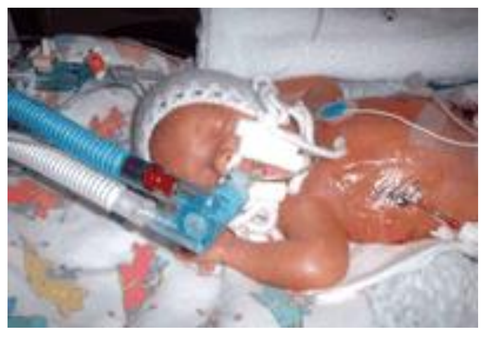
C-reactive protein for diagnosing late-onset infection in newborn infants: Cochrane Review of Diagnostic Test Accuracy

Late-onset (> 72 h after birth) infection is the most common serious complication of intensive care for preterm or sick newborn infants. Infection is associated with higher rates of mortality, morbidity, and neurodevelopmental disability.

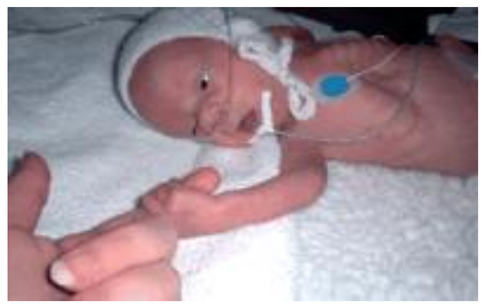


Index test

The most commonly used and established biomarker to diagnose infection is the serum level of C-reactive protein (CRP). CRP can be measured in laboratories within about one hour using a very small volume of serum. CRP levels are usually very low, but rise over 12-24 hours to detectable concentrations following an infectious or inflammatory stimulus.

Clinical pathway

Serum CRP is typically measured at the initial assessment of an infant with suspected late-onset infection, usually alongside other tests including microbiological culture of a blood sample ("blood culture"). Because the culture of a potentially pathogenic organism from a blood sample takes about 24-48 hours to complete (the reference standard), the purpose of measuring the serum CRP level is to make a more immediate assessment of the overall likelihood that an infant is truly infected.



Objective

To determine the diagnostic accuracy of serum CRP for late-onset invasive infection in newborn infants.

Table 1: **Inclusion criteria**

Types of studies	Cohort and cross-sectional studies
Participants	Hospitalised newborn infants older than 72 hours
Index test	Serum CRP level (threshold as defined by authors)
Target condition	Microbiologically-confirmed late-onset infection including bacteraemia, fungaemia, meningitis, osteomyelitis, septic arthritis, and peritonitis
Reference standard	Diagnosis of late-onset infection confirmed by culture from a normally sterile site, including CSF, blood, bone or joint

Methods

Search strategy

We searched MEDLINE, Embase, and Science Citation Index and examined reference lists of included studies as well as conference proceedings.

Data collection and analysis

Two reviewers screened titles and abstracts and examined full texts independently. Data extraction and quality assessment (using QUADAS-2) were conducted by one reviewer and checked by another. Any disagreements were resolved in discussion with input from clinical professionals as needed.

We constructed “2-x-2" diagnostic tables from the reference standard (infected/not infected) and the index test (cut-off level for serum CRP for a positive result as defined by each study). We created forest plots with 95% confidence intervals (CI) for sensitivity and specificity for each study.

We conducted bivariate random effects meta-analysis (using metandi commands, Stata 13), which takes into account correlation between sensitivity and specificity, and constructed a hierarchical summary receiver operating characteristic (SROC) curve.

Results

Out of 7,047 references identified by the database searches, 18 studies were included in our analyses.

Pooled estimates (Figure 1):

- Sensitivity 0.69 (95% CI 0.51 to 0.82)
- Specificity 0.80 (95% CI 0.69 to 0.87)
- Positive likelihood ratio 3.37 (95% CI 2.26 to 5.03)
- Negative likelihood ratio 0.39 (95% CI 0.24 to 0.63).

Figure 1: **Summary receiver operating curve**

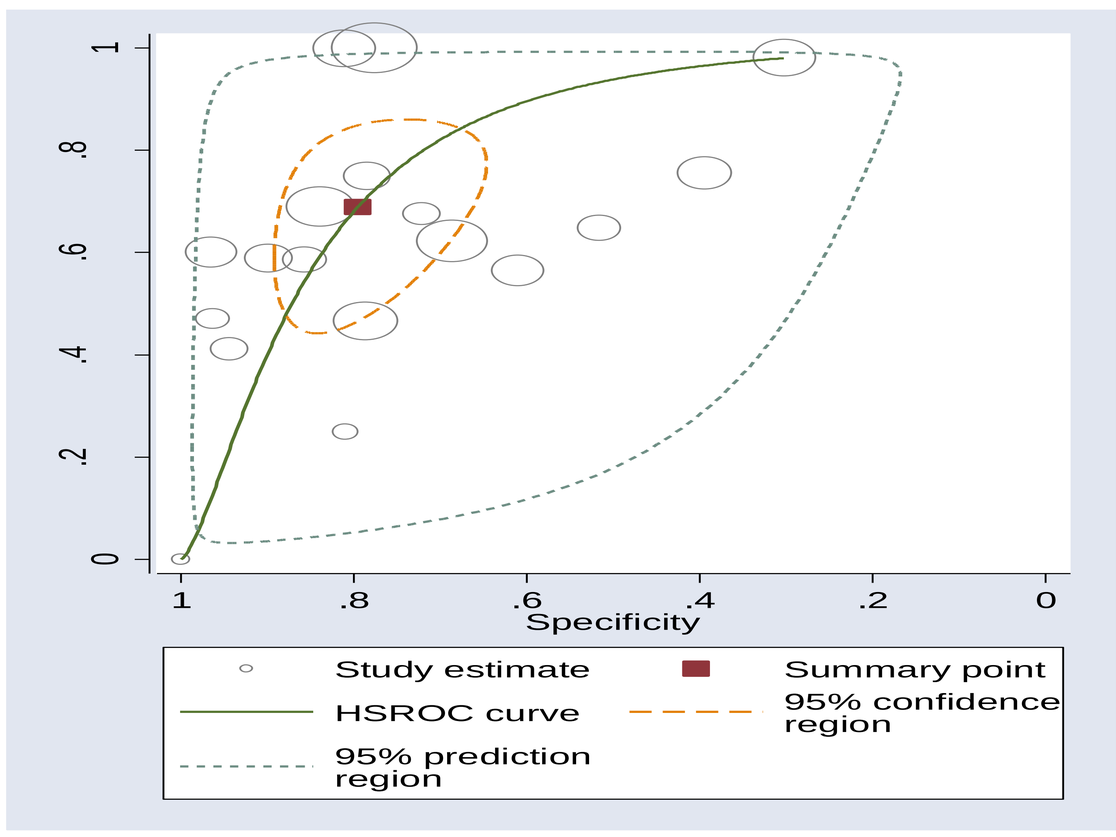


Table 2: **Overview of pre- and post-test probabilities**

Pre-test probability	Post-test probability after **positive** test[1]	Post-test probability after **negative** test[2]
20%	45.7%	8.9%
40%	69.2%	20.6%
60%	83.5%	36.9%
80%	93.1%	60.9%

[1]Positive likelihood ratio = 3.37
[2]Negative likelihood ratio = 0.39

Conclusions

Most included studies had small sample sizes a variety of methodological weaknesses. Meta-analysis shows that diagnostic accuracy of serum CRP level is modest with a positive likelihood ratio of 3.37 and a negative likelihood ratio of 0.39. Serum CRP level in this context is not sufficiently accurate to reliably confirm or exclude a diagnosis of infection.

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