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MATERNAL-FETAL MEDICINE

Procalcitonin in preterm rupture of membranes: a systematic review and meta-analysis

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Abstract

Purpose Early detection of infection is of supreme importance in obstetrics; however, during pregnancy it is not reliably predicted by standard laboratory tests.

We aimed to determine if procalcitonin (PCT) is a reliable predictor of chorioamnionitis (CA) in women with premature rupture of membranes (PPROM).

Methods An electronic search of Scopus, ISI, Medline, Embase, ClinicalTrials.gov and the Cochrane Library databases was performed using specified key words. We examined all English and French reports on PCT measurement after admission for PPROM and considered: human studies published between 1990 and 2019; observational studies; and randomized controlled trials.

A protocol was determined previously, registered at PROSPERO as CRD42019145464.

The eligibility was independently assessed by two researchers and literature search yielded 590 studies; after revision of the titles and abstracts, 46 articles were identified as potentially eligible; eight studies were included in the meta-analysis.

Primary data synthesis was performed in Review Manager Version 5.3 and average sensitivity and specificity was calculated using Midas, Stata.

Results From the eight studies included, 335 participants with PPROM were enrolled.

Our meta-analysis disclosed that PCT has a poor sensitivity (0.50; 95% CI 0.28–0.73) and a modest specificity (0.72; 95% CI 0.51–0.87) in diagnosing CA.

C-reactive protein (CRP) not only has better sensitivity (0.71; 95% CI 0.53–0.84), but also better specificity (0.75; 95% CI 0.55–0.88), compared with the other inflammatory parameters analyzed.

Procalcitonin does not seems to be better than CRP in preterm rupture of membranes for chorioamnionitis diagnosis.

Keywords Procalcitonin · Preterm premature rupture of membranes · PPROM · Chorioamnionitis

Introduction

Procalcitonin (PCT), is secreted by thyroid C-cells as a sepsis-induced protein. Its levels are markedly elevated in many bacterial infections but only slightly in focal inflammation [1], remaining low in viral infections and in non-specific inflammatory diseases [2]. In general, PCT can be detected in plasma in 2 h after beginning of an infection, increases in 6–8 h and reaches a plateau in 20–72 h. Also, it can be used as a prognostic indicator of sepsis [1].

During severe inflammation or sepsis, serum levels of PCT rapidly increase. For this reason, PCT is now generally accepted as a good predictive and diagnostic marker of the inflammatory process and as an additional tool to guide antibiotic prescription [3]. Serum PCT levels rise more rapidly

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than C-reactive protein (CRP) levels and peak within a short period before returning to normal levels, also more quickly [3].

Studies of PCT normal ranges during pregnancy are rather contradictory, with a recent study pointing out serum levels higher in healthy pregnant women than in non-pregnant women [1]; moreover, serum PCT levels increase rapidly during late pregnancy and delivery [1, 2].

Membrane rupture before labor and before 37 weeks of gestation is identified as PPROM. Its management is affected by gestational age and the existence of complicating factors [4]. Clinically apparent intraamniotic infection occurs in approximately 15–25% of women with PPROM, greater at earlier gestational ages [4]. Although complications of prematurity are the most significant risks to the fetus after PPROM, intrauterine inflammation has demonstrated to be a risk factor for neurodevelopmental injuries [4]. This means that early on detection of infection is of absolute importance in obstetrics; failure can lead to complications both for the mother and the baby. However, infection during pregnancy is not consistently calculated by standard laboratory tests, such as white blood cell (WBC) count, (with a physiological increase during pregnancy) [1]; or CRP levels. Moreover, clinical signs such as fever and tachycardia (maternal and fetal) usually appear at later stages [1].

So, PCT is gaining attention in the scientific community regarding its use not only during pregnancy, but more specifically in the preterm rupture of membranes.

The main aim of this systematic review and metanalysis was, therefore, to determine if the PCT level is a more reliable marker of chorioamnionitis in pregnant women with PPROM than CRP or WBC count. If so, it could be used in clinical practice to diagnose early chorioamnionitis in PPROM.

Materials and methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. A protocol was first prepared by the participating authors and registered at the PROSPERO registry as CRD42019145464.

A comprehensive electronic search (from conception 15 August 2019, to end-of-search date, 31 December 2019) of Scopus, ISI, Medline, Embase, ClinicalTrials.gov and the Cochrane Library databases was performed to extract relevant reports with the use of the following key words: Procalcitonin AND Premature rupture of membranes OR (PPROM, PR of fetal membranes, Membrane premature rupture, Preterm PROM, PROM, preterm) AND Pregnancy AND Chorioamnionitis.

A comprehensive electronic search was performed in August 2019; the reference lists of included reports were also scrutinized for further potentially eligible studies. The last search was run on 31 December 2019 and comprised all previous items in the selected databases (Appendix S1).

Eligibility criteria

This systematic literature review examined all English and French reports on PCT measurement in maternal blood after admission for PPROM.

We considered human studies published between 1990 and 2019, observational studies (prospective and retrospective), and randomized controlled trials.

We excluded non-human studies, literature reviews, and abstracts. Moreover, articles concerning patients with multiple pregnancies, congenital abnormalities, hypertensive disorders, known gestational diabetes mellitus and patients with active labor, were also excluded.

Subsequently, full text articles were retrieved, and authors were contacted to obtain additional information, if necessary.

No ethics approval was required as the analysis only involved published and anonymous data.

There was no funding or financial support for this review.

Study selection

The eligibility of the reviewed reports was independently assessed by two researchers (ALA and AMP) using a predefined model as follows: analysis of titles and abstracts; discussion of differences between the choices and arranging a consensual final choice; reading the full text of the chosen articles and analysis of the results. Disagreements were solved by the third author (MA). Additionally, the original authors were contacted for missing data.

The risk of bias for each included study was assessed based on the criteria outlined in *The Cochrane Collaboration*. Four domains related to risk of bias were assessed: (1) patient selection; (2) index test; (3) reference standard; and (4) flow and timing.

The quality rating for each item of all the included trials was categorized as 'low risk', 'high risk' or 'unclear risk' of bias.

A predefined data extraction form included: year of publication; type of study; number of patients; gestational age at inclusion; comparisons; main outcomes; results for PCT, CRP and WBC counts and corresponding thresholds; and risk of bias.

PPROM was defined as membrane rupture before 37 weeks of gestation and before labor. Normal range for PCT was defined as values below 0.05 ng/mL; for CRP as less than 1.6 mg/dL and for WBC as under 15,000/mm^3.

Analysis of individual patient-level data was not possible due to non-response of most contacted authors.

Chorioamnionitis was diagnosed using internationally specified histological (inflammation or necrosis) and/or clinical criteria (maternal symptoms including fever, abdominal pain, abnormal vaginal discharge and leukocytosis) [5].

Primary data synthesis was performed within the bivariate mixed-effects logistic regression modelling framework in Review Manager Version 5.3 (RevMan, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Average sensitivity and specificity were calculated using Midas, a Stata module for meta-analytical integration of diagnostic test accuracy studies (Stata version 16, StataCorp LLC, College Station, TX, USA), using random effects.

Results

The literature search yielded 590 studies published between 1990 and 2019, of which 565 remained after removal of duplicates. These 565 publications were further screened and 519 were excluded after revision of the titles and abstracts showed them to be not eligible, i.e. they were: case reports; review articles; editorials; non-human studies; non-English or non-French articles; articles not focusing on the review topic; and articles not meeting the inclusion criteria. This left a total of 46 articles as being potentially suitable for inclusion in our review. After reading the full texts, a further 32 studies were excluded because they did not meet the inclusion criteria in that the data concerned only newborns, or because the data between tables and text were inconsistent. Finally, 15 appropriate publications were selected. Of these, only eight studies [6–13] were used for the meta-analysis, as the other five [14–18] had to be excluded because the data could not be extracted (although several attempts were made to contact the authors) (Appendix S2).

Results of individual studies.

The study by Asadi et al. comprised 75 women with PPROM [24–34 weeks gestational age (GA)] and established that women with CA had significantly higher serum levels of CRP, both on admission ($p = 0.004$) and before termination of pregnancy ($p < 0.001$). The CRP cut-off value for diagnosis of CA was 16 mg/dl, with a sensitivity of 83%, specificity of 73%, positive predictive value (PPV) of 25% and a negative predictive value (NPV) of 97%. The area under the curve (AUC) for last CRP was 0.78 (95% confidence interval 0.57–0.84), indicating moderate accuracy. Procalcitonin and WBC had lower accuracy to predict CA [6].

On the other hand, Broumand et al. [7] concluded that there was no significant correlation between maternal infection with pathologic CA and the mean values of the WBC and PCT inflammatory indices on hospitalization ($p = 0.386$ and 0.191, respectively) in 48 women with PPROM (28–33 weeks GA), with PCT mean value of 0.041 ± 0.017 (0.02–0.1).

A previous study by Dulay et al. [8] found that levels of PCT did not differ for women with PPROM and that CRP was elevated to a similar extent in both groups (with or without intraamniotic infection), with a wide range of values and only five patients, rendering any conclusion difficult. Consequently, there was no correlation between PCT or CRP and CA. The authors, therefore, concluded that none of the studied maternal blood proteins had a diagnostic predictive value better than maternal blood WBC [8].

Nevertheless, after reviewing 21 cases of PPROM, Greksova et al. [9] concluded that both PCT and CRP were elevated in cases of CA, and thus concluded that measuring PCT and CRP levels in maternal blood may support an earlier diagnosis of intrauterine infection.

In 2014, a study by Gverić-Ahmetašević [10] evaluated 60 women with PPROM and found that the AUC for both PCT and CRP was relatively low, but still had significant predictive values (CRP = 0.78 and for PCT = 0.74). The predictive value of CRP was thus no different from the predictive value of PCT in chorioamnionitis (p = 0.378).

Ronzino-Dubost et al. [11], however, having studied 30 cases of PPROM (24–34 weeks GA) stated that there is no reason to use PCT in the prediction of CA in addition to clinical and biological monitoring based on the levels of CRP and leukocytes. Their study showed that the sensitivity of PCT for CA diagnosis was 54%, while that of the CRP was 81%. Moreover, the authors state that the association of CRP and PCT allowed an increase in specificity (reaching 85%), but at the expense of lowering the sensitivity to 45%.

In line with those results, Torbé et al. had also indicated previously that not only is PCT unsatisfactory in the diagnosis of CA [13], but that there was no correlation between the value of PCT and altered WBC ($r = 0.01$; $p = 0.930$) and CRP ($r = -0.14$; $p = 0.360$) in cases of CA [12].

The findings of each study are summarized in Table 1.

The overall risk of bias was low (Appendix S3). All but one study reported a low risk of bias for all the domains assessed, namely patient selection, index test, reference standard and flow and timing.

Main findings

From the eight studies, 335 participants were enrolled with PPROM between 24 and 37 weeks of gestational age. Of those studies, all reported results for PCT in the diagnosis of CA (after admission and before labor), only six had results for CRP, and five for WBC. All cases of PPROM were managed expectantly.

Our meta-analysis revealed that CRP has both better sensitivity (0.71; 95% CI 0.53–0.84) and better specificity (0.75;

Table 1 Results of individual studies

First author	Year of publication	Type of study	Number of patients	Comparisons	Results
Asadi [6]	2019	Prospective, cross-sectional	75	PCT, CRP, WBC	Maternal serum CRP was the most accurate predictor of CA in women with PPROM
Broumand [7]	2018	Prospective, cohort	48	PCT, CRP, WBC	There was no significant correlation between inflammatory indices and CA
Dulay [8]	2015	Case–control	5	PCT, CRP, WBC	PCT was not a useful biomarker for intraamniotic infection
Greksova [9]	2009	Prospective, cohort	21	PCT, CRP	Measure of PCT and CRP in maternal blood sample may support earlier diagnosis of intrauterine infection
Gverić-Ahmetašević [10]	2014	Case–control	60	PCT, CRP	Both markers are predictive of CA and neonatal infections, with almost similar significance
Ronzino-Dubost [11]	2015	Prospective, cohort	30	PCT, CRP, WBC	PCT in the diagnosis of CA is not useful for managing patients
Torbé et al. [13]	2005	Case–control	48	PCT	PCT is unsatisfactory in the diagnosis of CA
Torbé [12]	2007	Prospective, cohort	48	PCT, CRP, WBC	No correlation between value of PCT and altered WBC and CRP Comparable values of PCT with or without CA

PCT procalcitonin, *CRP* C-reactive protein, *WBC* white blood cells, *CA* chorioamnionitis

95% CI 0.55–0.88), compared with the other inflammatory parameters analyzed (Figs. 1, 2 and 3).

Although specificity did not differ greatly between CRP, WBC and PCT, CRP showed a substantial difference in sensitivity, with a good result. CRP was thus confirmed as the best parameter in CA diagnosis (Table S1).

Discussion

Calcitonin is a hormone implicated in inflammatory processes seldomly studied in pregnancy, as its reference values have not been unambiguously recognized. A study designed to establish reference limits for PCT in healthy pregnant women in the Chinese population revealed that serum PCT levels are considerably higher in pregnant versus non-pregnant women, and this difference is mostly apparent after delivery [1]. These studies can be substantiated by the placental production of PCT, namely its synthesis by trophoblast and decidual stromal cells [19]. Afterwards, an European study by Paccolat et al. concluded that a cut-off PCT level of 0.25 mg/L could be applied during the third trimester, at delivery, and in the immediate postpartum period to exclude infection [2].

Nevertheless, some authors argue that PCT is not relevant to predict maternal bacterial infection in pregnancy because, during chorioamnionitis, PCT is more likely to be released by the fetus rather than by placental tissue [20]. Furthermore, PCT although useful in bacterial sepsis, has no value in the assessment of fungal or viral infections with no response to intracellular microorganisms (i.e. *Mycoplasma*, one of the main genera of bacteria responsible for CA) or in local infections with no systemic response [2, 21].

Strengths and limitations

The main strength of the present study is the uniqueness of the meta-analysis, with distinct inclusion criteria and a thorough literature review using PRISMA guidelines.

Not only is this the first article addressing PCT use as a reliable predictor of chorioamnionitis in women with PPROM, but it has also been able to resolve the question as to whether CRP could be replaced by PCT in those cases.

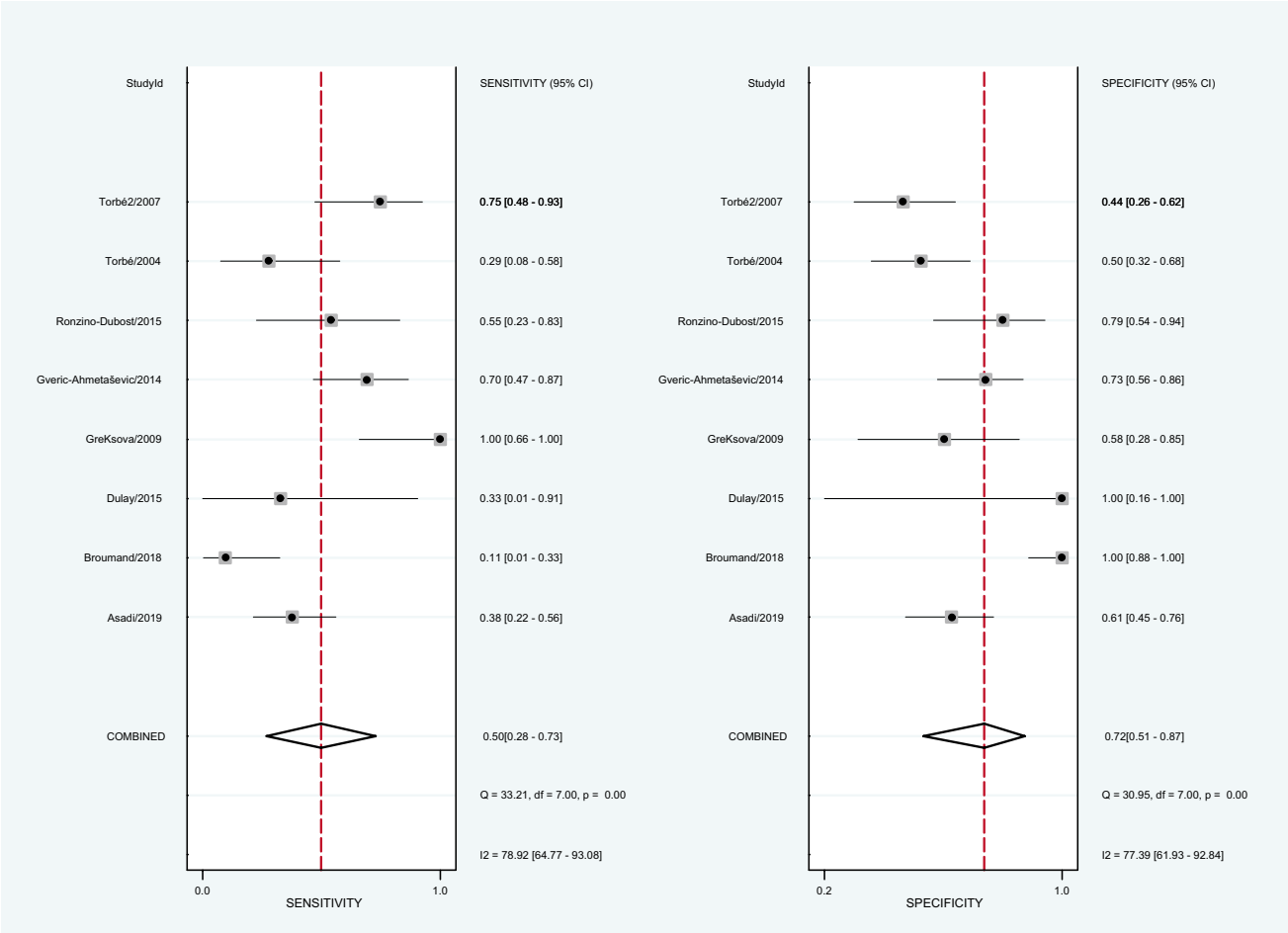

Fig. 1 Sensitivity and specificity of procalcitonin. Legend: included studies and meta-analysis combined sensitivity and specificity with 95% confidence intervals of procalcitonin value for the diagnosis of chorioamnionitis in women with premature rupture of membranes

However, some limitations in our meta-analysis need to be mentioned: the relatively small amount of articles with complete data included (including absence of mean or median values of the used parameters and gestational age of the women included); the variations between studies regarding cut-off values used for abnormal PCT (0.05–2.0 ng/mL) and abnormal CRP (1.0–2.5 mg/mL); the differences in the types of antibiotic used that could possibly influence the results; the inadequate amount of placental pathology in each study; and finally, the significant heterogeneity between studies ($I^2 > 70\%$ in all analyses). Moreover, we only included published studies, so publication bias is present.

Interpretation

Our meta-analysis aimed to respond to the question of whether PCT could/should replace the actual inflammatory parameters used in modern obstetrics to more accurately and safely predict chorioamnionitis.

We found that PCT is not a better inflammatory parameter than CRP in the diagnosis of CA, since it has only a poor sensitivity (0.50; 95% CI 0.28–0.73).

Based on the analysis of data in this meta-analysis, we can conclude that unlike in a normal, non-pregnant condition CRP is more relevant than PCT to predict maternal chorioamnionitis in PPROM, and only slightly better (as a predictor) than WBC.

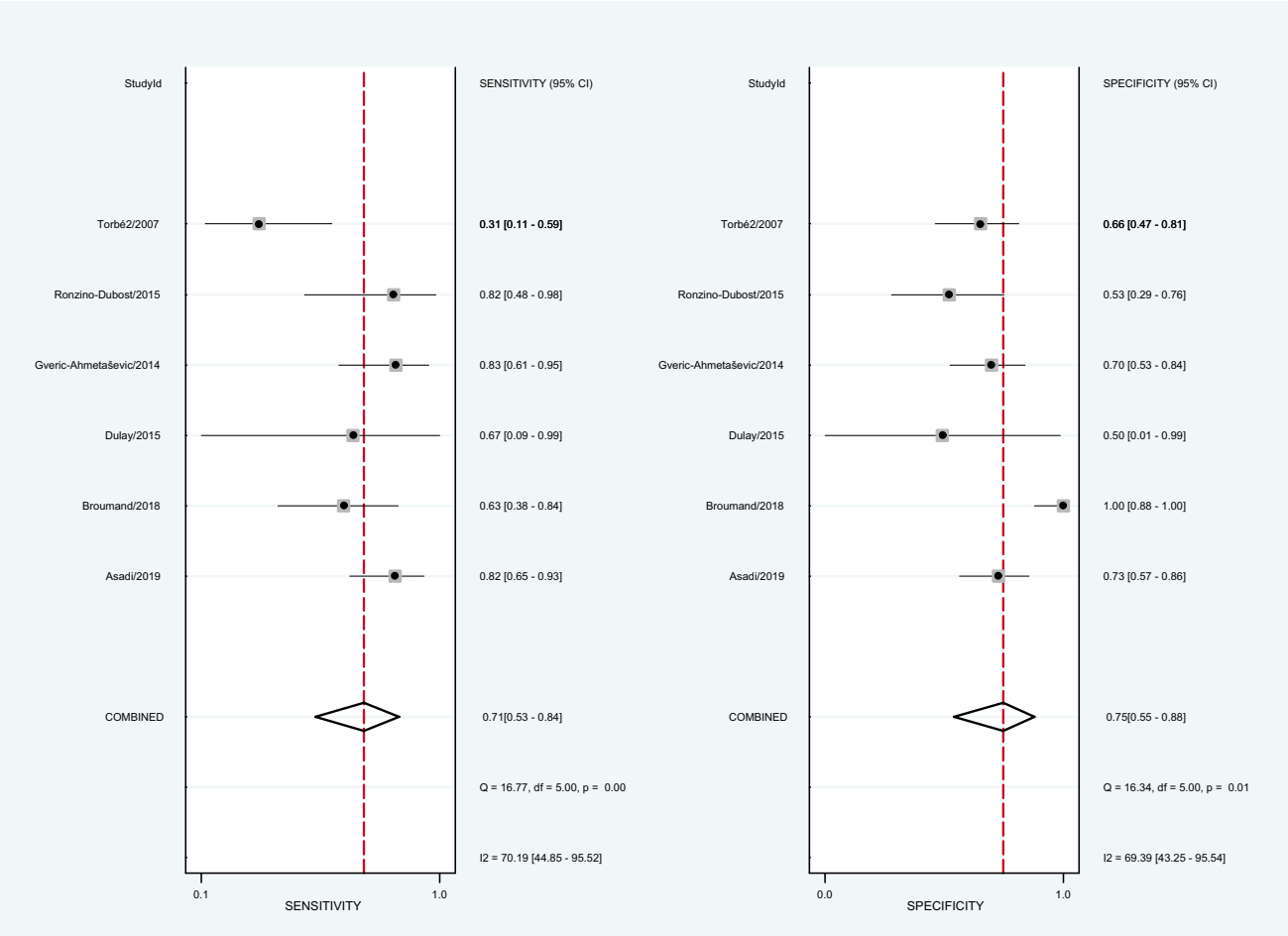

Fig. 2 Sensitivity and specificity of C-reactive protein. Legend: included studies and meta-analysis combined sensitivity and specificity with 95% confidence intervals of C-reactive protein value for the diagnosis of chorioamnionitis in women with premature rupture of membranes

Conclusions

Poorly timed diagnosis of infection is of the utmost importance in PPROM, because it can create serious problems not only for the mother and fetus, but for the newborn infant, too. Even though PCT is widely used in clinical practice in the diagnosis of systemic bacterial infections, our meta-analysis demonstrated that it should not be used to replace standard laboratory tests (CRP and WBC) for the diagnosis of chorioamnionitis, because PCT has poor sensitivity (0.50; 95% CI 0.28–0.73) and modest specificity (0.72; 95% CI 0.51–0.87).

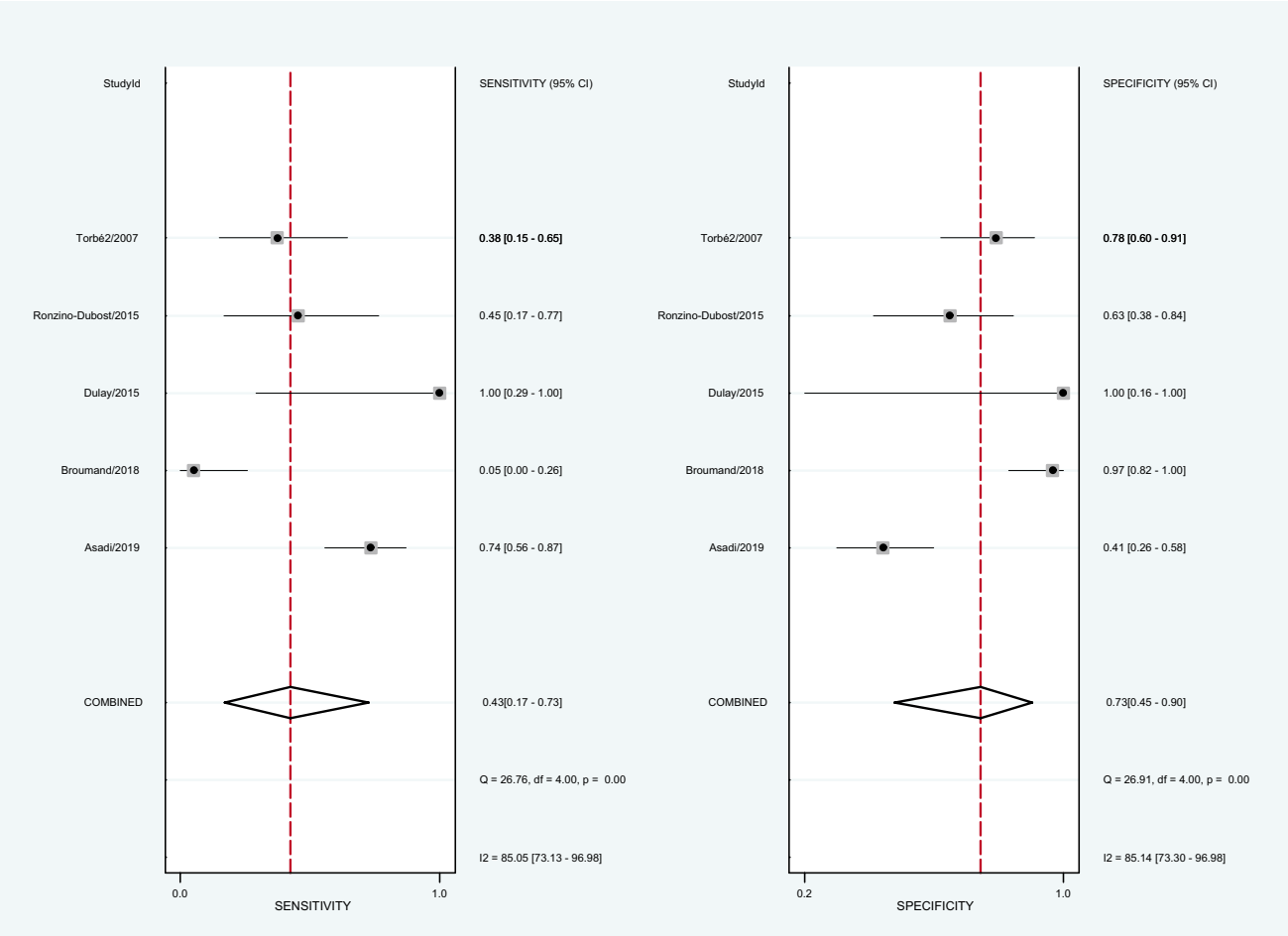

Fig. 3 Sensitivity and specificity of white blood cells. Legend: included studies and meta-analysis combined sensitivity and specificity with 95% confidence intervals of white blood cells count for the diagnosis of chorioamnionitis in women with premature rupture of membranes

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by ALA, MA, and AM-P. The first draft of the manuscript was written by ALA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval No ethics approval was required as the analysis only involved published and anonymous data.

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