 1 Odds R: IV, Fixed, S 0.1 1 0.1 1 Odds R: IV, Fixed, S	10 10 10 10 10 10 10 10 10 10
Heterogeneity: $Tau^2 = 1$ Test for overall effect: 2 Study 2.6 location of insertio Badheka 2021 Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 0 Study 2.7 location of insertio Shah 2015 Smitherman 2015 Total (95%CI) Heterogeneity: Chi ² = 1 Test for overall effect: 2 Study 2.8 location of insertio Gnannt 2018 Menendez 2016 Shin 2017 Total (95%CI) Heterogeneity: Chi ² = 0 Test for overall effect: 7	1.68; $Chi^2 = 11.52$, $df = Z = 2.07$ (P = 0.04) log[Odds Rat on 5 (Jugular VS Upp 0.9578 1.363 0.5737 0.95, $df = 2$ (P = 0.62); 1 log[Odds Ratio] on 6 (Subclavian VS U 0.4002 -0.6942 .59, $df = 1$ (P = 0.21); 1 Z = 0.96 (P = 0.33) log[Odds Ratio] on 7 (Brachial VS Bas -0.4839 -0.4889 -0.1472 0.63, $df = 2$ (P = 0.73); 1 Z = 1.60 (P = 0.11)	3 (P = 0.00 io] SE er extremity 0.8145 0.6924 0.4462 $l^2 = 0\%$ SE Dpper extre 0.7319 0.4656 $l^2 = 37\%$ SE ilic) 0.332 0.5304 0.3198 $l^2 = 0\%$	9), 1 = 74% Weight 17.5% 24.2% 58.3% 100% Weight mity) 28.8% 71.2% 100% Weight 40.5% 15.9% 43.6% 100%	0.01 Odds Ratio IV, Fixed, 95% Cl 2.61 [0.53, 12.86] 3.91 [1.01, 15.18] 1.77 [0.74, 4.26] 2.30 [1.18, 4.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 1.49 [0.36, 6.26] 0.50 [0.20, 1.24] 0.68 [0.32, 1.48] 0.01 Odds Ratio IV, Fixed, 95% Cl 0.62 [0.32, 1.18] 0.61 [0.22, 1.73] 0.86 [0.46, 1.62] 0.71 [0.47, 1.08]	0.1 1 Odds R: IV, Fixed, S 0.1 1 0.1 1 Odds R: IV, Fixed, S 0.1 1 0.1 1 Odds R: IV, Fixed, S	10 atio 10 10 10 10 10 atio 5% Cl 10 10 10 10 10 10 10 10 10 10

				Odds Ratio	Odd	s Ratio	
Study	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixe	d, 95% Cl	
2.9 location of insertion	on 8 (Brachial VS Cepl	halic)					
Gnannt 2018	-0.6698	0.5973	27.1%	0.51 [0.16, 1.65]			
Menendez 2016	-2.1972	1.7056	3.3%	0.11 [0.00, 3.14]	_		
Shin 2017	0.2033	0.3728	69.6%	1.23 [0.59, 2.54]			
Total (95%CI)			100%	0.89 [0.49, 1.64]			
Heterogeneity: Chi ² = 3	.08, df = 2 (P = 0.21); l ²	² = 35%					
Test for overall effect: Z	Z = 0.36 (P = 0.72)			H		l	
				0.01	0.1	1 10	100



				Odds Ratio	Odds Ratio	
Study	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI	
2.11 location of insertion	10 (Basilic VS Med	lian vein)				
Deng 2020	0.0953	0.6809	46.9%	1.10 [0.29, 4.18]		
Wei 2017	-0.1871	0.6399	53.1%	0.83 [0.24, 2.91]		
Total (95%CI)			100%	0.95 [0.38, 2.36]		
Heterogeneity: Chi ² = 0.09	, df = 1 (P = 0.76); l ²	= 0%				
Test for overall effect: Z = 0	0.12 (P = 0.91)			Ľ		
				0.01	0.1 1 10	100

				Odds Ratio	Odds Ratio	
Study	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% CI	
2.12 location of insertion	11 (Upper extremity	/ VS Lowe	er extremity))		
Noonan 2018	-1.5026	0.3314	38.7%	0.22 [0.12, 0.43]		
Onyeama 2018	1.2883	0.7571	31.2%	3.63 [0.82, 15.99]		_
Zhu 2022	-0.9542	0.8142	30.1%	0.39 [0.08, 1.90]		
Total (95%CI)			100%	0.63 [0.12, 3.39]		
Heterogeneity: $Tau^2 = 1.80$; Chi ² = 11.42, df = 2	(P = 0.003	3); l ² = 82%			
Test for overall effect: $Z = 0$	0.54 (P = 0.59)			—		 1
				0.01	0.1 1	10 100

Study	log[Odds Batio]	SE	Weight	Odds Ratio	Odds Ratio	
Study		<u> </u>	weight	IV, I IXEU, 33 /8 OI		
2.13 catheter size (<5F	VS ≥5F)					
Beck 1988	0.9343	0.8455	5.4%	2.55 [0.49, 13.35]		
Faustino 2013	-0.6439	0.6188	10.1%	0.53 [0.16, 1.77]		
Faustino 2015	-0.4024	0.523	14.1%	0.67 [0.24, 1.86]		
Gnannt 2018	-0.6578	0.3241	36.8%	0.52 [0.27, 0.98]		
Menendez 2016	0.9248	1.5547	1.6%	2.52 [0.12, 53.09]		
Smitherman 2015	-0.2559	0.3472	32.0%	0.77 [0.39, 1.53]		
Total (95%CI)			100%	0.68 [0.47, 1.00]	-	
Heterogeneity: Chi ² = 4.1	I7, df = 5 (P = 0.53); l ² :	= 0%				
Test for overall effect: Z =	= 1.94 (P = 0.05)			L		-
				0.01	0.1 1 10 1	00

Fig. 4 Continued

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Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% C	I	
2.14 catheter dysfunction	I						
Beck 1988	0.4877	0.872	3.1%	1.63 [0.29, 9.00]			
Jaffray 2020	0.502	0.2282	44.9%	1.65 [1.06, 2.58]			
Menendez 2016	0.6577	0.2724	31.5%	1.93 [1.13, 3.29]			
Ostlund 2019	0.5311	0.3371	20 6%	1.70 [0.88, 3.29]			
Total (95%CI)			100%	1.74 [1.29, 2.35]			
Heterogeneity: Chi ² = 0.21, Test for overall effect: Z = 3	df = 3 (P = 0.98); l ² = 3.64 (P = 0.0003)	= 0%		0.01	0.1 1		

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Study	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.15 side of insertion (right	t VS left)				
Chen 2016	0.409	0.6682	2.6%	1.51 [0.41, 5.58]	
Deng 2020	0.4704	0.5979	3.2%	1.60 [0.50, 5.17]	
Faustino 2013	0.8602	0.6795	2.6%	2.36 [0.62, 8.95]	
Gnannt 2018	-0.3356	0.4366	5.2%	0.71 [0.30, 1.68]	
Male 2003	-0.9295	0.4749	4.6%	0.39 [0.16, 1.00]	
Marquez 2016	0.7975	0.3772	6.4%	2.22 [1.06, 4.65]	
Menendez 2016	-0.1704	0.2618	9.7%	0.84 [0.50, 1.41]	
Noonan 2018	-0.5634	0.2466	10.2%	0.57 [0.35, 0.92]	
Onyeama 2018	0.0187	0.5932	3.2%	1.02 [0.32, 3.26]	
Patel 2020	-0.3083	0.1153	15.8%	0.73 [0.59, 0.92]	
Shin 2017	0.0214	0.1417	14.7%	1.02 [0.77, 1.35]	+
Wei 2017	0.9219	0.4623	4.8%	2.51 [1.02, 6.22]	
Wisecup 2015	0.1959	0.3618	6.7%	1.22 [0.60, 2.47]	
Zeng 2020	0.051	0.2947	8.6%	1.05 [0.59, 1.87]	
Zhu 2022	-0.5028	0.8097	1.9%	0.60 [0.12, 2.96]	
Total (95%CI)			100%	0.97 [0.77, 1.22]	•
Heterogeneity: Tau ² = 0.07;	Chi ² = 26.14, df = 1	4 (P = 0.02	2); l ² = 46%		
Test for overall effect: Z = 0.	24 (P = 0.81)				

Fig. 4 Continued

because PICC is often placed in smaller vessels and journeys through the arm or leg causing limb pain and swelling, whereas TLs are located in the chest.

The risk of CRT increases with the number of lumens. A possible explanation for this finding is that multilumen catheters tend to have larger catheter sizes and thus occupy more area within the vessel lumen, leading to obstruction of normal blood flow within the veins. The relationship between CRT and CLABSI is bidirectional. Following catheter insertion, a fibrin sheath forms around the catheter. Microorganisms, especially staphylococcus aureus, easily adhere to the fibrin sheaths, and may lead to CLABSI.⁷ Conversely, CLABSI can trigger inflammatory reactions, leading to further progression of thrombosis. CVAD duration is positively associated with the risk of CRT. Catheter placement may cause mechanical injury to the vein. As the indwelling duration increases, many damaged smooth muscle and endothelial cells become embedded within the fibrin, resulting in thrombus formation. In addition, prolonged indwelling increases the chance of platelet contact with the vessel lining, activating coagulation factors and thrombin, increasing the risk of thrombosis.²² Therefore, nurses should perform routine maintenance of the catheter in children who require long-term CVAD indwelling. The duration of CVAD should be monitored, the necessity of its indwelling should be assessed daily, and the catheter should be removed as early as possible while ensuring treatment.

As obstruction of venous blood flow from the CVAD is considered an essential causative mechanism for the development of VTE, a high ratio between catheter size and vein diameter

could be a risk factor for CRT. The 2012 international guidelines on pediatric CVC insertion recommend that the ratio between the catheter's external diameter and the cannulated vein's diameter should not exceed 0.33.75 However, this suggestion is only based on expert opinions and currently lacks relevant clinical data support. Therefore, further research is still needed to verify it. Catheter dysfunction is mainly caused by small clots or fibrous sheaths wrapping around the tip of the catheter. Prolonged accumulation may lead to incomplete or complete blockage of blood vessels, becoming a gathering point for thrombosis.⁷ Journeycake et al. observed that the risk of VTE was highest in pediatric cancer patients with multiple episodes of catheter dysfunction.⁷⁶ A study of pediatric brain tumor patients reported that VTE was more common in patients with catheter dysfunction.⁷⁷ Thus, these studies and the current data support the need to consider catheter dysfunction as a possible risk factor for CRT and to design further screening and intervention studies for early identification and prevention of catheter dysfunction.

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The rationale for studying the relationship between the insertion side of CVAD and the risk of CRT is based on the anatomy of the upper body venous system. The left brachiocephalic vein is longer and courses more horizontally than the right side, thus entering the superior vena cava at a sharper angle. The right jugular vein is the most direct and shortest route for the CVAD to enter the heart. By contrast, the CVAD located in the left jugular vein has a greater distance to the heart and passes through 2 angles in the venous system, which may cause endothelial damage and increase the

				Odds Ratio	Odds Ratio
Study	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.16 type of catheter 1 (P	ICC VS tunnedlled	CVC)			
Chen 2016	0.1001	0.7839	10.4%	1.11 [0.24, 5.14]	
Derderian 2019	1.2204	1.0509	6.8%	3.39 [0.43, 26.58]	
Patel 2020	1.1679	0.4386	19.1%	3.22 [1.36, 7.60]	
Shah 2015	-1.5254	0.6088	14.1%	0.22 [0.07, 0.72]	
Smitherman 2015	0.2934	0.4381	19.2%	1.34 [0.57, 3 16]	
Tran 2018	0.4487	0.0844	30.4%	1.57 [1.33, 1.85]	-
Total (95%CI)			100%	1.34 [0.73, 2 46]	-
Heterogeneity: Tau ² = 0.31 Test for overall effect: Z =	l; Chi ² = 14.03, df = 5 0.95 (P = 0.34)	5 (P = 0.02); l ² = 64%	F	

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				Odds Ratio	Odds Ratio
Study	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.17 type of catheter 2 (P	PICC VS nontunnele	d CVC)			
Derderian 2019	-0.9016	0.375	17.4%	0.41 [0.19, 0.85]	
Patel 2020	0.5769	0.168	21.2%	1.78 [1.28, 2.47]	-
Shah 2015	-2.4315	0.4822	15.2%	0.09 [0.03, 0.23]	
Smitherman 2015	1.1682	1.028	7.1%	3.22 [0.43, 24.12]	
Tran 2018	0.327	0.043	22.3%	1.39 [1.27, 1.51]	
Zeng 2020	1.5015	0.4051	16.8%	4.49 [2.03, 9.93]	
Total (95%CI)			100%	1.00 [0.52, 1.93]	
		- /	aa.u. 12 a		

Heterogeneity: Tau² = 0.49; Chi² = 54.72, df = 5 (P < 0.00001); l² = 91% Test for overall effect: Z = 0.01 (P = 0.99)

				Odds Ratio	Odds Ratio	
Study	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% CI	
2.18 type of catheter 3	(PICC VS Tunneled li	nes)				
Charny 2018	2.0433	0.7596	9.6%	7.72 [1.74, 34.20]		
Derderian 2019	1.4022	0.7762	9.3%	4.06 [0.89, 18.61]		
Jaffray 2020	0.8362	0.2613	22.5%	2.31 [1.38, 3.85]		
Shah 2015	-1.5254	0.6088	12.5%	0.22 [0.07, 0.72]		
Smitherman 2015	0.2154	0.3619	19.3%	1.24 [0.61, 2.52]		
Tran 2018	0.8547	0.0734	26.9%	2.35 [2.04, 2.71]		
Total (95%CI)			100%	1.81 [1.02, 3.21]		
Hotorogonoity: $T_{0}u^{2} = 0$	$21 \cdot Chi^2 = 21 \cdot 01 \cdot df = 6$	(P _ 0 00	00), 12 - 76	- · ·		

Heterogeneity: Tau² = 0.31; Chi² = 21.01, df = 5 (P = 0.0008); l² = 76% Test for overall effect: Z = 2.04 (P = 0.04)



Heterogeneity: $Chi^2 = 3.67$, df = 2 (P = 0.16); $l^2 = 45\%$

Test for overall effect: Z = 0.00 (P = 1.00)

Fig. 5 Meta-analysis of CVAD-related risk factors (2). Forest plots of odds ratios (OR) that were included in the quantitative meta-analysis and the associated overall OR. For each OR, the size of the red square region is proportional to the corresponding study weight. Diamond shape intervals represent the overall OR. I² represents the fraction of variability among the individual OR that cannot be explained by sampling variability.

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				Odds Ratio		Odds Ratio	
Study	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	ľ	V, Random, 95% Cl	
2.21 type of catheter 6 (No	ON-PICC)						
Badheka 2021	0.2414	0.3387	21.9%	1.27 [0.66, 2.47]			
Longo 2021	0.9282	0.4635	19.4%	2.53 [1.02, 6.28]			
Noonan 2018	-1.0177	0.2549	23.4%	0.36 [0.22, 0.60]			
Onyeama 2018	-2.0604	0.7563	13.7%	0.13 [0.03, 0.56]			
Smitherman 2015	-0.331	0.3523	21.6%	0.72 [0.36, 1.43]			
Total (95%CI)			100%	0.70 [0.31, 1.56]			
Heterogeneity: $Tau^2 = 0.66$; Chi ² = 22.53, df = 4	(P = 0.000	02); I ² = 82%	5			
Test for overall effect: $Z = 0$.88 (P = 0.38)			F			<u> </u>
				0.0	1 0.1	1 1	0 100

				Odds Ratio	Odds Ratio
Study	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.22 type of catheter 7 (t	unnedlled CVC VS n	ontunnele	d CVC)		
Derderian 2019	-2.1221	1.0212	6.9%	0.12 [0.02, 0.89]	
Patel 2020	-0.591	0.4125	23.3%	0.55 [0.25, 1.24]	
Shah 2015	-0.9061	0.4489	21.4%	0.40 [0.17, 0.97]	
Smitherman 2015	0.8748	1.0763	6.3%	2.40 [0.29, 19.77]	
Tran 2018	-0.1217	0.0827	42.1%	0.89 [0.75, 1.04]	
Total (95%CI)			100%	0.62 [0.35, 1.10]	
Heterogeneity: $Tau^2 = 0.2$	0. $Chi^2 = 8.67 df = 4$	(P = 0.07)	$l^2 = 54\%$		

Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 8.67$, df = 4 (P = 0.07); $I^2 = 54\%$ Test for overall effect: Z = 1.63 (P = 0.10)



Study	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	l
2.23 type of catheter 8 (T	IVAP VS tunnedlled	CVC)			
Chen 2016	0.1542	0.5876	24.2%	1.17 [0.37, 3.69]	
Derderian 2019	-0.3355	1.4162	7.3%	0.71 [0.04, 11.48]	
Smitherman 2015	0.1985	0.5947	23.9%	1.22 [0.38, 3.91]	
Tran 2018	-0.9965	0.1459	44.6%	0.37 [0.28, 0.49]	
Total (95%CI)			100%	0.68 [0.30, 1.54]	
Heterogeneity: $Tau^2 = 0.36$	6; Chi ² = 7.16, df = 3	(P = 0.07);	$l^2 = 58\%$		
Test for overall effect: Z =	0.92 (P = 0.36)	· · · · · · · · · · · · · · · · · · ·			

Odds Ratio Odds Ratio IV, Random, 95% CI IV, Random, 95% CI Study log[Odds Ratio] SE Weight 2.24 type of catheter 9 (TIVAP VS nontunneled CVC) Derderian 2019 1.0207 25.7% 0.09 [0.01, 0.63] -2.4576 Smitherman 2015 1.0734 1.1038 23.7% 2.93 [10.34, 25.45] Tran 2018 -1.1182 0.1265 50.5% 0.33 [0.26, 0.42] Total (95%CI) 100% 0.39 [0.09, 1.64] Heterogeneity: $Tau^2 = 1.05$; $Chi^2 = 5.66$, df = 3 (P = 0.06); $l^2 = 65\%$ Test for overall effect: Z = 1.28 (P = 0.20) 0.01 0.1 10 100 1

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Fig. 5 Continued

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				Odds Ratio	Odds Ratio
Study	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.26 number of lumens ((Multiple VS Singer)				
Gnannt 2018	1.0384	0.2448	10.9%	2.82 [1.75, 4.56]	
Gray 2012	2.9874	0.4096	9.1%	19.83 [8.89, 44.27]	
Jaffray 2020	0.9233	0.2167	11.2%	2.52 [1.65, 3.85]	
Lambert 2019	-0.1054	0.5438	7.6%	0.90 [0.31, 2.61]	
Li 2021	0.2137	0.1744	11.5%	1.24 [0.88, 1.74]	+
Longo 2021	1.0613	0.6184	6.8%	2.89 [0.86, 9.71]	
Menendez 2016	0.015	0.2693	10.7%	1.02 [0.60, 1.72]	
Noonan 2018	-0.5035	0.2494	10.9%	0.60 [0.37, 0.99]	
Ostlund 2019	0.5365	0.185	11.5%	1.71 [1.19, 2.46]	
Wisecup 2015	0.12	0.3466	9.8%	1.31 [0.57, 2.22]	
Total (95%CI)			100%	1.82 [1.13, 2.93]	-
Heterogeneity: Tau ² = 0.4 Test for overall effect: Z =	8; Chi ² = 70.93, df = 9 2.46 (P = 0.01)) (P < 0.000	001); l ² = 87	%	

Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% Cl	Odds Ratio IV, Fixed, 95% Cl
2.27 number of cath	eters (Multiple VS Singe	r)			
Jiang 2022	0.6429	0.3482	21.9%	1.90 [0.96, 3.76]	
Sol 2015	1.8326	0.6843	5.7%	6.25 [1.63, 23.90]	
Steen 2019	1.1632	1.1912	72.5%	3.20 [2.20, 4.66]	
Total (95%CI)			100%	2.97 [2.16, 4.08]	•
Llataraganaitu Chi ²	$0.07 df 0.00 0.00) 1^2$	000/			

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Heterogeneity: $Chi^2 = 2.97$, df = 2 (P = 0.23); $I^2 = 33\%$ Test for overall effect: Z = 6.68 (P < 0.00001)

				Odds Ratio	Odds Ratio
Study	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.28 catheter indwell	ing time				
Dubois 2007	0.0488	0.0352	1.9%	1.05 [0.98, 1.13]	r
Jiang 2022	0.1587	0.0709	0.5%	1.17 [1.02, 1.35]	-
Lovett 2023	0.0198	0.0256	3.6%	1.02 [0.97, 1.07]	•
Marquez 2016	0.0488	0.03	2.6%	1.05 [0.99, 1.11]	<u>+</u>
Menendez 2016	0.01	0.0051	91.3%	1.01 [1.00, 1.02]	—
Pei 2016	0.3723	0.2336	0.0%	1.45 [0.92, 2.29]	
Total (95%CI)			100%	1.01 [1.00, 1.02]	
Heterogeneity: $Chi^2 =$	9 46 df = 5 (P = 0.09) \dot{f}	$^{2} = 47\%$			

= 9.46, df = 5 (P = 0.09); l' Heterogeneity: Chi² 47% Test for overall effect: Z = 2.66 (P = 0.008)



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Odds Ratio Odds Ratio log[Odds Ratio] SE IV, Fixed, 95% CI IV, Fixed, 95% CI Study Weight 2.29 CLABSI Dubois 2007 0.26 [0.02, 4.56] -1.3323 1.4543 3.0% Jaffray 2020 5.60 [1.90, 16.51] 1.7228 0.5515 20.6% Lambert 2019 9.85 [1.99, 48.90] 2.2878 0.8173 9.4% Ostlund 2019 0.8589 0.8307 9.1% 2.36 [0.46, 12.03] Rooden 2005 2.8679 0.7433 11.4% 17.60 [4.10, 75.55] Sol 2015 2.5735 0.7693 10.6% 13.11 [2.90, 59.22] Steen 2019 1.8563 0.7754 10.4% 6.40 [1.40, 29.26] Verheij 2018 1.1236 0.7844 10.2% 3.08 [0.66, 14.31] Zeng 2020 0.5187 0.6395 15.3% 1.68 [0.48, 5.88] Total (95%CI) 100% 4.93 [3.02, 8.05] Heterogeneity: $Chi^2 = 13.47$, df = 8 (P = 0.10); $I^2 = 41\%$ Test for overall effect: Z = 6.37 (P < 0.00001) 0.01 0.1 10 100 1

Fig. 5 Continued

0.01

0.1

Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% C	Odds Ratio IV, Random, 95% Cl
2.30 difficult insertion					
Chen 2016	0.6348	0.5013	14.0%	1.89 [0.71, 5.04]	
Deng 2020	0.0883	0.4953	14.2%	1.09 [0.41, 2.88]	
Kim 2022	1.7272	0.5439	13.0%	5.62 [1.94, 16.33]	
Li 2022	0.3237	1.2283	4.4%	1.38 [0.12, 15.35]	
Menendez 2016	0.8246	0.2696	20.3%	2.28 [1.34, 3.87]	
Ostlund 2019	-0.2231	0.2101	21.9%	0.80 [0.53, 1.21]	
Wang 2021	-0.0899	0.5839	12.1%	0.91 [0.29, 2.87]	
Total (95%CI)			100%	1.57 [0.90, 2.73]	
Heterogeneity: $Tau^2 = 0.3$ Test for overall effect: Z =	32; Chi ² = 17.94, df = = 1.58 (P = 0.11)	6 (P = 0.00	06); l ² = 67%		

Fig. 5 Continued

likelihood of blood flow obstruction and venous wall adhesion.²⁶ However, our meta-analysis did not find a statistically significant increase in the risk of CRT with left-sided placement compared to right-sided placement. The ideal location for the catheter tip is the junction of the superior vena cava and the right atrium. This location is preferred because of the higher blood flow rate, which may be protective against thrombosis.⁴³ Currently, the pediatric literature on the effect of optimal tip position on CRT is scarce and inconclusive. In addition, catheter tips do not always remain in that position after initial placement. Therefore, tip movement should be a significant concern in pediatric patients, especially active, growing, and requiring longterm catheter use.

Providing renal replacement therapy is a lifelong task for pediatric end-stage renal disease (ESRD) patients. Although successful transplantation can be achieved even in young patients, the lifespan of the graft is limited. Consequently, many transplant recipients may be put back on dialysis as part of their ESRD treatment.⁷⁸ CVC remains the main vascular access for hemodialysis in children. Long-term reliance on CVC is related to a high incidence of catheter dysfunction and failure. The frequent need for recurrent CVC placement in such patients leads to an elevated risk of central vein stenosis and CRT. Cardiac catheterization is also a possible risk factor for CRT. Appropriate anticoagulation is required during catheterization, without which the risk of thrombosis is up to 40%. However, the use of unfractionated heparin in pediatric patients is challenging because the coagulation system and heparin response are different from that of adults.⁷⁹ There's a need for further research to determine if children are receiving adequate doses of heparin during cardiac catheterization to prevent thrombosis without increasing the risk of bleeding complications. The incidence of VTE in adult patients who are chronically bedridden and braked is 3.59 times higher than in patients with normal activity levels.⁸⁰ In critically ill or surgical children, mechanical ventilation is often performed in the early stages, requiring continuous use of multiple sedative or inotropic drugs to reduce cardiac load and protect pulmonary function. During sedation, the child is in a braked state, limb activity is reduced or even inactive, blood flow slows down, and blood stagnates in the veins, increasing the chance of platelet adhesion to the endothelium, which may increase the risk of CRT. Therefore, passive movements such as limb abduction, internal rotation, elbow flexion and elbow extension should be performed appropriately when the child's condition permits.

Nutritional support is an important part of critical illness treatment, including enteral and parenteral nutrition (PN). CVAD is the supply channel for total parenteral nutrition (TPN), and some children may even need this method to provide calories for a long time. High glucose and calcium concentrations in PN are both possible triggers of CRT, and PN has been shown to upregulate the extrinsic coagulation cascade, especially with long-term use.⁶⁰ Diamanti et al. reported that the incidence rate of TPN complicated with CRT was 20%.81 Mannitol or glycerol fructose are widely used as hypertonic drugs in clinical practice, which can increase plasma osmolality to dehydrate tissues after entering the body. At the same time, it may cause a cellular stress response, induce apoptosis, and can activate inflammatory cytokines and coagulation pathways to induce thrombosis. Jiang et al.²² found vasoactive drugs to be a risk factor for CRT. The possible reason is that vasoactive drugs can cause strong vasoconstriction, endothelial function damage or impairment, and promote fibrinogen synthesis. However, this is contrary to the findings of Marquez et al.²⁸ and Faustino et al.²¹ Therefore, larger prospective studies are still needed to assess this risk factor more precisely.

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The strengths of this study include the systematic identification of all relevant studies of risk factors for CRT in hospitalized children and the classification of risk factors into three categories, patient-related risk factors, CVAD-related risk factors, and treatment-related risk factors, to offer a logical progression of the possible causes of CRT in children. However, several limitations of this systematic review should be stated. Firstly, as most of the studies originate from Western countries, extrapolating these results to Eastern populations is questionable. Second, significant heterogeneity was encountered in our analysis, potentially stemming from variations in regimen, duration, population enrolled, and center setting, among other factors. This diversity necessitates a cautious interpretation of the results. In addition, only a few high-quality studies with a low risk of bias, and many of the studies suffer from significant sources of bias. Furthermore, the effect in many occasions was assessed by very few studies. Therefore, the evidence to support it is low, which needs to be validated in future studies. Finally, risk factors for CRT could not be made causal assertions since the majority of studies were retrospective.

CONCLUSIONS

In conclusion, we have identified several critical factors that affect CRT, including D-dimer, location of insertion, type of catheter, number of lumens, catheter indwelling time, and CLABSI. Nevertheless, none of the included studies considered the impact of socio-demographic factors on CRT, such as parental education level, occupation, and family economic status. Therefore, larger sample sizes and well-designed prospective studies are still needed to clarify the predictors affecting CRT in the future. In addition, there is a lack of pediatric-specific CRT risk assessment

Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI		Odds IV, Fixe	Ratio d, 95% Cl	
3.1 TPN								
Beck 1988	0.4738	0.7445	2.2%	1.61 [0.37, 6.91]				
Deng 2020	-0.5108	0.5973	3.5%	0.60 [0.19, 1.93]				
Dubois 2007	-0.9867	1.0489	1.1%	0.37 [0.05, 2.91]				
Faustino 2013	0.7069	0.656	2.9%	2.03 [0.56, 7.33]		-		
Gnannt 2018	-0.0756	0.2572	18.8%	0.93 [0.56, 1.53]		-	-	
Jiang 2022	0.2187	0.3166	12.4%	1.24 [0.67, 2.31]				
Lambert 2019	1.7357	1.4363	0.6%	5.67 [0.34, 94.71]				
Marquez 2016	0.5306	0.3846	8.4%	1.70 [0.80, 3.61]				
Menéndez 2016	-0.0558	0.261	18.2%	0.95 [0.57, 1.58]		-	-	
Smitherman 2015	1.0647	0.4502	6.1%	2.90 [1.20, 7.01]				
Verheij 2018	0.7747	0.592	3.5%	2.17 [0.68, 6.92]				
Wang 2021	-0.0492	0.727	2.3%	0.95 [0.23, 3.96]				
Wisecup 2015	0.7787	0.3845	8.4%	2.18 [1.03, 4.63]				
Zeng 2020	0.8746	0.3283	11.5%	2.40 [1.26, 4.56]				
Total (95%CI)			100%	1.37 [1.10, 1.71]				
Heterogeneity: Chi ² =	17.55, df = 13 (P = 0.18	3); I ² = 26%	, ,					
Test for overall effect:	Z = 2.85 (P = 0.004)				 		++	I
					0.01	0.1	1 10	100

Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI		Odds Ratio IV, Random, 95% CI	
3.2 surgery							
Badheka 2021	1.0112	0.477	6.7%	2.75 [1.08, 7.00]			
Faustino 2015	-0.806	0.5091	6.4%	0.45 [0.16, 1.21]			
Kim 2015	0.1313	0.4674	6.8%	1.14 [0.46, 2.85]			
Lambert 2019	1.1414	0.5374	6.0%	3.13 [1.09, 8.98]			
Li 2021	-1.0033	0.1389	10.7%	0.37 [0.28, 0.48]		-	
Longo 2021	1.335	0.4413	7.1%	3.80 [1.60, 9.02]			
Lovett 2023	0.1948	0.6456	5.0%	1.22 [0.34, 4.31]			
Marquez 2016	-0.734	0.3579	8.2%	0.48 [0.24, 0.97]			
Menéndez 2016	-0.4574	0.4092	7.5%	0.63 [0.28, 1.41]			
Östlund 2019	0.174	0.1598	10.5%	1.19 [0.87, 1.63]			
Sol 2015	1.0745	0.6728	4.8%	2.93 [0.78, 10.95]			
Steen 2019	-1.3863	0.2958	9.0%	0.25 [0.14, 0.45]			
Tran 2018	-0.4155	0.0659	11.2%	0.66 [0.58, 0.75]		-	
Total (95%CI)			100%	0.90 [0.62, 1.32]		•	
Heterogeneity: Tau ²	= 0.33, Chi ² = 83.85, df =	= 12 (P < 0.	.00001); l ² :	= 86%			
Test for overall effect	:: Z = 0.53 (P = 0.59)				L		
					0.01 0	.1 1 10	100
				Odds Ratio		Odds Ratio	
Study	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	

Study	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI			
3.3 dialysis									
Li 2021	0.4	0.2294	13.9%	1.49 [0.95, 2.34]			+		
Smitherman 2015	1.1632	0.5495	2.4%	3.20 [1.09, 9.40]					
Tran 2018	0.6254	0.094	83.0%	1.87 [1.55, 2.25]					
Wisecup 2015	1.8617	1.093	0.6%	6.43 [0.76, 54.81]			+	-	
Total (95%CI)			100%	1.85 [1.56, 2.19]			•		
Heterogeneity: Chi ² =	3.19, df = 3 (P = 0.36);	$l^2 = 6\%$							
Test for overall effect:	Z = 7.18 (P < 0.00001)	1			—				
					0.01	0.1	1	10	100

Fig. 6 Meta-analysis of treatment-related risk factors. Forest plots of odds ratios (OR) that were included in the quantitative meta-analysis and the associated overall OR. For each OR, the size of the red square region is proportional to the corresponding study weight. Diamond shape intervals represent the overall OR. I^2 represents the fraction of variability among the individual OR that cannot be explained by sampling variability.

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Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Odds Ratio IV, Random, 95% Cl
3.4 mechanical ventila	ation				
Badheka 2021	-0.1222	0.3882	12.9%	0.88 [0.41, 1.89]	
Faustino 2013	1.1314	0.7592	5.5%	3.10 [0.70, 13.73]	
Faustino 2015	-0.565	0.6227	7.3%	0.57 [0.17, 1.93]	
Li 2021	0.545	0.2114	19.4%	1.72 [1.14, 2.61]	
Marquez 2016	0.3784	0.4051	12.3%	1.46 [0.66, 3.23]	
Östlund 2019	-0.0551	0.3319	14.8%	0.95 [0.49, 1.81]	
Pei 2016	0.9571	0.8607	4.5%	2.60 [0.48, 14.07]	
Tran 2018	0.9083	0.0922	23.4%	2.48 [2.07, 2.97]	*
Total (95%CI)			100%	1.50 [1.01, 2.22]	•
Heterogeneity: $Tau^2 = 0$	0.17; Chi ² = 20.35, df =	= 7 (P = 0.0	$(005); I^2 = 6$	6%	
T 1 C 11 C 1 T					

Odds Ratio IV, Random, 95% CI

5.98 [1.56, 22.95]

0.54 [0.15, 1.89]

0.56 [0.38, 0.82]

2.04 [0.76, 5.49]

Test for overall effect: Z = 2.01 (P = 0.04)

3.5 mechanical thromboprophylaxis / limb exercises

Study

Li 2022

Faustino 2013

Faustino 2015

Lovett 2023

Total (95%CI)



Heterogeneity: Tau² = 0.90; Chi² = 15.69, df = 3 (P = 0.001); l² = 81% Test for overall effect: Z = 0.45 (P = 0.65)

log[Odds Ratio]

1.7892

-0.6168

-0.5861

0.7143

SE

0.6857

0.6406

0.1962

0.5048

Weight

21.3%

22.3%

31.1%

25.3%

100%

Odds Ratio Random, 95% Cl		Odds Ra IV, Random,	ntio 95% Cl	
⊢— 0.01	0.	.1 1	1	 0 100
1.27 [0.44, 3.67]				

1

10

100

Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Odds Ratio IV, Random, 95% Cl
3.6 tissue plasminoger	n activator				
MacLean 2018	0.6917	0.3098	53.1%	2.00 [1.09, 3.67]	
Onyeama 2018	-3.2425	1.0336	46.9%	0.04 [0.01, 0.30]	←
Total (95%CI)			100%	0.32 [0.01, 14.82]	
Heterogeneity: $Tau^2 = 7$.	.16; Chi ² = 13.29, df =	= 1 (P = 0.0	$(0003); I^2 = 1$	92%	

Heterogeneity: Tau² = 7.16; Chi² = 13.29, df = 1 (P = 0.0003); l² = 92% Test for overall effect: Z = 0.59 (P = 0.56)

Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% Cl
3.7 glucocorticoid					
Chen 2016	0.9489	0.5542	18.8%	2.58 [0.87, 7.65]	
Zeng 2020	0.7362	0.2663	81.2%	2.09 [1.24, 3.52]	
Total (95%CI)			100%	2.17 [1.36, 3.48]	•
Heterogeneity: Chi ² = 0.1	12, df = 1 (P = 0.73);	$l^2 = 0\%$			

0.01

0.1

Test for overall effect: Z = 3.23 (P = 0.001)

Heterogeneity: $Chi^2 = 9.54$, df = 6 (P = 0.15); l² = 37% Test for overall effect: Z = 3.12 (P = 0.002)

log[Odds Ratio]

0.3567

0.401

1.4171

-0.0765

0.4187

1.0296

0

SE

0.5464

0.5111

0.3606

0.6522

0.3339

0.3693

0.9291



Fig. 6 Continued

Study

3.8 vasoactive drugs Faustino 2013

Faustino 2015

Jiang 2022

Lovett 2023

Marquez 2016

Wisecup 2015

Total (95%CI)

Zhu 2022

Study log[Odds Ratio]		SE	Weight	Odds Ratio IV, Random, 95% CI		Odds IV, Rando	Ratio om, 95% Cl	
3.9 hypertonic liqu	id							
Li 2022	0.4656	0.2088	55.4%	1.59 [1.06, 2.40]				
Lovett 2023	1.2669	1.1139	26.1%	3.55 [0.40, 31.50]				-
Pei 2016	3.4702	1.4764	18.5%	32.14 [1.78, 580.5]				•>
Total (95%CI)			100%	3.42 [0.76, 15.46]		-		
Heterogeneity: Tau ²	² = 1.03; Chi ² = 4.49, df = 2	2 (P = 0.11); I ² = 55%					
Test for overall effect	ct: Z = 1.60 (P = 0.11)				1	1		
					0.01	0.1	1 10	100

				Odds Ratio	Odds Ratio
Study	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
3.10 blood products					
Dubois 2007	-1.3323	1.4543	2.0%	0.26 [0.02, 4.56]	
Faustino 2013	-0.1054	0.55	14.0%	0.90 [0.31, 2.64]	
Gnannt 2018	0.2828	0.7355	7.8%	1.33 [0.31, 5.61]	
Jiang 2022	0.1737	0.3811	29.1%	1.19 [0.56, 2.51]	_
Lambert 2019	0.3982	0.4889	17.7%	1.49 [0.57, 3.88]	
Lovett 2023	-0.1823	0.7555	7.4%	0.83 [0.19, 3.66]	
Marquez 2016	0.9821	0.4387	22.0%	2.67 [1.13, 6.31]	
Total (95%CI)			100%	1.36 [0.91, 2.03]	
Heterogeneity: Chi ² = 4	.78, df = 6 (P = 0.57);	l ² = 0%			
Test for overall effect: Z	= 1.48 (P = 0.14)			L	

Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl		Odds Ratio IV, Random, 95% Cl	
3.11 cardiac cather	terization						
Steen 2019	1.6563	0.3018	45.5%	5.24 [2.90, 9.47]			
Tran 2018	0.7227	0.1101	54.5%	2.06 [1.66, 2.56]			
Total (95%CI)			100%	3.15 [1.27, 7.83]			
Heterogeneity: Tau ²	² = 0.38; Chi ² = 8.45, df =	1 (P = 0.00	4); l ² = 88%	6			
Test for overall effect	ct: Z = 2.47 (P = 0.01)			F			
				0.01	1 0.1	1 10	100

0.1

1

10

100

Study	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI		Odds I IV, Rand	Ratio om, 95% Cl	
3.12 length of hospita	al admission							
Kim 2015	1.0986	0.5605	36.8%	3.00 [1.00, 9.00]				
Verheij 2018	0.01	0.0206	63.2%	1.01 [0.97, 1.05]				
Total (95%CI)			100%	1.51 [0.54, 4.22]				
Heterogeneity: Tau ² =	0.44; Chi ² = 3.77, df =	1 (P = 0.05); I ² = 73%					
Test for overall effect:	Z = 0.78 (P = 0.43)							
					0.01	0.1	1 10	100

Fig. 6 Continued

tools, which need to be further developed and validated. Machine learning (ML), as a method for designing risk assessment models that help to efficiently explore and mine useful information, has been widely used in recent years to solve a variety of challenging medical problems. Likewise, the application of ML in CRT risk diagnosis may contribute to a more precise assessment. In clinical practice, it is necessary to take appropriate stratified preventive measures according to the level of CRT risk assessment of children, to improve the efficiency of clinical work, reduce the burden of clinical work, and minimize the occurrence of CRT under the premise of ensuring the safety of children.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

GY and YL framed the review questions on the basis of input from MF and QY. YY and XQ conducted the literature search. MF, WS, and QY screened and evaluated the identified papers. GY and YY performed data extraction and analysis. MF, WS, XQ and QY prepared the initial manuscript with revisions and comments from GY, YL, and XX. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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COMPETING INTERESTS

The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Genzhen Yu.

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