Review

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Accuracy of chest radiography compared to ultrasound for positioning the umbilical venous catheter in neonates: A meta-analysis and systematic review

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Abstract

This study was aimed to investigate the accuracy of anteroposterior chest radiography for tip position verification for the umbilical venous catheters in neonates compared to ultrasound. A search in the PubMed, Embase, the Cochrane Library, and EBSCO was conducted to evaluate all the related articles on umbilical venous catheter (UVC), ultrasound AND neonates updated to August, 2020. Study selection, data extraction, and quality assessment were performed independently by two investigators. Random effects model was used to estimate the pooled sensitivity, specificity, and diagnostic odds ratio (DOR). The summary receiver operator characteristic (SROC) curve was constructed, and the area under the SROC curve (AUC) was calculated. Fourteen related studies were finally included for meta-analysis. The overall diagnostic sensitivity and specificity of X-ray on tip verification of UVC were 0.90 (95% CI 0.71–0.97) and 0.82 (95% CI 0.53–0.95), respectively. The pooled DOR was 3.69 (95% CI 1.64–5.71). The AUC was 0.93 (95% CI 0.90–0.95). The meta-regression analysis suggested that study sample size, study design, different US confirming method, and different gold standard in original design might be potential sources of heterogeneity. Our conclusion is that the commonly used anteroposterior X-ray is not reliable in identifying the exact anatomical location of UVC tip in neonates. Studies suggested ultrasound or echocardiography with saline contrast injection could be the gold standard for verification of catheter location and should be considered whenever possible, especially in premature patients. More studies are needed to expand the use of ultrasound or echocardiography in tip position confirming of UVCs.

Keywords

Chest radiography, ultrasound, neonates, umbilical venous catheter, tip position, meta-analysis

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Introduction

Umbilical venous catheters (UVCs) are usually used in neonatal intensive care units (NICUs) to provide intravenous fluids, medication, and total parenteral nutrition.[1] UVC is introduced into the umbilical vein, joining the inferior vena cava (IVC) by venous portal system, and the ductus venosus (DV).[2] They are widely used in neonatal care, especially in premature or critically ill newborns.[3,4] However, the use of UVCs has many complications, including myocardial perforation, cardiac tamponade, pericardial effusion, and cardiac arrhythmia and thrombosis, even pulmonary embolism.[5–7] These complications were reported mostly associated with tip malposition of the catheter.[8–10] The most advocated tip position of UVC is in the thoracic portion of IVC or at the

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junction of the IVC with right atrium (RA)[10–12] although there is still inconsistence, and many researchers also accept tip position in RA.[2,4,7] Low-lying UVC is defined as a catheter tip position below the junction of the IVC.[13] It was reported that low-lying UVC was associated with higher risk of UVC associated infection, formation of thrombosis, extravasation, and hepatic injuries.[13–15]

Anteroposterior chest radiography (X-ray) is the most frequently used method to assess catheter tip position. Chest radiography is regarded as gold standard to confirm the tip position of central venous catheters (CVCs), using the diaphragm, cardiac silhouette, and mostly the vertebral bodies as anatomical landmarks.[16,17] However, many studies on UVC for newborns questioned the accuracy of X-ray used for verifying the correct tip position by these anatomical landmarks.[2–4,10–12,18] It was reported that ultrasound (US), especially echocardiography revealed a significant number of umbilical venous catheters malpositioned into the left atrium (LA), even though these catheters were considered to be in the ideal position by X-ray.[10,19] The tip of UVC located in the left atrium was reported associated with thrombosis formation.[10] Some studies have suggested that ultrasound, especially echocardiography should be the "gold standard" to verify the tip position of UVCs on newborns, and sometimes with saline contrast injection to contribute to verify the position of the tip.[4,12,20] Ultrasound allows real-time imaging of the catheter tip relative to identifiable anatomical structures.[18] However, many of these studies had limited number of patients and the accuracy of anteroposterior chest radiography to confirm the tip position of UVC compared to ultrasound was not well defined. There is no related meta-analysis and systematic review.

Thus, we conducted a meta-analysis and systematic review to evaluate the accuracy of the anteroposterior chest radiography in determining the umbilical venous catheter tip position, with ultrasound as the gold standard.

Methods

The meta-analysis and systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[18]

Search strategy

A search in the PubMed, Embase, the Cochrane Library, and EBSCO was conducted to evaluate all the related articles on umbilical venous catheter, ultrasound AND neonates updated to August, 2020 for human studies without language restriction. Relevant articles were identified by combining the following medical subject headlines (MeSH) and keywords: (radiography OR radioactive rays OR radial ray OR "X-line" OR "X-ray") AND (UV OR umbilical venous catheter OR Umbilical catheter OR umbilical vein catheter OR umbilical line) AND (ultrasound OR ultrasonography OR ultrasonographic OR supersound OR ultrasonic OR TnECHO OR echocardiography OR echocardiogram OR ECHO OR ultrasonic cardiogram) AND (pediatry OR pediatric OR pediatric OR neonatal OR neonatus OR Child OR chit OR baby OR children OR infant OR infants OR newborn OR toddler OR neonate). In addition, the reference lists of relevant reviews were manually searched to obtain additional articles.

Inclusion criteria and exclusion criteria

Eligible studies included in this meta-analysis and systematic review had to fulfill the three predefined criteria: (1) prospective or retrospective observational studies on UVC tip position verification among neonates or infants; (2) studies comparing at least two procedures on tip position confirmation: US or echocardiography, and X-ray; (3) studies that reported sufficient data to reconstruct the diagnostic 2×2 table by test of X-ray and US. Articles were excluded for the following reasons: (1) reviews and case reports; (2) studies not related to UVC tip position verification among neonates or infants; (3) studies not reconstruct the diagnostic 2×2 table by test of X-ray and US; and (4) studies without valid data or with improper data.

Data extraction

Two reviewers (Yuxiu Liu and Yanling Yin) independently screened titles, abstracts, and full texts. All disagreements or discrepancies about the inclusion were resolved following discussion by consensus or by consulting a third reviewer (Yuzhen Zhang). We asked for information from the authors of the studies for unpublished data. In case of multiple publications from one dataset or of cross data, we included the most proper study for our analysis. For each eligible study, two reviewers (Yanling Yin and Yuxiu Liu), blind to each other, extracted the relevant data using standardized data extraction form. Variables abstracted included: first author, year of publication, country, study design, study population, best tip position, catheter tip malposition, X-ray tip position confirming method, ultrasound device, ultrasound tip position diagnosis method, and data needed for meta-analysis, true positive (TP), false positive (FP), false negative (FN), and true negative (TN) for the testing of X-ray compared ultrasound for the tip position confirming of UVCs.

Quality evaluation

Two reviewers (Yanling Yin and Yuxiu Liu) used the revised quality assessment of diagnostic accuracy studies

(QUADAS-2) criteria to assess the methodological quality of the included studies.[21] The tool is composed of four domains: patient selection, index test, reference standard, and flow and timing. Every domain is evaluated in terms of risk of bias. Moreover, the first three domains are assessed with applicability to clinical practice. For both categories, risk of bias, and concern for applicability were classified as low risk, high risk, or unclear. The results were presented by using tables from the QUADAS web site (www.quadas.org).

Statistical analysis

The pooled sensitivity, specificity, positive likelihood ratios (PLR), negative likelihood ratios (NLR), and diagnostic odds ratio (DOR) with the 95% confidence intervals (CIs) were calculated using the DerSimonian-Laird random effects model.[22] The summary receiver operator characteristic (SROC) curve was constructed, and the area under the SROC curve (AUC) was calculated. The hierarchical summary receiver operating characteristic (HSROC) was used to identify the X-ray accuracy for the confirmation of CVC tip position compared to ultrasound. Meta-regression and subgroup analyses were conducted to evaluate the source of heterogeneity. Publication bias was assessed by using funnel plot and Egger's test.[23] All the analyses were performed using Stata 12.0 and Metadisc 1.4 software. All statistical tests were two sided with the significance level at 0.05 and add 1/2 to all cells of the studies with zero.

Results

Study identification and study characteristics

After a comprehensive literature search in PubMed, Embase, the Cochrane Library, and EBSCO databases, a total of 470 studies were retrieved. Seven additional articles were identified by reference literature review. After duplicates removal, title, abstract and full-text checking, 14 related studies were finally included for meta-analysis.[2–4,7,8,10–12,18–20,24–26] A flowchart on the detailed study selection process is shown in Figure 1.

A total of 979 umbilical venous catheters were assessed the tip positions by X-ray and ultrasound in the 14 included studies. Of the 14 studies, 11 studies were prospective observational design,[2–4,7,11,12,18,20,24–26] 2 studies were retrospective design,[8,10] and 1 study was cross-sectional observational design.[19] These studies were from seven countries, in United States of America ($n=7$), Canada ($n=2$), Israel ($n=1$), France ($n=1$), Australia ($n=1$), United Arab Emirates ($n=1$), and Brazil ($n=1$). Eight of the studies explored the accuracy of ultrasound or echocardiography on the confirmation of umbilical venous tip position using X-ray as gold standard.[3,7,11,12,20,24–26] Five studies evaluated the accuracy of the X-ray in determining the position of the umbilical venous catheter tip position using echocardiography or ultrasound as a reference standard.[4,8,10,18,19] One study compared ultrasound and X-ray in determining the position of umbilical venous catheters using "actual position" of the catheter tip as gold standard based on the results of the two methods.[2] For X-ray evaluation methods, six studies used antero-posterior chest radiography and only thoracic vertebra as landmarks.[2,8,11,12,18,25,26] Two studies used two kinds of X-ray for verifying the tip position by X-ray, antero-posterior chest radiography and lateral chest radiography.[4,10] One study used cardiac silhouette method and vertebral body method to confirm the tip position by X-ray respectively, thus, we regarded these data as two separate data.[18] Five studies used more than two types of anatomical landmarks from diaphragm, cardiac silhouette, and vertebral bodies to confirm the tip position of UVCs by X-ray.[3,7,19,20,24] The related data in the 14 studies for meta-analysis are shown in online data and Table 1.

Quality of included studies. Of the 14 studies included in the meta-analysis, eight studies presented low risk in all the domains of risk of bias and applicability concerns.[2–4,7,11,18,25,26] Regarding the internal validity, two of studies were rated as high risk of bias in the patient selection domain; 21.42% were rated as high risk of bias or unclear in index test, reference standard, and flow and timing domain. A few studies were retrospective or case–control design which raised the patient's selection bias,[10,24] and a few were not blinded on both tests or the time gap between the two tests was unclear or not described which raised risk of bias on the internal validity.[8,10,12,19] Regarding the external validity, all studies were rated as low risk of bias in the patient selection, index test, and reference standard domain. Study quality on risk of bias assessment and applicability concerns assessment is showed in Table 2.

Accuracy of X-ray on tip position verification by meta-analysis. Fourteen studies with 15 groups of data were included in the meta-analysis. The overall diagnostic sensitivity and specificity of X-ray on tip verification of umbilical venous catheter were 0.90 (95% CI 0.71–0.97) and 0.82 (95% CI 0.53–0.95), respectively (Figure 2). The pooled PLR, NLR, and DOR were 5.03 (95% CI 1.55–16.31), 0.13 (95% CI 0.04–0.42), and 3.69 (95% CI 1.64–5.71), respectively. I^2 values for sensitivity was 93.19% (95% CI 90.81–95.57), and I^2 values for specificity was 96.12% (95% CI 94.98–97.26), with $p < 0.01$. A random effects model was used to estimate the pooled data because great heterogeneity existed among the included studies. The area under the SROC was 0.93 (95% CI 0.90–0.95) (Figure 3).

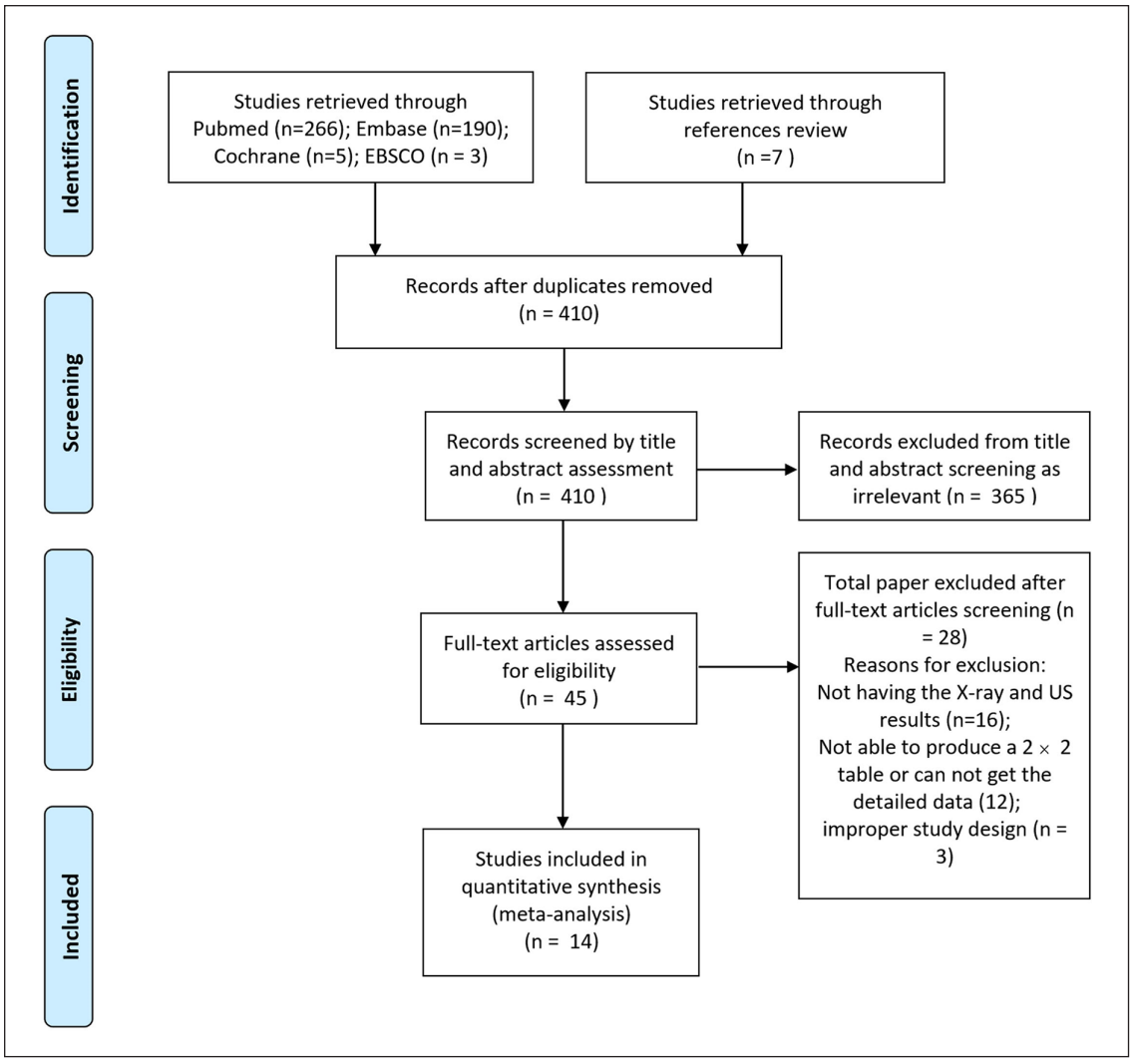

Figure 1. Flow chart of systematic literature search and study selection process.

Table 1. Test performance characteristics.

Study	Country	X-ray (*n*)	Ultrasound (*n*)	TP	FP	FN	TN
George et al.[20]	USA	15	15	3	6	3	3
Greenberg et al.[12]	USA	95	95	60	0	0	35
Raval et al.[10]	USA	31	31	27	17	4	14
Ades et al.[4]	USA	50	50	23	14	4	9
Simanovsky et al.[3]	Israel	75	75	46	0	0	29
Michel et al.[2]	France	61	61	19	1	2	39
Pulickal et al.[7]	USA	30	30	25	5	0	1
Hoellering et al.[18,*]	Australia	200	200	21	4	9	166
Hoellering et al.[18]	Australia	200	200	17	46	11	126
Harabor and Soraisham[8]	Canada	51	51	8	8	21	14
El-Maadawy et al.[11]	UAE	75	75	21	2	3	50
Saul et al.[24]	USA	18	18	15	0	0	3
Guimarães et al.[19]	Brazil	162	162	25	34	19	84
Karber et al.[26]	USA	51	51	22	28	0	1
Franta et al.[25]	Canada	65	65	11	8	14	32

TP: true positive; FP: false positive; FN: false negative; TN: true negative.
*The study used two methods to confirm the tip position by X-ray.

Table 2. Quality assessment of risk of bias and applicability concerns of 14 studies included in meta-analysis.

Study (authors)	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
George et al.[20]	+	+	+	−	+	+	+
Greenberg et al.[12]	+	?	?	+	+	+	+
Raval et al.[10]	−	?	?	?	+	+	+
Ades et al.[4]	+	+	+	+	+	+	+
Simanovsky et al.[3]	+	+	+	+	+	+	+
Michel et al.[2]	+	+	+	+	+	+	+
Pulickal et al.[7]	+	+	+	+	+	+	+
Hoellering et al.[18]	+	+	+	+	+	+	+
Harabor and Soraisham[8]	+	?	?	+	+	+	+
El-Maadawy et al.[11]	+	+	+	+	+	+	+
Saul et al.[24]	−	+	+	+	+	+	+
Guimarães et al.[19]	+	+	+	−	+	+	+
Karber et al.[26]	+	+	+	+	+	+	+
Franta et al.[25]	+	+	+	+	+	+	+

+: low risk/concern; −: high risk/concern; ?; unclear risk/concern.

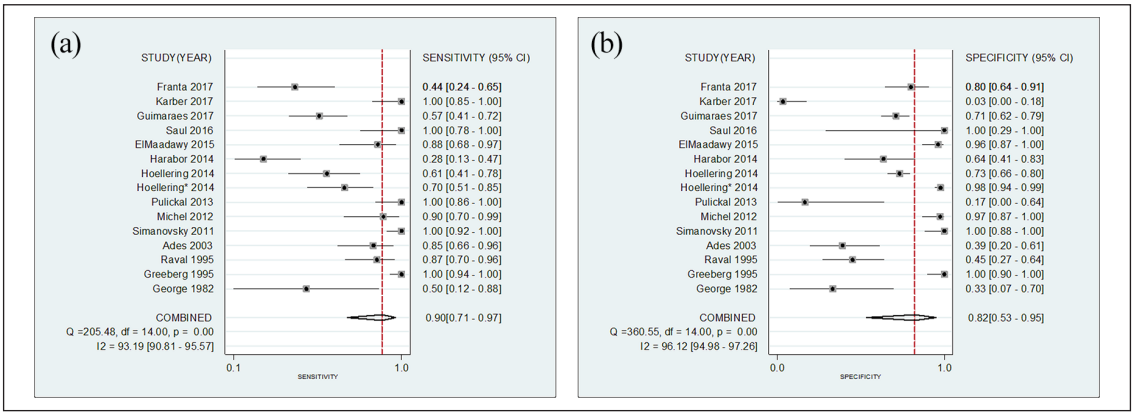

Figure 2. Forest plots of sensitivity (a) and specificity (b) for the umbilical venous catheter tip position by X-ray.

In the model of hierarchical summary receive operating characteristic, β was 0.16 (95% CI −0.56 to −0.87), $p=0.662$, indicating that SROC was symmetric. The Lambda value of HSROC was 3.74 (95% CI 1.70–5.78), which indicating that X-ray has higher accuracy to confirm the tip position of UVC (Figure 4).

Heterogeneity analysis and publication bias. In order to identify the potential sources of heterogeneity, subgroup analyses and meta-regression were conducted based on study sample size, study design, different anatomical landmarks for X-ray method, different US confirming method, and different gold standard. The meta-regression analysis suggested that study sample size (⩾75 or <75), study design (retrospective or prospective), different US confirming method (with saline injection or without saline injection), and different gold standard in original design (US or X-ray) might be potential sources of heterogeneity. Table 3 presents the detailed results of subgroup analyses and meta-regression analysis. Assessment for the publication bias by Begg's test showed $\Pr > Z = 1.000$ and Egger's test showed $P > t = 0.806$. Based on these results, no publication bias was identified in this meta-analysis (Figure 5).

Discussion

In this quantitative meta-analysis, we evaluated the accuracy of the anteroposterior chest radiography in determining the umbilical venous catheter tip position, with ultrasound as the gold standard. To the best of our knowledge, this is the first meta-analysis and systematic review that determined the accuracy of X-ray performance on umbilical venous catheters for the newborns. As more and

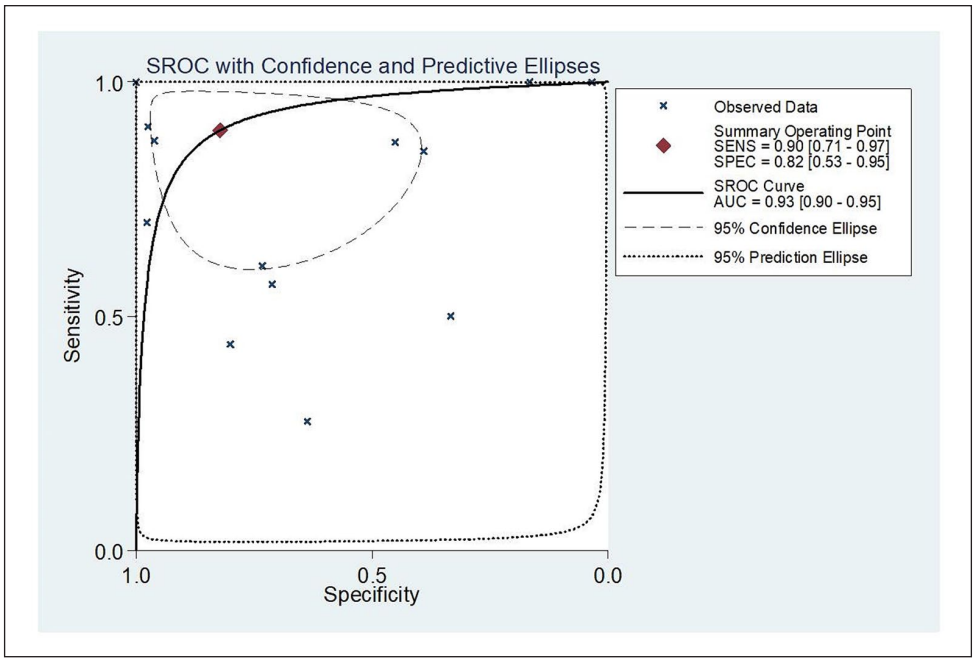

Figure 3. The overall SROC of X-ray in determining the umbilical venous catheter tip position.

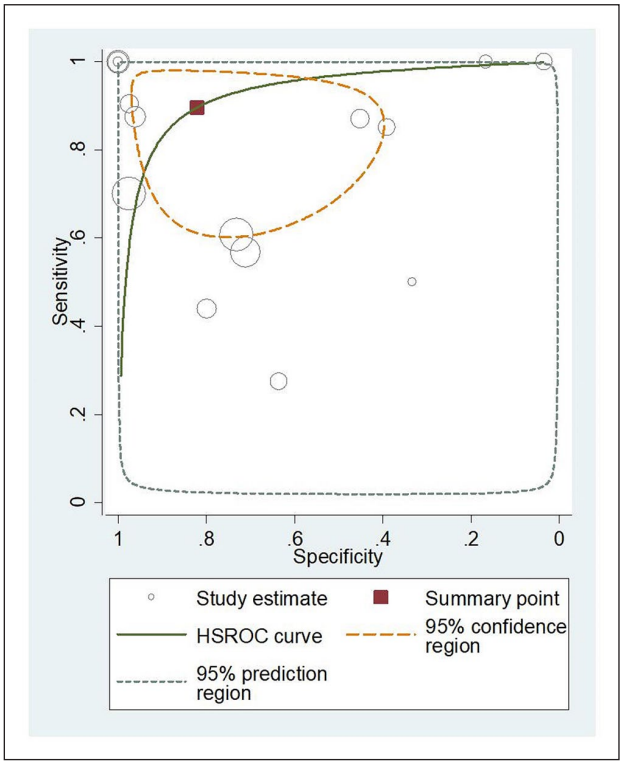

Figure 4. HSROC curve of X-ray in determining the umbilical venous catheter tip position. The sizes of the dots for 1-specificity and sensitivity of the single studies in the ROC space were derived from the respective sample size.

more studies questioned the accuracy of X-ray for verification of tip position of UVCs in newborns and suggested US, especially echocardiography should be the "gold standard" to confirm the tip position of UVCs,[12,20] it became necessary to conduct this meta-analysis. The pooled results of our meta-analysis using bivariate random effects model showed that X-ray had a sensitivity of 0.90 (95% CI 0.71–0.97) and a specificity of 0.82 (95% CI 0.53–0.95) with AUC of SROC of 0.93 (95% CI 0.90–0.95) and DOR of 3.69 (95% CI 1.64–5.71). This result indicated that compared to US, X-ray may produce 10% false-negative and 18% false-positive test results. As reported, in newborns, especially low birth weight infants, when the UVC tip was judged to be in the RA or the IVC-RA junction by X-ray, there were a large number of UVC tips actually in the LA,[4,8] which could result in the increase of complications. The anteroposterior chest radiography, which is routinely used to assess catheter positioning, is not reliable in identifying the exact anatomical location of UVC tip.

Radiography used for UVC position verification was introduced by Peck and Lowman in 1967,[27] and the technique remains the most often used in central venous catheter tip assessment. After the 1980s, various studies which evaluated the catheter by US or echocardiography found that the chest anteroposterior radiography alone was not enough to ensure a reliable UVC positioning.[3,7,10,12,18,20] Anatomical landmarks were used to access the tip position of UVC by X-ray, with thoracic vertebra used most.

Table 3. Subgroup analyses and meta-regression exploring effects on heterogeneity and pooled sensitivity and specificity.

Subgroup	*n*	Pooled sensitivity (95% CI)	I^2%	Pooled specificity (95% CI)	I^2%	Diagnostic odds ratio (95% CI)	I^2%	RDOR (95% CI)	*p*-Value
Sample size									
⩾75	6	0.82 (0.76–0.87)	92.5	0.85 (0.82–0.88)	94.4	74.46 (10.68–518.91)	91.5	0.03 (0.00–0.66)	0.03
<75	9	0.76 (0.70–0.82)	90.5	0.57 (0.50–0.64)	92.0	5.03 (1.54–16.44)	73.4		
Different anatomical landmarks for X-ray method									
Only one method by thoracic vertebrae	7	0.76 (0.69–0.81)	93.7	0.76 (0.72–0.80)	95.2	18.53 (3.01–114.11)	89.1	5.19 (0.35–77.16)	0.20
Others	8	0.83 (0.77–0.87)	87.4	0.79 (0.75–0.83)	94.4	13.12 (3.10–55.57)	83.5		
Different US confirming method									
With saline injection	6	0.80 (0.72–0.84)	89.6	0.82 (0.79–0.85)	95.1	26.67 (5.30–134.21)	89.5	113.73 (1.43–9071.83)	0.04
Without saline	9	0.80 (0.74–0.85)	92.4	0.67 (0.60–0.73)	93.7	10.03 (2.04–49.24)	83.3		
Different gold standard									
Echocardiography or US	6	0.64 (0.57–0.71)	84.3	0.77 (0.73–0.81)	94.8	5.02 (1.65–15.25)	85.1	0.00 (0.00–0.06)	0.01
X-ray	8	0.91 (0.87–0.94)	89.2	0.79 (0.74–0.84)	94.8	53.41 (6.32–451.30)	85.0		
Study design									
Retrospective	2	0.58 (0.45–0.71)	95.7	0.53 (0.39–0.67)	43.8	1.90 (0.24–15.24)	82.6	609.79 (1.20–310,576.80)	0.04
Prospective	13	0.83 (0.78–0.86)	89.5	0.80 (0.76–0.82)	94.8	22.36 (6.74–74.16)	85.5		

RDOR: relative diagnostic odds ratio; US: ultrasound.

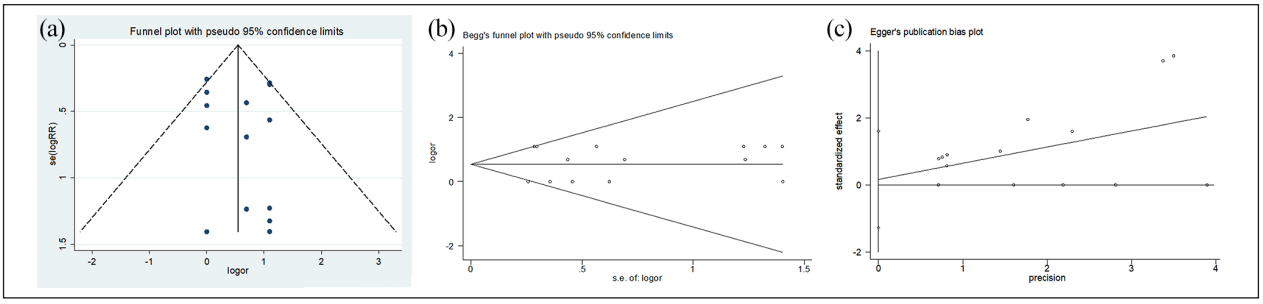

Figure 5. Publication bias was analyzed by drawing funnel plots, Begg's and Egger's publication bias plots: (a) evaluation of publication bias by funnel plot, (b) Begg's publication bias plot, and (c) Egger's publication bias plot.

However, it was reported that the target area of UVC tip may be located in a wide range of vertebral bodies, from T6 to T11 or even at T4.[2,4] The cardiac silhouette method was reported more accurate in predicting UVCs tip than vertebral body level in newborns.[18] However, X-ray images obtained with different exposure settings and with different positions may result in catheter tip projections at different locations.[19] Lateral X-ray has been suggested as being superior to anteroposterior X-ray in assessing distal catheter position.[4] Only two of the studies included in the meta-analysis attempted to use anteroposterior X-ray and lateral X-ray to confirm the tip position of UVCs[4,10] and suggested lateral X-ray was more sensitive, but less specific, than anteroposterior X-ray for detection of left atrial catheter location.[4] Compared to X-ray, which do not allow the direct visualization of the veins, and the location of the catheter tip is assessed indirectly, US or echocardiography allows direct visualization of the catheter tip, which is more accurate at this point. What's more, US or echocardiography avoids radiation exposure of the newborns and medical staff since fluoroscopy is not considered appropriate in NICU. Ultrasound is non-invasive, completely safe and readily available for neonates. Ultrasound provides real-time assessment and can be an effective follow-up checking method while x-ray is a post-procedural methodology. Being post-procedural, X-ray can be used only for tip location, but not for tip navigation.[26] It was reported that about 50% of UVC tips could migrate during the first week of life in preterm infants.[25] Some studies have highlighted the importance of confirming the position of the catheter tip, tip navigation, and follow-up for tip position check by an ultrasound. US is suggested as a means of routine and repeated method to assess UVC placement.[25,28] Some studies suggest that confirmation of the tip position by a X-ray examination alone is insufficient, and a US examination is indispensable.[25,29] Although ultrasound scanning can be expensive and is not routinely available on a 24-h basis in most units, but recent studies have suggested that training on the use of real-time US is easy and feasible[26,30] Recent guidelines strongly recommend real-time method for tip location,[31] and in Barone's protocol, real-time ultrasound is suggested the most promising tool for tip navigation and location during placement of UVC in the neonate.[32] We recommend the use of the Neo-ECHOTIP protocol published by Barone to standardize the UVC tip localization procedure by US.[32]

As for the different designs described above, subgroup analyses and meta-regression were performed to identify the accuracy of X-ray in different situations and the potential sources of heterogeneity. X-ray had higher diagnostic efficiency in the studies with sample size $\geqslant$75, prospective design, US confirming method with saline injection. It was suggested that a small volume of saline solution (0.5 mL) be injected through the catheter as contrast medium, to determine the exact position of the tip.[18,19] Different gold standard in original design (US or X-ray) might also be potential sources of heterogeneity.

Limitations

Some limitations must be taken into consideration while explaining the results of the meta-analysis. First, we failed to get some unpublished data from the authors. Second, we pooled the publication data from different methods even from one population. Two different methods, X-ray and US were assessed the sensitivity and specificity in one study.[18] We could not remove these important data. Third, a significant heterogeneity was present in the 14 studies. Several reasons could account for this. (a) There were differences in study design among the 14 studies, including sample size, prospective or retrospective design, and the gold standard in original design. (b) Different ultrasound tip position confirming methods were used. Ultrasound tip position confirming method with a small volume of saline injection was reported higher diagnosis efficiency.

Conclusion

In summary, this meta-analysis showed relatively high accuracy of anteroposterior radiography for confirming the tip of umbilical venous catheters among newborns

compared to ultrasound. However, current methods commonly used to confirm correct placement by X-ray are inadequate. Studies suggested ultrasound or echocardiography with saline contrast injection could be the gold standard for verification of catheter location and should be considered whenever possible, especially in premature patients. Catheter positioning can be accomplished with radiography in the situation when ultrasonography is not available. Moreover, more studies are needed to expand the use of ultrasound or echocardiography in tip position confirming of UVCs and other CVCs among newborns.

Author contributions

Yuxiu Liu conceived and designed the study. All authors contributed to data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Declaration of conflicting interests

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