Cumulative Evidence of Randomized Controlled and Observational Studies on Catheter-Related Infection Risk of Central Venous Catheter Insertion Site in ICU Patients: A Pairwise and Network Meta-Analysis

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Background: Selection of central venous catheter insertion site in ICU patients could help reduce catheter-related infections. Although subclavian was considered the most appropriate site, its preferential use in ICU patients is not generalized and questioned by contradicted meta-analysis results. In addition, conflicting data exist on alternative site selection whenever subclavian is contraindicated.

Objective: To compare catheter-related bloodstream infection and colonization risk between the three sites (subclavian, internal jugular, and femoral) in adult ICU patients.

Data Source: We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled trials, CINAHL, and clinicaltrials.gov.

Study Selection: Eligible studies were randomized controlled trials and observational ones.

Data Extraction: Extracted data were analyzed by pairwise and network meta-analysis.

Data Synthesis: Twenty studies were included; 11 were observational, seven were randomized controlled trials for other outcomes, and two were randomized controlled trials for sites. We evaluated 18,554 central venous catheters: 9,331 from observational studies, 5,482 from randomized controlled trials for other outcomes, and 3,741 from randomized controlled trials for sites. Colonization risk was higher for internal jugular (relative risk, 2.25 [95% CI, 1.84–2.75]; $I^2 = 0\%$) and femoral (relative risk, 2.92 [95% CI, 2.11–4.04]; $I^2 = 24\%$), compared with subclavian. Catheter-related bloodstream infection risk was comparable for internal jugular and subclavian, higher for femoral than subclavian (relative risk, 2.44 [95% CI, 1.25–4.75]; $I^2 = 61\%$), and lower for internal jugular than femoral (relative risk, 0.55 [95% CI, 0.34–0.89]; $I^2 = 61\%$). When observational studies that did not control for baseline characteristics were excluded, catheter-related bloodstream infection risk was comparable between the sites.

Conclusions: In ICU patients, internal jugular and subclavian may, similarly, decrease catheter-related bloodstream infection risk, when compared with femoral. Subclavian could be suggested as the most appropriate site, whenever colonization risk is considered and not, otherwise, contraindicated. Current evidence on catheter-related bloodstream infection femoral risk, compared with the other sites, is inconclusive. (*Crit Care Med* 2016; XX:00–00)

Key Words: catheter-related infections; central venous catheter; insertion site; intensive care unit; meta-analysis; network meta-analysis

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Insertion of central venous catheters (CVCs) in ICUs is associated with infectious (1, 2), mechanical (3, 4), and thrombotic (5, 6) complications. Catheter-related bloodstream

infection (CRBSI) and colonization are the commonest adverse outcomes among catheter-related infections (CRIs), raising mortality and cost of hospitalization (7, 8). Preventive efforts have been undertaken to reduce their occurrence rate (9–11), combining inexpensive measures with costly devices and materials (12). Insertion site selection integrated in a preventive bundle may contribute to CRI reduction (9, 11). In 2011, published guidelines for CRI prevention hospital-wide, proposed subclavian as the site with the lowest CRI risk (13). Ever since, the recommended site was not commonly chosen in ICUs (14–16). Two meta-analyses of randomized controlled trials (RCTs) and observational trials were published in 2012. The first evaluated the CRI risk and supported the protective effect of subclavian when compared with the other sites (17), whereas the second found comparable CRBSIs between femoral and subclavian and favored internal jugular in comparison with femoral (18). In 2013, a secondary analysis of data retrieved from two RCTs, not randomized for CVC site, presented comparable CRBSI and colonization risk of femoral and internal jugular (19). In 2014, an update of Infectious Diseases Society of America and Society for Healthcare Epidemiology of America's practice recommendations on Central-Line Associated Bloodstream Infections prevention, based on studies published before 2011, proposed avoiding femoral in obese patients, recommendation that was contradicted (19, 20). In 2015, intention to treat analysis of an RCT for the site reported lower colonization risk of subclavian compared with the other sites and of jugular compared with femoral. Subclavian was associated with lower CRBSI risk when compared with femoral and similar when compared with internal jugular. In per-protocol CRBSI risk analysis, subclavian was favored when compared with femoral and internal jugular, whereas, in sensitivity analysis of one random catheter per patient, no CRBSI risk difference was observed between sites (21). Overall, in four studies (17–19, 21) published after 2011 guidelines, discrepant data were reported regarding CRBSI risk, two evaluated colonization (19, 21), and one compared the three sites with each other (21).

In the present analysis, we aimed to evaluate CRBSI and colonization risk related to the insertion site of short-term, nontunnelled CVCs exclusively in ICU patients. We reappraised available data and compared sites using pairwise and network meta-analysis (NMA). Relevant RCTs and observational studies were included. PRISMA and MOOSE statements were followed (22, 23).

METHODS

Data Sources

We searched MEDLINE (1966 to May 2016), EMBASE (1977 to May 2016), Cochrane Central Register of Controlled trials (CENTRAL) (1948 to May 2016), CINAHL (1982 to May 2016), and clinicaltrials.gov (May 2016). For additional studies, we manually searched bibliographies of relevant reviews and meta-analyses (8, 12, 17, 18, 24–26) and reference lists of eligible articles. No restrictions to calendar day or language were adopted. Search was conducted in September 2015, and analyzed data were retrieved. Additional search was conducted in May 2016 to identify any recent studies eligible for inclusion (**Supplement Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C171).

Study Selection

Studies referring to adult ICU patients with short-term, noncuffed, nontunnelled CVCs inserted in the ICU were included. RCTs for sites or other outcomes and observational studies were selected. Observational trials were included whether or not they provided multivariable analyses' results. We excluded studies with animals, volunteers, pediatric, or burn patients, crossover studies, studies with zero events in all arms (27), studies using exclusively guidewire-exchange technique and data from abstracts, conference proceedings, reviews, or comments. We excluded peripherally inserted central catheters, pulmonary artery catheters, and hemodialysis catheters. For studies not reporting CRBSI or colonization per site, corresponding authors were contacted and, if data were not provided, studies were excluded. Initial screening by study title and abstract (phase 1) plus full-text screening (phase 2) and data retrieval were performed separately by two investigators (K.A., D.L.); disagreements were resolved by consensus.

Outcome Selection

We prespecified two primary outcomes, colonization and CRBSI. Secondary outcomes were mechanical complications and CVC-related thrombosis.

Definitions

U.S. and French definitions were applied for primary outcomes (28–31). Definitions for colonization, CRBSI, and CVC-related thrombosis are presented in the **Supplement-Only online material** (Supplemental Digital Content 2, http://links.lww.com/CCM/C172).

Data Extraction

For every eligible study, we extracted study-related data (authorship, study design, number of centers, and sample size), CVC characteristics (type, number of lumens, number of CVCs per patient, and guidewire exchange), CVC-oriented infection prevention strategy, definitions used, CRBSI and colonization per site, insertion-related complications, duration of catheterization, and microorganisms.

Individual Study Quality Assessment

The risk of bias for each study was evaluated with the Cochrane Collaboration's risk of bias tool (32) for RCTs and Newcastle-Ottawa Scale (33) for observational studies. RCTs were evaluated regardless if there were randomized for the site or other outcomes. We used GRADE approach to rate the quality of treatment effect estimates from pairwise meta-analyses (34).

Quantitative Data Synthesis

The risk of colonization and CRBSI per site was compared with the risk associated with the other two sites by pairwise

meta-analysis. Subgroup analyses were conducted according to study design. Data from RCTs for other outcomes were treated as those from observational studies. We conducted pairwise analysis of studies published after 2011 guidelines and after exclusion of observational studies that did not control for baseline characteristics. Cumulative meta-analysis was performed to evaluate the potential influence of publication year on each effect estimate. Catheter-related thrombosis risk between femoral and subclavian was evaluated by pairwise meta-analysis.

For each comparison of binary outcomes, we calculated pooled effect sizes with the Der Simonian and Laird random effects model (35) and relative risks (RRs) with their 95% CIs. We used random-effects models because of the obvious heterogeneity (different study design) across included trials.

Heterogeneity was assessed with Cochrane *Q* statistic and estimated with I^2 measure; published guidelines were used to define not important (I^2 = 0–40%), moderate (I^2 = 30–60%), substantial (I^2 = 50–90%), or high/considerable ($I^2 \geq 75\%$) heterogeneity (36, 37).

Sensitivity analysis was conducted to evaluate potential confounding variables (number of centers, number of CVCs per patient, CRBSI and colonization definitions used, use of guidewire technique, administration of parenteral nutrition or blood products through catheters, full barrier precautions, CVC insertion and maintenance protocol, skin antisepsis type, impregnated CVCs, dressing type, and studies, with an increased risk of bias) and explain heterogeneity.

Additional Analyses

We compared the mean duration of CVC catheterization between the sites by calculating mean differences and 95% CIs. The inverse-variance method was used to obtain summary mean differences (37). The units of analysis were mean and SD per study.

Meta-regression analysis was performed to explore the potential effect of publication year, patient age, and Acute Physiology and Chronic Health Evaluation (APACHE) score (38, 39).

Publication bias was assessed with the Harbord test and visually inspected with the counter-enhanced plots for asymmetry (40).

NMA was performed to estimate every possible comparison's effect in a network combining all three sites. We included RCTs and observational studies to evaluate the largest possible data sample, and we used naive pooling methodology that does not differentiate between the two study designs (41, 42). We calculated the surface under the cumulative ranking curve (SUCRA) to estimate cumulative probability for each site to rank in each place (first, second, and third) (38). Femoral was considered as the reference site.

Pairwise analyses were performed using Review Manager (RevMan version 5.3. Copenhagen: the Nordic Cochrane Centre, The Cochrane Collaboration, 2008) and replicated by

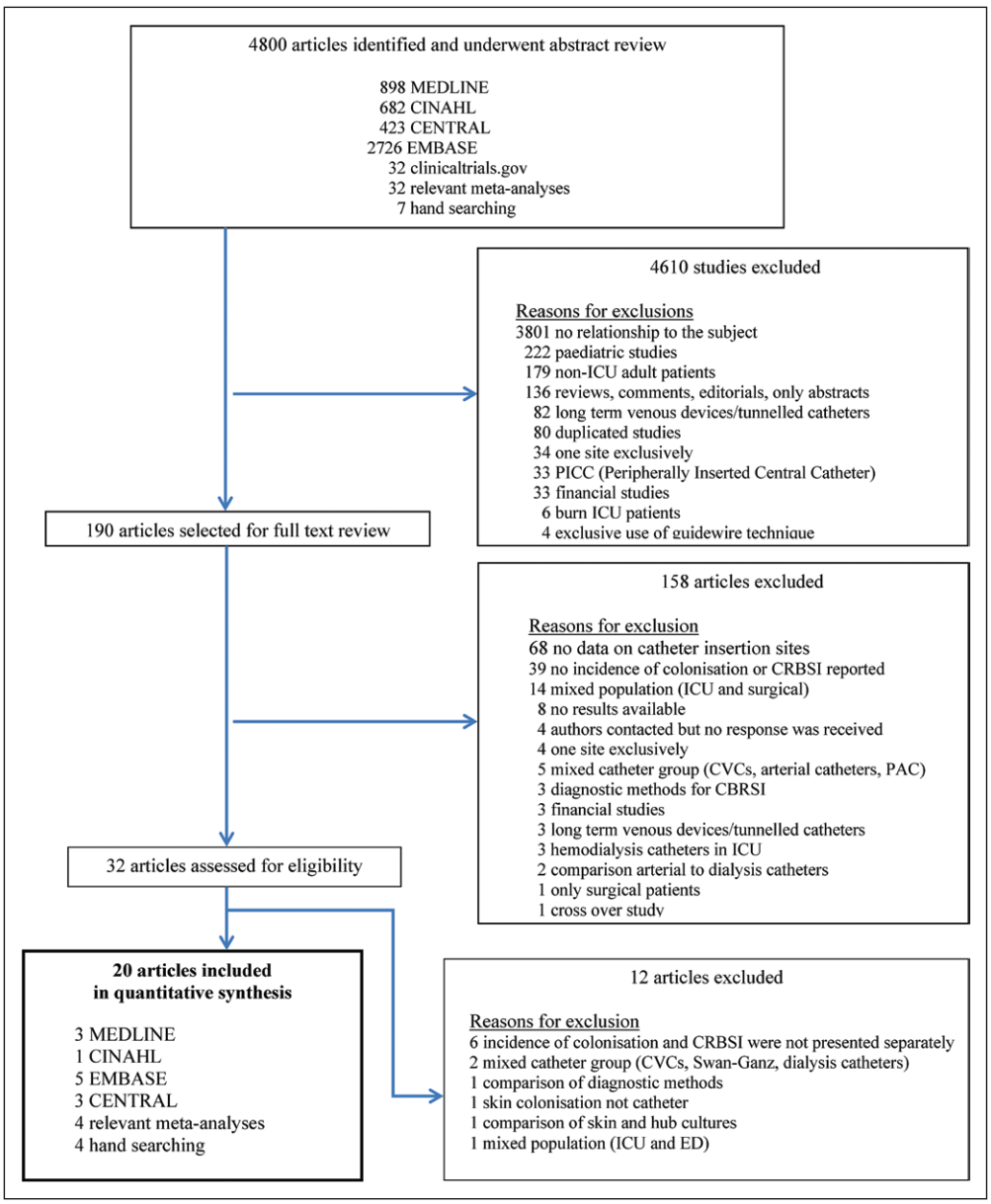

Figure 1. Flowchart of included studies. CRBSI = catheter-related bloodstream infection, CVC = central venous catheter, ED = emergency department, PAC = pulmonary artery catheter.

STATA, version 12.0. STATA, version 12.0, was used for NMA. We considered *p* value less than or equal to 0.05 (two sided) as significant.

RESULTS

Study Selection

Twenty studies were included in quantitative synthesis (**Fig. 1**). Of them, 11 were observational (43–53), seven RCTs for other outcomes (19, 54, 55), and two RCTs for sites (21, 56). We evaluated 18,554 CVCs: 9,331 from observational studies, 5,482 from RCTs for other outcomes, and 3,741 from RCTs for sites (**Supplement-Digital Content-Table 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/C172; and **Supplement-Table 2**, Supplemental Digital Content 3, http://links.lww.com/CCM/C173). Nine studies presented data for CRBSI (43, 44, 48–53, 55), six for colonization (46, 47, 57–60), and five for both outcomes (19, 21, 45, 54, 56). In 18 studies, protocols for CVC insertion and maintenance, as well as reasons for catheter removal, were reported (Supplement-Table 2, Supplemental Digital Content 3, http://links.lww.com/CCM/C173). All studies reported colonization and CRBSI definitions, only five CRBSI definitions in the case of coagulase-negative staphylococci (19, 21, 44, 54, 58) (Supplement-Digital Content-Table 1, Supplemental Digital Content 2, http://links.lww.com/CCM/C172).

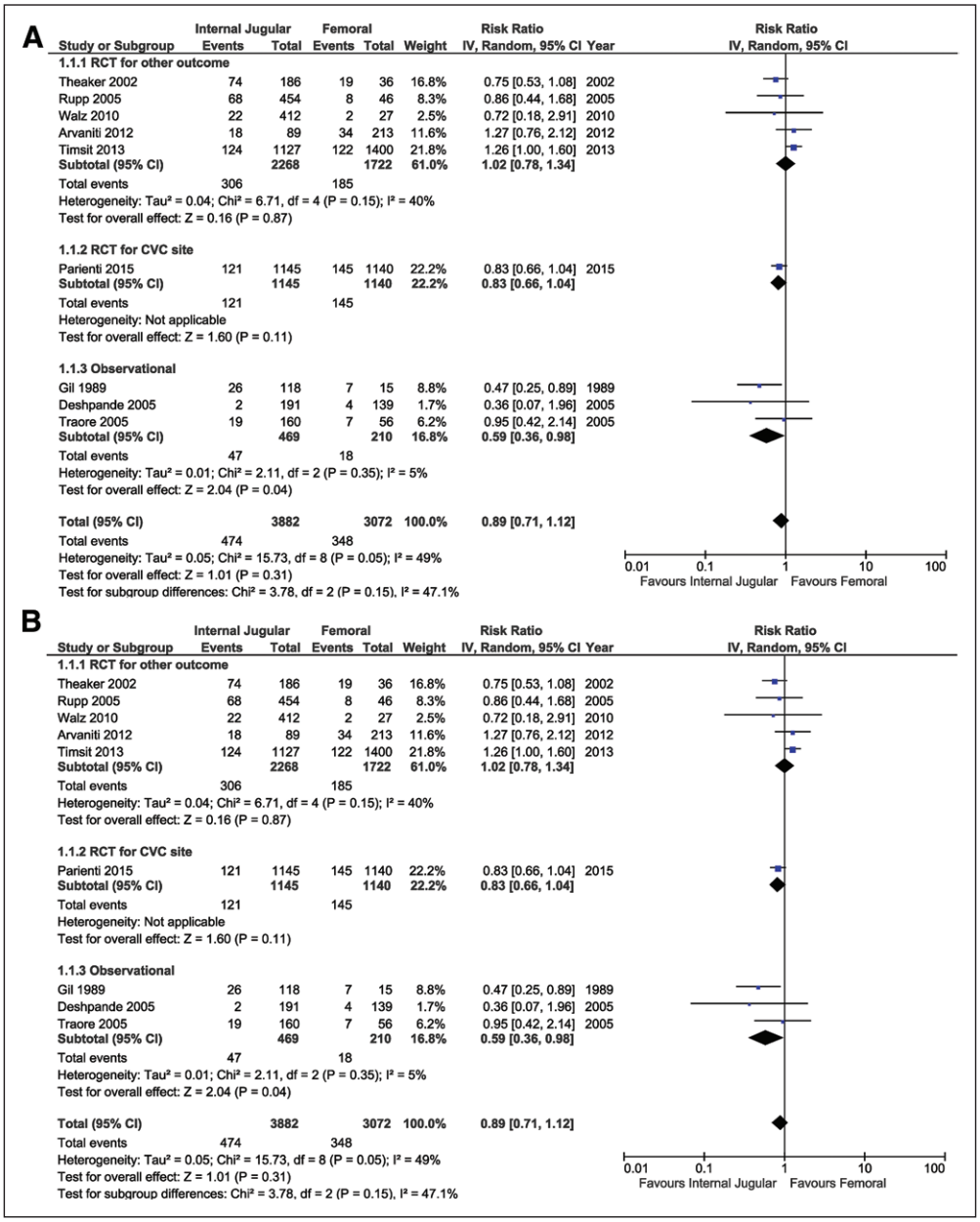

Figure 2. Central venous catheter colonization risk in studies comparing internal jugular to femoral (**A**), internal jugular to subclavian (**B**), and

Quality of Included Studies

Only three studies provided adjusted hazard ratios (19, 21, 54). Two RCTs had a high risk of bias (55, 59). Six of 11 observational studies did not control for baseline characteristics (46, 47, 49, 51–53) (**Supplement-Tables 2–4**, Supplemental Digital Content 2, http://links.lww.com/CCM/C172).

Primary Outcomes and Subgroup Analysis

Colonization. Colonization risk was higher for internal jugular (RR, 2.25 [95% CI, 1.84–2.75]; I^2 = 0%) and femoral (RR, 2.92 [95% CI, 2.11–4.04]; I^2 = 24%), compared with subclavian. There was no significant difference between internal jugular and femoral (**Fig. 2**). Comparing the subgroups of study designs, there was no significant difference in any of the pooled estimates (χ^2 = 3.78; p = 0.15, χ^2 = 0.62; p = 0.73, and χ^2 = 2.23; p = 0.33, respectively). Discrepancy between study designs was observed in internal jugular-femoral comparison in two observational studies with increased risk of bias (Fig. 2; and **Supplement-Fig. 1*A***, Supplemental Digital Content 2, http://links.lww.com/CCM/C172).

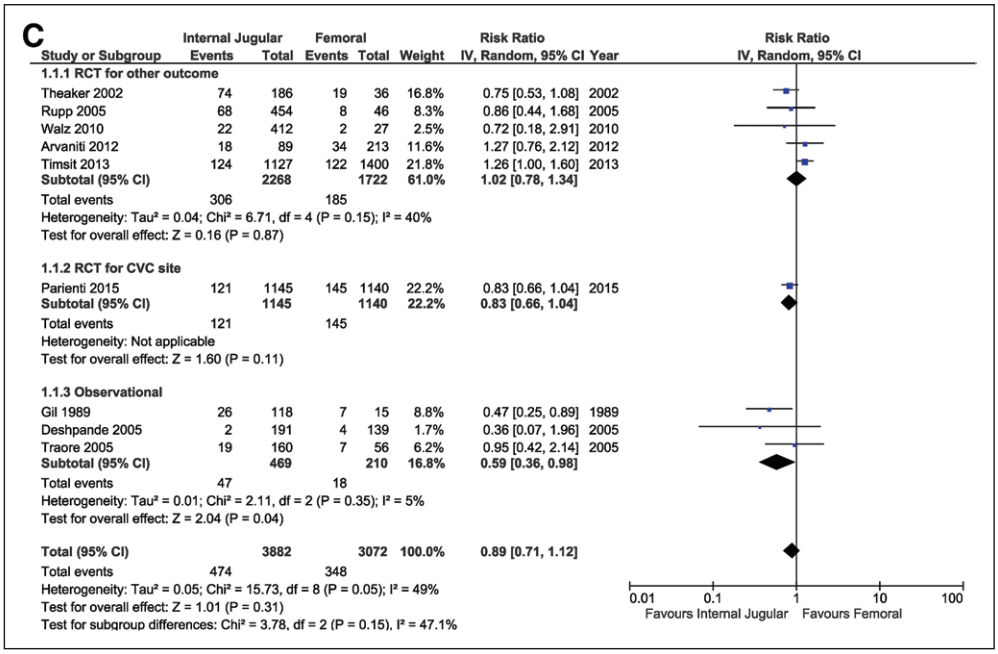

Figure 2. (*Continued*). femoral to subclavian insertion site (**C**). *Vertical lines* indicate no difference between the two intervention groups. Pooled risk ratios were calculated from random-effects models with Der Simonian and Laird method. IV = inverse variance.

CRBSI. No significant difference was found in CRBSI risk between internal jugular and subclavian and between study design estimates (χ^2 = 1.99; p = 0.37). CRBSI risk was lower for internal jugular compared with femoral (RR, 0.55 [95% CI, 0.34–0.89]; I^2 = 61%), and there seemed to be a significant difference in pooled estimates between study designs (observational studies: RR = 0.40, RCT for other outcomes: RR = 1.32, and RCT for CVC sites: 1.39; χ^2 = 13.77; p = 0.001). CRBSI risk was higher for femoral compared with subclavian (RR, 2.44 [95% CI, 1.25–4.75]; I^2 = 61%), and there was a borderline significance in the difference in pooled estimates between study designs (observational studies: RR = 2.94; RCT for other outcomes: RR = 0.07, and RCT for sites: RR = 2.61; χ^2 = 6.07; p = 0.05) (**Fig. 3**). In internal jugular-femoral comparison, when observational studies that did not control for baseline characteristics were excluded, the point estimate was increased by 40% (from RR, 0.40 [0.27–0.59]; I^2 = 25% to RR, 0.56 [0.37–0.84]; I^2 = 0%), whereas the overall point estimate was comparable between the two sites (RR, 0.79 [0.53–1.18]; I^2 = 26%). Similarly, in femoral-subclavian comparison, CRBSI risk was comparable between the two sites in subgroup analysis of observational studies (from RR, 2.94 [1.38–6.25]; I^2 = 65% to RR, 1.51 [0.78–2.92]; I^2 = 27%) and in the overall analysis (from RR, 2.44 [1.25–4.75]; I^2 = 61% to RR, 1.56 [0.78–3.11]; I^2 = 40 %; (**Supplement-Table 7*B***, Supplemental Digital Content 2, http://links.lww.com/CCM/C172; and **Supplement-Fig. 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/C172). When only studies after 2011 guidelines and, also, studies that reported adjusted hazard ratios were analyzed, CRBSI risk was comparable between the sites (Supplement-Table 7*B*, Supplemental Digital Content 2, http://links.lww.com/CCM/C172).

Sensitivity Analyses

In sensitivity analyses, pooled estimates were similar to primary analyses, for both outcomes, when the number of centers, number of CVCs per patient, CRBSI and colonization definitions used, use of guidewire technique, administration of parenteral nutrition or blood products, full barrier precautions, CVC insertion and maintenance protocol, and skin antisepsis type were evaluated. However, the reduced number of studies that used impregnated catheters and lack of homogeneity on dressing selection did not permit their appraisal (**Supplement-Tables 5–7**, Supplemental Digital Content 2, http://links.lww.com/CCM/C172).

According to GRADE approach, the quality of evidence was either low or very low for observational studies and RCTs for other outcomes and moderate for RCTs for the site, mainly because of the absence of blinding for patients and personnel. The overall quality of evidence for all observed outcomes was low for all comparisons (**Supplement-Table 8**, Supplemental Digital Content 2, http://links.lww.com/CCM/C172).

Additional Analyses

Indwelling Time. The mean duration of catheterization was reported in 10 studies. Subclavian catheters were kept longer compared with internal jugular (mean difference: –1.76; 95% CI, –3.74 to 0.22) or femoral (mean difference: –0.43; 95% CI, –1.03 to 0.16). No difference in indwelling time was observed between internal jugular and femoral. Important heterogeneity was found in internal jugular-femoral (I^2 = 88%) and internal jugular-subclavian (I^2 = 92%) comparisons (**Fig. 4**).

Risk of Bias. Bias related to distribution of studies' effect estimate was observed only in femoral-subclavian comparison for colonization. No bias related to small study effects according to Harbord modified test was shown in any other comparison (**Supplement-Figs. 3–6**, Supplemental Digital Content 2, http://links.lww.com/CCM/C172).

Meta-regression showed a positive effect of publication year only on CRBSI risk (**Supplement-Figs. 7 and 8**) in internal jugular-femoral comparisons (p = 0.001). No effect of APACHE score was observed in either comparison (**Supplement-Figs. 9** and **10**, Supplemental Digital Content 2, http://links.lww.com/CCM/C172). The risk ratio of CRBSI risk in older ages was shown larger in internal jugular-femoral comparison (p = 0.009) (**Supplement-Figs. 11** and **12**, Supplemental Digital Content 2, http://links.lww.com/CCM/C172).

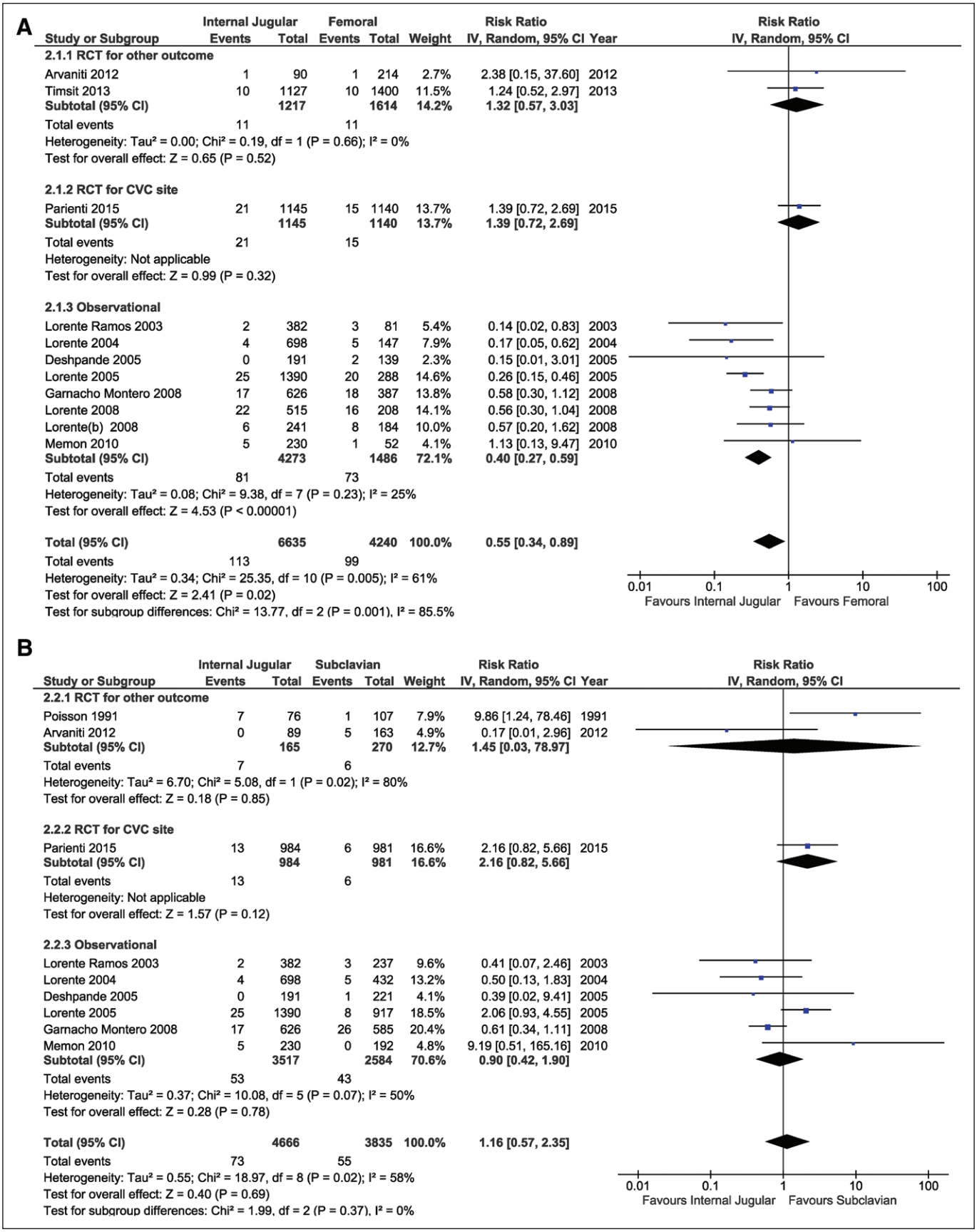

Figure 3. Catheter-related blood stream infection risk in studies comparing internal jugular to femoral (**A**), internal jugular to subclavian (**B**), and

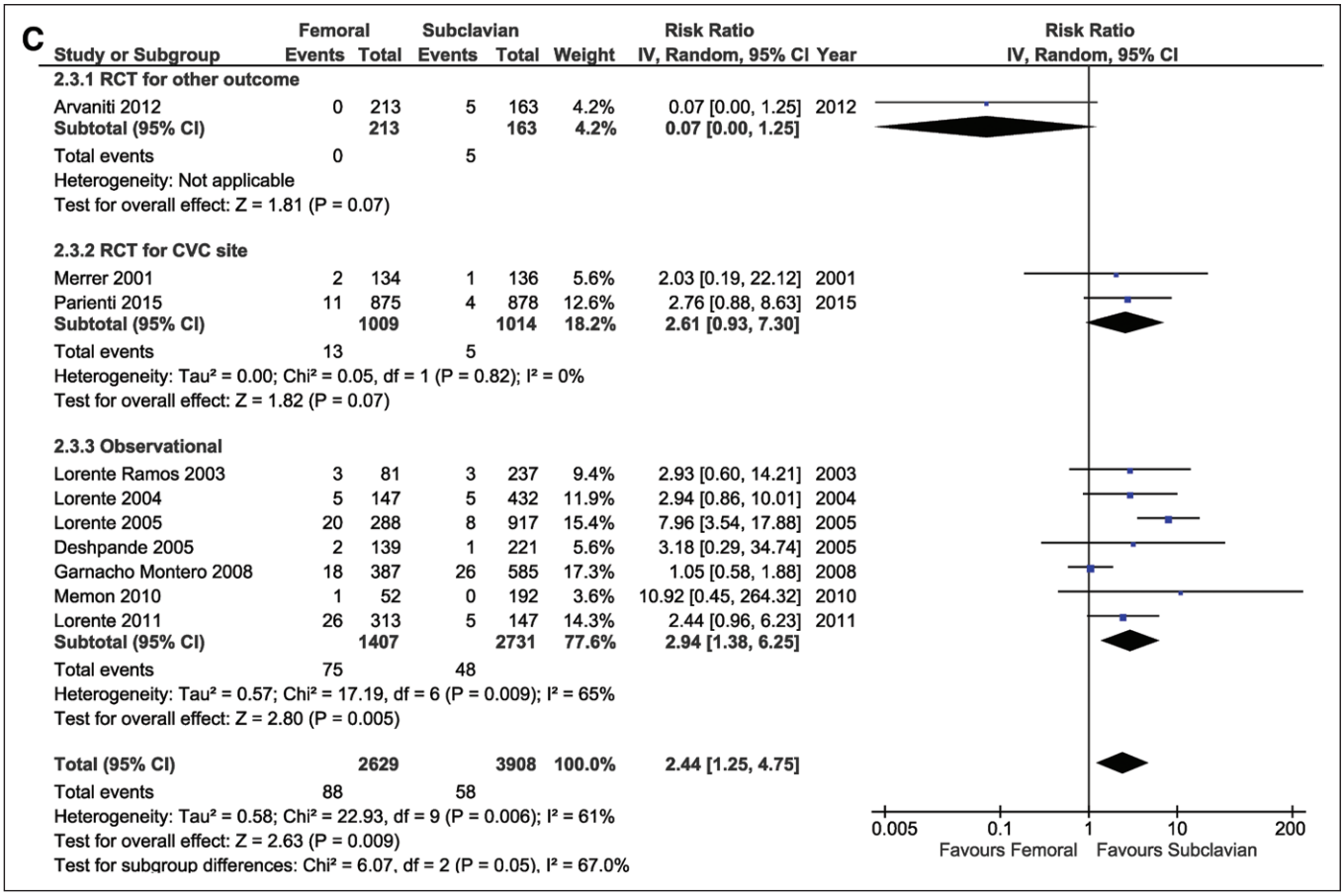

Figure 3. (*Continued*). femoral to subclavian insertion site (**C**). *Vertical lines* indicate no difference between the two intervention groups. Pooled risk ratios were calculated from random-effects models with Der Simonian and Laird method. IV = inverse variance.

In cumulative meta-analysis, considerable influence of studies published after 2011 was observed only in colonization risk point estimates in internal jugular-femoral comparisons with a tendency toward nondifference (**Supplement-Figs. 13** and **14**, Supplemental Digital Content 2, http://links.lww.com/CCM/C172).

Network Meta-Analysis

In individual comparisons for colonization, femoral and internal jugular were more probable to increase the risk than subclavian (NMA: RR, 3.01 [95% CI, 2.18–4.16] and RR, 2.50 [95% CI, 1.98–3.16], respectively), whereas subclavian presented the lowest risk (SUCRA, 100%). CRBSI risk was increased for femoral compared with subclavian (NMA: RR, 2.40 [95% CI, 1.35–4.26]), and no difference was observed between internal jugular and subclavian (NMA: RR, 1.19 [95% CI, 0.65–2.19]). There was no inconsistency for either outcome, indicating that NMA comparisons seem to be in agreement with calculated indirect estimates by pairwise analysis (**Fig. 5**; **Supplement-Table 9**, Supplemental Digital Content 2, http://links.lww.com/CCM/C172; and **Supplement-Figs. 15** and **16**, Supplemental Digital Content 2, http://links.lww.com/CCM/C172).

Secondary Outcomes

Three studies (21, 53, 56) reported noninfectious complications; in one (21), pneumothorax was more frequent in subclavian (14/981) compared with internal jugular (4/984), in the second (53), pneumothorax events between subclavian (1/192) and internal jugular (1/230) were similar, and in the third (56), four events (4/144) in subclavian were observed. Only one study (21) used ultrasound guidance for CVC insertion, mainly for internal jugular.

Two studies (21, 56) reported thrombotic complications per site (Supplement-Table 2, Supplemental Digital Content 3, http://links.lww.com/CCM/C173).Quantitative synthesis was possible solely for comparison of thrombotic risk between femoral and subclavian. The risk was higher for femoral considering CVC-related thrombosis (RR, 4.58 [95% CI, 1.02–20.52]; I^2 = 76) and major CVC-related thrombosis (RR, 3.57 [95% CI, 1.38–9.22]; I^2 = 0%; **Supplement-Fig. 17**, Supplemental Digital Content 2, http://links.lww.com/CCM/C172).

DISCUSSION

According to our findings, in the ICU setting, when CRBSI risk is considered, subclavian is no longer the incontestable site of choice in ICU patients; internal jugular can be, also, chosen initially. Subclavian retains its first-choice rank when colonization risk is regarded and not otherwise contraindicated. Excess CRBSI risk of femoral remains arguable.

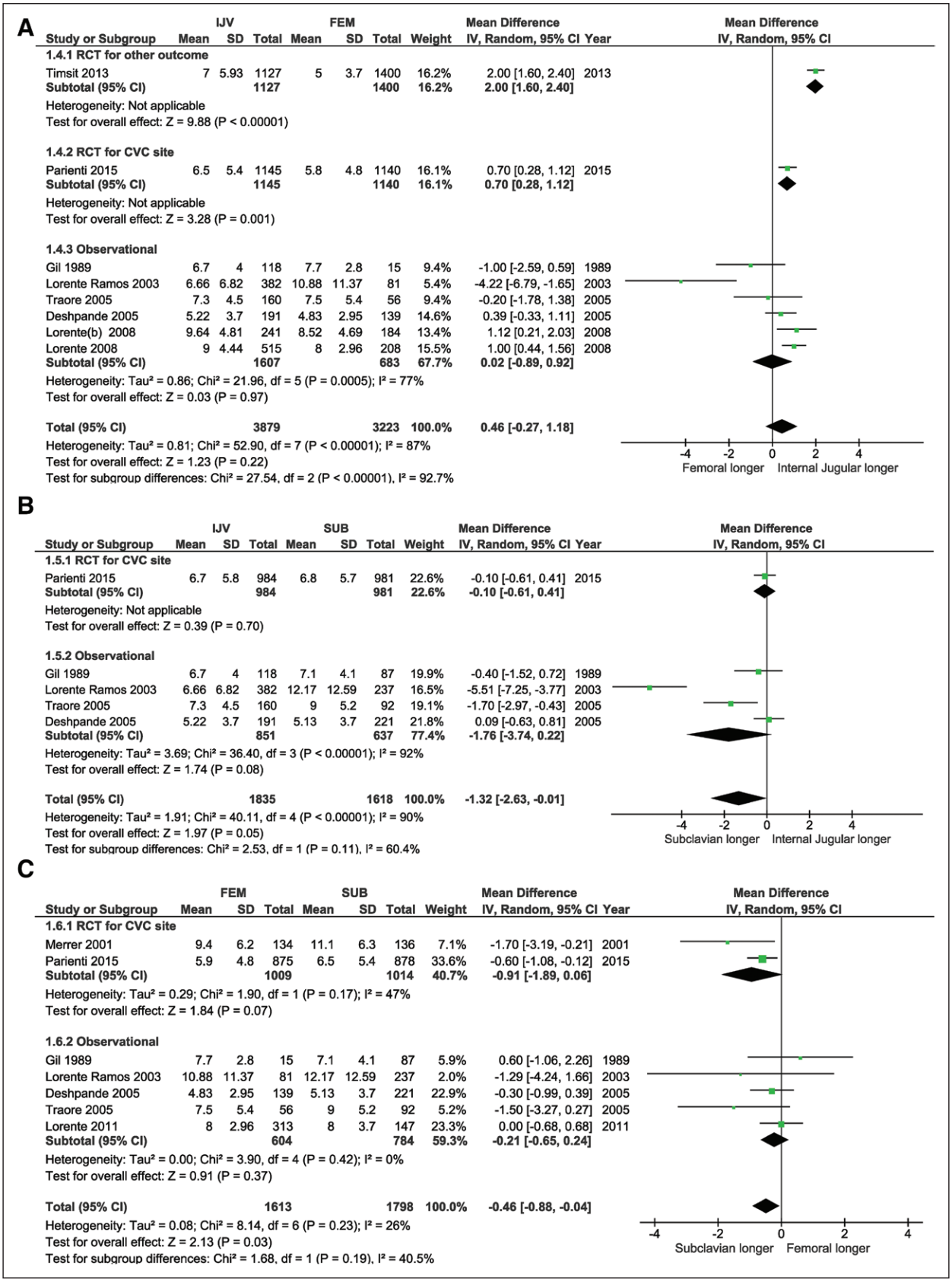

Figure 4. Comparison of central venous catheter indwelling time between internal jugular and femoral (**A**), internal jugular and subclavian (**B**), and femoral and subclavian insertion site (**C**). *Vertical lines* indicate no difference between the two intervention groups. Pooled mean difference was calculated from random-effects models with Der Simonian and Laird method.

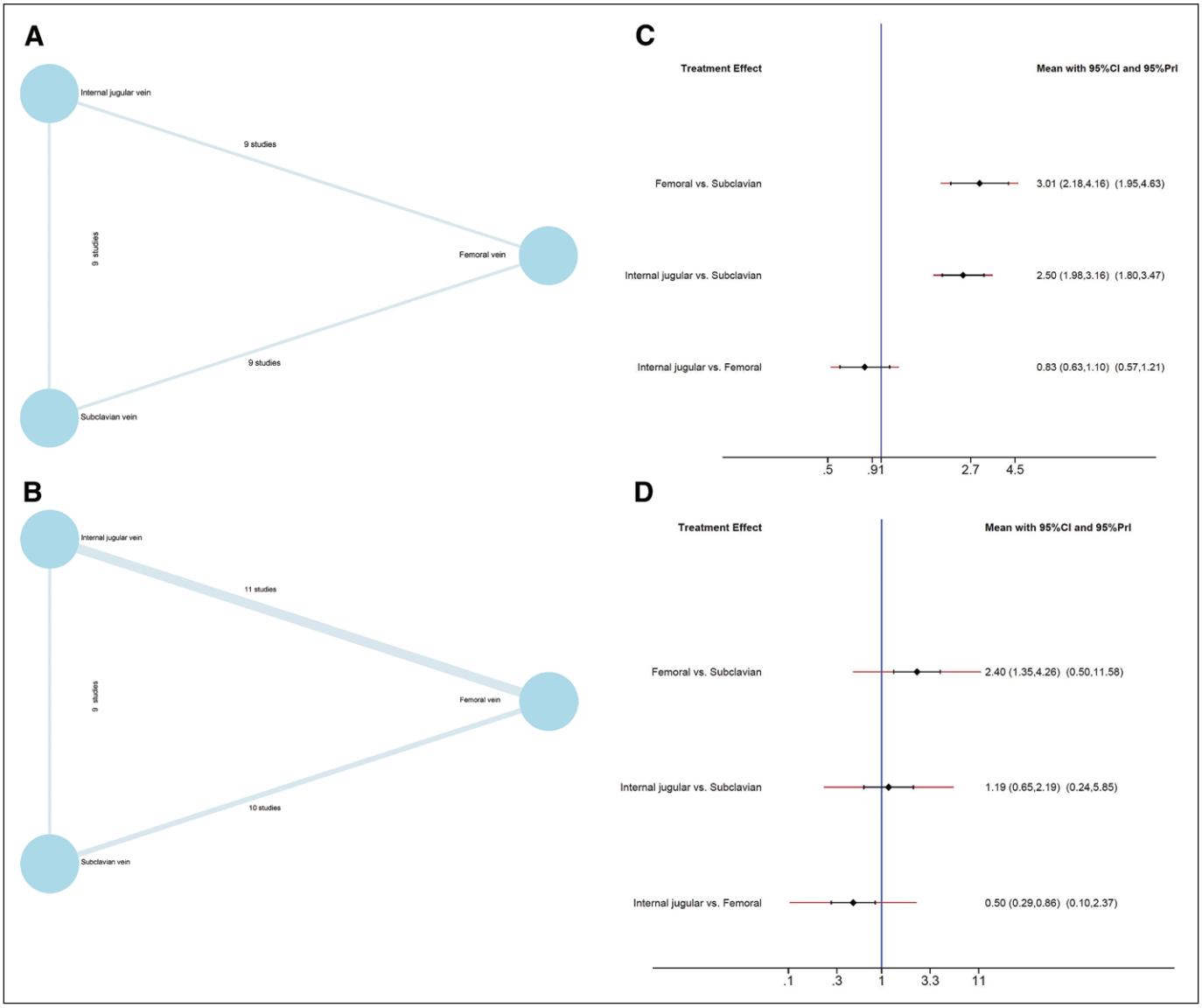

Figure 5. Network estimates (network meta-analysis [NMA]): from the trial by Parienti et al (21), only central venous catheters (CVCs) inserted in the insertion sites assigned in three-choice randomization scheme (subclavian, internal jugular, and femoral) were analyzed in the NMA. **A**, NMA plot of the three insertion sites for CVC colonization. **B**, Network plot of the three insertion sites for catheter-related bloodstream infections (CRBSIs). The width of the lines is proportional to the number of trials comparing each pair of insertion sites and the size of each node is proportional to the number of participants. **C**, Network estimates of summary risk ratios for CVC colonization. **D**, Network estimates of summary risk ratios for CRBSI. The *black solid lines* represent the CIs for summary risk ratios for each comparison and the *red lines* the respective predictive intervals (PIs). The *blue line* is the line of no effect (risk ratio = 1).

The present meta-analysis differs from the two former ones (17, 18). It is the first that included the largest RCT for sites, compared separately each site with the remaining ones, assessed the quality of evidence, and analyzed CRBSI and colonization as distinct outcomes. Contrary to the findings of Parienti et al (17), our findings support subclavian, as the preferred site, only for colonization and not for CRBSI risk reasons. Contrary to the study by Marik et al (18), we found that femoral has higher CRBSI risk than subclavian and, in agreement to their results, higher CRBSI risk than internal jugular, which merits further evaluation. In contrast to the present meta-analysis, in the study by Parienti et al (17), CRBSI and colonization risk data were not separately analyzed; one of the 10 included studies was a crossover trial, and two studies included catheters inserted in wards or emergency departments, whereas internal jugular was not compared with femoral. In addition, statistical significance was guided by one, observational, single-center study that did not control for baseline characteristics (51). In the study by Marik et al (18), five of 10 studies analyzed CVCs inserted in wards, as well as in the ICU, and one included catheters for renal replacement therapy; furthermore, subclavian was not compared with internal jugular. Compared with the study by Timsit et al (19), we observed different CRBSIs, yet, comparable colonization risk for internal jugular and femoral. Our results for CRBSI and colonization risk agree with the recent RCT for sites by Parienti et al (21) with differences, only in internal jugular-femoral comparisons.

Full barrier precautions and protocols for CVC insertion and maintenance were reported in almost all studies, highlighting their wide application. Two studies (49, 57) used exclusively chlorhexidine solutions for skin antisepsis, two used chlorhexidine-impregnated sponges (19, 54), and one (19) evaluated chlorhexidine-dressings' effect on femoral and internal jugular CRIs, which did not permit quantitative analysis. The relevance between the site and chlorhexidine dressings for CRI prevention remains controversial (61). None of the studies evaluated chlorhexidine bathing. Five studies used impregnated catheters as comparators; none of them evaluated CRBSI or colonization in patients with exclusive use of these catheters; instead, relative CRBSI risk was comparable when studies with these catheters in more than 40% of their populations were analyzed separately. Probably, antimicrobial catheters reduce CRBSI and colonization risk in the ICU (62); however, our study was not designed to evaluate CRI risk differences between sites, when only antimicrobial catheters were used. Even in the latest RCT for sites, no antimicrobial catheters or chlorexidine dressings were used, whereas chlorexidine for skin antisepsis and ultrasound guidance were applied only for a proportion of patients (21). This observation signifies that newer preventive policies have not yet gained general acceptance in the ICU, which merits further evaluation.

Mechanical complications were rarely reported in included studies. Ultrasound-guided CVC insertion can probably reduce mechanical complications, mainly for internal jugular and secondarily for subclavian (63). Nevertheless, this approach has not shown any positive effect on CRBSI prevention (64).

The present study has several limitations. First, we included crude incidence numbers of outcome measures because only three studies reported adjusted hazard ratios; nonetheless, even with adjusted outcome measures, residual confounding may still exist. Second, the included studies did not provide data on site skin colonization, dressing disruptions, and—with one exception (19)—on gender, possible confounding variables (65). We could not estimate the influence of duration of CVC catheterization on CRBSI and colonization risk, as this could be achieved only by individual patient data meta-analysis. Third, because the majority of included studies were observational, the risk of overrated pooled estimates exists, as nonsignificant outcomes from observational studies are more expected to be published than from RCTs (66). Nevertheless, in a recent meta-analysis, significant effect estimate differences between RCTs and observational studies were not demonstrated, suggesting that other than study design issues should be evaluated whenever discrepancies between RCTs and observational studies are speculated (66, 67). Fourth, the NMA of randomized and observational studies permitted the evaluation of a large sample size, at the cost, however, of a possibly enhanced risk of bias because of low-quality nonrandomized assignments (68). Consequently, our NMA results, though valid, should not be used for the elaboration of definitive conclusions.

CONCLUSIONS

The present meta-analysis for short-term, nontunneled CVCs in the ICU suggests that subclavian, as well as, internal jugular could be chosen initially when CRBSI risk is considered. Subclavian could be proposed as the most appropriate site, whenever colonization risk is assumed and not otherwise contraindicated. Conclusions were derived from a large data sample including trials with considerable heterogeneity of CRBSI risk comparisons, small number of RCTs for site, limited sample size of observational studies to detect rare events as CRBSIs, and low GRADE quality of evidence for all comparisons. A RCT for femoral compared with the other two sites, incorporating other than site selection preventive measures, like ultrasound guidance for CVC insertion, timely discontinuation of catheterization, antimicrobial catheters, could help elucidate the veritable place of femoral in a site selection procedure.

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Definitions: USA and French definitions were applied for primary outcomes (29,30). Colonisation was defined as positive semi-quantitative tip culture [≤15 cfu/mL, roll plate (31)] or positive quantitative culture [$\leq 10^3$ cfu/mL vortex (32)], without evidence of clinical sepsis; CRBSI as colonisation plus one positive blood culture from peripheral puncture growing the same microorganism as the catheter tip. CVC-related thrombosis was considered when a partial thrombus was found or when symptomatic site-related deep vein thrombosis was observed. Major CVC-related thrombosis was defined as complete site-related thrombosis of at least one vessel.