Procalcitonin, a Biomarker for Diagnosing and Differentiating Infection among Liver Transplant Recipients: a systematic review and meta-analysis

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Research

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Abstract

Background Infection has long been the major cause for death after liver transplantation. Diagnosing this deadly disease in time can be of great help to support the patients in intensive care units. However, tests like blood culture would take too much time to generate an outcome. Procalcitonin seems to be a promising biomarker in such clinical settings these days. To evaluate its diagnostic value as a biomarker in identifying and differentiating infectious complications in liver transplant recipients.

Methods PUBMED, Scopus, Web of Science, Cochrane Library were searched for articles published from January 1990 to September 2019 without language limitation. Cohort or case-control study investigating the value of PCT in distinguishing postoperative infectious complications among liver transplant recipients were included, followed by measurement using QUADAS-2 tool to estimate the risk of bias of each study. Bivariate approach and random-effects model were performed to generate the pooled outcomes.

Results 8 studies (studying 560 liver transplant recipients) from 6 populations were reviewed and included, one of which is later excluded due to huge heterogeneity it caused. No significant threshold effect was found, suggesting that heterogeneity returned by the I 2 was not due the various cutoff values. The pooled DOR was 18.65 (95%CI 9.85-35.31) and the area under HSROC was 0.857 (θ =-0.024; β =-0.203). The positive likelihood ratio and negative likelihood ratio are 3.472 (95% 2.352-5.127) and 0.289 (95% 0.192-0.434).

Conclusion Current articles suggest a reasonable diagnostic value for the procalcitonin test in identifying infectious complications among patients undergoing liver transplantation. However, the reason why no threshold effect was found remained explored.

Background

Significant infection accounts for most of the morbidity and mortality after liver transplantation (LT)[1], risk factors of which relate to operation procedures, recipients and donors. Specifically, these include intra-operative ischemia-reperfusion damage, quality of donated organs, level and type of immunosuppression, preoperatively impaired nutritional status, as well as recipients' scores of Model for End-stage Liver Disease (MELD) or other criteria[2, 3]. Following this multi-factorial disease, lung infection, sepsis, systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction syndrome (MODS) tend to arise in clinical settings, causing an inflammatory cascade of vicious circles[4].

Early recognition of an altered inflammatory condition, timely diagnosis, and prompt treatment with antimicrobial agents in the post-transplant period are therefore for improving post-transplant outcomes. However, being not capable of individually identifying post-transplant infections, current clinical manifestations and laboratory tests like as white blood cells (WBC) or C-reactive protein (CRP) generally fail to satisfy such needs. Thus, inflammatory markers of higher sensitivity and specificity are needed to

provide prompt diagnosis and treatment. More importantly, a biomarker with ability to differentiate post-transplant complications, such as rejection and infection, could provide further guidance on regimen design and therefore improve their prognostic performance.

Serum Procalcitonin (PCT) seems to meet these requests in intensive care and emergency room settings due to its pathophysiological characteristics[5, 6]. In conditions like allergy, virus infection, local fungal infection and chronic inflammation, serum PCT concentration tends to remain steady. On the contrary, it will soon be secreted by macrophages and monocytes in different organs when subjects are under severe bacterial- or fungi-induced infection like sepsis, SIRS or MODS[7–10].Another advantage of PCT over other biomarkers such as CRP, ILs, and WBCs lies in its rapid rise following an inciting physiological insult (6-hour peak) and relatively shorter half-life (24 hours)[11, 12]. In recent literature, PCT has shown relatively good sensitivity and specificity for demonstrating infectious complications among organ transplant recipients[13–16]. Of note, early detection of infection and differentiation from non-infectious complications, such as rejection was also addressed[17–19]. However, due to substantial heterogeneity of current publications, its role among liver transplant recipients has not been well established. Therefore, this article performed a systematic review and meta-analysis on the published studies to determine the diagnostic value of PCT in post-liver-transplant infectious complications.

Methods

Guideline and Search Strategy

This meta-analysis was strictly carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[20], checklist of which is presented in Additional file 1:Table S1, S2. Studies conducted before July, 2019 were systematically searched on PubMed, Scopus, Science Citation Index Expanded from Web of Science and Cochrane Library without language limitation. Detailed search strategy, terms and queries are presented in Additional file 1: Table S3. Additional articles were identified through a manual search of the reference lists of the papers obtained.

Literature selection

Before this procedure, definitions for certain items were set to avoid unnecessary discrepancies: index test was defined as a method using PCT alone or combined with other inflammatory markers; and gold standard was referred to microbiological detection or combined with other clinical evidence. Rejection is defined by histopathology criteria for the biopsy specimen, and infection is defined by clinical symptoms with pathologic proof from culture of blood or body fluid specimens.

Articles were reviewed by two authors (WD, DYW) independently. Potentially relevant studies with cohort or case-control design were then included if comparison between index tests and gold standards were made. Ultimately, articles were excluded if data can’t be extracted to set 2 × 2 contingency table. After the selection, evidence qualities were accessed using Quality Assessment of Diagnostic Accuracy Studies

(QUADAS-2) tool[21]. Of note, every unclear item was marked as “no” and therefore, the final result presents the floor level of the study quality.

Any discrepancy between reviewers was resolved by an additional reviewer’s (ZWZ) assessing. Corresponding author would be contacted if any information was missing.

Data analysis

The following data was extracted from the primary papers: author, year of publication, patient characteristics, study design, number of subjects etc (Additional file 1: Table S4). Separate diagnostic odds ratio (DOR) of each study was then calculated to generate pooled variables with 95% confidence intervals (CI). Hierarchical summary receiver operating characteristic (HSROC) curve was generated and the area under the curve (AUC) as well as the DOR was considered as the main indicator of the diagnostic performance. P-value less than 0.05 is recognized to be of statistical significance and an AUC more than 0.8 indicates a good diagnostic accuracy. Statistical analysis was carried out using the R software/environment (version 3.4.2. R Foundation for Statistical Computing)[22]. The numerical and graphical outputs were obtained by using mada[23], and metaphor[24]R packages. For additional analysis, Spearman correlation was generated by Meta-DiSc (version 1.4) software to measure the threshold effects of the included studies.

Results

After removing duplicates from the 311 articles identified, 34 studies were assessed for eligibility (Additional file1: Table S5). On detailed full-text reading, 8 pieces of research[17–19, 25–29]representing 6 distinct populations of 560 recipients were included (Fig. 1). All evaluations were observational and single center in nature, with 6 prospective and 2 retrospective designs. Main characteristics of the selected studies, including study design, etiology of transplantation, cut-off value, sampling time and diagnostic accuracy parameters, were summarized in Additional file 2: Table S1.

Quality of Study and risk of bias

Figure 2 and 3 represent the results of QUADAS-2 tools. In terms of risk of bias, studies conducted by Grammatikopouslos et. al.[27] has potential bias related to patient selection as it was a case-control study. There were 4 articles that were judged as having high bias in the index tests for not prespecifying a cutoff value. None studies were considered to have potential bias in reference test and flow and timing sections. In terms of applicability, only four articles raised certain concerns related to patient selections. No concerns about index test as well as reference test were proposed. Of note again, the results of QUADAS-2 tool show the worst condition of each study as an uncertain domain was marked as “high risk” rather than “unclear”.

Publication bias and heterogeneity of the included studies

Publication bias was not tested as false positive result is likely to come out when less than 10 articles are used for analysis. The Spearman correlation and p-value for PCT were 0.595 and 0.12, suggesting that no significant threshold effect existed. Then we computed the pooled DOR. An I^2 measuring 41.66% was returned by the mefor R package, suggesting the moderate heterogeneity. We also generated the Cochran's Q reaching 12.5354 with a p-value of 0.0843, furthering confirming the heterogeneity among the included studies. Sensitivity analysis was then carried out. By deleting the included studies one at a time, we found that when a study[17] in which the sampling time was before the transplantation was deleted, the I^2 dramatically dropped to 0.00%, and the Cochran's Q as well as the p-value showed corresponding changes, which became 5.148 and 0.525. As the article raised huge heterogeneity that can't be ignored, we removed it and conducted another analysis, results of which are described below.

Overall analysis of Individual Studies

We identified 7 studies that simultaneously estimated sensitivity and specificity among liver transplant patients with suspected infection. Overall, the studies' pooled DOR was 18.65 (95%CI 9.85–35.31) (Fig. 4). HSROC curve for the PCT test was shown in Fig. 5, revealing an AUC of 0.857 (θ=-0.024; β=-0.203). The positive likelihood ratio and negative likelihood ratio are 3.472 (95% 2.352–5.127) and 0.289 (95% 0.192–0.434).

Discussion

Studies have shown that PCT can effectively diagnose infectious complication among solid organ transplant recipients[30–32]. Unfortunately, these studies were sporadic and there were few analyses focusing on single organ, liver, for example. Worse still, drawbacks such as certain methodological flaw, small sample size and lack of united cut-off value existed in these published articles. In this study, we managed to perform a random-effects model analysis on 7 clinical trials from 6 countries to investigate PCT's utility in differentiating infection among LT recipients. To the best of our knowledge, there have been no previous evidence on this field of concern.

Our results presented a pooled DOR of 18.65 (95%CI 9.85–35.31), suggesting a good diagnostic accuracy for PCT, which was further confirmed by an AUC measuring 0.857, strengthening its reliability for diagnosing infectious complications following LT. Apart from demonstrating the diagnostic value, more importantly, the article also reveals several meaningful but not well understood aspects of PCT's utility.

Before performing the meta-analysis, PCT concentration, a continuous variable whose cutoff varied among studies, was considered as a potential resource for heterogeneity. Surprisingly, Spearman correlation returned by the Meta-DiSc suggested that no significant threshold effect existed, which meant that different thresholds of various studies were not the main causes for heterogeneity. One possible explanation is that the methods to detect PCT concentration in the included studies somehow neutralized the effect due to the different cutoff settings, leaving an evenly balanced result that passed the threshold effect test which produced a Spearman correlation measuring 0.429 with a p-value of 0.337. Unfortunately, the true reason of it remains unknown and therefore wide discussion as well as more

studies is needed. Of note, we found the cutoff value set in the early years are relatively high, which gradually fell down at 0.5 ng/ml in the recent years which presented a high DOR as well as the AUC. Hence researchers are advised to adopt this standard and to verify it in the following studies.

Sensitivity analysis showed that the research conducted by Hara et al[17] led a huge heterogeneity, by deleting which, the I^2 was reduced to 0%. The reason accounting for it may be that it's the only one study evaluated the PCT value as a predictive biomarker. Hara sampled the patients on the day before transplantation while others sampled on the day of diagnosis of infectious disease. It's a retrospective cohort of 136 liver transplant patients which demonstrated that, to some degree, sepsis can be predicted by pretransplant serum PCT level, for which the authors suggested a re-evaluation of the general condition and rescheduling of LT of a patient whose pretransplant serum PCT > 0.5 ng/ml. Though this study was not included into the meta-analysis due to heterogeneity, it still remains a positive direction to explore.

However, a note of caution is due here since some limitation existed. Due to the inherent flaws in study design, this meta-analysis can only evaluate and combine the size effects measuring the diagnostic accuracy instead of the clinical benefits. Therefore, we call for more studies using random control design with double-blind method to provide solid evidence so as to evaluate the clinical effects from which LT patients may benefit. Besides, as shown in Fig. 3, certain studies have high risk in index test in terms of risk of bias. It is because that in the early years, the universal cut-off was not settled for reasons like different testing methods and incomplete understanding of PCT, resulting in the wide usage of receiver operating characteristic curve for generating an optimal cut-off, which has been overcome in the recent years. Another limitation in this article was that the amount of the included studies is very limited, lowering the level of evidence.

Conclusions

Still, in conclusion, PCT can serve as a biomarker for infectious complication among liver transplant recipients. Importantly, further studies are warranted to provide corroboration due to the small sample size and heterogeneity of these included studies. Besides, the reason why no threshold effect was found remained explored.

Abbreviations

LT: liver transplantation; MELD: Model for End-stage Liver Disease; SIRS: systemic inflammatory response syndrome; MODS: multiple organ dysfunction syndrome; WBC: white blood cells; CRP: C-reactive protein; PCT: procalcitonin; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies; DOR: diagnostic odds ratio; CI: confidence intervals; HSROC: hierarchical summary receiver operating characteristic; AUC: area under the curve;

Declarations

Ethics approval and consent to participate

Formal ethical approval was not required as primary data were not collected.

Consent for publication

Not applicable as no personal data is presented in this meta-analysis.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Research design: ZWZ, WD, DYW, JG; Design of Search Strategy: JG; Discrepancy resolving: ZWZ; Writing the article: ZWZ, WD, DYW; Title and abstract screening: WD, DYW, XZ, XYL, YMW; Full-text reading: WD, DYW; Data extraction: WD, DYW, XYL, YMW; Evaluating risk of bias: WD, DYW, MF; Data analysis: WD, DYW, XZ, JG, XYL.

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Not applicable

References

1. Kaido, T., et al., *In-hospital mortality in adult recipients of living donor liver transplantation: experience of 576 consecutive cases at a single center.* Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society, 2009. **15**(11): p. 1420-1425.
2. van Hoek, B., B.-J. de Rooij, and H.W. Verspaget, *Risk factors for infection after liver transplantation.* Best practice & research. Clinical gastroenterology, 2012. **26**(1): p. 61-72.
3. Antunes, M., et al., *Infections After Liver Transplantation: A Retrospective, Single-center Study.* Transplantation proceedings, 2015. **47**(4): p. 1019-1024.

4. Hotchkiss, R.S. and I.E. Karl, *The pathophysiology and treatment of sepsis.* The New England journal of medicine, 2003. **348**(2): p. 138-150.
5. Schuetz, P., et al., *Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial.* JAMA, 2009. **302**(10): p. 1059-1066.
6. Bouadma, L., et al., *Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial.* Lancet (London, England), 2010. **375**(9713): p. 463-474.
7. Assicot, M., et al., *High serum procalcitonin concentrations in patients with sepsis and infection.* Lancet (London, England), 1993. **341**(8844): p. 515-518.
8. Mimoz, O., et al., *Procalcitonin and C-reactive protein during the early posttraumatic systemic inflammatory response syndrome.* Intensive care medicine, 1998. **24**(2): p. 185-188.
9. Schneider, H.-G. and Q.T. Lam, *Procalcitonin for the clinical laboratory: a review.* Pathology, 2007. **39**(4): p. 383-390.
10. Endo, S., et al., *Usefulness of procalcitonin serum level for the discrimination of severe sepsis from sepsis: a multicenter prospective study.* Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy, 2008. **14**(3): p. 244-249.
11. Gendrel, D. and C. Bohuon, *Procalcitonin as a marker of bacterial infection.* The Pediatric infectious disease journal, 2000. **19**(8).
12. Dumea, R., et al., *Procalcitonin: diagnostic value in systemic infections in chronic kidney disease or renal transplant patients.* International urology and nephrology, 2014. **46**(2): p. 461-468.
13. Desmard, M., et al., *Post-operative kinetics of procalcitonin after lung transplantation.* The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation, 2015. **34**(2): p. 189-194.
14. Franeková, J., et al., *Serial measurement of presepsin, procalcitonin, and C-reactive protein in the early postoperative period and the response to antithymocyte globulin administration after heart transplantation.* Clinical transplantation, 2017. **31**(1).
15. Mazo, C., et al., *Procalcitonin accurately predicts lung transplant adults with low risk of pulmonary graft dysfunction and intensive care mortality.* Journal of critical care, 2018. **44**: p. 142-147.
16. Kuse, E.R., et al., *Procalcitonin in fever of unknown origin after liver transplantation: a variable to differentiate acute rejection from infection.* Critical care medicine, 2000. **28**(2): p. 555-559.
17. Hara, T., et al., *Pretransplant serum procalcitonin level for prediction of early post-transplant sepsis in living donor liver transplantation.* Hepatology research : the official journal of the Japan Society of Hepatology, 2018. **48**(5): p. 383-390.
18. Kaido, T., et al., *Perioperative changes of procalcitonin levels in patients undergoing liver transplantation.* Transplant infectious disease : an official journal of the Transplantation Society, 2014. **16**(5): p. 790-796.

19. Perrakis, A., et al., *Prognostic and diagnostic value of procalcitonin in the post-transplant setting after liver transplantation.* Archives of medical science : AMS, 2016. **12**(2): p. 372-379.
20. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* PLoS medicine, 2009. **6**(7): p. e1000097.
21. Whiting, P.F., et al., *QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies.* Annals of internal medicine, 2011. **155**(8): p. 529-536.
22. Team, R.C., *R: A language and environment for statistical computing*. 2019: R Foundation for Statistical Computing, Vienna, Austria.
23. Doebler, P., *mada: Meta-Analysis of Diagnostic Accuracy*. 2019.
24. Viechtbauer, W., *Conducting meta-analyses in R with the metafor package.* Journal of Statistical Software, 2010. **36**: p. 1-48.
25. Kuse, E.R., et al., *Procalcitonin-a new diagnostic tool in complications following liver transplantation.* Intensive care medicine, 2000. **26 Suppl 2**: p. S187-S192.
26. Chen, J., et al., *Early diagnostic value of plasma PCT and BG assay for CRBSI after OLT.* Transplantation proceedings, 2011. **43**(5): p. 1777-1779.
27. Grammatikopoulos, T., et al., *Baseline evaluation of serum markers of inflammation and their utility in clinical practice in paediatric liver transplant recipients.* Clinics and research in hepatology and gastroenterology, 2012. **36**(4): p. 365-370.
28. Gür, A., et al., *Prognostic Value of Procalcitonin, CRP, Serum Amyloid A, Lactate and IL-6 Markers in Liver Transplant Patients Admitted to ED with Suspected Infection.* In vivo (Athens, Greece), 2017. **31**(6): p. 1179-1185.
29. Ghiasvand, F., et al., *Positive Role of Procalcitonin Level in the Diagnosis of Infectious Diseases After Liver Transplantation.* Hepat Mon, 2019. **19**(5): p. e85668.
30. Sammons, C. and C.T. Doligalski, *Utility of procalcitonin as a biomarker for rejection and differentiation of infectious complications in lung transplant recipients.* The Annals of pharmacotherapy, 2014. **48**(1): p. 116-122.
31. Hammer, S., et al., *Procalcitonin for differential diagnosis of graft rejection and infection in patients with heart and/or lung grafts.* Intensive care medicine, 2000. **26 Suppl 2**: p. S182-S186.
32. Hammer, C., et al., *Procalcitonin: a new marker for diagnosis of acute rejection and nonviral infection of heart and lung transplant patients.* Transplantation proceedings, 2001. **33**(3): p. 2204-2206.

Additional Files

Additional file 1: Table S1. PRISMA-DTA checklist. **Table S2.** Abstract checklist for PRISMA-DTA. **Table S3**. Search strategy performed. **Table S4**. Extracted data in each study assessed for eligibility. **Table S5**. Full text articles excluded, not fitting eligibility criteria. **Table S6**. Diagnostic accuracy parameters estimated for each included study.

Additional file 2: Table S1. Main Characteristics of Included Studies

Figures

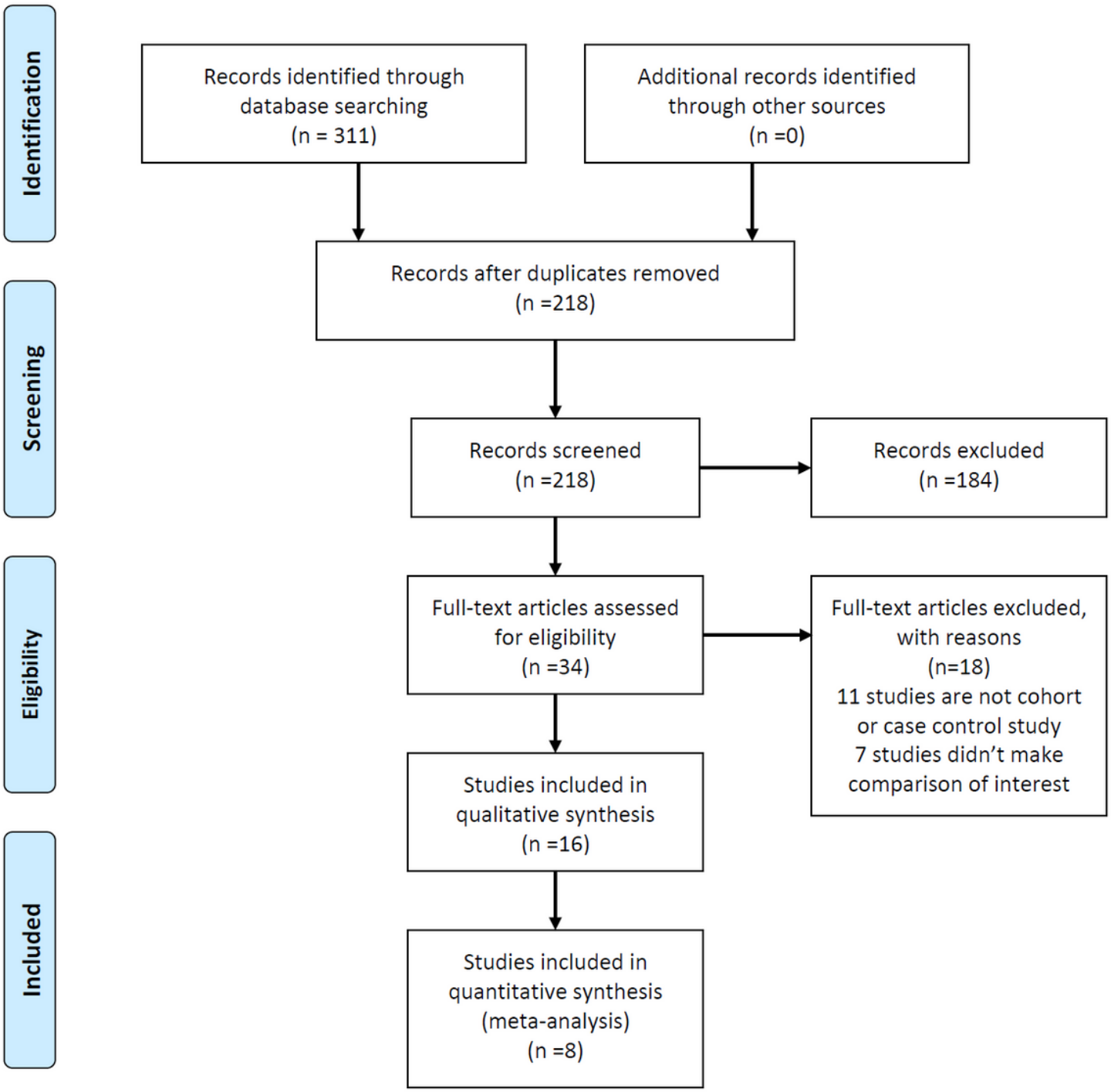

Figure 1

PRISMA flow diagram for literature search and screening process

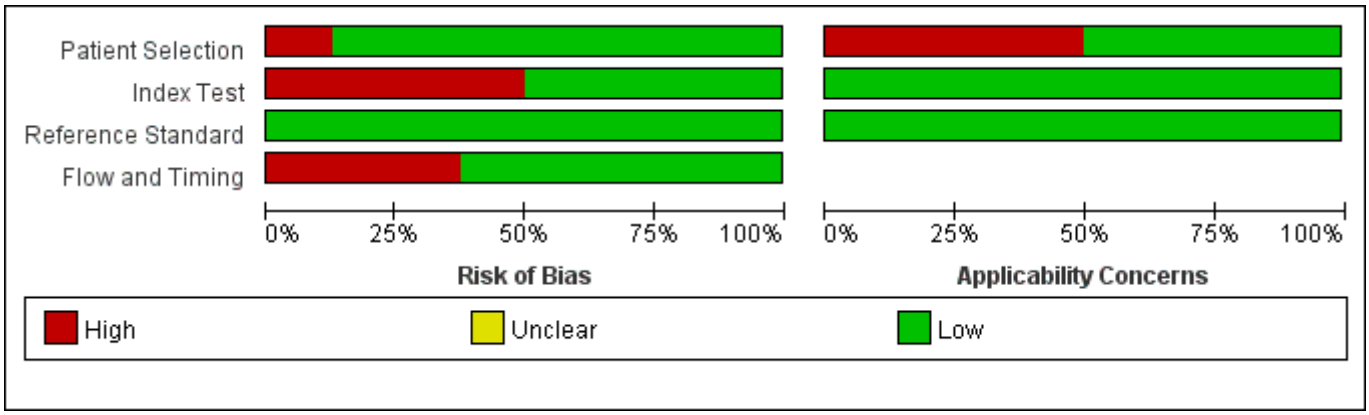

Figure 4

Risk of bias and applicability concerns.

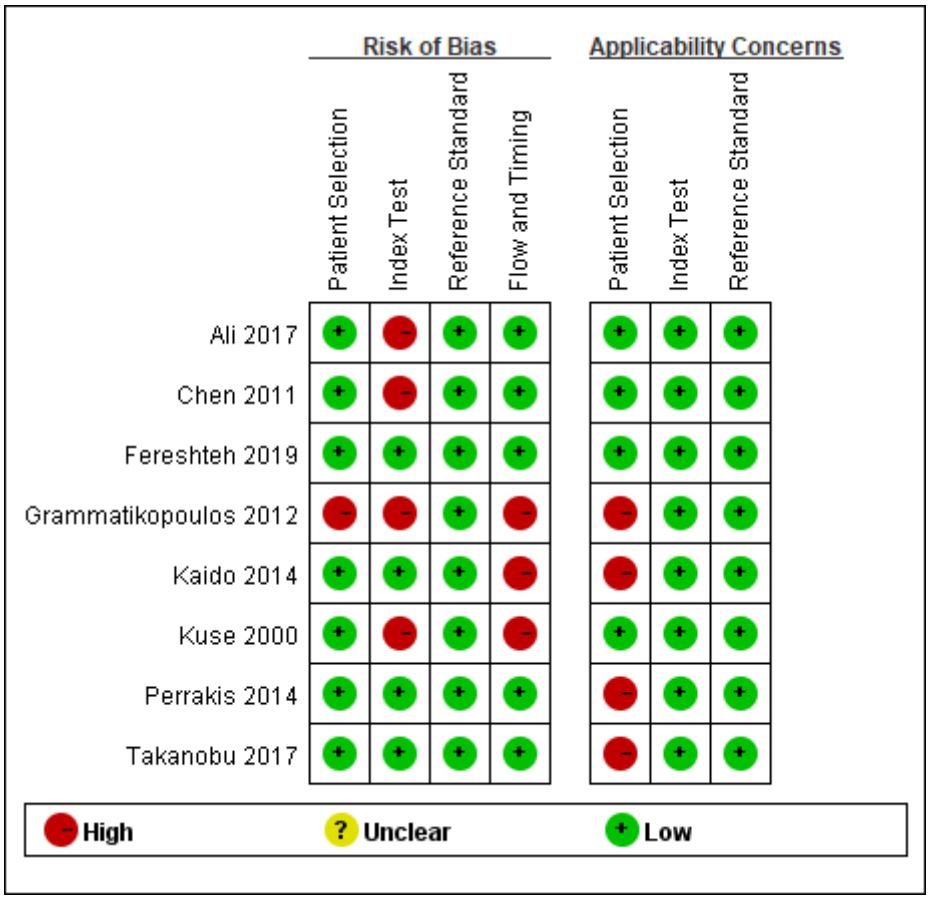

Figure 6

Risk of bias and applicability concerns – summary

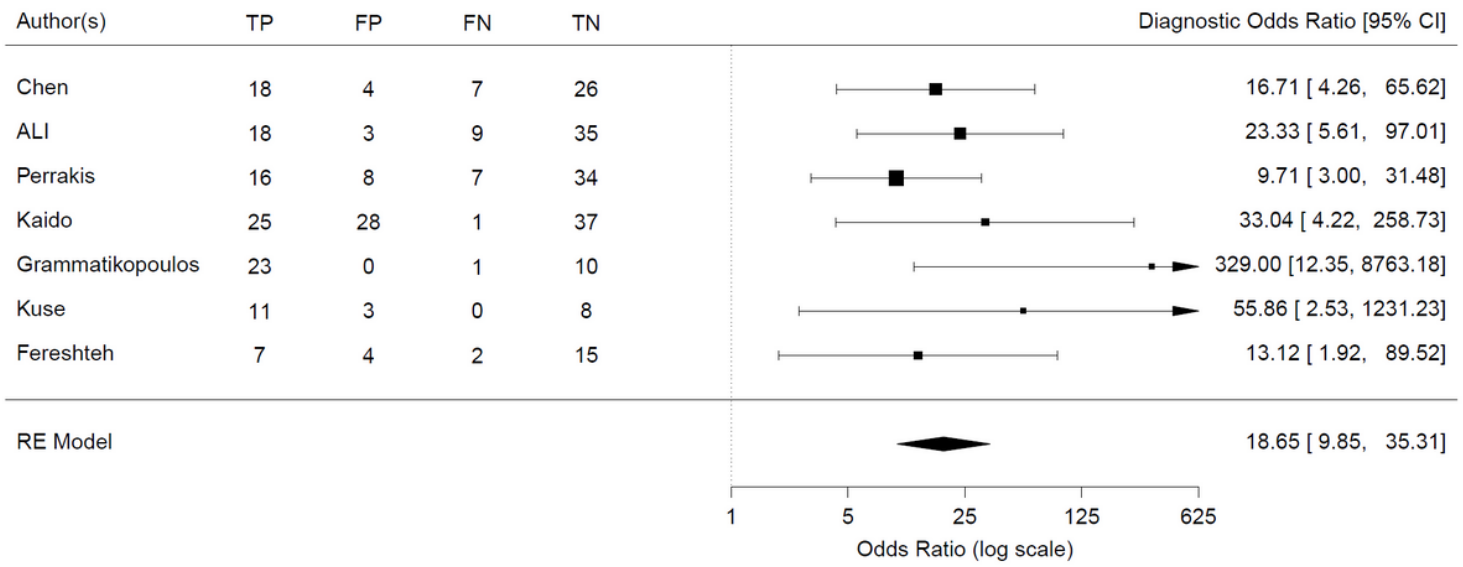

Figure 7

DOR in studies examining PCT testing.

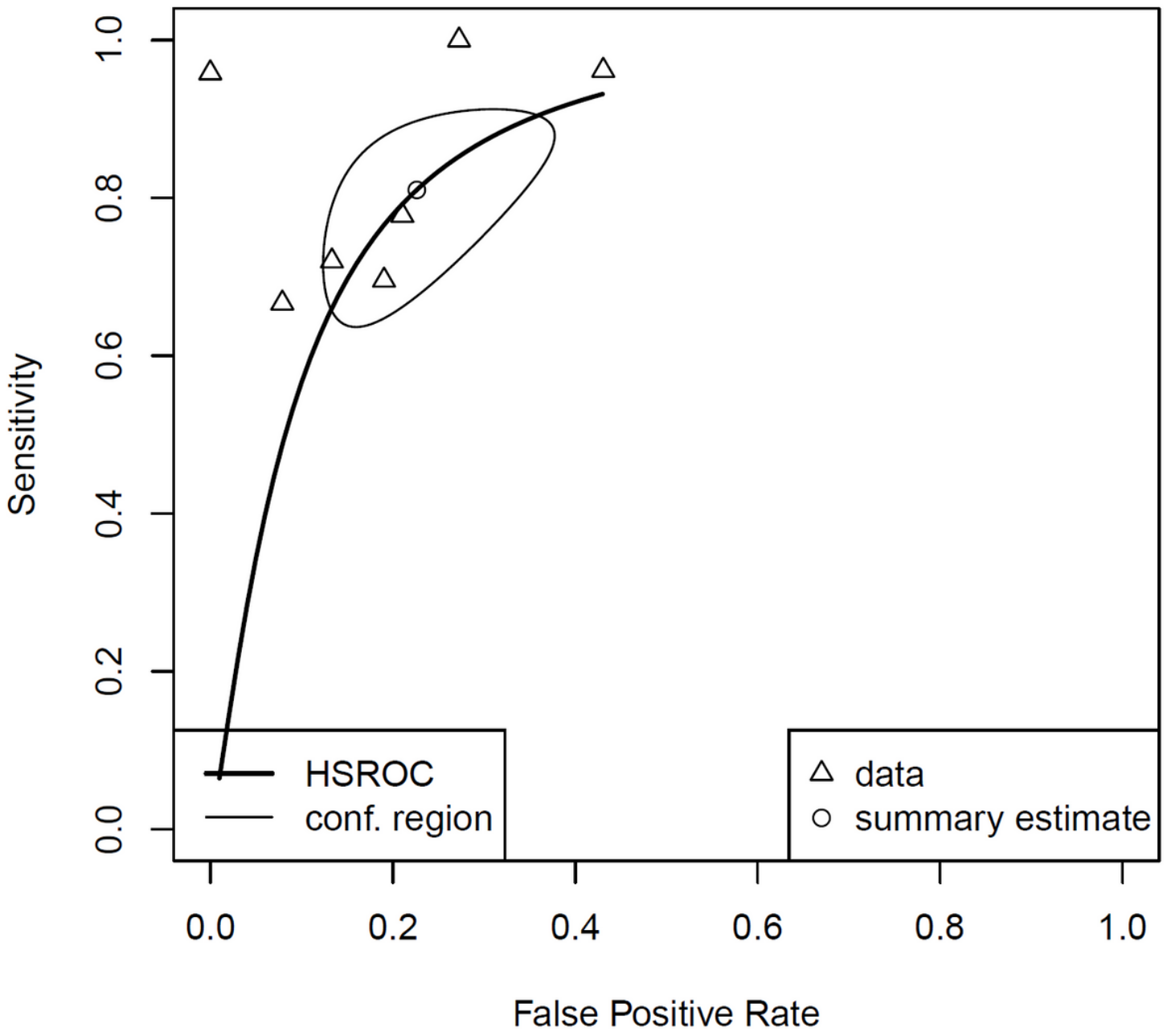

Figure 9

HSROC curve of studies examining PCT testing.

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