# Procalcitonin for predicting catheter-associated bloodstream infection
## A meta-analysis

Chun Mei Jia, MD, Shun Yi Feng, MD, Yong Li, MD, Zong Xun Cao, MBBS, Cheng Pu Wu, MBBS, Yan Zhao Zhai, MBBS, Jie Cui, MBBS, Meng Zhang, MD, Jie Gao, MBBS[*]

## Abstract

**Objective:** The predictive accuracies of procalcitonin (PCT) in the diagnosis of catheter-associated bloodstream infection (CABSI) vary widely. This meta-analysis aimed to explore the predictive value of PCT for CABSI.

**Methods:** We searched PubMed, EMBase, Web of Science, ScienceDirect, Cochrane Library, and studies published up to 10 March 2019. Odds ratios (ORs) with 95% confidence intervals (95%CIs) were calculated to evaluate PCT predictive value using Stata 14.0 software.

**Results:** The meta-analysis was composed of 7 studies, consisting of 347 subjects. Pooled analysis demonstrated that a high PCT was significantly correlated with CABSI (pooled OR = 23.36, 95%CI 12.43–43.91, $P < .001$) and medium heterogeneity ($I^2 = 36.9\%$, $P = .147$). The pooled sensitivity and specificity were 85% (95%CI 0.76–0.91) and 89% (95%CI 0.68–0.97), respectively. Although Begg funnel plot ($P = .007$) indicated the presence of publication bias among the included studies, the stability of the pooled outcomes was verified by the trim-and-fill method. Furthermore, sensitivity analyses did not show important differences in effect estimation.

**Conclusion:** PCT is an effective predictor of CABSI. However, high-quality randomized controlled trials are needed to determine whether PCT could predict CABSI.

**Abbreviations:** AUC = area under the curve, CABSI = catheter-associated bloodstream infection, CI = confidence interval, CVCs = Central venous Catheters, OR = odds ratio, PCT = procalcitonin, PQ = paraquat, QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2 tool.

**Keywords:** catheter-associated bloodstream infection, prediction, procalcitonin

## 1. Introduction

Central venous Catheters (CVCs) play an important role in facilitating infusion, drug administration, blood sampling, and close monitoring in seriously ill patients. The reported prevalence of CVC utilization in intensive care patients is 48%.[1] CVC use has been associated with many complications.[2–4] Catheter-associated bloodstream infection (CABSI) is one of the most common intractable healthcare-associated infections because catheters can be easily contaminated by bacteria and are associated with high mortality.[3,5–7] An estimated 250,000 cases of CABSI occur in the United States annually, with 10% mortality rate.[8,9] The alarmingly high rates of CABSI have forced changes in clinical practices, including increased adoption of catheter lock solutions and improved anti-infective and anti-microbial surveillance protocols to reduce catheter-related infection rates.[10,11] Controlling and managing these infections have imposed a heavy financial burden on the government.

Procalcitonin, a 116-amino-acid peptide, which undergoes posttranslational proteolysis into calcitonin, is synthesized in C cells of the thyroid gland and secreted from leukocytes of the peripheral blood. The rise of PCT in bacterial infection is remarkable, but its incidence in viral infections only showed a negligible increment.[12,13] Increased PCT level is considered a key laboratory indication of acute infection, and PCT is confirmed as a marker of CABSI among patients with CVCs.[14–20] Although PCT is implied to have superb specificity and sensitivity for CABSI, controversies remain due to inconsistent opinions. Therefore, we performed a meta-analysis from clinical trials to investigate the predictive value of PCT for CABSI.

## 2. Materials and methods

The manuscript has been prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses

guidelines for protocols.[21] Ethical approval was unnecessary in this study, because it was a meta-analysis of existing articles, and no individual patient data were handled. This protocol has been registered in the PROSPERO network (registration number: CRD42019129219).

### 2.1. Search strategy

We searched PubMed, EMBase, Web of Science, ScienceDirect, Cochrane Library, and studies published up to March 20, 2019. The search terms were as follows: "catheter associated bloodstream infection" AND "procalcitonin." The reference lists of relevant literature were manually searched for additional eligible articles. Searching language was restricted to English and Chinese.

### 2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: all the subjects included in the study were given definitive diagnoses of CABSI; all prospective and retrospective full-text studies detecting the predictive value of PCT for CABSI; sufficient survival data were provided for the odds ratios (ORs) with 95% confidence intervals (CIs); The exclusion criteria were as follows: duplicated studies, letters, case report abstracts, comments, reviews, and conference papers. Only the study with the largest number of subjects was included, when multiple studies were based on the same case series.

### 2.3. Data extraction

Data were extracted independently by two reviewers from the included studies. When conflicts or different opinions arise during data extraction, a resolution was achieved by consensus with a third reviewer. Data were abstracted from included studies, including first author, year of publication, study design, country of origin, gender, sample size, cutoff values, PCT level, and study period.

### 2.4. Risk of bias

Risk of bias assessment of the included studies was independently fulfilled by 2 reviewers using the Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2),[22–24] which consisted of four domains, as follows: patient selection, index test, reference standard, and flow and timing. Discrepancies were resolved by discussion.

### 2.5. Statistical analysis

Data analysis for this meta-analysis was performed using STATA version 14. Statistical heterogeneity was assessed through the Chi-square test and $I$-square test, which were checked through the Q test, and a $P > 0.10$ indicated a lack of heterogeneity. The percentages of $I^2$ of approximately 25%, 50%, and 75% indicate low, medium, and high heterogeneity, respectively.[25] Without statistical heterogeneity ($I^2 < 50\%$, $P > .1$), a fixed-effects model was employed to calculate the pooled HRs with 95% CIs. Otherwise, a random-effects model was used. Publication bias was estimated using Begg test and a funnel plot with the trim-and-fill method to adjust for publication bias from potential unpublished studies. Sensitivity analysis was used to evaluate the robustness of the pooled

results. Sensitivity analysis was performed by removing individual study at each turn to investigate the influence of any single study on the pooling summary. Fagan plot analysis was also performed to assess the relationship among an estimated pretest probability of the disease, the likelihood ratio of the diagnostic test, and the post-test probability of the disease. A pre-test probability was calculated depending on the included studies, and the corresponding positive and negative post-test probabilities were calculated. $P < 0.05$ was considered statistically significant.

## 3. Result

### 3.1. Search strategy

The detailed selection procedure is listed in Figure 1 According to the search strategy, a total of 133 potentially eligible studies were identified. After excluding duplication and reading the texts for further examination, a total of seven studies[14–20] were included for analysis.

### 3.2. Study characteristics

Table 1 revealed the main characteristics of the included studies. All 7 prospective studies consisting of 347 subjects were published between 2011 and 2018. Among the included studies, three studies[14,18,20] were from China. Turkey,[17] Egypt,[15] USA,[16] and Greece[19] had 1 study each. Six studies[14–17,19,20] were published in English, and 1 study[18] was published in Chinese.

### 3.3. Assessment of risk of bias for included studies

QUADAS-2 assessment is summarized in Figure 2. The patient selection risk of bias domain in 6 studies[14,16–20] was labeled as unknown, because the authors did not report whether the subjects were consecutively enrolled. One study[15] was labeled as high risk, because the authors did not report whether the subjects were consecutively enrolled in the study period. The index test domain of all studies[14–20] was labeled as high risk, because a pre-specified threshold was not used.

### 3.4. Association of PCT and CABSI

Pooled analysis showed that a high PCT was significantly correlated with CABSI (pooled OR = 23.36, 95%CI 12.43–43.91, $P < .001$; Fig. 3) and with medium heterogenicity ($I^2 = 36.9\%$, $P = .147$). The pooled sensitivity and specificity were 85% (95%CI 0.76–0.91) and 89% (95%CI 0.68–0.97), respectively. The positive likelihood ratio was 7.4 (95%CI 2.3–23.6), the negative likelihood ratio was 0.17 (95%CI 0.10–0.29), and diagnostic OR was 43 (95%CI 9–189). AUC of PCT for CABSI was 0.90 (95%CI 0.87–0.93; Fig. 4)

### 3.5. Meta-regression analysis for heterogeneity

The following specific variables were separately evaluated for their effects on heterogeneity: sample size (≥50 or <50), publication year (before 2016 or after 2016), prevalence (43%), and cutoff (≥3.96 or <3.96). Meta-regression showed that these variables did not explain heterogeneity observed for specificity (Table 2).
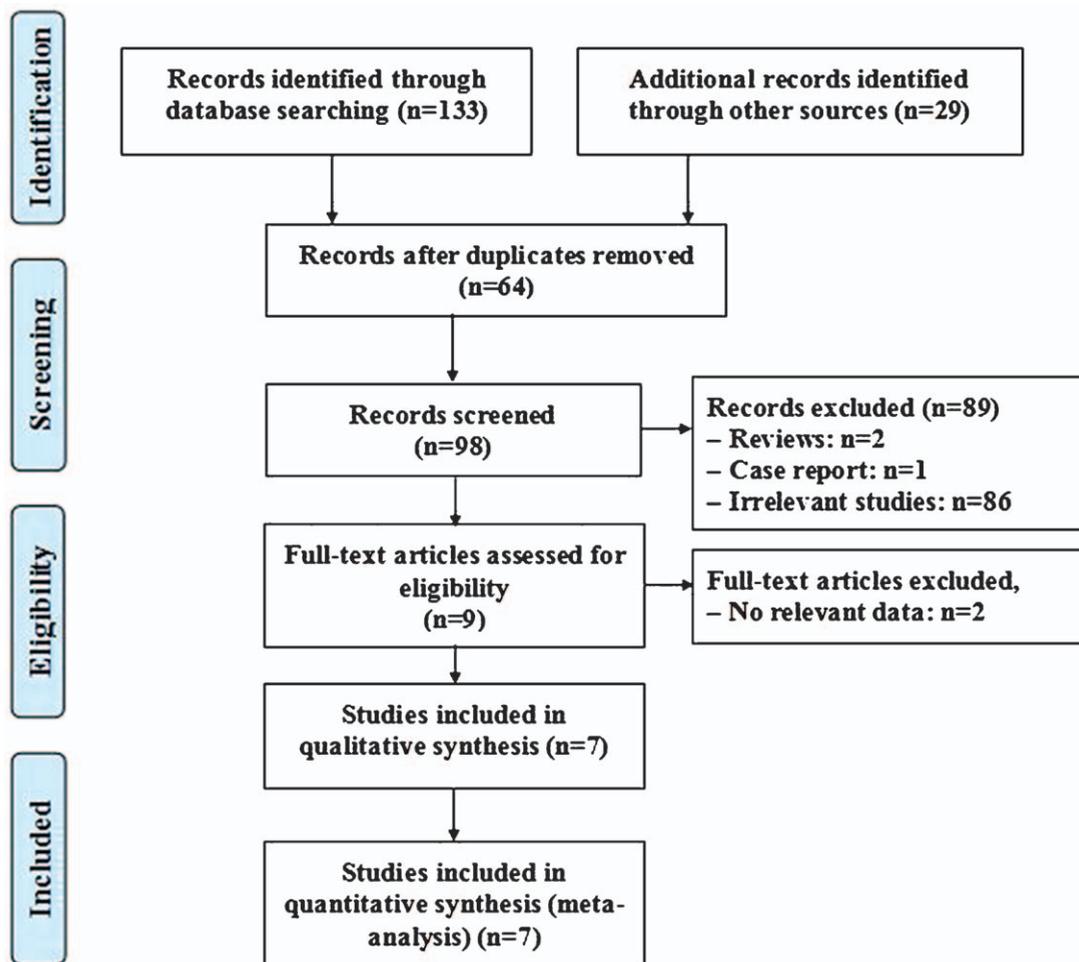
**Figure 1.** Flowchart of study selection.

### 3.6. Sensitivity analysis and publication bias

Sensitivity analysis was performed by removing all included studies sequentially to detect the influence of each study on the pooled OR. The corresponding pooled ORs were not significantly changed after excluding the studies one by one, thereby suggesting the significant stability of our results (Fig. 5). Although Begg funnel plot ($P = .007$; Fig. 6A) indicated the presence of publication bias among the included studies, the adjusted fixed-effects pooled OR of 20.59 (95%CI 10.58–40.08, $P < .001$)

calculated using trim-and-fill method was consistent with the original analysis (OR = 15.64, 95%CI 8.26–29.61, $P < .001$) (Fig. 6B).

### 3.7. Fagan plot analysis

When a pre-test probability of 43% (149/347) was calculated depending on these included studies, the probability of a correct diagnosis following a positive measurement of PCT was 85% for

---

| Table 1 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|

**Characteristics of included studies.**

| Author (Year) | Region | Design | No. of patients | GNB/GPB/fungemia | Cutoff value (ng/mL) | Procalcitonin (ng/mL) | | Study period |
|---|---|---|---|---|---|---|---|---|
| | | | | | | CABSI | Non-CABSI | |
| Chen et al 2011[14] | China | Prospective | 55 | 13/11/1 | 3.1 | 5.48 ± 4.50 | 1.32 ± 1.19 | 2008–2009 |
| Hamada Imam et al 2017[15] | Egypt | Prospective | 31 | NA | 15.5 | 40.0 ± 21.9 | 1.1 ± 1.0 | NA |
| Kasem et al 2012[16] | USA | Prospective | 62 | 10/3/0 | 0.3 | 19.16 | 0.65 | 2010 |
| Ozsurekci et al 2016[17] | Turkey | Prospective | 49 | 10/12/2 | 0.86 | 1.76 | 0.57 | 2013–2014 |
| Sui et al 2013[18] | China | Prospective | 36 | 8/8/1 | 4.30 | 0.19 | 0.11 | 2012–2013 |
| Theodorou et al 2012[19] | Greece | Prospective | 46 | 22/6/0 | 0.70 | 7.70 | 0.10 | 2012–2011 |
| Zhou et al 2018[20] | China | Prospective | 68 | NA | 2.98 | NA | NA | 2014 |

CABSI = catheter-associated bloodstream infection, GNB = gram-negative bacteremia, GPB = gram-positive bacteremia, NA = not available.
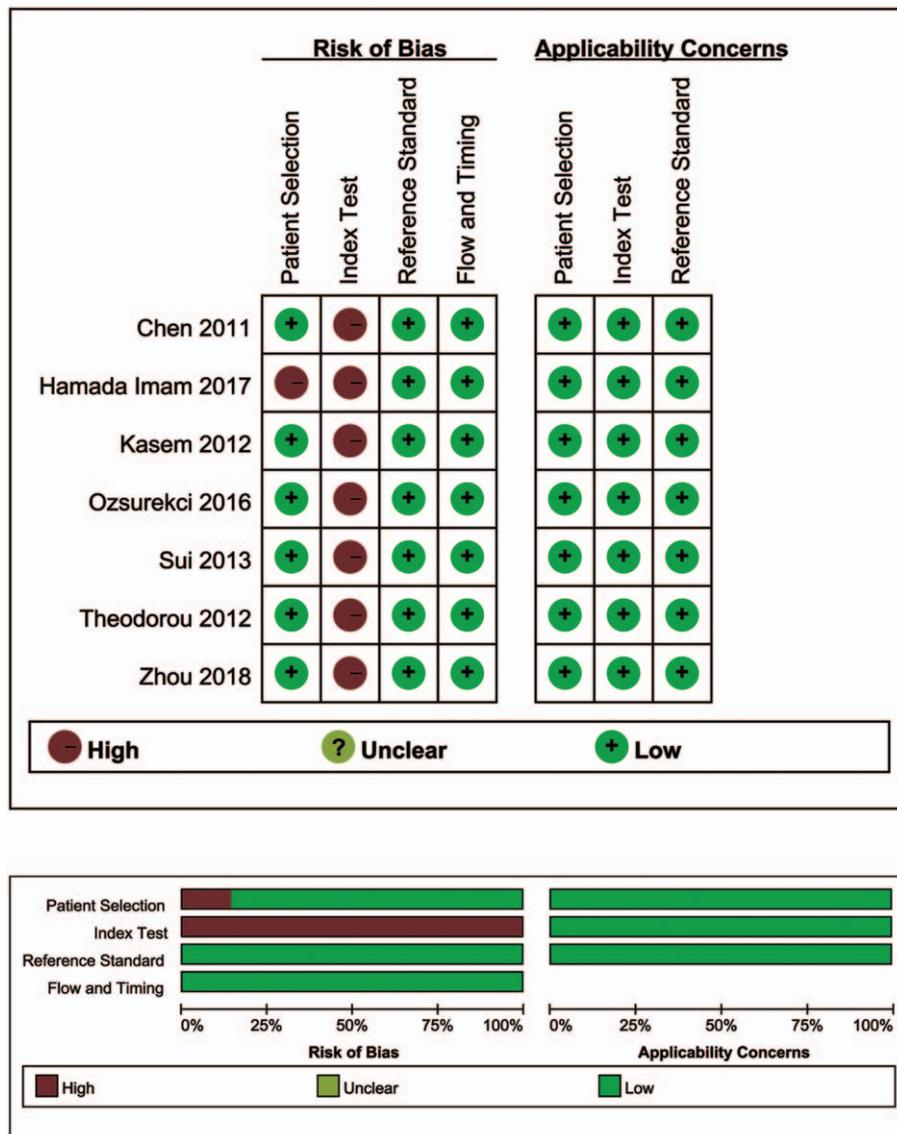
**Figure 2.** Quality assessment of the included studies by using QUADAS-2 graph.

CABSI. The misdiagnosis rate was 11% for patients under a negative measurement (Fig. 7).[26]

## 4. Discussion

To the best of our knowledge, the present study is the first meta-analysis to investigate the predictive value of PCT for CABSI, which might provide useful information for clinicians. The results from the combined data of 7 studies should that a 22-fold risk increase of CABSI is present among clinically suspected CABSI with high PCT level, with a diagnostic sensitivity of 85%, a specificity of 89%, and 0.90 AUC.

Early diagnosis of CABSI is of primary importance, because when an appropriate antimicrobial regimen is administered after accurate diagnosis in infected patients, a better outcome is expected.[27] Clinical findings are unreliable for establishing the diagnosis of CABSI because of their poor sensitivity and specificity. Establishing a true "gold standard" for the diagnosis of CABSI is a challenge. The practical use of blood cultures has a significant limitation due to the delay in reporting of culture results, the issues with colonization and contamination, and the inability to grow atypical pathogens in standard cultures.

Colonization of the lumen of an intravascular catheter precedes infection in many cases. Schuetz et al[28] showed the increased values of PCT 1 day prior to clinical manifestation of BSI and collection of blood cultures. The early increase of PCT might reflect the colonization of the catheter with subclinical infection ultimately leading to bloodstream infection.[29] Notably, nonspecific increases in the absence of bacterial infection can be observed in stress conditions, such as severe trauma and surgery. Under these conditions, the increases are moderate and a rapid decrease might ensue.[30] Thus, dynamic observation on change of PCT is objective and stable.
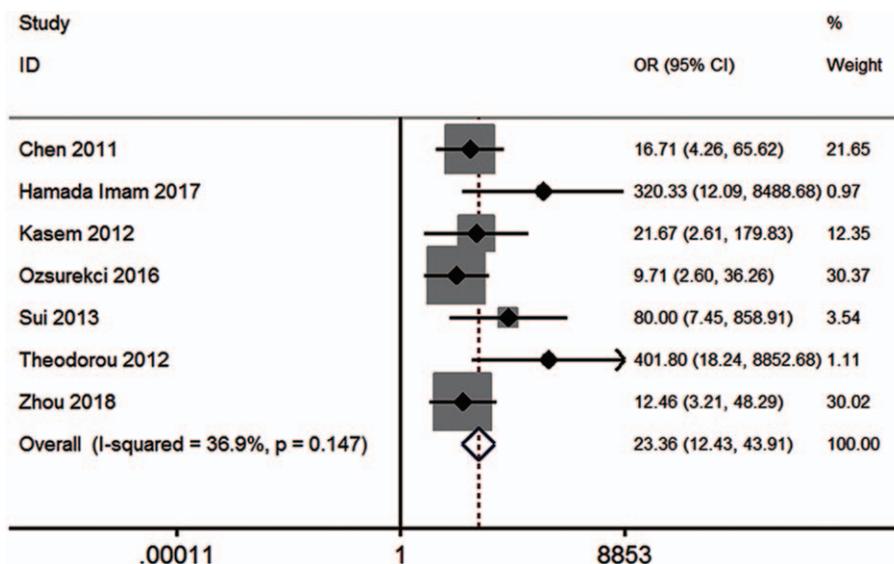
**Figure 3.** Forest plot of the association between procalcitonin and catheter-associated bloodstream infection.
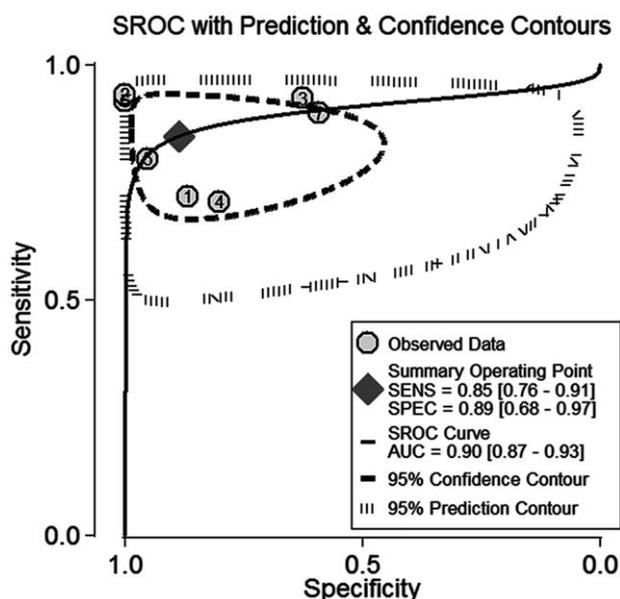


**Figure 4.** SROC of procalcitonin for the prediction of catheter-associated bloodstream infection. The area under the SROC curve (dashed line) is 0.90, the pooled sensitivity is 85%, and the specificity is 89%. The 95% confidence region displays the 95% confidence interval of the pooled sensitivity and specificity. SROC = summary receiver operating characteristic curve.

PCT's role as a biomarker for bacterial infection in adults is well documented, but its role in infections affecting neonatal children remains controversial.[31,32] The number of studies interpreting the worth of PCT as a diagnostic and screening test in pediatric infections is insufficient. The pooled OR with 95% CI was OR = 13.17 (95% CI 4.33–40.08, $P < .001$) on the basis of 2 studies in children[16,17] and OR = 30.97 (95% CI 14.19–67.59, $P < .001$) on the basis of 5 studies in adults. Our results demonstrated that a high PCT is significantly correlated with CABSI in children and adults.[14,15,18–20] However, further research is needed due to the insufficient number of studies, especially in children.

A comprehensive evaluation of every patient with a bloodstream infection includes an attempt to identify the infectious source. Pathogens can originate from various sites, including the lung, biliary tract, urinary tract, surgical site, skin, or catheter. Biomarkers are used for identifying the presence of infection, but not the specific sites.

Missing comorbidity data result in uncertainties; under-/overestimation of PCT level; or failure to address confounding factors such as burn injury, trauma, and chronic heart failure. Notably, all seven studies included in our meta-analysis did not adjust for comorbidity. Thus, to improve research on comorbidity, studies should include information on the variety and severity of comorbidity.

**Table 2**

**Meta-regression analysis of potential sources of heterogeneity.**

| Heterogeneity factors | Coefficient | SE | Z | P value | 95% CI (lower limit, upper limit) |
|---|---|---|---|---|---|
| Sample size | −0.008 | 0.079 | −0.10 | .929 | −0.351, 0.062 |
| Publication year | −0.714 | 1.803 | −0.40 | .730 | −0.872, 7.044 |
| Prevalence | −0.661 | 1.580 | −10.42 | .717 | −7.460, 6.139 |
| Cutoff value | 2.157 | 2.111 | 1.02 | .414 | −6.927, 11.241 |

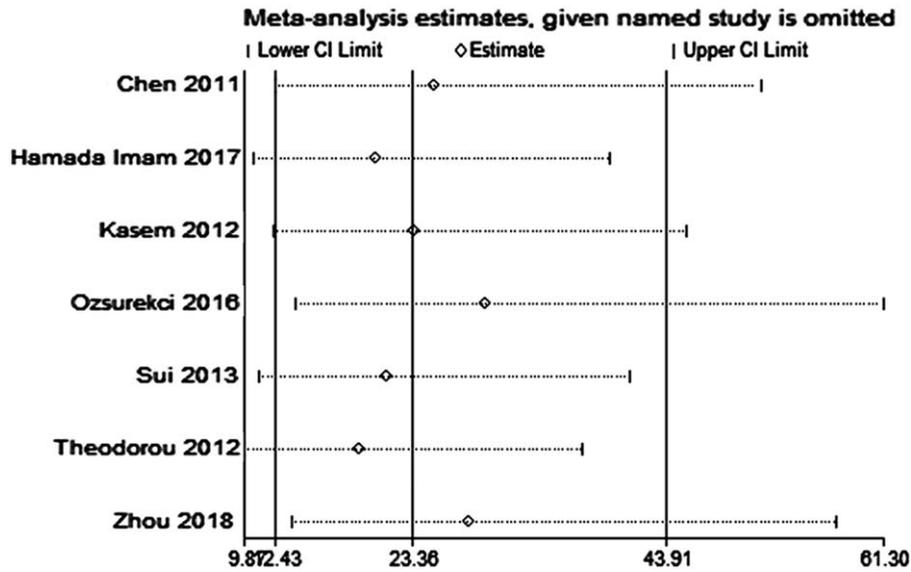CI = confidence interval, OR = odds ratio.

**Figure 5.** Sensitivity analysis of procalcitonin for catheter-associated bloodstream infection prediction. Leave-one-out method was used to confirm the stability of the results. No single study was detected to incur undue weight in the analysis.

The strength of our study is the use of Fagan plot analysis to explore the clinical utility of PCT. At 43% pre-test probability, the probability of a correct diagnosis following a positive measurement of PCT was 85% for CABSI. The misdiagnosis rate of patients under negative measurement was 11%. Fagan plot analysis further supports the importance of PCT for diagnosing CABSI.

The cutoff value of PCT level varied across different studies, and a consensus value was difficult to reach. The range of cutoff value among the seven included studies was from 0.3 ng/mL to 15.5 ng/mL. The discrepancy could be attributed to differences in the proportions of bacterial species. Infection by different pathogens can induce different levels of PCT production.[33] GNB can produce endotoxins that can be released upon cell death, resulting in persistently high levels of PCT.[34,35]

Nonetheless, several limitations should be considered when interpreting our results. First, our meta-analysis included a total of published studies with 347 subjects, which might decrease statistical power. Second, some potent reports in other languages might have been missed due to language limitation in search strategy. Thus, Begg funnel plot might have not detected possible publication bias. Third, medium heterogeneity was found in this meta-analysis.

In conclusion, the interesting but preliminary data of this meta-analysis demonstrate that PCT is an effective diagnostic method for detecting CABSI in patients. Our study has several limitations and further investigation is needed; however, these findings might help clinicians identify CABSI early and formulate treatment strategies.
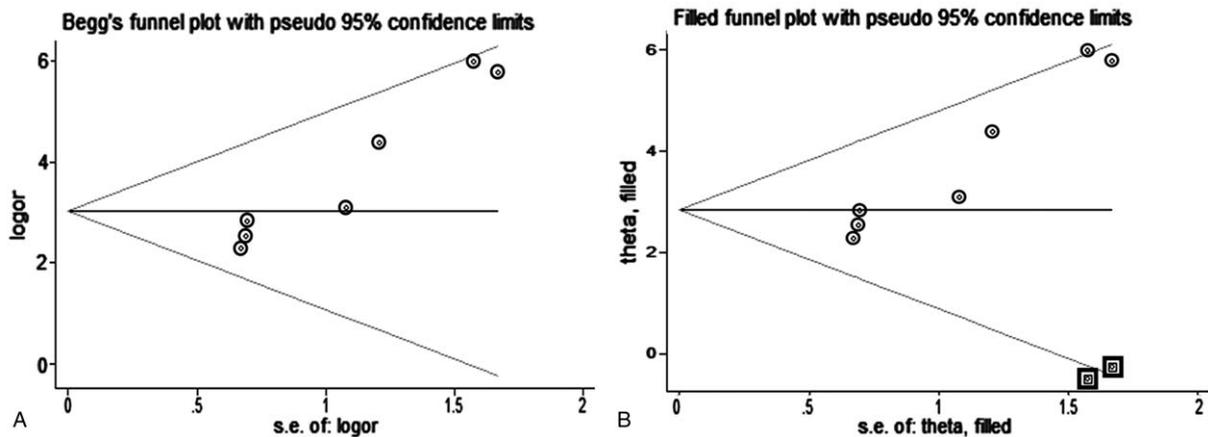


**Figure 6.** Funnel plot of publication bias. (A) Begg test; (B) Trim-and-fill method.
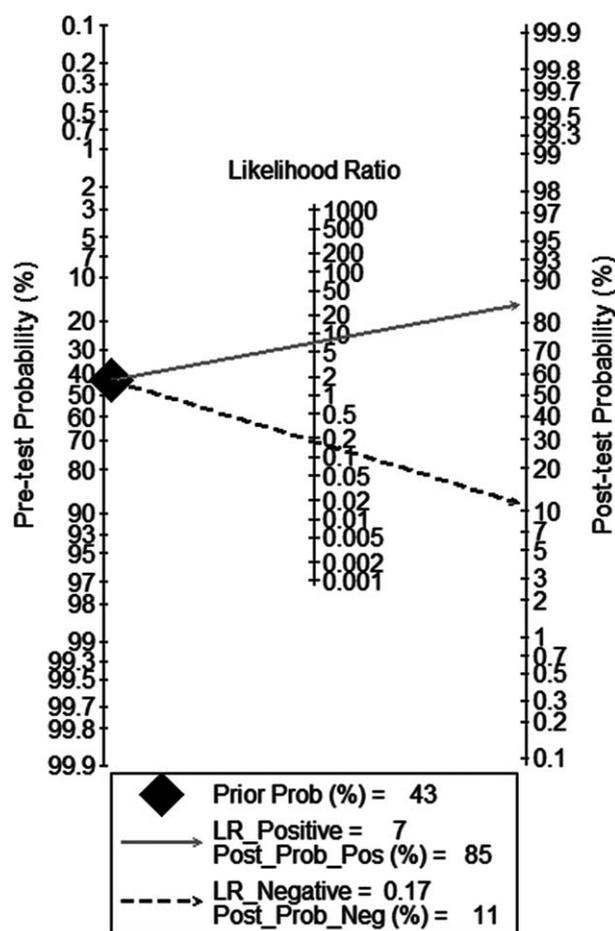
**Figure 7.** Fagan plot analysis of procalcitonin for the prediction of catheter-associated bloodstream infection.

## Author contributions

**Conceptualization:** Chun Mei Jia.
**Data curation:** Chun Mei Jia, Shun Yi Feng, Zong Xun Cao, Cheng Pu Wu, Yan Zhao Zhai, Meng Zhang.
**Methodology:** Yong Li.
**Project administration:** Yong Li.
**Software:** Shun Yi Feng.
**Writing – original draft:** Chun Mei Jia, Shun Yi Feng.
**Writing – review & editing:** Jie Cui, Jie Gao.

## References

[1] Salama MF, Jamal W, Al Mousa H, et al. Implementation of central venous catheter bundle in an intensive care unit in Kuwait: Effect on central line-associated bloodstream infections. J Infect Public Health 2016;9:34–41.
[2] Chen IC, Yang SC, Liu KT, et al. Delayed malposition of a double-lumen hemodialysis catheter that caused hemorrhage and hypovolemic shock: A case report. Medicine (Baltimore) 2019;98:e14192.
[3] Glied S, Cohen B, Liu J, et al. Trends in mortality, length of stay, and hospital charges associated with health care-associated infections, 2006-2012. Am J Infect Control 2016;44:983–9.
[4] Al-Asadi O, Almusarhed M, Eldeeb H. Predictive risk factors of venous thromboembolism (VTE) associated with peripherally inserted central catheters (PICC) in ambulant solid cancer patients: retrospective single centre cohort study. Thromb J 2019;17:2.
[5] Siempos II, Kopterides P, Tsangaris I, et al. Impact of catheter-related bloodstream infections on the mortality of critically ill patients: a meta-analysis. Crit Care Med 2009;37:2283–9.
[6] Ye H, Zeng J, Qin W, et al. A totally implantable venous access port associated with bloodstream infection caused by Mycobacterium fortuitum: A case report. Medicine (Baltimore) 2018;97:e11493.
[7] Prowle JR, Echeverri JE, Ligabo EV, et al. Acquired bloodstream infection in the intensive care unit: incidence and attributable mortality. Crit Care 2011;15:R100.
[8] Fisher BT, Vendetti N, Bryan M, et al. Central venous catheter retention and mortality in children with candidemia: A retrospective cohort analysis. J Pediatric Infect Dis Soc 2016;5:403–8.
[9] Brunelli SM, Turenne W, Sibbel S, et al. Clinical and economic burden of bloodstream infections in critical care patients with central venous catheters. J Crit Care 2016;35:69–74.
[10] Wang K, Wang P, Liang X, et al. Epidemiology of haemodialysis catheter complications: a survey of 865 dialysis patients from 14 haemodialysis centres in Henan province in China. BMJ Open 2015;5:e007136.
[11] Murea M, James KM, Russell GB, et al. Risk of catheter-related bloodstream infection in elderly patients on hemodialysis. Clin J Am Soc Nephrol 2014;9:764–70.
[12] Ibrahim KA, Abdel-Wahab AA, Ibrahim AS. Diagnostic value of serum procalcitonin levels in children with meningitis: a comparison with blood leukocyte count and C-reactive protein. J Pak Med Assoc 2011;61: 346–51.
[13] Gendrel D, Raymond J, Assicot M, et al. Measurement of procalcitonin levels in children with bacterial or viral meningitis. Clin Infect Dis 1997;24:1240–2.
[14] Chen J, Wang Y, Shen Z, et al. Early diagnostic value of plasma PCT and BG assay for CRBSI after OLT. Transplant Proc 2011;43:1777–9.
[15] Hamada Imam M, Gamal E. Procalcitonin level as a surrogate for catheter-related blood stream infection among hemodialysis patients. J Vasc Access 2017;18:498–502.
[16] Kasem AJ, Bulloch B, Henry M, et al. Procalcitonin as a marker of bacteremia in children with fever and a central venous catheter presenting to the emergency department. Pediatr Emerg Care 2012;28:1017–21.
[17] Ozsurekci Y, Oktay Arikan K, Bayhan C, et al. Can procalcitonin be a diagnostic marker for catheter-related blood stream infection in children? J Pediatr (Rio J) 2016;92:414–20.
[18] Sui ML, Wu CJ, Huang CF, Zhu TJ. Early diagnostic and prognostic value of procalcitonin and interleukin 6 for catheter-related bloodstream infections in critically ill patients. Journal of Shanghai Jiaotong University 2013;33:1491–5.
[19] Theodorou VP, Papaioannou VE, Tripsianis GA, et al. Procalcitonin and procalcitonin kinetics for diagnosis and prognosis of intravascular catheter-related bloodstream infections in selected critically ill patients: a prospective observational study. BMC Infect Dis 2012; 12:247.
[20] Zhou B, Zhu J, Mao Z, et al. Roles of procalcitonin and N-Terminal Pro-B-Type Natriuretic Peptide in predicting catheter-related bloodstream infection in severe burn injury patients. Dis Markers 2018;2018: 5607932.
[21] McInnes MDF, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: The PRISMA-DTA statement. JAMA 2018;319:388–96.
[22] Guo Y, Wang L, Hu J, et al. Diagnostic performance of choline PET/CT for the detection of bone metastasis in prostate cancer: A systematic review and meta-analysis. PLoS One 2018;13:e0203400.
[23] Shao H, Ma X, Gao Y, et al. Comparison of the diagnostic efficiency for local recurrence of rectal cancer using CT, MRI, PET and PET-CT: A systematic review protocol. Medicine (Baltimore) 2018;97:e12900.
[24] Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
[25] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[26] Pu K, Shi JH, Wang X, et al. Diagnostic accuracy of transient elastography (FibroScan) in detection of esophageal varices in patients with cirrhosis: A meta-analysis. World J Gastroenterol 2017;23: 345–56.
[27] Kollef MH, Sherman G, Ward S, et al. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462–74.

[28] Schuetz P, Mueller B, Trampuz A. Serum procalcitonin for discrimination of blood contamination from bloodstream infection due to coagulase-negative staphylococci. Infection 2007;35:352–5.

[29] Catton JA, Dobbins BM, Kite P, et al. In situ diagnosis of intravascular catheter-related bloodstream infection: a comparison of quantitative culture, differential time to positivity, and endoluminal brushing. Crit Care Med 2005;33:787–91.

[30] Schuetz P, Haubitz S, Mueller B. Do sepsis biomarkers in the emergency room allow transition from bundled sepsis care to personalized patient care? Curr Opin Crit Care 2012;18:341–9.

[31] Giulia B, Luisa A, Concetta S, et al. Procalcitonin and community-acquired pneumonia (CAP) in children. Clin Chim Acta 2015;451:215–8.

[32] van Rossum AM, Wulkan RW, Oudesluys-Murphy AM. Procalcitonin as an early marker of infection in neonates and children. Lancet Infect Dis 2004;4:620–30.

[33] Yan ST, Sun LC, Jia HB, et al. Procalcitonin levels in bloodstream infections caused by different sources and species of bacteria. Am J Emerg Med 2017;35:579–83.

[34] Castelli GP, Pognani C, Cita M, et al. Procalcitonin as a prognostic and diagnostic tool for septic complications after major trauma. Crit Care Med 2009;37:1845–9.

[35] Maruna P, Frasko R, Gürlich R. Plasma procalcitonin in patients with ileus. Relations to other inflammatory parameters. Physiol Res 2008;57:481–6.