

C-Reactive Protein in Early Diagnosis of Neonatal Late-Onset Sepsis: A Systematic Review and Meta-analysis

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Abstract

Background: C-reactive protein (CRP) is an acute-phase protein reactant that rises especially in response to infectious processes in adults and neonates. It has been used for decades as a tremendous indicator of sepsis in Neonatal in-depth Care devices (NICUs). **Aim:** This work aims to determine the accuracy of C - reactive protein (CRP), in early diagnosis of late-onset sepsis in infants. **Materials and Methods:** A systematic search was performed over different medical databases to identify Pediatrics studies, which studied the outcome of CRP in early diagnosis of late-onset sepsis (LOS) in infants. Using the meta-analysis process, either with fixed or random-effects models, we conducted a meta-analysis on sensitivity as a primary outcome, and on specificity as a secondary outcome. **Results:** Six studies were identified involving 1203 infants. The meta-analysis process revealed that the pooled sensitivity of CRP for diagnosis of late-onset infection=71.7% (p<0.001), and the pooled specificity of CRP for diagnosis of late-onset infection=76.1% (p<0.001). **Conclusion:** To conclude, late-onset sepsis represents significant morbidity and mortality in the neonatal intensive care unit, CRP plays an important role in the diagnosis of LOS.

Keywords: C - reactive protein; Infants; Late-onset sepsis

Introduction

Neonatal sepsis is a common, fatal trouble with worldwide impact including significant morbidity and mortality, even in high-resource nations. The best prevalence and impact of neonatal sepsis is visible within the smallest, most prematurely born infants. In a cohort of 5100 extremely preterm infants (born before 29 finished weeks of gestation), 34% experienced late-onset sepsis (LOS, a positive blood culture with a bacterial or fungal organism after seventy-two h of life), which was associated with 18% mortality. LOS survivors demonstrate the significant neurodevelopmental effect, that's superimposed on the effect of premature delivery and extends into the second decade of life.^[1]

Late-onset neonatal sepsis becomes defined by one or more clinical features of sepsis: hypothermia, or temperature instability, apnea, bradycardia, elevated oxygen requirement, feed intolerance, lethargy, or hypotonia, plus a pure growth of a single organism from blood or CSF accumulated after 3 days (72 hours) of life.^[2]

C-reactive protein (CRP) is an acute-phase protein reactant that rises especially in response to infectious processes in adults and neonates. It has been used for decades as a tremendous indicator of sepsis in Neonatal in-depth Care devices (NICUs). Lately, it has to turn out to be a point of debate. a few studies advocate that

ELBW infants present with decrease CRP levels in comparison to full-terms, following a septic attack. Whilst others support the concept that ELBW babies are capable of mounting significant CRP responses in the course of a septic event.^[3]

The measurement of biomarkers associated with different chance elements represents substantial prediction in diagnosing neonatal sepsis early. Even though the usage of biomarkers in assisting diagnose sepsis has been explored and observed to be promising, there may be a paucity of data regarding since most of such research had been carried out in developed nations. Therefore, they evaluated the usefulness of CRP as an inflammatory biomarker in the prediction of neonatal sepsis.^[4]

This work aims to determine the accuracy of C-Reactive Protein (CRP), in early diagnosis of late-onset sepsis in infants.

Literature Review

Our review came following the (PRISMA) statement guidelines.^[5]

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Study eligibility

The included studies should be in English, a journal published article, and a human study describing infected neonates. The excluded studies were non-English or animal studies or describing older children.

Study identification

Basic searching was done over the PubMed, Cochrane library, and Google scholar using the following keywords: C - reactive protein, Infants, and Late-Onset Sepsis.

Data extraction and synthesis

RCTs, clinical trials, and comparative studies, which studied the outcome of CRP, in early diagnosis of late-onset sepsis in infants, will be reviewed. Outcome measures included sensitivity (as a primary outcome), and specificity (as a secondary outcome).

Study selection

We found 250 records, 190 excluded based on title and abstract review; 60 articles are searched for eligibility by full-text review; 18 articles cannot be accessed; 20 studies were reviews and case reports; the desired marker (CRP) not used in 16 studies leaving 6 studies that met all inclusion criteria.

Statistical methodology

The pooling of data, Sensitivity, and Specificity, with 95% confidence intervals (CI) was done, using MedCalc ver. 18.11.3 (MedCalc, Belgium). According to heterogeneity across trials using the I²-statistics; a fixed-effects model or random-effects model were used in the meta-analysis process.

Results

The included studies published between 2008 and 2020. Regarding the type of included studies, 3 studies (out of 6

studies) were prospective, 2 studies were cross-sectional, while 1 study was retrospective [Table 1]. Regarding infants' characteristics, the total number of infants in all the included studies was 1203 infants [Table 1]. The mean gestational age of all infants was (32 weeks), and the median CRP cut-off value for the diagnosis of late-onset infection was 10 mg/dl [Table 1].^[4,6-10]

A meta-analysis study was done on 6 studies that described the diagnostic accuracy of CRP for diagnosis of late-onset infection; with an overall number of infants (N=1203) [Table 2].^[4,6-10]

Each outcome was measured by:

Pooled Proportions (%) for:

- For sensitivity
- For specificity

Concerning the primary outcome measure, we found 6 studies reported sensitivity with a total number of infants (N=1203).

I₂ (inconsistency) was 88.7% with a highly significant Q test for heterogeneity (p<0.0001), so random-effects model was carried out; with overall pooled sensitivity=71.7% (95% CI=55.2 to 88.3). Using the random-effects model, the meta-analysis process revealed that the pooled sensitivity of CRP for diagnosis of late-onset infection=71.7% (p<0.001) [Figure 1].

Concerning the secondary outcome measure, we found 6 studies reported specificity with a total number of infants (N=1203).

I₂ (inconsistency) was 0% with a non-significant Q test for heterogeneity (p>0.05), so fixed-effects model was carried out; with overall pooled specificity=76.1% (95% CI=69.6 to 82.6). Using the fixed-effects model, the meta-analysis process revealed that the pooled specificity of CRP for diagnosis of late-onset infection=76.1% (p<0.001) [Figure 2].

Table 1: Infants and study characteristics.

N	Authors	Type of study	Number of infants Total	CRP cut-off value (mg/dl)	Gestational Age (GA) (Average weeks)
1	Sherwin et al. ^[6]	Prospective	52	>18	42
2	Bohnhorst et al. ^[7]	Prospective	170	>10	28
3	Kordek et al. ^[8]	Prospective	52	>5	30
4	Beltempo et al. ^[9]	Retrospective	590	>10	27.9
5	Lamichhane and Mishra ^[10]	Cross-sectional	51	>10	---
6	Bunduki and Adu-Sarkodie ^[4]	Cross-sectional	288	≥ 6	---

#Studies arranged via publication year.

Table 2: Summary of outcome measures in all studies.

N	Authors	Primary outcome Sensitivity		Secondary outcome Specificity	
		Average Sensitivity (%)	SE	Average Specificity (%)	SE
1	Sherwin et al. ^[6]	41	17	73	13.5
2	Bohnhorst et al. ^[7]	69	12.5	84	12
3	Kordek et al. ^[8]	68	17	72	21.5
4	Beltempo et al. ^[9]	49	8	76	4
5	Lamichhane and Mishra ^[10]	88.5	5.5	46.1	18
6	Bunduki and Adu-Sarkodie ^[4]	95.7	2.5	82.4	9.5

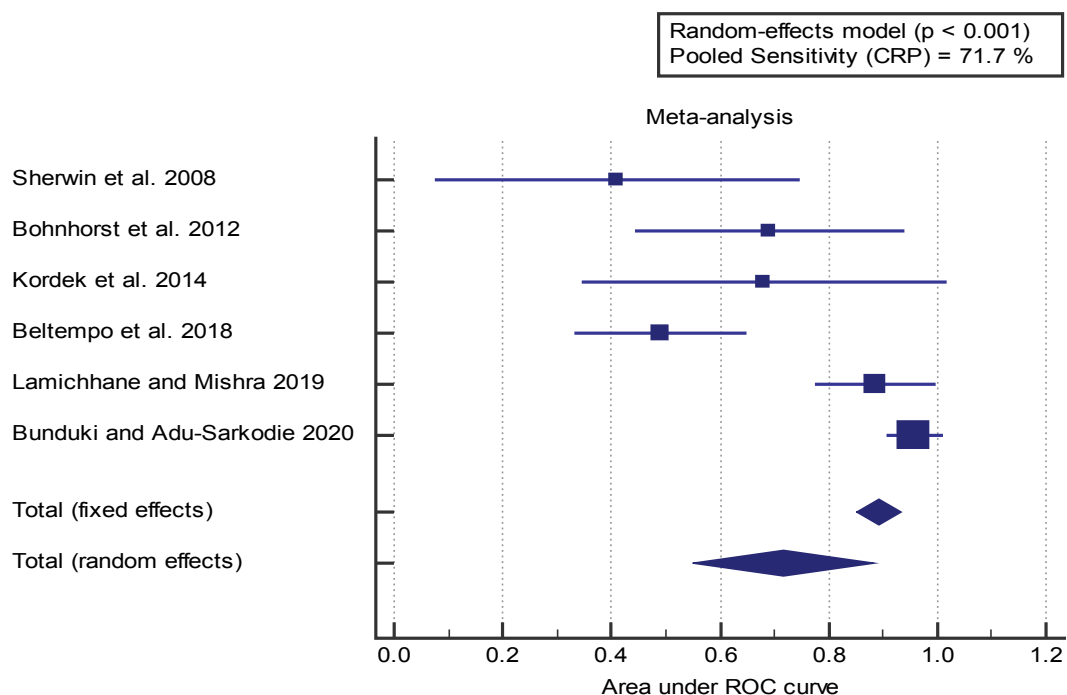


Figure 1: Forest plot demonstrating (Sensitivity).

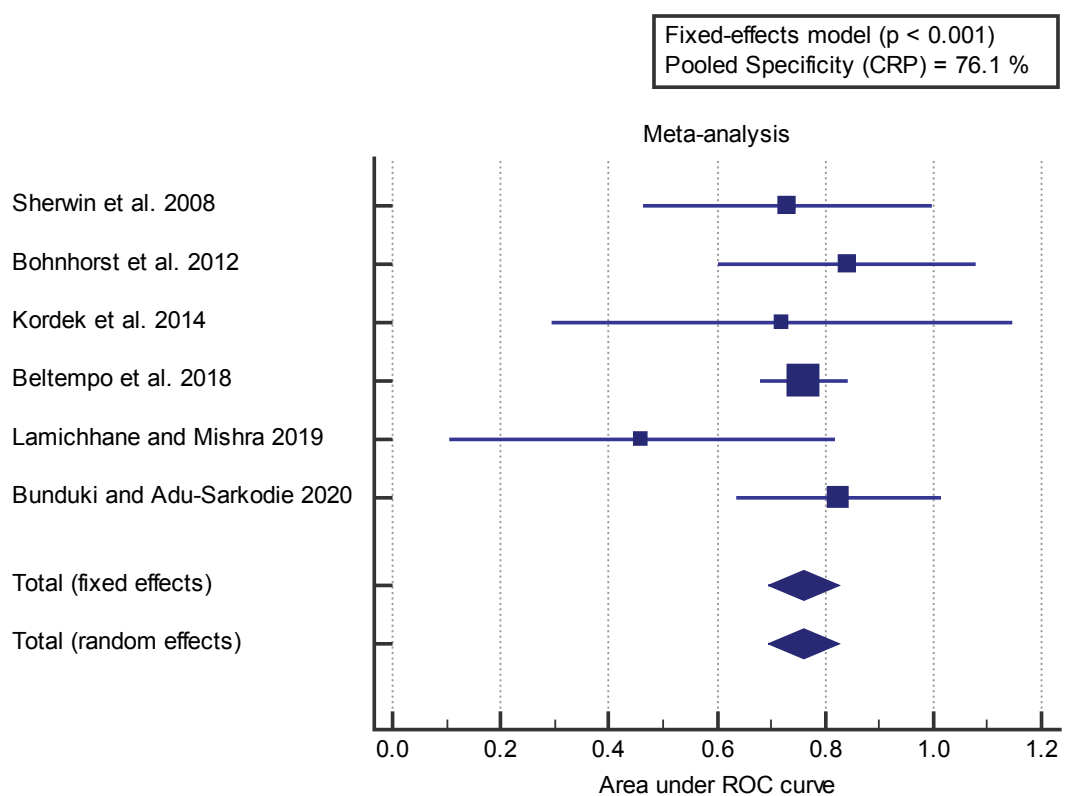


Figure 2: Forest plot demonstrating (Specificity).

Discussion

This work aims to determine the accuracy of C - reactive protein (CRP), in early diagnosis of late-onset sepsis in infants. The included studies published between 2008 and 2020. Regarding the type of included studies, 3 studies (out of 6 studies) were prospective, 2 studies were cross-sectional, while 1 study was retrospective. Regarding infants' characteristics, the total

number of infants in all the included studies was 1203 infants. The mean gestational age of all infants was (32 weeks), and the median CRP cut-off value for the diagnosis of late-onset infection was 10 mg/dl. A meta-analysis study was done on 6 studies which described diagnostic accuracy of CRP for diagnosis of late-onset infection; with an overall number of infants (N=1203). Concerning the primary outcome measure,

we found 6 studies reported sensitivity with a total number of infants (N=1203).

Using the random-effects model, the meta-analysis process revealed that the pooled sensitivity of CRP for diagnosis of late-onset infection=71.7% ($p<0.001$), which came in agreement with Beltempo et al.,^[9] Cantey and Bultmann,^[11] Brown et al.,^[12] Kipfmüller et al.,^[13] Bunduki and Adu-Sarkodie^[4] and Eschborn and Weitkamp.^[14]

Beltempo et al. reported that, at preliminary sepsis work-up (T_0), combining the CBC and CRP presented the highest sensitivity for late-onset sepsis diagnosis (65%) which was statistically superior to CRP (49%, $p<0.001$) and CBC (49%, $p<0.001$). At T24, the sensitivity of the CRP increased and became not statistically significantly different than when combined with the CBC (84% vs. 87%, $p=0.36$). At T24, the sensitivities of the person components of the CBC have been 50% for the I/T ratio, 4% for leukopenia, and 12% for thrombocytopenia. As compared to its performance at T24, the sensitivity of the CRP at T48 reduced (84% vs. 73%, $p=0.08$).^[9]

Cantey and Bultmann reported that the sensitivity of the CRP test can be lowest amongst infants with lower gestational age and birth weight, which means that CRP performs the worst amongst infants with the highest hazard for sepsis, median sensitivity was 0.62.^[11]

Brown et al. reported that, in total, 22 research with 2255 infants have been included (sample size range, 11-590 infants). Participants in most research were preterm (<37 weeks) or very-low-birth-weight (<1500 g) infants. Two researches moreover enrolled infants born at term. Most studies (14 of 16) used a pre-specified CRP stage cutoff for a “positive” index test (5-10 mg/L) and the culture of a pathogenic microorganism from blood as the reference trend. The hazard of bias became low with an independent evaluation of index and reference tests. At median specificity (0.74), pooled sensitivity was 0.62.^[12]

Kipfmüller et al. reported that, higher sensitivity and negative predictive value of IL-6 in comparison to CRP for diagnosing sepsis in VLBW infants. They determined CRP to be of decrease sensitivity for diagnosis of infection, however of increased sensitivity and specificity whilst measured 24 and 48 hours after diagnosis. CRP becomes helpful for the assessment of the course of an infection and for monitoring the efficacy of antibiotic therapy.^[13]

Bunduki and Adu-Sarkodie reported that, 69 (30.3%) of 228 neonates screened for sepsis, had a positive blood culture. Of the 228 sepsis infants, 94 (41.2%) had a positive CRP. Among the 69 cases with positive blood culture, CRP identified 66 cases. The sensitivity and specificity of CRP were 95.7%, 82.4% respectively. The accuracy (AUC) for the CRP was 94.8%. CRP showed its usefulness in the diagnosis of neonatal sepsis.^[4]

Eschborn and Weitkamp reported that, they identified 39 studies directly comparing CRP and PCT, but only four in very low birth weight (VLBW) neonates. The mean sensitivity for LOS was 77.4%.^[14] Concerning the secondary outcome measure,

we found 6 studies reported specificity with a total number of infants (N=1203).

Using the fixed-effects model, the meta-analysis process revealed that the pooled specificity of CRP for diagnosis of late-onset infection=76.1% ($p<0.001$), which came in agreement with Bunduki and Adu-Sarkodie,^[4] Cortese et al.,^[15] Beltempo et al.,^[9] Cantey and Bultmann,^[11] Chauhan, Tiwari, and Jain^[16] and Pammi and Weisman.^[17]

Bunduki and Adu-Sarkodie reported that the sensitivity, specificity, positive, and negative predictive values of the CRP were 95.7%, 82.4%, 70.2%, and 97.8%, respectively. The ROC curve of the CRP shows that the area under the curve (AUC) is 0.948 ($P<0.0001$).^[4]

Cortese et al. reported that CRP, a peptide synthesized by the liver in response to infection or inflammatory processes, was proven to be the best diagnostic marker of neonatal sepsis, with higher sensitivity and specificity than total PMN count and immature-to-total-PMN ratio.46 but, it presents a low sensitivity for the duration of the early levels of infection due to the time needed for release (about 6 hours). Serial determinations improve diagnostic accuracy and are useful for assessing the response to treatment.^[15]

Beltempo et al. reported that the sensitivity, specificity, positive, and negative predictive values of the CRP, CBC, and their combinations had been calculated at each time point and compared specificity was 76% (72–80).^[9] Cantey and Bultmann reported that, analyzed 22 studies including 2255 infants, the majority being 32weeks or less gestational age or 1500 g or less birth weight. The median specificity of CRP was 0.74.^[11]

Chauhan, Tiwari, and Jain reported that CRP is the most widely used biomarker in the laboratory settings for the detection of neonatal sepsis. CRP comes below the category of acute-phase proteins that are produced through the liver. CRP stages take 10 to 12 h to adjust, after the inception of infection. CRP has 24 h to 48 h of half of life, with a specificity of 94.8% and sensitivity of 67.1%.^[16]

Pammi and Weisman reported that CRP is an acute phase reactant synthesized within the liver in the first 6–8 h of the infective process with low sensitivity (60%) early in sepsis. however, serial CRP measurements at 24 h and 48 h enhance sensitivity to 82% and 84%, and specificity and positive predictive values range from 83 to 100%.^[17]

Conclusion

To conclude, late-onset sepsis represents significant morbidity and mortality in the neonatal intensive care unit, CRP plays an important role in the diagnosis of LOS.

Competing Interests

The authors declare that they have no competing interests. All the listed authors contributed significantly to the conception and design of study, acquisition, analysis, and interpretation of data and drafting of the manuscript, to justify authorship.

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