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# Accuracy of C-Reactive Protein Test for Neonatal Septicemia: A Diagnostic Meta-Analysis

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Data Collection B  
Statistical Analysis C  
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**Background:** The aim of this study was to evaluate the diagnostic value of C-reactive protein (CRP) test in detecting neonatal septicemia.





**Material/Methods:** We searched the Cochrane Library, PubMed, Springer, MBASE, Elsevier Science Direct, and Medline databases up to March 2017. To collect relevant data on CRP testing in patients with neonatal septicemia, we performed a meta-analysis of positive likelihood ratio (LR), sensitivity, negative LR, specificity and diagnostic odds ratio (dOR) of CRP testing, using Stata 12.0 and Meta-DiSc 1.4 data analysis software.

**Results:** Ten studies including 1819 participants were considered in this study. We found that positive LR, sensitivity, negative LR, specificity, and dOR of the CRP test for neonatal septicemia were 5.63 (95% CI=2.86 to 11.09), 0.70 (95% CI=0.66 to 0.75), 0.36 (95% CI=0.21 to 0.60), 0.89 (95% CI=0.87 to 0.91), and 17.99 (95% CI=6.50 to 49.83), respectively. The AUC and Q\* index of this meta-analysis were 0.90 and 0.83, respectively.

**Conclusions:** The area under the curve (AUC), negative LR, positive LR, Q\* index, specificity, and dOR of the CRP test suggest that it is appropriate for detecting neonatal septicemia.

**MeSH Keywords:** **C-Reactive Protein • Meta-Analysis • Neonatal Screening**

**Full-text PDF:** <https://www.medscimonit.com/abstract/index/idArt/916968>

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## Background

Neonatal sepsis is the leading cause of morbidity and mortality of children during the neonatal period worldwide [1–5]; therefore, early diagnosis and timely treatment are needed. However, lack of clinical specificity can delay correct diagnosis. It is therefore of great importance to detect reliable biomarkers for early diagnosis of neonatal septicemia [6]. In the intensive care unit, neonatal septicemia, which is mainly caused by drug-resistant bacteria, is not only life-threatening, but may also lead to long-term sequelae [7]. C-reactive protein (CRP) is a sensitive indicator of inflammation in humans; it activates the complement system and promotes granulocyte and macrophage phagocytosis, which is the most commonly used test for diagnosis of neonatal sepsis.

Whether the diagnostic value of the CRP test is appropriate for detecting neonatal septicemia is controversial [8–11]. The objective of this study was to assess the diagnostic accuracy of CRP as a single test for the early detection of neonatal sepsis. We performed a meta-analysis to assess the sensitivity, specificity, positive LR, negative LR, and diagnostic odds ratio (dOR) in patients tested by CRP.

## Material and Methods

### Source of material

We searched the electronic databases Cochrane Library, PubMed, Springer, Mbase, Elsevier Science Direct, and Medline (up to October 2017) using the following terms: “C-reactive protein” or “CRP” or “neonatal septicemia” or “neonatal sepsis” and “diagnosis” or “diagnostic” and “study” or “trial” or “research”, limiting the search to English-language articles.

### Study selection

Inclusion criteria were: (1) The internal standard mainly pertains to investigations of patients with neonatal septicemia; (2) The diagnosis of neonatal septicemia was pathologically confirmed, (3) The CRP test used for diagnosis for neonatal septicemia was included in the report; and the effect size included positive LR, sensitivity, negative LR, specificity, and dOR. We excluded reviews, case reports, and duplicate studies.

### Date extraction

A standardized reporting form was used to abstract the data from each study, including study year, year of the publication, country, cutoff value, case/control, detection of CRP, TP, and FP FN TN. Data were extracted independently by 2 investigators. The results were compared and disagreements were resolved by consensus.

## Evaluation of quality

Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria were evaluated to determine the quality of included studies [12,13]. The QUADAS identifies 4 key domains – “patient selection”, “index test”, “reference standard”, and “flow and timing” – which are combined to assess the risk of bias.

## Meta-analysis methods

A summarized receiver operating characteristic curve (SROC) was used to represent the performance of the diagnostic test [14]. The SROC curve includes multiple points, and the cutoff points are determined by selecting the maximum point, which is the sum of the sensitivity and the specificity [15]. The area under the curve (AUC) and exponential  $Q^*$  are potential useful summaries of the curve. Based on the exact analysis of the expression, the upper limit is derived and the lower limit of the  $Q^*$  is based on the limit, which is defined by the sensitivity equal to the feature point:  $Q^*$  is not equal to heterogeneity [14]. We measured the asymmetry of the funnel by the natural logarithmic scale of effect size, and we used Egger linear regression [16] to assess publication bias.

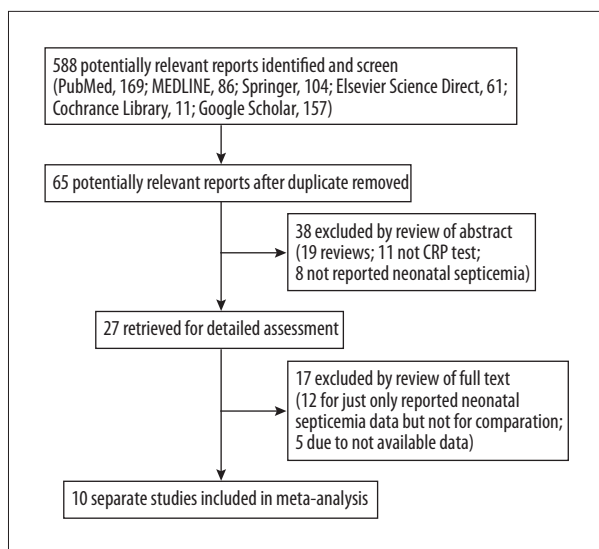
We performed statistical analysis using STATA software package v.13.0 (Stata Corporation, College Station, TX, USA). All P values are bilateral. P values less than 0.05 were considered to be statistically significant.

## Results

### Characteristics of eligible studies

Our literature search identified 588 papers in total. The flow chart of the literature screening is shown in Figure 1. After deleting irrelevant or duplicate papers, a total of 65 possible studies were found. After reading the abstracts, we excluded 38 articles (19 for the commentary; 11 for CRP testing; 8 did not report neonatal sepsis). The remaining 27 studies were assessed in full, and 17 of them were excluded (12 did not apply to CRP test and 5 were not available); therefore, we finally included 10 papers met our criteria.

As is shown in Table 1, there were 10 studies [8–11,17–22] in which sample sizes were between 26 and 1002 and CRP threshold values were between 5.82 and 10 mg/L. Quality assessment is shown in Table 2. In combination with this meta-analysis, the accepted criterion standard for diagnosis of neonatal septicemia includes confirmation by blood culture, and thus entry 7 does not apply; CRP test results were interpreted by instruments, so entry 9 does not apply.



**Figure 1.** Flow diagram for selection of studies for the meta-analysis.

**Analysis of diagnostic threshold**

The cutoff values used in the included studies (see Table 1, column 4) cause differences in sensitivity and specificity, called threshold effects. A premise of our study is that there is no threshold effect in the combination of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and other

indicators. The first step in the meta-analysis of diagnostic tests is to explore the threshold effect and other heterogeneity sources. Using Meta-disc software, the Spearman correlation coefficient for the study was -0.418 and the p value was 0.229, suggesting that there was no threshold effect in this study.

**Overall effects of diagnostic parameters of CRP test for neonatal septicemia in the meta-analysis**

The overall results of our meta-analysis of neonatal septicemia with CRP is summarized in Table 3. A total of 10 studies were included in the study, including 1819 participants. We used the random-effects model ( $Q^2=12.98$ ,  $I^2=84.6\%$ ,  $P<0.01$ ) to combined the data on true positive (TP), false positive (FP), false negative (FN), and true negative (TN). The overall estimates of the meta-analysis showed that the CRP test may be appropriate for detecting neonatal septicemia among patients, in which sensitivity, specificity, positive LR, negative LR, and dOR were 0.70 (95% CI=0.66 to 0.75), 0.89 (95% CI=0.87 to 0.91), 5.63 (95% CI=2.86 to 11.09), 0.36 (95% CI=0.21 to 0.60), and 17.99 (95% CI=6.50 to 49.83), respectively. The  $Q^*$  index and AUC were 0.83 and 0.90, respectively (Figure 2).

**Publication bias**

Egger’s test was performed to assess the publication bias of our study, showing there was no publication ( $t=-1.87$ ,  $P>0.05$ ).

**Table 1.** Characteristics of studies included in the meta-analysis.

Study	Year of publication	Country	Cutoff value (mg/L)	Case/control	Detection of CRP	CRP test			
						TP	FP	FN	TN
Sharma A, et al. [20]	1993	India	>6	10/16	LA	8	1	2	15
Benitz WE, et al. [17]	1998	American	≥10	20/982	NA	7	98	13	884
Manucha V, et al. [19]	2002	India	>6	21/129	LA	16	27	5	102
Vazzalwar R, et al. [21]	2005	American	>8	18/16	NA	14	6	4	10
Schrama A, et al. [11]	2008	The Netherlands	>10	24/55	NA	22	1	2	54
Boo NY, et al. [18]	2008	Malaysia	NA	18/69	NA	10	7	8	62
Zaki Mel-S, et al. [22]	2009	Egypt	>8	58/62	PENIA	50	2	8	60
Celik IH, et al. [10]	2010	Turkey	>5.82	170/50	ITM	121	1	49	49
Hotoura E, et al. [9]	2011	Greece	>10	25/50	FNM	16	11	9	39
Choo YK, et al. [8]	2012	Korea	≥10	12/14	Standard sterile techniques	1	2	11	12

TP – true positive; FP – false positive; FN – false negative; TN – true negative; NA – not available; PENIA – particle-enhanced nephelometric immunoassay; LA – latex agglutination; ITM – immune turbidimetric method; FNM – flow nephelometry method.

**Table 2.** Quality assessment of the included articles.

QUADAS list item	Reference number of the included studies									
	1	2	3	4	5	6	7	8	9	10
1. Did the spectrum of patients represent the patients who will receive the test in practice?	+	0	+	0	+	+	0	+	+	+
2. Were selection criteria clearly described?	+	+	+	+	+	+	+	+	+	+
3. Is the reference standard likely to correctly classify the target condition?	+	+	+	+	+	+	+	+	+	+
4. Is the period between the reference standard and index test short enough to be reasonably sure that the target condition did not change between the 2 tests?	+	0	+	+	+	+	+	+	0	+
5. Did the entire sample or a random selection of the sample receive verification using a reference standard of diagnosis?	+	+	+	+	+	+	+	+	+	+
6. Did patients receive the same reference standard regardless of index test result?	+	+	+	+	+	+	+	+	+	+
7. Was the reference standard independent of the index test (i.e., index test did not form part of the reference standard)?	0	0	0	0	0	0	0	0	0	0
8. Was execution of the index test described in sufficient detail to permit replication of the test?	+	+	+	+	+	+	+	+	+	+
9. Was execution of the reference standard described in sufficient detail to permit its replication?	+	+	+	0	+	+	+	+	+	+
10. Were index test results interpreted without knowledge of results of the reference standard?	0	0	+	+	0	+	+	+	+	+
11. Were reference standard results interpreted without knowledge of results of the index test?	0	+	+	0	0	+	+	+	+	+
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	0	0	0	0	0	0	0	0	0	0
13. Were uninterruptable/intermediate test results reported?	0	0	+	+	+	0	+	0	+	+
14. Were withdrawals from the study explained?	+	+	+	+	+	+	+	+	+	+

**Table 3.** The indexes of neonatal septicemia diagnosed by CRP test.

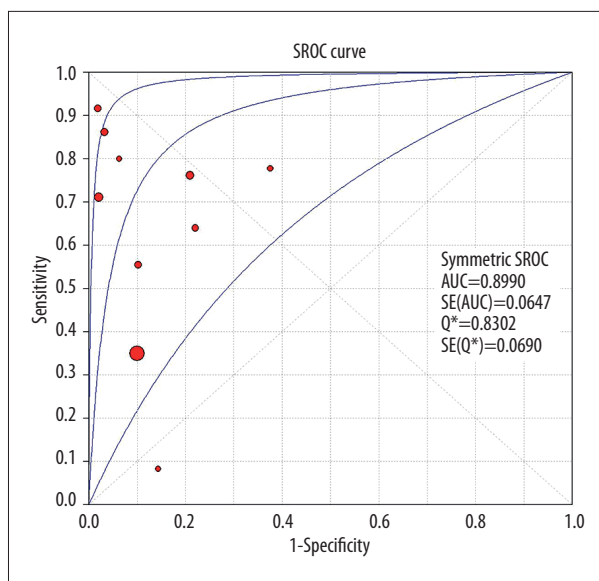
Parameter	Test of association		Test of heterogeneity			Model	Egger's test for publication bias	
	Estimates	95% CI	Q	P value	I <sup>2</sup> (%)		t	P value
Overall	–	–	12.98	<0.01	84.6	Random	–1.87	0.10
Sensitivity	0.70	0.66 to 0.75	49.47	<0.01	81.8	–	–	–
Specificity	0.89	0.87 to 0.91	43.03	<0.01	79.1	–	–	–
Positive LR	5.63	2.86 to 11.09	49.54	<0.01	81.8	Random	–	–
Negative LR	0.36	0.21 to 0.60	100.94	<0.01	91.1	Random	–	–
dOR	17.99	6.50 to 49.83	41.98	<0.01	78.6	Random	–	–

LR – likelihood ratio; dOR – diagnostic odds ratio.

## Discussion

This meta-analysis evaluated the diagnostic value of the CRP test in detecting neonatal septicemia. After a comprehensive

analysis of 10 papers, we found that sensitivity, specificity, positive LR, negative LR, and dOR of the CRP test for neonatal septicemia were 0.70 (95% CI=0.66 to 0.75), 0.89 (95% CI=0.87 to 0.91), 5.63 (95% CI=2.86 to 11.09), 0.36 (95%



**Figure 2.** The summary receiver operating characteristic (SROC) curve of CRP test.

CI=0.21 to 0.60), and 17.99 (95% CI=6.50 to 49.83), respectively, which suggest that the CRP test has a good diagnostic value for neonatal sepsis.

Neonatal sepsis, which is defined as a 30-day infection after birth, remains an important clinical syndrome and is characterized by symptomatic systemic illness. Disease progression in neonates is rapid and mortality and morbidity rates are high [10]. Clinically inoculation of premature neonates with sepsis and late-onset neonatal sepsis were divided into 3 days and 4–28 days after birth [23]. Due to diagnostic procedures, early identification of neonatal sepsis is still a global problem [8]. Studies have shown that serum procalcitonin (PCT) has high specificity and sensitivity in diagnosing early neonatal sepsis, but the cost is high.

Under normal circumstances, serum CRP levels are very low; the body of a person infected by bacteria due to WBC and other inflammatory cells releases endogenous neurotransmitters to stimulate liver cells. Synthesis of CRP occurs within 4–6 h and

peaks at 36–50 h, so the inflammatory process generally begins 6–12 h after the detection of CRP [24]. Neonatal sepsis, in which bacteria invade the blood, release toxins, and stimulates systemic inflammatory response, can lead to elevated CRP.

There are several limitations of this study that should be discussed. Neonatal sepsis was not divided into early-onset and late-onset in this study. In early-onset neonatal sepsis, bacteria are derived from the intrauterine and postpartum periods, and these pathogens are concentrated. For example, in Australia, 80% of sepsis occurs within 48 h of birth and is mostly caused by *B streptococcus* (GBS) and gram-negative bacteria, so the time is defined at 48 h in order to guide the clinical selection of antibiotics and predict prognosis. In addition, significant between-study heterogeneities were detected in our meta-analysis, and this may have affected our results. Heterogeneity is one of the main problems of the meta-analysis method [25], mainly due to misleading outcomes due to non-uniform data. In addition, the studies we included had differences in populations, including healthy newborns, premature children, low-birth-weight children, high-risk factors, neonatal hemolysis, intracranial hemorrhage, and wet lungs, and these differences may have affected our results. Different CRP detection methods, neonatal gestational age, and other factors may also have affected the results of this study.

## Conclusions

The CRP test appears to be appropriate for use in detecting neonatal septicemia. The CRP test can help diagnose neonatal septicemia to guide rational drug use in clinical practice.

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## Conflict of interest

None.

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