Real-time Two-dimensional Ultrasound Guidance for Central Venous Cannulation

A Meta-analysis

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CME This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Background: Use of ultrasound-guided techniques to facilitate central venous cannulation (CVC) may reduce the risk of misplacement and complications. A meta-analysis was conducted to compare real-time two-dimensional ultrasound (RTUS) guidance technique with anatomical landmark technique for CVC to determine whether RTUS has any advantages.

Methods: Randomized studies comparing outcomes in patients undergoing CVC with either RTUS or landmark technique were retrieved from PubMed, ISI Web of Knowledge, EMBASE, and OVID EBM Reviews from their inception to March 2012.

Results: Twenty-six studies involving 4,185 CVC procedures met the inclusion criteria. Compared with landmark technique, patients with RTUS had a pooled relative risk (RR) of 0.18 (95% CI: 0.10–0.32) for cannulation failure, 0.25 (95% CI: 0.15–0.42) for arterial puncture, 0.30 (95% CI: 0.19–0.46) for hematoma, 0.21 (95% CI: 0.06–0.73) for pneumothorax, and 0.10 (95% CI: 0.02–0.54) for hemothorax from random-effects models. However, RTUS did not show a reduction in the risk of cannulation failure

What We Already Know about This Topic

- Use of ultrasound-guided techniques to facilitate central venous cannulation may reduce the risk of misplacement and complications

What This Article Tells Us That Is New

- The current meta-analysis showed that compared to the use of an anatomical landmark technique for central venous cannulation, real-time, two-dimensional ultrasound guidance was associated with decreased risks of cannulation failure, arterial puncture, hematoma, and hemothorax in adults

(RR = 0.26, 95% CI: 0.03–2.55), arterial puncture (RR = 0.34, 95% CI: 0.05–2.60), hematoma (RR = 0.13, 95% CI: 0.01–2.42), pneumothorax (RR = 0.40, 95% CI: 0.02–9.61), and hemothorax (RR = 0.40, 95% CI: 0.02–9.61) in children or infants when the limited data were analyzed.

Conclusions: Among adults receiving CVC, RTUS was associated with decreased risks of cannulation failure, arterial puncture, hematoma, and hemothorax. Additional data of randomized studies are necessary to evaluate these outcomes in pediatric patients.

CENTRAL venous cannulation (CVC) is a commonly followed procedure for hemodynamic monitoring (such as central venous pressure), long-term administration of fluids, antibiotics, total parenteral nutrition, hemodialysis, and so on.[1–3] The internal jugular, subclavian, and femoral veins (FV) are commonly used sites.[4] However, it may be technically difficult due to anatomical and morphological variations among patients or because of previous catheterization.[5] Attempting CVC may be unsafe or even fatal in some rare cases because of various complications, including cardiac tamponade,[6] massive cervical hematoma,[7] and puncture of endotracheal tube cuff.[8]

Ultrasound guidance for CVC has gained popularity among practitioners. Ultrasound modalities usually include color flow Doppler sonography, auditory Doppler

Table 1. Baseline Characteristics of the Trials Included in the Meta-Analysis

		Participants					
Study	Yr	Mean Age, yr	Country	Puncture Site	Ultrasound Device	RTUS	ALM
Mallory[27]	1990	NR	America	IJV	Hewlett Packed 7702A	12	17
Troianos[28]	1991	NR	America	IJV	SiteRite or Sonos 500	77	83
Soyer[29]	1993	44.5	French	IJV	Sono Diagnost R unit, Philips	24	23
Gualtieri[30]	1995	NR	America	SCV	SiteRite	25	27
Hilty[31]‡	1997	64	America	FV	Aloka 650CL	20	20
Slama[32]	1997	65.5	French	IJV	Sonos 100	37	42
Teichgräber[10]	1997	NR	Germany	IJV	Toshiba	50	50
Verghese[33]	1999	0.5	America	IJV	SiteRite	43	52
Sulek[34]	2000	59.0	America	IJV	Hewlett Packard	60	60
Verghese[35]	2000	0.56	America	IJV	SiteRite	16	16
Cajozzo[36]	2004	NR	Italy	SCV/IJV	Prisma-Diasonics	105	91
Grebenik[37]‖	2004	<8	America	IJV	Baird Site Rite III	59	65
Bansal[38]	2005	41.0	India	IJV	NR	30	30
Milling[39]	2005	71.9	America	IJV	SonoSite	60	69
Karakitsos[18]	2006	58.7	Greece	IJV	ATL 3500	450	450
Leung[40]	2006	54.5	Australia	IJV	SonoSite	65	65
Agarwal[41]	2009	NR	India	IJV	SonoSite	40	40
Palepu-1[4]††	2009	48.7	India	IJV	SonoSite	205	194

| | | Jadad Scale* | | | |
Randomization	Blind	Withdrawals and Dropouts Described (n)	Jadad Score	Operator Experience	Reported Outcome Measures
1	0	1(0)	2	Senior	Cannulation failure
1	0	1(0)	2	NR	Cannulation failure Arterial puncture
1	0	1(0)	2	NR	Cannulation failure Arterial puncture
2	0	1(1)	3	Junior	Cannulation failure Arterial puncture Hematoma Pneumothorax†
1	0	1(0)	2	Junior	Cannulation failure Arterial catheterization§
1	0	1(0)	2	Junior	Cannulation failure Arterial puncture
1	0	1(0)	2	Senior	Arterial puncture Hematoma
2	0	1(0)	3	Senior	Cannulation failure Arterial puncture Hematoma Pneumothorax Hemothorax
1	0	1(0)	2	Senior	Cannulation failure Arterial puncture Hematoma
2	0	1(0)	3	Junior	Cannulation failure Arterial puncture
1	0	1(0)	2	Senior	Cannulation failure Arterial puncture Pneumothorax
2	0	1(10)	3	Senior	Cannulation failure Arterial puncture
1	0	1(0)	2	Junior	Cannulation failure Arterial puncture Hematoma
2	0	1(0)	3	NR**	Cannulation failure
2	0	1(0)	3	Senior	Cannulation failure Arterial puncture Hematoma Hemothorax Pneumothorax
2	0	1(0)	3	NR	Cannulation failure Arterial puncture Hematoma Pneumothorax
1	0	1(0)	2	Senior	Arterial puncture Pneumothorax
2	0	1(0)	3	Senior/ Junior	Cannulation failure Arterial puncture Hematoma Pneumothorax†

(*continued*)

Table 1. (Continued)

Study	Yr	Mean Age, yr	Country	Puncture Site	Ultrasound Device	RTUS	ALM
Palepu-2[4]††	2009	51.0	India	SCV	SonoSite	17	28
Turker[2]	2009	47.5	Turkey	IJV	Toshiba	190	190
Aouad[42]	2010	2.9	America	FV	SonoSite 180 Plus	24	24
Ovezov[43]	2010	4.4	Russia	IJV	US navigation	107	102
Prabhu[3]	2010	49.5	India	FV	SonoSite	55	55
Fragou[19]	2011	57.5	Greece	SCV	HD11 XE Philips	200	201
Shrestha[44]	2011	38.5‡‡	Nepal	IJV	Toshiba	60	60
Zhang[45]§§	2011	55.0	China	IJV	SonoSite	50	50

* The basis of scoring each item (randomization, blind, and withdrawals and dropouts described) is presented in detail in appendix 2.
† The incidences of these endpoints in both groups were zero, and the corresponding studies were excluded from the meta-analysis.
‡ Each patient served as his or her own control. § The complication of arterial catheterization was categorized into arterial puncture.
‖ The complication of hematoma was not clarified in the text, and this endpoint in this study was not extracted. #This study was a three-armed trial and the complication rates of each group in this study was not extracted because there might exist some confusing information that has discrepancy between the table and text. ** Experience levels of operators varied. †† This study included two randomized control trials, which were considered separately to facilitate analysis. ‡‡ The patients involved were all older than 17 yr, and we classified the population into adults. §§ The study was a three-armed trial (RTUS *vs.* prelocation *vs.* ALM). The data from the arms of RTUS and ALM were used in the meta-analysis.
ALM = anatomical landmark technique; FV = femoral vein; IJV = internal jugular vein; NR = not reported; RTUS = real-time two-dimensional ultrasound guidance technique; SCV = subclavian vein.

guidance, two-dimensional ultrasound guidance (2-DUS), and the state-of-the-art technique three-dimensional ultrasound guidance.[9] Color flow Doppler sonography is a reliable method for detecting thrombosis but it is not necessary for cannulation.[10] With advances in ultrasound technology, auditory Doppler guidance, which includes SMART® needle[11] and fingertip pulsed Doppler,[12,13] is not recommended for CVC and is almost outmoded in practice.[14] Real-time 2-DUS technique (RTUS), by which arteries, veins, and surrounding structures could be visually distinguished by their relative positions, is increasingly popular in clinical practice

as safer and more portable ultrasound devices are introduced. Three-dimensional ultrasound guidance has appeared in case reports recently.[15] A meta-analysis by Hind *et al.*[16] 9 yr ago reported that the use of 2-DUS was associated with increased success of cannulation of internal jugular vein (IJV) and subclavian vein (SCV). However, other endpoints, such as the incidences of arterial puncture, hematoma, pneumothorax, and hemothorax, were not reported, and the success rate of FV cannulation under RTUS were not found to be different from those by anatomical landmark technique (ALM) due to limited data. During the past 9 yr, the number of randomized

| Jadad Scale* | | | | | |
Randomization	Blind	Withdrawals and Dropouts Described (n)	Jadad Score	Operator Experience	Reported Outcome Measures
2	0	1(0)	3	Senior/ Junior	Cannulation failure Arterial puncture Hematoma Pneumothorax
1	0	1(0)	2	Junior	Cannulation failure Arterial puncture Hematoma Pneumothorax† Hemothorax†
2	0	1(0)	3	Senior	Cannulation failure Arterial puncture
2	1	1(0)	4	NR	Cannulation failure Arterial puncture
2	0	1(0)	3	Senior / Junior	Cannulation failure Arterial puncture Hematoma
2	0	1(62)	3	Senior	Cannulation failure Arterial puncture Hematoma Pneumothorax Hemothorax
1	0	1(0)	2	NR	Cannulation failure Arterial puncture Hematoma Pneumothorax† Hemothorax†
2	0	1(0)	3	Senior	Cannulation failure Arterial puncture Hematoma

controlled trials (RCTs) on this issue has doubled. Given the newly emerging evidence, we conducted a meta-analysis to investigate the effects of RTUS on the clinical outcomes of patients receiving CVC.

Materials and Methods

Search Strategy

We conducted a literature search using PubMed, ISI Web of Knowledge, EMBASE, and OVID EMB Reviews (Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED) from the inception to March 2012. A variety of synonyms for "ultrasound", "CVC", "IJV", "SCV", and "FV" were combined in the search process. The complete search strategy is presented in appendix 1. Potentially eligible studies were also identified through a manual search of the references and citations in the articles retrieved for full review. No language restrictions were made in this process. No attempts were made to contact the study authors for identifying missing and confusing data. This meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[17]
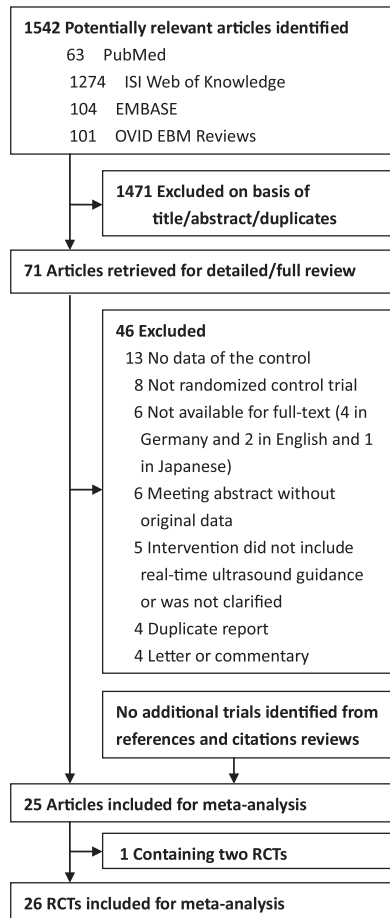
1542 Potentially relevant articles identified
- 63 PubMed
- 1274 ISI Web of Knowledge
- 104 EMBASE
- 101 OVID EBM Reviews

1471 Excluded on basis of title/abstract/duplicates

71 Articles retrieved for detailed/full review

46 Excluded
- 13 No data of the control
- 8 Not randomized control trial
- 6 Not available for full-text (4 in Germany and 2 in English and 1 in Japanese)
- 6 Meeting abstract without original data
- 5 Intervention did not include real-time ultrasound guidance or was not clarified
- 4 Duplicate report
- 4 Letter or commentary

No additional trials identified from references and citations reviews

25 Articles included for meta-analysis

1 Containing two RCTs

26 RCTs included for meta-analysis

Fig. 1. Flowchart of the literature search and selection. RCTs = randomized control trials.

Selection Process

Two reviewers (Drs. Wu and Cao) independently screened all titles and abstracts to identify potentially eligible studies, and two reviewers (Drs. Wu and Ling) independently screened the potentially eligible studies by detailed review of the article in full text to determine eligibility for the review. Dilemmas on whether to include or exclude a study were resolved by consensus with other investigators (Drs. Wang, Xu, and Zeng).

Clinical studies meeting the following criteria were considered eligible for this meta-analysis: (1) studies adopting a randomized, controlled design; (2) studies with participants who underwent CVC, no matter what the indication was, and who were assigned to a RTUS group or an ALM group; and (3) studies reporting cannulation failure and clinical adverse events (arterial puncture, hematoma, pneumothorax, or hemothorax). ALM was defined as the patients undergoing central venous access (including IJV, SCV, and FV) using "blind" punctures, relying on anatomical landmarks without any ultrasound guidance. RTUS was defined as the patients undergoing venous access with real-time 2-DUS guidance, but not including the use of 2-DUS for prelocation (defined as obtaining static ultrasound imaging before cannulation, obviating the need

for sterile probe covering, sterile ultrasound gels, and needle guides)[9] or auditory Doppler guidance.

Studies were excluded on the basis of the following criteria: if group allocation was not randomized or the randomization method was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, *etc.*); the intervention technique used was auditory Doppler guidance or 2-DUS prelocation, or was not clarified; the control technique was not ALM; the puncture site was elsewhere, such as axillary vein or external jugular vein rather than central veins (IJV, SCV, or FV); or the data of full-text were not available.

Data Extraction Process

Data were extracted independently by three investigators (Drs. Wang, Ling, and Cao) from the full-text articles (including the articles published in the form of meeting abstract) of each included study using a standardized data-collection form, including the name of the first author, publication year, country of publication, ultrasound devices used, sample size, quality of each study (Jadad scale), operator experience, and reported outcome measurements. Operator experience (senior or junior) in each study was determined by discussion among four reviewers (Drs. Wang, Ling, Cao, and Zeng). The principal endpoints for the current analysis were cannulation failure, arterial puncture, hematoma, pneumothorax, and hemothorax. The definition of each endpoint mentioned above was the same as that used in each study. Several rare complications, such as catheter-associated infection[18] and cardiac tamponade,[19] were excluded. In addition, access time (the time needed for CVC) was also excluded from analysis because its definition varied greatly among studies and would generate enormous heterogeneity.

Quality Assessment of Studies

Quality assessment was independently performed by two investigators (Drs. Wang and Ling) using an established tool—Jadad scale.[20] Jadad scale is the most widely used tool to assess the methodological quality of a clinical trial.[21,22] It contains three questions (about randomization, blinding, description of withdrawals and dropouts, respectively) and generates a Jadad score (a scale of 0–5) for every trial (table 1 and appendix 2). Discrepancies were addressed by re-reading the study and discussions between the two authors and, if necessary, with the help of a third senior researcher (Dr. Zeng).

Statistical Analysis

The heterogeneity of outcomes across the trials was estimated by Q statistic (significance level at $P < 0.10$) and the I^2 statistic (a scale of 0–100%, greater than 75% indicating high heterogeneity), which is a quantitative measure of inconsistency across studies.[23,24] Fixed-effects and random-effects models generated similar findings; however, between-study heterogeneity was detected for some outcomes. Consequently, results from the random-effects models, which
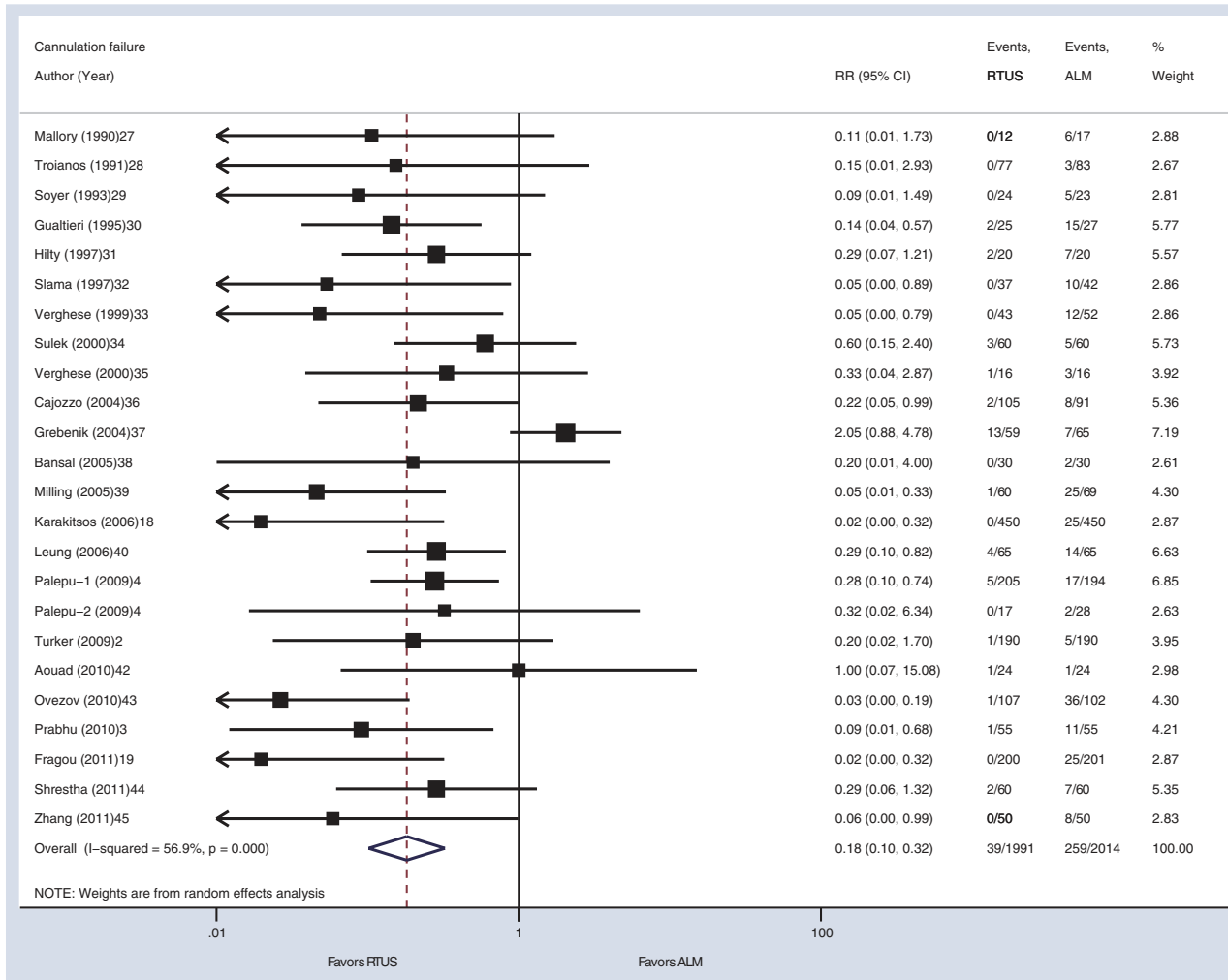
Fig. 2. Pooled relative risk for central venous cannulation failure. ALM = anatomical landmark technique; RR = relative risk; RTUS = real-time two-dimensional ultrasound guidance technique.

produced more conservative and cautious estimates with wider 95% CIs when between-study heterogeneity existed, are presented. We conducted a series of subgroup analyses stratified by puncture site, patients' age, and Jadad score to explore the impacts of these variables on the endpoints. Sensitivity analyses were investigated to determine the influence of a single study on overall risk estimate by omitting one study in each turn. Publication bias was assessed by Begg adjusted rank correlation test[25] and Egger's regression asymmetry test.[26] The meta-analysis was performed with Stata software (release 12.0; StataCorp., College Station, TX). For a study without an event in one group of patients, neither the relative risk (RR) nor its standard error could be calculated. The metan command in the Stata software was used to address this problem automatically by adding 0.5 to all cells of the 2×2 table before analysis. However, when there were no events in one whole column of the 2×2 table, any measurement of the effect summarized as a ratio could not be estimated, and the trial was given zero weight and excluded from the meta-analysis. P value less than 0.05 was regarded

statistically significant, except otherwise specified. All statistical tests were two-sided.

Results

A detailed flowchart of the search and selection results is shown in figure 1. Of 1,542 potentially relevant articles identified, 25 were included in the meta-analysis.[2–4,10,18,19,27–45] As one article contained two RCTs, investigating the real-time 2-DUS use in IJV and SCV respectively,[4] a total of 26 eligible RCTs with 4,185 CVC procedures met all the inclusion criteria and were included in the meta-analysis. Among these included 26 studies, the vein catheterized included the IJV in 19 trials,[2,4,10,18,27–29,32–35,37–41,43–45] the SCV in three trials,[4,19,30] either IJV or SCV in one trial,[36] and the FV in three trials.[3,31,42] Although one patient in one study[30] might undergo more than one CVC procedure during the study period, and every patient in another study even served as his or her own control,[31] it should be pointed out that each procedure (RTUS *vs.* ALM) would be considered as an independent event, and that the
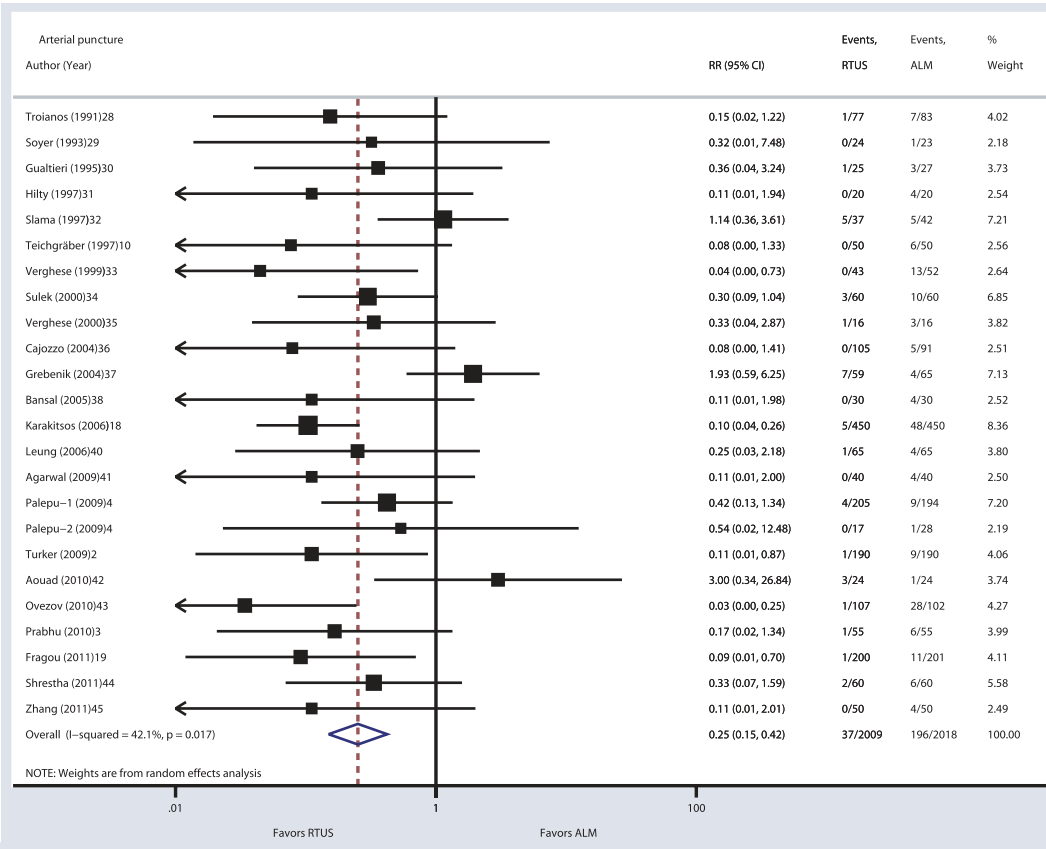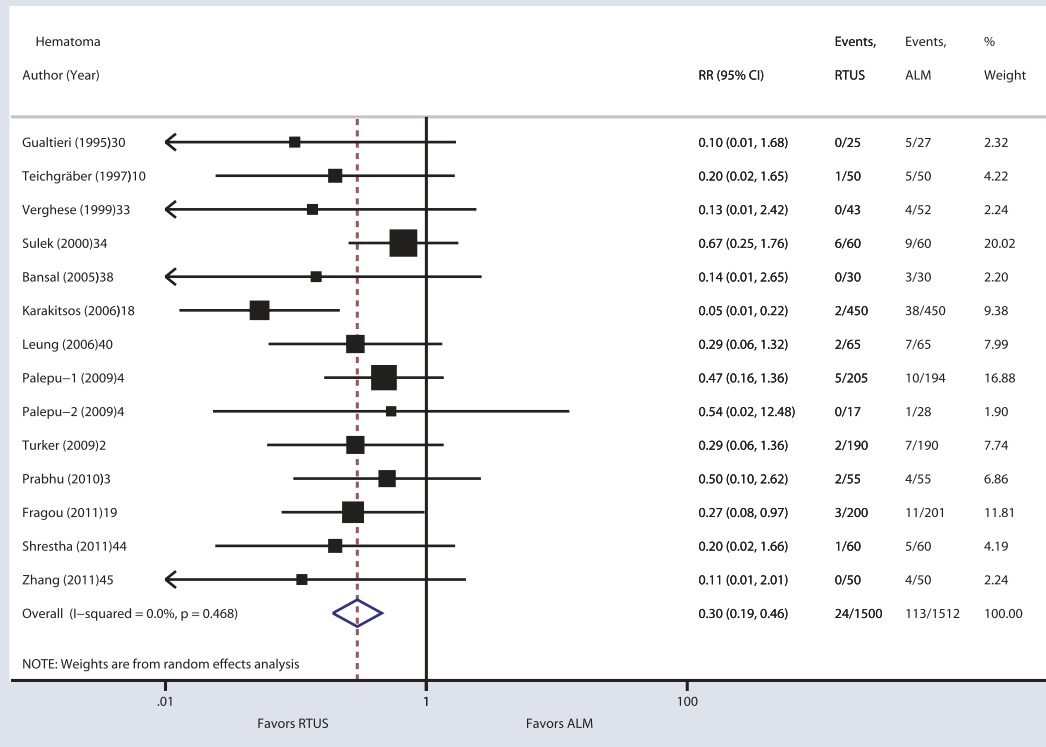
Fig. 3. Pooled relative risks for clinical adverse events, including arterial puncture (*A*), hematoma (*B*), pneumothorax (*C*), and hemothorax (*D*). ALM = anatomical landmark technique; RR = relative risk; RTUS = real-time two-dimensional ultrasound guidance technique. (*Continued*)
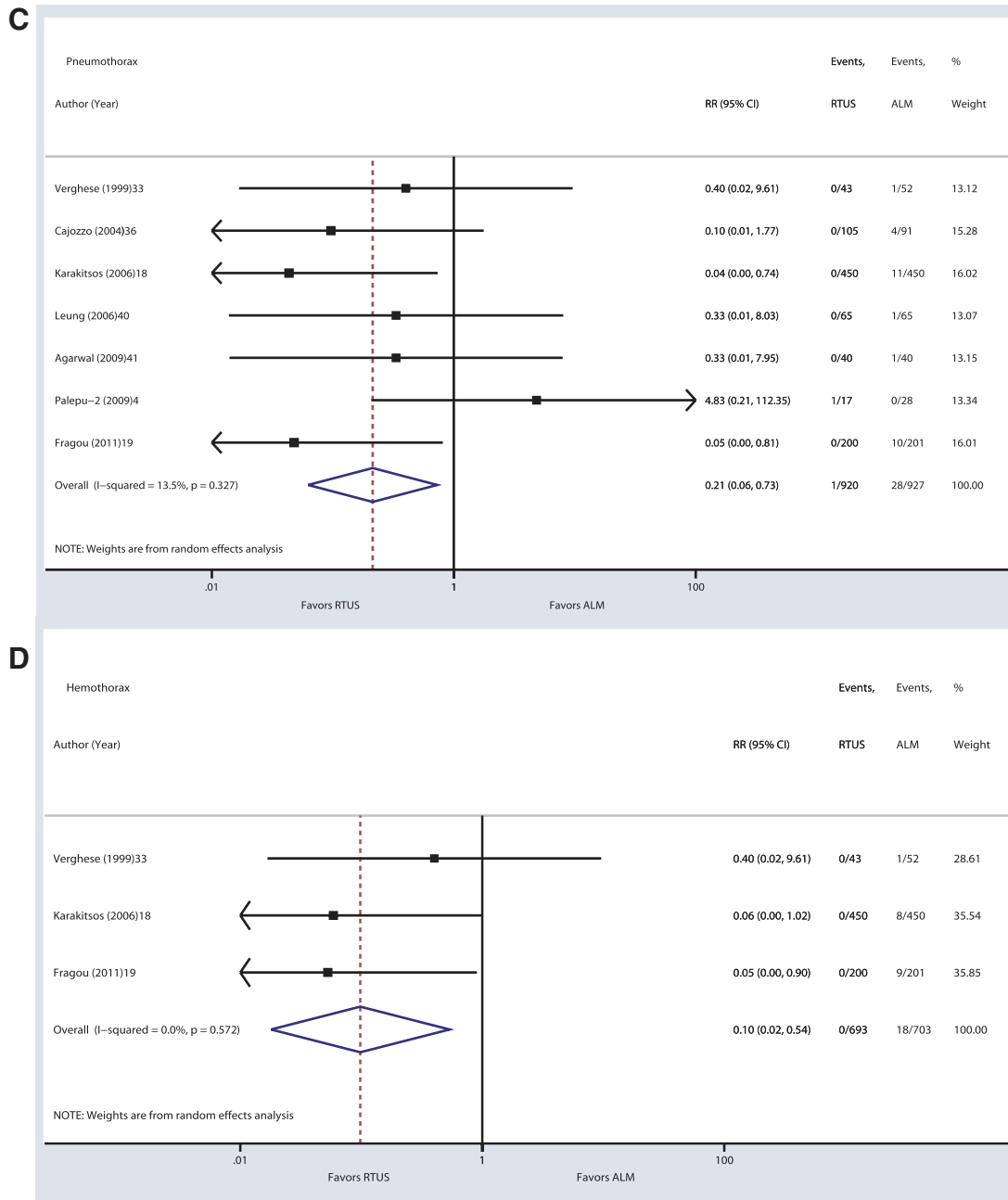
Fig. 3. (*Continued*)

number of procedures, which was used as the denominator for calculation of success and complication rates by each method,[30] was converted to the same number of participants artificially in this meta-analysis, mainly for the convenience of calculation. The characteristics of the included studies are shown in table 1.

Main Analysis
Pooled overall RRs are shown in figures 2 and 3 for all study outcomes. The analysis showed that RTUS significantly

reduced the risk of cannulation failure (RR = 0.18, 95% CI: 0.10–0.32, *P* < 0.001, fig. 2) and reduce the occurrence of clinical adverse events, including the risk of arterial puncture (RR = 0.25, 95% CI: 0.15–0.42, *P* < 0.001, fig. 3A), hematoma (RR = 0.30, 95% CI: 0.19–0.46, *P* < 0.001, fig. 3B), pneumothorax (RR = 0.21, 95% CI: 0.06–0.73, *P* = 0.014, fig. 3C), and hemothorax (RR = 0.10, 95% CI: 0.02–0.54, *P* = 0.007, fig. 3D).

I^2 values were calculated to quantify the extent of heterogeneity between studies. The I^2 values were 0.0%

Table 2. Subgroup of Cannulation Failure, Arterial Puncture

Group		Cannulation Failure				Arterial Puncture		
	N*	RR (95% CI)	$P_{heterogeneity}$	I² (%)	N*	RR (95% CI)	$P_{heterogeneity}$	I² (%)
Total	24	0.18 (0.10, 0.32)	<0.001	56.9	24	0.25 (0.15, 0.42)	0.017	42.1
Puncture site								
IJV	17	0.19 (0.08, 0.37)	<0.001	65.2	17	0.24 (0.13, 0.45)	0.009	50.7
SCV	3	0.11 (0.03, 0.46t)	0.270	23.6	3	0.21 (0.06, 0.82)	0.526	0.0
FV	3	0.25 (0.08, 0.77)	0.349	5.1	3	0.41 (0.05, 3.33)	0.095	57.5
Mean age†								
<8 yr	5	0.26 (0.03, 2.55)	<0.001	85.9	5	0.34 (0.05, 2.60)	<0.001	81.3
>18 yr	15	0.18 (0.11, 0.31)	0.260	17.3	14	0.25 (0.15, 0.40)	0.334	10.8
Jadad score								
2	10	0.25 (0.13, 0.45)	0.906	0.0	11	0.30 (0.17, 0.53)	0.443	0.0
≥3	14	0.15 (0.06, 0.38)	<0.001	73.9	13	0.26 (0.12, 0.58)	0.003	59.4

* The number of studies included in the meta-analysis, with the study given zero weight excluded. † Studies with patients at the mean ages between 8 and 18 were not found.

FV = femoral vein; IJV = internal jugular vein; RR = relative risk; SCV = subclavian vein.

(P = 0.468) for hematoma, 13.5% (P = 0.327) for pneumothorax, and 0.0% (P = 0.572) for hemothorax, indicating low heterogeneity between studies. Moderate heterogeneity was detected for cannulation failure (I^2 = 56.9% [P < 0.001 from Q test]) and arterial puncture (I^2 = 42.1% [P = 0.017]).

Sensitivity Analyses

Sensitivity analyses suggested that the overall risk estimates for cannulation failure, arterial puncture, and hematoma were not substantially modified by any single study, with a range of RRs from 0.17 (95% CI: 0.09–0.31) to 0.20 (95% CI: 0.12–0.36) for incidence of cannulation failure, from 0.22 (95% CI: 0.14–0.35) to 0.28 (95% CI: 0.16–0.47) for incidence of arterial puncture,

and from 0.24 (95% CI: 0.15–0.39) to 0.35 (95% CI: 0.22–0.56) for incidence of hematoma. Sensitivity analyses were not performed for the outcomes of pneumothorax and hemothorax because of the small number of studies and low heterogeneity.

Subgroup Analyses

We conducted subgroup analyses to investigate the influence of puncture site, patients' age, and Jadad score of each trial on the risks of cannulation failure and arterial puncture (table 2), as well as the risks of hematoma, pneumothorax, and hemothorax (table 3).

For the risk of cannulation failure, the superiority of RTUS was significant in adult patients (RR = 0.18, 95% CI: 0.11–0.31), but not in pediatric patients (RR = 0.26,

Table 3. Subgroup Analyses of Hematoma, Pneumothorax, and Hemothorax

Group		Hematoma				Pneumothorax				Hemothorax		
	N*	RR (95% CI)	$P_{heterogeneity}$	I² (%)	N*	RR (95% CI)	$P_{heterogeneity}$	I², %	N*	RR (95% CI)	$P_{heterogeneity}$	I², %
Total	14	0.30 (0.19, 0.46)	0.468	0.0	7	0.21 (0.06, 0.73)	0.327	13.5	3	0.10 (0.02, 0.54)	0.572	0.0
Puncture site												
IJV	10	0.26 (0.14, 0.48)	0.232	22.9	4	0.19 (0.04, 0.89)	0.627	0.0	2	0.14 (0.02, 1.15)	0.360	0.0
SCV	3	0.26 (0.09, 0.76)	0.712	0.0	2	0.46 (0.00, 47.91)	0.028	79.3	1	0.05 (0.00, 0.90)	NA	NA
FV	1	0.50 (0.10, 2.62)	NA	NA	0	NA	NA	NA	0	NA	NA	NA
Mean age†												
<8 yr	1	0.13 (0.01, 2.42)	NA	NA	1	0.40 (0.02, 9.61)	NA	NA	1	0.40 (0.02, 9.61)	NA	NA
>18 yr	11	0.30 (0.18, 0.50)	0.307	14.4	4	0.22 (0.03, 1.95)	0.095	52.8	2	0.06 (0.01, 0.42)	0.959	0.0
Jadad score												
2	5	0.40 (0.20, 0.80)	0.621	0.0	2	0.17 (0.02, 1.45)	0.566	0.0	0	NA	NA	NA
≥3	9	0.24 (0.13, 0.44)	0.358	9.2	5	0.24 (0.04, 1.38)	0.158	39.4	3	0.10 (0.02, 0.54)	0.572	0.0

* The number of studies included in the meta-analysis, with the study given zero weight excluded. † Studies with patients at the mean ages between 8 and 18 were not found.

FV = femoral vein; IJV = internal jugular vein; NA = not applicable; RR = relative risk; SCV = subclavian vein.
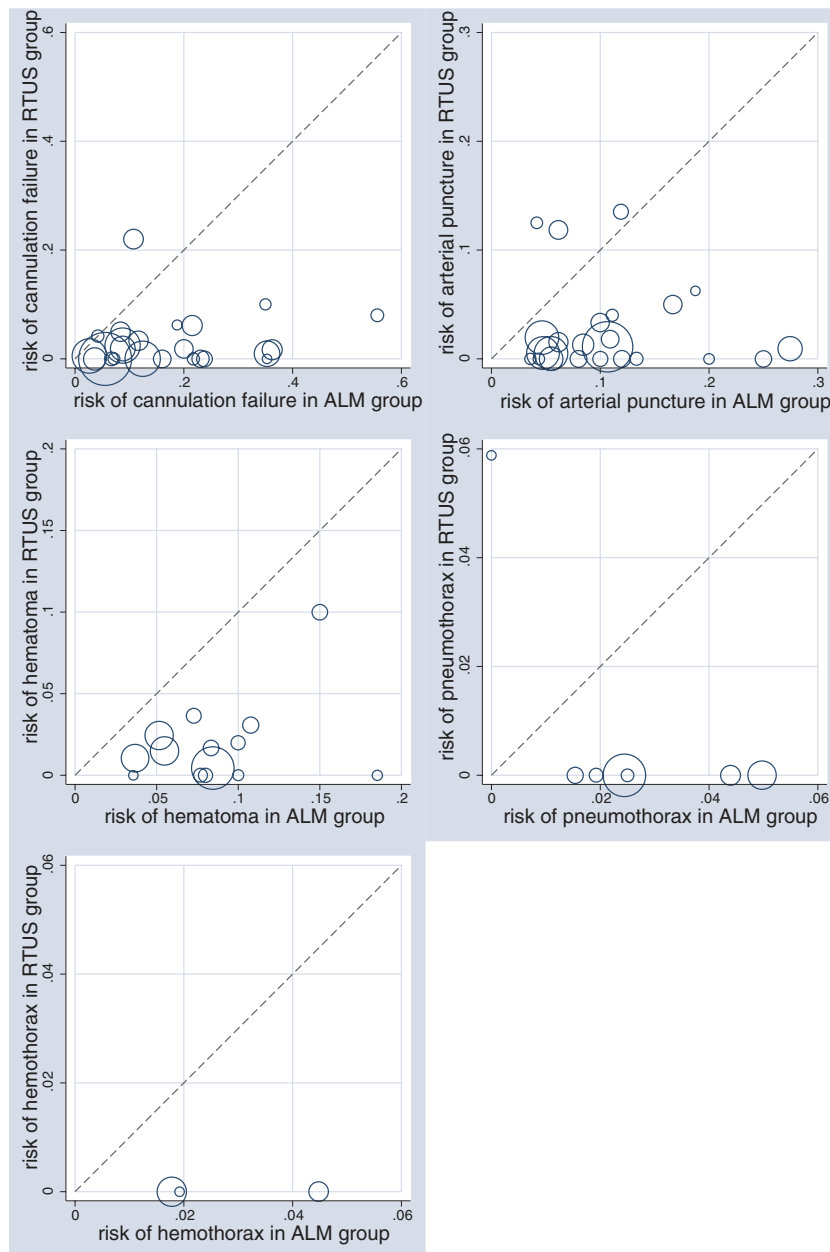
Fig. 4. L'Abbé plots for ALM and RTUS group for the five endpoints. In L'Abbé plots, each symbol stands for one trial and the size of the symbol is appropriate to the sample size of the trial. ALM = anatomical landmark technique; RTUS = real-time two-dimensional ultrasound guidance technique.

95% CI: 0.03–2.55). In addition, use of RTUS was not associated with a reduced risk of arterial puncture and hematoma in pediatric patients (RR = 0.34, 95% CI: 0.05–2.60; RR = 0.13, 95% CI: 0.01–2.42, respectively), but it could decrease the risks of accidental arterial puncture and hematoma in adults (RR = 0.25, 95% CI: 0.15–0.40; RR =0.30, 95% CI: 0.18–0.50, respectively). Moreover, compared with the data of adults, high heterogeneity was found in the data of pediatric patients for the risks of cannulation failure (I^2 = 85.9% [P < 0.001 from Q test]) and arterial puncture (I^2 = 81.3% [P < 0.001]). We also observed moderate heterogeneity in the subgroup of IJV

both for cannulation failure (I^2 = 65.2% [P < 0.001]) and arterial puncture (I^2 = 50.7% [P = 0.009]) (table 2), high heterogeneity in the subgroup of SCV for pneumothorax (I^2 = 79.3% [P = 0.028]) (table 3), and moderate heterogeneity in the subgroup of FV for arterial puncture (I^2 = 57.5% [P = 0.095]) (table 2).

Subgroup analyses stratified by Jadad score showed that the significant heterogeneity for the outcomes of cannulation failure and arterial puncture was from the studies with higher quality (Jadad score was more than two) (table 2), indicating that heterogeneity was due to other factors, rather than lower quality of studies.

Publication Bias and L'Abbé Plots

Neither Begg adjusted rank correlation test nor Egger's regression asymmetry test yields evidence of significant publication bias for any of the three endpoints (cannulation failure, arterial puncture, and hematoma). Publication bias evaluation on the pneumothorax and hemothorax were not conducted due to limited trials involved. L'Abbé plots are shown in figure 4, which plot the event rates in the treatment (RTUS) and the control (ALM) groups by study. Each of them provides an alternative way of displaying the data that allow inspection of the variability in treatment and control group event rates.

Discussion

Our meta-analysis of 26 RCTs shows that patients receiving CVC can obtain significant benefit from RTUS. Our overall pooled results for RTUS compared with ALM showed statistically significant reductions in incidence of cannulation failure, and the risk for accidental arterial puncture, hematoma, pneumothorax, and hemothorax.

Cannulation of the central veins is an important aspect of patient care for the administration of fluid, medications, and nutrients, and for monitoring central venous pressure, central venous blood analysis, and so on.[9,46] However, CVC has an inherent risk itself. A recent report by Maecken *et al.*[47] reminds us of the importance of understanding and correctly identifying the relevant structures, of the fact that the anatomy at these sites is not always consistent, and that ALM cannot take this variability into account.[48] Operators generally choose the venous access site based on personal experience, clinical needs, and the most recent data from the literature. For example, SCV catheterization is associated with a lower risk of infectious and thrombotic complications than FV catheterization in intensive care unit patients,[49] and hence the SCV may be a first choice for some intensive care unit physicians. Our meta-analysis suggested that both the IJV and SCV access site could benefit from the use of RTUS in terms of reducing risks of cannulation failure, arterial puncture, and hematoma. RTUS was associated with an increased cannulation success rate in those receiving FV access, but could not be shown to significantly reduce the risk of arterial puncture and hematoma (due to limited data).

Several other important findings emerged from this meta-analysis. First, we observed a significant reduction in the incidences of cannulation failure, arterial puncture, hematoma, and hemothorax in adults. Second, pediatric patients might not benefit from RTUS based on subgroup analyses. While this finding indicates that patients' age might serve as a potential effect modifier, the interpretation of these differences by patients' age is challenging. The benefits of RTUS in pediatric patients should not be simply denied and these results of subgroup analyses should be interpreted cautiously because of the limited number of trials in this subgroup. Until now, only five trials reported the outcomes of cannulation failure

and arterial puncture,[33,35,37,42,43] and only one trial reported the outcome of hematoma, pneumothorax, and hemothorax in the subgroup of pediatric patients.[33] In those five trials, IJV was the most commonly used puncture site (four in five) and only one trial investigated the use of RTUS for FV. Although the latest guidelines recommend that trained clinicians use real-time ultrasound during IJV and FV cannulation whenever possible to improve cannulation success and reduce the incidence of complications in pediatric patients,[9] more well-designed and large-scale RCTs are necessary to assess the value of RTUS in pediatric patients.

Significant heterogeneity was observed across the studies in the association between RTUS use and cannulation failure and arterial puncture. This is not surprising because of variation in study designs and characteristics of patients and operators among the different studies. As indicated by our subgroup analyses, age likely contributed largely to the observed heterogeneity. The heterogeneity was low in adults ($I^2 < 20\%$), but high in pediatric patients ($I^2 > 80\%$), both for cannulation failure and arterial puncture. Other factors, such as puncture site, could not explain well the source of the observed heterogeneity.

We believe our study has strengths. First, with more and better data available than in previous meta-analyses,[16,50] we have enhanced statistical power to identify an association between the use of RTUS and increased cannulation success rate and reduced incidence of clinic adverse events (accidental arterial puncture, hematoma, pneumothorax, and hemothorax). Second, all studies included in the current meta-analysis used a randomized control design, which decreased spurious causality and bias. Additionally, the same conclusions were made that RTUS was beneficial to reduce the risks of cannulation failure, arterial puncture, hematoma, pneumothorax, and hemothorax when studies were restricted within the latest 10 yr (2003–2012) as few people work with ultrasound devices older than 10 yr. Furthermore, to our knowledge, this is the first meta-analysis to assess the value of RTUS in CVC, which is increasingly popular as safer and more portable ultrasound devices are available in practice.

Several important limitations should be considered when interpreting our findings. First, most of the included studies were not blinded, which might have generated a high risk of observer bias for the endpoints. Second, we applied a concise and popular method (Jadad scale) to assess the quality of each study, which presents the best validity and reliability evidence among as many as 21 scales that are being used.[22] However, the Jadad scale gives more weight to the quality of reporting than to actual methodological quality and ignores assessing allocation concealment.[51] These limitations should be taken into consideration and the results provided by subgroup analyses stratified by Jadad score should be interpreted with caution. Third, the definitions of operator experience varied widely across studies, making it hard and at times somewhat subjective

to judge whether the operators in each study were senior or junior. Thus, subgroup analyses stratified by operator experience were not conducted. Fourth, other endpoints, such as access time, were not included in our analysis because of heterogeneity in the definition. Fifth, meta-regression was not conducted due to the number of missing data on variables, such as patients' age, which might affect the interpretation of the statistical heterogeneity between results of multiple studies.

In conclusion, the current meta-analysis indicates that the use of RTUS is associated with a reduced incidence of cannulation failure, arterial puncture, hematoma, and hemothorax in adult patients undergoing CVC. A lack of good data in the pediatric population underscores the urgent need for more well-designed RCTs to clarify the role of RTUS in pediatric patients.

Appendix 1

Database
PubMed

Searchfilter
"Ultrasonography, Interventional"(Mesh) AND (inter* jugul*[tiab] OR femoral*[tiab] OR subclavian* [tiab] OR "Catheterization, Central Venous"[Mesh]) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR random* [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR trial [ti]) NOT (animals [mh] NOT humans [mh])

Database
ISI Web of knowledge

Searchfilter
Title=(ultrasound* or ultrasonic* or imag* guid* or ultrasonograph*) AND Title=(central venous or venous cannulation or venous catheter* or vein* cannulation or vein*catheter* or pulmonary arter* flotation* or central line* or hickman line* or inter* jugul* OR femoral* OR subclavian*)
Timespan = All Years. Search language = English. Lemmatization = On.

Database
EMBASE

Searchfilter
1. exp central venous catheterization/ or exp central venous catheter/
2. central venous line$.tw.
3. Catheterization, Central Venous/
4. ((venous or vein*) adj3 (cannulation or access or catheter*)).mp.
5. central line* insertion*.mp.
6. hickman line*.
7. (ultrasonography* or ultrasonics* or ultrasound* or ultrasonic*).mp.
8. (imag* adj guid*).mp.
9. (jugul* or subclavia* or femoral*).mp.
10. random*.mp.
11. limit 10 to human
12. (1 or 2 or 3 or 4 or 5 or 6)
13. (7 or 8)
14. (9 and 10 and 11 and 12 and 13)

Database
All OVID Evidence-Based Medicine Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED

Searchfilter
1. catheterization-central-venous*.mp. (mp = ti, ot, ab, tx, kw, ct, sh, hw)
2. central venous line$.tw.
3. (venous or vein*) adj3 (cannulation or access or catheter*).mp. (mp = ti, ot, ab, tx, kw, ct, sh, hw)
4. central line* insertion*.mp. (mp = ti, ot, ab, tx, kw, ct, sh, hw)
5. hickman line*.mp. (mp = ti, ot, ab, tx, kw, ct, sh, hw)
6. (ultrasonography* or ultrasonics* or ultrasound* or ultrasonic*).mp. (mp=ti, ot, ab, tx, kw, ct, sh, hw)
7. (imag* adj guid*).mp. (mp=ti, ot, ab, tx, kw, ct, sh, hw)
8. (jugul* or subclavia* or femoral*).mp. (mp = ti, ot, ab, tx, kw, ct, sh, hw)
9. random*.mp. (mp = ti, ot, ab, tx, kw, ct, sh, hw)
10. limit 9 to humans (Limit not valid in Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register; records were retained)
11. (1 or 2 or 3 or 4 or 5)
12. (6 or 7)
13. (8 and 9 and 10 and 11 and 12)

Appendix 2: Jadad scale

Jadad *et al.* [20] published a three-point questionnaire that formed the basis for the Jadad scale. A clinical trial could receive a Jadad score of between zero and five. The Jadad scale is concise and has only three questions which are as follows:

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?
   A. The method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, *etc.*). (+2 Points)
   B. The study was described as randomized, but the method to generate the sequence of randomization was not described. (+1 Point)
   C. The method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, *etc.*). (+0 Point)
2. Was the study described as double blind?
   A. The method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, *etc.*). (+2 Points)
   B. The study was described as double blind, but the method of blinding was not described. (+1 Point)
   C. The study was described as double blind but the method of blinding was inappropriate (*e.g.,* comparison of tablet *vs.* injection with no double dummy). (+0 Point)
3. Was there a description of withdrawals and dropouts?
   A. Yes. The number of withdrawals and dropouts and the reasons were stated in each of the comparison groups. (+1 Point)
   B. No. (+0 Point)

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