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The role of the complete blood count in the diagnosis of culture-proven neonatal sepsis: a systematic review and meta-analysis

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Abstract

Objective: Neonatal sepsis is a significant cause of morbidity and mortality, particularly in preterm infants. Despite its routine use in adults, the diagnostic utility of the complete blood count (CBC) in neonatal sepsis remains debated. This systematic review and meta-analysis aimed to evaluate the diagnostic accuracy of CBC parameters for neonatal sepsis.

Methods: This review was registered on PROSPERO (CRD42023476510). MEDLINE, Embase, CINAHL and the Cochrane Library were searched from database inception to 28th October 2024. Observational studies of neonates with sepsis, published in English, were included. Pooled diagnostic accuracy metrics were calculated for CBC parameters, including the white cell count (WCC), neutrophil count, and immature-to-total neutrophil ratio (ITR). Bias was assessed using a modified QUADAS-2 tool.

Results: Functional CBC parameters like ITR and mean neutrophil volume (MNV) showed moderate diagnostic accuracy. Pooled analysis revealed that an ITR >0.20 had 66% sensitivity and 85% specificity for neonatal sepsis. MNV also showed promising diagnostic utility, but substantial heterogeneity across studies ($I^2 > 0.90$) limited its generalisability. Traditional parameters like the WCC and platelet count had lower diagnostic accuracy.

Conclusions: The CBC is a rapid, cost-effective test requiring minimal blood volume, making it a practical adjunct in neonatal diagnostics. Functional parameters like ITR and MNV show the potential to complement existing approaches but are insufficient as standalone diagnostic tools. Further research is needed to validate their clinical utility and address heterogeneity in study designs.

What is already known on this topic:

The complete blood count (CBC) is widely used in adults but is often dismissed in neonatal diagnostics due to perceived limited utility. Current NICE guidelines exclude the CBC from sepsis evaluation, citing low-quality evidence for the diagnostic values of the white cell count. However, these guidelines do not consider the full scope of parameters available from the CBC, including novel immune cell activation parameters available from modern analysers.

What this study adds:

This study highlights the diagnostic potential of functional CBC parameters, specifically the immature-to-total neutrophil ratio and mean neutrophil volume, which exhibit higher accuracy than traditional cell counts. These findings suggest that these parameters could complement existing diagnostic tools for neonatal sepsis.

How this study might affect research, practice or policy:

Integrating CBC functional parameters into diagnostic protocols could improve the detection of neonatal sepsis and reduce unnecessary antibiotic usage. This study highlights the need for future research on CBC-based diagnostics in neonates and a re-evaluation of the current guidelines.

Introduction

Approximately 100,000 babies are admitted to neonatal units (NNU) in the UK each year, primarily due to preterm birth (gestational age <37 weeks) and suspected infections. Neonatal sepsis, a significant cause of morbidity and mortality, accounted for 4,640 cases in the UK and 6.31 million cases globally in 2019, as defined by ICD-10 codes for bacterial infections [1].

Accurate and timely diagnosis of neonatal sepsis is critical to improving outcomes. Current UK guidelines, published by the National Institute for Health and Care Excellence (NICE) in 2021, recommend blood cultures as the gold standard [2]. However, blood cultures are often negative in neonatal sepsis, with sensitivities as low as 40%, and results can take up to 72 hours, delaying definitive treatment decisions [3]. Baseline C-reactive protein (CRP) measurements are recommended to monitor treatment efficacy, but their delayed sensitivity limits their role in early diagnosis [4].

Despite its widespread use outside neonatal care, the complete blood count (CBC) is not included in the NICE guidelines for diagnosing sepsis due to insufficient evidence supporting the diagnostic utility of the white cell count (WCC)[5]. In contrast, the CBC is a well-established diagnostic tool in adults with suspected sepsis [6]. Studies in adults have demonstrated significant differences in neutrophil counts between infected and non-infected patients at various time points after diagnosis ($p < 0.0001$ at 2 days, $p = 0.0001$ at 4 days, and $p = 0.013$ at 7 days)[6].

The CBC is a rapid, inexpensive test that requires minimal blood volume (as little as 20 µL) and is routinely measured in neonates to monitor haemoglobin levels and detect anaemia [7]. Recent innovations in automated haematology analysers enable to measurement of functional parameters such as immature-to-total neutrophil ratio (ITR) and mean neutrophil volume (MNV), providing a fresh perspective on the diagnostic utility of the CBC. ITR is a measure of neutrophil regeneration - a higher ITR indicates an increase in immature neutrophil production in response to infection [8]. Immature neutrophils are larger than mature neutrophils, so an increase in MNV also occurs [8].

This systematic review and meta-analysis aims to evaluate the diagnostic accuracy of CBC parameters, particularly functional markers, for neonatal sepsis. By leveraging recent advances in CBC technology and addressing limitations of prior diagnostic approaches, our study seeks to reframe the CBC as a potential adjunctive tool for improving early detection and management of neonatal sepsis.

Methods

This review follows the Cochrane Library guidelines for conducting a diagnostic accuracy systematic review [9] and was registered prospectively with PROSPERO (CRD42023476510) on 05/12/2023.

Eligibility criteria, information sources and search strategy

We conducted an electronic search for studies reporting the diagnostic accuracy of the CBC for neonatal sepsis. Eligibility criteria included prospective, retrospective, and cross-sectional observational studies conducted on humans and published in English. Case-control studies were included despite their limitations, as they provide valuable insights into diagnostic test performance under specific conditions. Studies with heterogeneous sepsis definitions (e.g., non-culture-proven cases) were excluded to ensure diagnostic consistency, thus only studies providing culture-proven sepsis as a case definition were included. Abstracts, case reports, and conference proceedings were excluded due to insufficient detail on diagnostic accuracy measures.

Searches were performed in MEDLINE and Embase via Ovid, Cochrane, and CINAHL from inception to 28th October 2024. Full search strategies for each database are provided in the Appendix. To identify additional studies, reference lists of included studies and previously published reviews were manually screened. All search results were imported into Covidence (Melbourne, Australia) for screening.

Study selection

Two reviewers (EH, MA) independently screened titles and abstracts for relevance, with discrepancies resolved by a third assessor (MV). Full texts of selected studies were reviewed to confirm eligibility. Heterogeneous sepsis definitions were mitigated by excluding studies that did not define cases using culture-proven sepsis. Studies with undefined control groups or inadequate reporting of CBC parameters were also excluded.

Data extraction

For each study, diagnostic accuracy measures including sensitivity (the proportion of correctly identified septic patients), specificity (the proportion of correctly identified non-septic patients),

positive predictive value (PPV; the probability that a positive result is correct), and negative predictive value (NPV; the probability that a negative result is correct) were recorded in an Excel spreadsheet. Where PPV and NPV were not directly reported, they were calculated using sensitivity, specificity, and the prevalence of sepsis in each study. True positives, true negatives, false positives, and false negatives were also derived. Case definitions for neonatal sepsis (e.g. positive culture with or without clinical signs of sepsis) and control definitions were also documented.

Assessment of applicability

Applicability was assessed using a modified tool derived from QUADAS-2 [10], the Critical Appraisal Skills Programme (CASP) diagnostic checklist [11], and the Newcastle-Ottawa scale [12]. Selected questions ensured relevance to the research objective. Two reviewers (EH, MA) independently applied the tool, with disagreements resolved by a third reviewer (MV). Studies scoring ≥6/8 were deemed applicable, although all studies were included regardless of score. The use of culture-proven sepsis as a case definition was required for inclusion.

Data synthesis

All analyses were performed using RStudio (2023.06.1.524, R version 4.3.0). Patient characteristics and biomarker values were summarised as means ± standard deviations or medians with inter-quartile ranges (IQR), according to underlying distributions. Optimal thresholds (the threshold at which a test result is considered positive or negative) for each parameter were identified by the highest Youden index (a measure of overall test performance). Diagnostic accuracy was assessed using a bivariate model (mada::reitsma), incorporating sensitivity, specificity and the area under the curve (AUC; a quantification of overall performance, where values closer to 1 indicate better discrimination between groups). This model was employed to account for study-level differences in diagnostic thresholds. Heterogeneity was quantified using the I^2 statistic.

A minimum of three studies was required to perform a meta-analysis for each parameter. Subgroup analyses were not conducted to explore variability across study designs and sampling times due to low study numbers. Publication bias was assessed visually through funnel plots.

Results

Study selection

In total, 428 studies were identified through database searches (Figure S1). After title and abstract screening, 259 studies were excluded, leaving 169 for full-text assessment. Ultimately, 24 studies were included in this systematic review: 14 studies from database screening [13–26] and 10 additional studies identified through reference list screening of systematic reviews (n = 5)[27–31] and included studies (n = 5)[32–36]. The reasons for exclusion are presented in Figure S1. Studies with heterogeneous sepsis definitions (e.g., those including non-culture-proven sepsis) were excluded to ensure comparability.

Study characteristics

Among the 24 studies included in this review, 16 were prospective [13–16,18,19,21–24,26,29,32–34,36] and eight were retrospective [17,20,25,27,28,30,31,35](Table 1). All studies defined neonatal sepsis based on a positive blood culture. Nineteen studies also included clinical signs [14–19,21–24,26–31,34–36], and four included additional laboratory indicators [15–17,27]. The median prevalence of sepsis across the included studies was 50.0% (IQR: 40.9% - 51.7%).

Fifteen studies defined the control group as an absence of clinical signs of sepsis [13–16,18,19,22–24,27,28,30,31,34,35], and six studies included the absence of laboratory markers [13,14,18,22,24,27]. Nine did not specify the criteria used to define the control group [17,20,21,25,26,29,32,33,36].

In total, 1377 neonates with sepsis were included across the 24 studies (Table 1). The median gestational age at birth was 34.3 weeks (IQR: 31.1 – 38.0 weeks), and the median age at sampling was 8.0 days (IQR: 7.0 – 15.0 days). The control group consisted of 1865 neonates, with a median gestational age at birth of 35.6 weeks (IQR: 31.3 – 38.0 weeks) and a median age at sampling of 7.0 days (IQR: 2.6 – 9.6 days). No significant differences in gestational age (P = 0.705) or age at sampling (P = 0.355) were observed between sepsis and control groups.

Level of applicability of included studies

Sixteen of the 24 included studies scored 6/8 or higher on the quality assessment tool [13,15–17,20–24,27,28,30–32,34,36](Table 1). Nine studies did not report when samples were taken [17–19,21,25,27–29,36], and nine studies did not specify how the CBC was measured [14,19,20,23,25–28,35]. Five studies included a sample size or power calculation [13,21,27,29,32]. While the overall applicability of the included studies was high (Figure 1), the lack of detailed reporting in some studies made the assessment of certain aspects of applicability more challenging.

Synthesis of results

The included studies assessed various CBC parameters: WCC (n = 8)[13,14,16,18,19,33,35,36], neutrophil count (n = 5)[13,16,18,33,36], ITR (n = 8)[13,16,18,23,24,27,33,36], neutrophil-to-lymphocyte ratio (NLR; n = 5)[21,25,26,30,31], delta neutrophil index (DNI; n = 2)[15,17], neutrophil activation markers (MNV (n = 3)[13,16,22]; MNC: mean neutrophil conductivity (n = 2)[16,22]; MNS: mean neutrophil scatter (n = 2)[16,22]), platelet count (n = 6)[13,18,32–34,36], mean platelet volume (MPV; n = 6)[20,24,28,29,32,34], and platelet-to-lymphocyte ratio (PLR; n = 3 [21,26,27](Table S1).

Meta-analyses were conducted for the WCC, neutrophil count, ITR, NLR, MNV, platelet count, and MPV (Table 2). Due to insufficient studies reporting diagnostic accuracy data, meta-analyses were not performed for DNI, MNC, and MNS. Additionally, a reliable meta-analysis could not be conducted for PLR due to substantial heterogeneity in reported values (15.00, 62.40, and 99.57). One study [21] was excluded from the NLR analysis due to extreme variability compared to other studies (0.80 vs 2.10 – 4.16) which suggested methodological differences. Therefore, three studies were not included in any meta-analyses [16,17,21].

MNV showed the highest diagnostic accuracy for neonatal sepsis, with a sensitivity of 76.6%, specificity of 90.9%, and an optimal threshold of 157.90 au [22] (Figure 2). Substantial heterogeneity was observed for MNV ($I^2 = 0.85$), underscoring the need for standardisation in future research.

In contrast, studies reporting on ITR exhibited much less heterogeneity (I^2 < 0.10) (Figure 3). ITR demonstrated high specificity (85%) and moderate sensitivity (66%), suggesting its utility as a diagnostic adjunct test. Subgroup analysis of studies reporting an optimal threshold of 0.20 (n = 5) [13,18,23,27,36] revealed a higher pooled sensitivity (72.5%) compared to the full cohort (66.3%) while specificity remained similar (85.3% vs 85.4%) and the AUC was higher (0.816 vs 0.773)(Figure S2).

Platelet count demonstrated moderate diagnostic accuracy, with a sensitivity of 66.5%, specificity of 81.4%, and an optimum threshold of 278 $x10^9$/L [32] (Figure S3). Subgroup analysis of studies reporting an optimal threshold of 150 $x10^9$/L reduced the I^2 statistic (< 0.10) and resulted in slightly lower diagnostic accuracy (sensitivity: 51.2%; specificity: 82.0%)(Figure S4).

NLR had the lowest diagnostic accuracy, with a sensitivity of 69.1%, specificity of 72.6%, and AUC of 0.685, at an optimal threshold of 3.17 [26] (Figure S5). The results of meta-analyses for WCC (Figure S6), neutrophil count (Figure S7), and MPV (Figure S8) are presented in Table 2. Subgroup analyses based on study design or onset of sepsis could not be conducted due to the low number of studies available for each parameter.

Discussion

Principal findings

This systematic review and meta-analysis evaluated the diagnostic utility of CBC parameters for neonatal sepsis, with a particular focus on functional markers. Although ITR and MNC showed moderate diagnostic accuracy, they are insufficient as standalone markers. ITR achieved a sensitivity of 66.3% and specificity of 85.4%, with minimal heterogeneity ($I^2 < 0.10$), suggesting consistent diagnostic performance across studies. However, its moderate sensitivity means it would miss a significant proportion of true sepsis cases.

MNV demonstrated promising utility, with a pooled sensitivity of 76.6% and specificity of 90.9%. However, the heterogeneity of included studies ($I^2 = 0.85$) raises concerns about generalisability. Differences in study design, diagnostic thresholds, and analytical techniques likely contribute to this variability. Traditional markers including the WCC displayed lower diagnostic accuracy, reflecting their susceptibility to physiological factors such as perinatal stress, neonatal colonization, and steroid exposure [37].

Comparison with existing literature

Our study builds upon and differentiates itself from prior systematic reviews. Earlier reviews primarily focused on traditional CBC parameters such as the WCC and platelet count, which were found to have limited diagnostic accuracy for neonatal sepsis [38,39]. Fowlie et al. identified a high variability in the WCC, which could be due to factors like perinatal stress and postnatal physiological changes, or due to variability in the methodology of included papers, including case definitions or timing of measurements. Rees et al. highlighted the need for novel biomarkers, particularly in resource-constrained settings where the cost and availability of tests, especially PCT, pose challenges.

In contrast, this review emphasises functional parameters such as ITR and MNV. Previous reviews have concluded that both the MNV and ITR have high diagnostic accuracy for neonatal sepsis [40,41]. However, Mishra et al. [40] included studies evaluating culture-proven and suspected sepsis, while

Zhang et al. [41] evaluated studies that defined the control group as neonates with suspected sepsis. These reviews highlight the heterogeneity of definitions within the literature. In contrast, the current study excluded all studies with overlapping case and control definitions to ensure a robust evaluation of the neonatal CBC.

The current gold standard for diagnosing sepsis in neonates, as defined by the NICE guidelines, is a positive blood culture [2]. However, up to 60% of true sepsis cases are culture-negative becoming positive only in severe cases of sepsis. Serial CRP measurements are recommended to monitor the progression of sepsis, although CRP levels only begin to rise 12 hours after infection onset, making it unsuitable for early diagnosis [4]. Moreover, the accuracy of CRP varies significantly, with reported sensitivities ranging from 30% to 80% at symptom onset [4].

The guidelines also recommend starting antibiotics while awaiting laboratory results [2]. However, the inappropriate use of antibiotics, especially in culture-negative cases, can have both short- and long-term health consequences for neonates. For example, a seven-day course of antibiotics increases the risk of necrotising enterocolitis twofold [42], and long-term antibiotic exposure has been linked to higher risks of inflammatory bowel disease (OR: 6.34)[43].

The CBC's affordability, rapid processing and minimal blood volume requirements make it a practical adjunctive tool, even in low-resource settings where advanced technology is becoming more readily available. Functional parameters such as ITR and MNV could enhance early detection and guide antibiotic stewardship, especially when existing tools such as CRP and PCT yield inconclusive or conflicting results.

One application of the CBC, which has been previously investigated by both Narasimha and Kumar [44] and Huang et al. [45], is the development of diagnostic algorithms incorporating the CBC parameters. Narasimha and Kumar created a scoring system for the CBC whereby all neonates with culture-positive sepsis scored at least five out of ten. Similarly, Huang et al. combined CBC parameters with clinical variables using machine learning. Their highest-performing models achieved specificities greater than

70% with sensitivities of 40 - 60%. Since these studies utilised the CBC in different ways, it is not possible to compare them directly. However, they provide good evidence for investigating the use of the CBC in more sophisticated diagnostic models.

By focusing on functional CBC parameters and leveraging advancements in analyser technology, our study reframes the CBC as more than a traditional diagnostic tool. While its standalone utility is limited, integrating CBC parameters with other diagnostic approaches offers a promising pathway for improving neonatal sepsis outcomes. Future research should aim to standardise the use of these parameters, explore their role in combined diagnostic algorithms, and validate their performance in prospective clinical settings.

Strengths and limitations

Decision-making in neonatal sepsis is a critical challenge for neonatologists. A strong evidence base is essential, given the vulnerability of this patient cohort due to their immature immune systems. A key challenge is the lack of a standard definition for neonatal sepsis, with many studies relying solely on clinical signs. However, signs such as tachycardia, tachypnoea, and jaundice are non-specific and commonly present in healthy neonates. Our review highlights the challenge of addressing inter-study variability in diagnostic accuracy studies. To enhance the accuracy of our findings, we excluded all studies that did not include a positive culture as part of the sepsis diagnosis, accounting for 42 excluded studies.

The breadth of definitions for control groups in the literature also posed a significant challenge. Thirty-two studies were excluded because their control groups were inadequately defined, often including neonates with clinical signs of sepsis but negative blood cultures. This highlights the overlap between case and control groups in neonatal sepsis research. By excluding these studies, we believe our study provides the most accurate picture of the CBC's diagnostic utility for neonatal sepsis to date. However, even within the included studies, it is likely that misclassification occurred due to culture-negative

250 septicaemia and blood culture contaminants. The lack of a gold standard sepsis definition continues to
251 weaken the literature on this subject.
252 Finally, a substantial limitation of this review is the insufficient number of relevant studies available
253 for analysis. There is a clear need for further research on all the parameters evaluated to confirm our
254 findings.

255 **Conclusion**

256 Building upon earlier reviews, our systematic review and meta-analysis evaluates the diagnostic
257 accuracy of the CBC for neonatal sepsis, providing novel insights into their diagnostic potential. The
258 CBC, particularly functional parameters such as ITR and MNV, has potential as a low-cost adjunctive
259 tool in neonatal sepsis diagnosis. However, its moderate diagnostic accuracy underscores the need for
260 further validation and integration with established biomarkers.

Statement of Ethics

This review follows the guidelines for conducting a diagnostic accuracy systematic review from the Cochrane Library. Informed consent was not required for this study as it involved the analysis of previously published data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

EH: Article conception, data extraction and analysis, manuscript drafting and reviewing

MA: Data extraction, manuscript drafting and reviewing

SK: Manuscript drafting and reviewing

MV: Guarantor, article conception, manuscript drafting and reviewing

Data Availability Statement

The data analysed in the current study are available from the corresponding studies. Additionally, the completed data extraction Excel file for this study is available upon request.

References

1 Li J, Xiang L, Chen X, Li S, Sun Q, Cheng X, et al. Global, regional, and national burden of neonatal sepsis and other neonatal infections, 1990–2019: findings from the Global Burden of Disease Study 2019. Eur J Pediatr. 2023;182(5):2335–43.

2 National Institute for Health and Care Excellence (NICE). Neonatal infection: antibiotics for prevention and treatment | Guidance [Internet]. 2021 [cited 2024 Jan 10]. Available from: https://www.nice.org.uk/guidance/ng195

3 Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. J Trop Pediatr. 2015;61(1):1–13.

4 Sharma D, Farahbakhsh N, Shastri S, Sharma P. Biomarkers for diagnosis of neonatal sepsis: a literature review. J Matern Fetal Neonatal Med. 2018;31(12):1646–59.

5 NICE Guideline Updates Team. Evidence review for investigations before starting treatment for late-onset neonatal infection: Neonatal infection: antibiotics for prevention and treatment. London: National Institute for Health and Care Excellence (NICE); 2021; [cited 2025 Feb 7].Available from: https://www.nice.org.uk/guidance/ng195/evidence

6 Nierhaus A, Linssen J, Wichmann D, Braune S, Kluge S. Use of a weighted, automated analysis of the differential blood count to differentiate sepsis from non-infectious systemic inflammation: the intensive care infection score (icis). Inflamm Allergy-Drug Targets. 2012 Apr;11(2):109–15.

7 Nassin ML, Lapping-Carr G, de Jong JLO. Anemia in the neonate: the differential diagnosis and treatment. Pediatr Ann. 2015;44(7):e159–63.

8 Siti Nur Azwa S, Azlin I, Raja Zahratul Azma RS, Hafiza A, Toh Leong T. Evaluation of mean neutrophil volume and immature to total neutrophil ratio as a biomarker for bacterial sepsis in adult patients. Malays J Pathol. 2023

9 Deeks J, Bossuyt P, Leeflang M, Takwoingi Y. Cochrane handbook for systematic reviews of diagnostic test accuracy. 2.0. Cochrane; 2023.Available from: https://training.cochrane.org/handbook-diagnostic-test-accuracy/current

10 Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529–36.

11 Critical Appraisal Skills Programme. CASP diagnostic test study checklist [Internet]. 2018 [cited 2022 Jan 20]. Available from: https://casp-uk.net/casp-tools-checklists/diagnostic-study-checklist/

12 Wells G, Shea B, O'Connell D, Robertson J, Peterson J, Welch V, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis [Internet]. 2021 [cited 2022 Feb 21]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

13 Abiramalatha T, Santhanam S, Mammen JJ, Rebekah G, Shabeer MP, Choudhury J, et al. Utility of neutrophil volume conductivity scatter (VCS) parameter changes as sepsis screen in neonates. J Perinatol. 2016;36(9):733–8.

14 Aboud MI, Waise MMA, Shakerdi LA. Procalcitonin as a marker of neonatal sepsis in intensive care units. Iran J Med Sci. 2010;35(3):205–10.

15 Buyukeren M, Celik HT, Yigit S, Portakal O, Sancak B, Yurdakok M. The role of the delta neutrophil index in determining the etiology of neonatal sepsis. Turk J Biochem. 2021;46(1):73–9.

16 Celik HT, Portakal O, Yigit S, Hascelik G, Korkmaz A, Yurdakok M. Efficacy of new leukocyte parameters versus serum C-reactive protein, procalcitonin, and interleukin-6 in the diagnosis of neonatal sepsis. Pediatr Int. 2016;58(2):119–25.

17 Celik IH, Arifoglu I, Arslan Z, Aksu G, Bas AY, Demirel N. The value of delta neutrophil index in neonatal sepsis diagnosis, follow-up and mortality prediction. Early Hum Dev. 2019;131:6–9.

18 Elawady S, Botros SK, Sorour AE, Ghany EA, Elbatran G, Ali R. Neutrophil CD64 as a diagnostic marker of sepsis in neonates. J Investig Med. 2014;62(3):644–9.

19 Kumar P, Anjula C, Bhardwaj P, Chauhan L, Karol M. D-dimer: a useful marker in neonatal sepsis. J Clin Neonatol. 2015;4(2):101–3.

20 Leibovitch L, Zohar H, Gavri-Beker A, Goshen A, Strauss T. Mean platelet volume in preterm infants as a predictor of late-onset neonatal sepsis: a retrospective comparative study. BMJ Paediatr Open. 2024;8(1):e002698.

21 Mahmoud NMS, Abdelhakeem M, Mohamed HHA, Baheeg G. Validity of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio in diagnosing early-onset neonatal sepsis in full-term newborns. J Compr Pediatr. 2022;13(1):e115378.

22 Nesargi P, Niranjan HS, Bandiya P, Benakappa N. Neutrophil volume, conductivity and scatter (VCS) as a screening tool in neonatal sepsis. Sci Rep. 2020;10(1):4457.

23 Schrama AJJ, de Beaufort AJ, Poorthuis BHJM, Berger HM, Walther FJ. Secretory phospholipase A2 in newborn infants with sepsis. J Perinatol. 2008;28(4):291-296.

24 Tosson AMS, Koptan DMT, Kamal M, Elhady MA. Assessment of serum interleukin-27 and mean platelet volume in late-onset neonatal sepsis. Am J Perinatol. 2024;41(9):1232–7.

25 Vardar G, Ozek E. Carboxyhemoglobin levels in preterm neonatal late-onset sepsis: to predict or not to predict. Mediterr J Hematol Infect Dis. 2023;15(1):e2023017.

26 Zhang S, Luan X, Zhang W, Jin Z. Platelet-to-lymphocyte and neutrophil-to-lymphocyte ratio as predictive biomarkers for early-onset neonatal sepsis. J Coll Physicians Surg. 2021;31(7):821–4.

27 Arcagok BC, Karabulut B. Platelet to lymphocyte ratio in neonates: a predictor of early onset neonatal sepsis. Mediterr J Hematol Infect Dis. 2019;11(1):e2019055.

28 Hanaganahalli SB, Sreeram S, Bompada M, Kuppannagari SK, Suresh PK, Philipose CS. Is MPV a predictive marker for neonatal sepsis? A pilot study. J Pediatr Hematol Oncol. 2018;40(7):548–52.

29 Madani SH, Amiri S, Khazaei S, Khadem Erfan MB, Rostami-Far Z, Tarlan M, et al. Platelet indices as useful indicators of neonatal sepsis. J Evol Med Dent Sci. 2019 May;8(20):1612–7.

30 Panda SK, Nayak MK, Rath S, Das P. The utility of the neutrophil-lymphocyte ratio as an early diagnostic marker in neonatal sepsis. Cureus. 2021;13(1):e12891.

31 Guney Varal I, Dogan P. Can neutrophil-lymphocyte ratio be a predictor of late-onset sepsis in preterm infants? Ann Med Res. 2020;27(1):23–8.

32 Guney Varal I, Dogan P, Acar Celik E, Güler Kazancı E. Mean platelet volume and mean platelet volume/platelet count ratio are predictors of late-onset sepsis in preterm infants: a case-control study. Fetal Pediatr Pathol. 2023;42(1):44–54.

33 Manucha V, Rusia U, Sikka M, Faridi MMA, Madan N. Utility of haematological parameters and C-reactive protein in the detection of neonatal sepsis. J Paediatr Child Health. 2002;38(5):459–64.

34 Panda SK, Nayak MK, Thangaraj J, Das P, Pugalia R. Platelet parameters as a diagnostic marker in early diagnosis of neonatal sepsis - seeking newer answers for older problems. J Fam Med Prim Care. 2022 May;11(5):1748–54.

35 Yang A-P, Liu J, Yue L-H, Wang H-Q, Yang W-J, Yang G-H. Neutrophil CD64 combined with PCT, CRP and WBC improves the sensitivity for the early diagnosis of neonatal sepsis. Clin Chem Lab Med. 2016 Feb;54(2):345–51.

36 Zaki MES, El Sayed H. Evaluation of microbiologic and hematologic parameters and E-selectin as early predictors for outcome of neonatal sepsis. Arch Pathol Lab Med. 2009;133(8):1291–6.

37 Riley LK, Rupert J. Evaluation of patients with leukocytosis. Am Fam Physician. 2015;92(11):1004–11.

38 Fowlie PW, Schmidt B. Diagnostic tests for bacterial infection from birth to 90 days - a systematic review. Arch Dis Child - Fetal Neonatal Ed. 1998 Mar;78(2):F92–8.

39 Rees CA, Lim J, Westbrook AL, El Helou R, Schmid A, Rubin-Smith J, et al. Systematic review and meta-analysis of the diagnostic value of four biomarkers in detecting neonatal sepsis in low- and middle-income countries. BMJ Paediatr Open. 2023 Jan;7(1):e001627.

40 Mishra A, Jena PK, Panda SK. The diagnostic performance of mean neutrophil volume in neonatal sepsis: a systematic review and meta-analysis. Pediatr Neonatol. 2025 Jan;66(1):71–5.

41 Zhang J, Zeng J, Zhang L, Yu X, Guo J, Li Z. The utility of peripheral blood leucocyte ratios as biomarkers in neonatal sepsis: a systematic review and meta-analysis. Front Pediatr. 2022 Jul;10. DOI: 10.3389/fped.2022.908362

42 Esmaeilizand R, Shah PS, Seshia M, Yee W, Yoon EW, Dow K. Antibiotic exposure and development of necrotizing enterocolitis in very preterm neonates. Paediatr Child Health. 2018;23(4):e56–61.

43 Canova C, Ludvigsson JF, Di Domenicantonio R, Zanier L, Barbiellini Amidei C, Zingone F. Perinatal and antibiotic exposures and the risk of developing childhood-onset inflammatory bowel disease: a nested case-control study based on a population-based birth cohort. Int J Environ Res Public Health. 2020;17(7):2409.

44 Narasimha A, Harendra Kumar ML. Significance of hematological scoring system (HSS) in early diagnosis of neonatal sepsis. Indian J Hematol Blood Transfus. 2011 Mar;27(1):14–7.

389 45 Huang B, Wang R, Masino AJ, Obstfeld AE. Aiding clinical assessment of neonatal sepsis using
390 hematological analyzer data with machine learning techniques. Int J Lab Hematol.
391 2021;43(6):1341–56.

392 46 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020
393 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar;372:n71.

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Figures

Figure 1: The risk of bias and applicability of the studies included in this systematic review, adapted from the QUADAS-2 tool [10], the CASP diagnostic checklist [11], and the Newcastle-Ottawa scale [12].

Figure 1: Diagnostic accuracy of mean neutrophil volume (au) for neonatal sepsis. A) Forest plot showing differences in values between cases and controls across individual studies; B) Summary receiver operating characteristic curve showing overall diagnostic performance across included studies – individual studies are labelled by their study number; C) funnel plot providing a visual assessment of publication bias.

Figure 2: Diagnostic accuracy of immature to total neutrophil ratio for neonatal sepsis. A) Forest plot showing differences in values between cases and controls across individual studies; B) Summary receiver operating characteristic curve showing overall diagnostic performance across included studies – individual studies are labelled by their study number; C) funnel plot providing a visual assessment of publication bias.

Supplementary Figures

Figure S1: PRISMA [46] flowchart for the study selection process for this systematic review and meta-analysis

Figure S2: Diagnostic accuracy of immature to total neutrophil ratio > 0.20 for neonatal sepsis. A) Forest plot showing differences in values between cases and controls across individual studies; B) Summary receiver operating characteristic curve showing overall diagnostic performance across included studies – individual studies are labelled by their study number; C) funnel plot providing a visual assessment of publication bias.

Figure S3: Diagnostic accuracy of platelet count ($x10^9$/L) for neonatal sepsis. A) Forest plot showing differences in values between cases and controls across individual studies; B) Summary receiver operating characteristic curve showing overall diagnostic performance across included studies – individual studies are labelled by their study number; C) funnel plot providing a visual assessment of publication bias.

Figure S4: Diagnostic accuracy of platelet count < 150 $x10^9$/L for neonatal sepsis. A) Forest plot showing differences in values between cases and controls across individual studies; B) Summary receiver operating characteristic curve showing overall diagnostic performance across included studies – individual studies are labelled by their study number; C) funnel plot providing a visual assessment of publication bias.

Figure S5: Diagnostic accuracy of neutrophil to lymphocyte ratio for neonatal sepsis. A) Forest plot showing differences in values between cases and controls across individual studies; B) Summary receiver operating characteristic curve showing overall diagnostic performance across included studies – individual studies are labelled by their study number; C) funnel plot providing a visual assessment of publication bias.

Figure S6: Diagnostic accuracy of white cell count ($x10^9$/L) for neonatal sepsis. A) Forest plot showing differences in values between cases and controls across individual studies; B) Summary receiver operating characteristic curve showing overall diagnostic performance across included studies – individual studies are labelled by their study number; C) funnel plot providing a visual assessment of publication bias.

Figure S7: Diagnostic accuracy of neutrophil count ($x10^9$/L) for neonatal sepsis. A) Forest plot showing differences in values between cases and controls across individual studies; B) Summary receiver operating characteristic curve showing overall diagnostic performance across included studies – individual studies are labelled by their study number; C) funnel plot providing a visual assessment of publication bias.

Figure S8: Diagnostic accuracy of mean platelet volume (fL) for neonatal sepsis. A) Forest plot showing differences in values between cases and controls across individual studies; B) Summary receiver operating characteristic curve showing overall diagnostic performance across included studies – individual studies are labelled by their study number; C) funnel plot providing a visual assessment of publication bias.

Tables

Table 1: Characteristics of studies included in this systematic review. Abbreviations: Pro – prospective; Retro – retrospective; BC+ - positive blood culture; CS – clinical signs of sepsis; LS – laboratory signs of sepsis; SUS – suspicion of sepsis; WCC – white cell count (x10^9/L); NEUT – neutrophil count (x10^9/L); ITR – immature to total neutrophil ratio; NLR – neutrophil to lymphocyte ratio; DNI – delta neutrophil index; MNV – mean neutrophil volume (au); MNC – mean neutrophil conductivity (au); MNS – mean neutrophil scatter (au); PLT – platelet count(x10^9/L); MPV – mean platelet volume (fL); PLR – platelet to lymphocyte ratio. [a]mean or median value.

				Cases					Controls						
No	**Study Author and Year**	**Setting**	**Design**	**Definition**	**No**	**Sex (M/F)**	**Age[a] (Days)**	**GA[a] (Weeks)**	**Definition**	**No**	**Sex (M/F)**	**Age[a] (Days)**	**GA[a] (Weeks)**	**Applicability Score**	**Biomarkers**
#1	Abiramalatha 2016 [13]	India	Pro	BC+	38	25/13	4.0	35.5	No CS/LS	360	195/165	1.0	36.5	8.00	WCC, NEUT, ITR, MNV, PLT
#2	Aboud 2010 [14]	Syria	Pro	BC+/CS	25	13/12	8.6	36.4	No CS/LS	22	8/14	9.6	37.3	5.50	WCC
#3	Arcagok 2019 [27]	Turkey	Retro	BC+/CS/LS	67	33/34		39.1	No CS/LS	92	43/49		40.1	6.00	ITR, PLR
#4	Buyukeren 2021 [15]	Turkey	Pro	BC+/CS/LS	77	38/39	15.0	34.3	No CS	131	60/71	9.0	34.8	6.00	DNI
#5	Çelik 2016 [16]	Turkey	Pro	BC+/CS/LS	40	26/14	4.5	32.5	No CS	111	70/41	1.0	34.4	7.00	WCC, NEUT, ITR, MNV, MNC, MNS
#6	Celik 2019 [17]	Turkey	Retro	BC+/CS/LS	110	64/46	8.0	28.0	No SUS	87	40/47	7.0	30.0	6.50	DNI
#7	Elawady 2013 [18]	Egypt	Pro	BC+/CS	25	17/8			No CS/LS	25	15/10			5.50	WCC, NEUT, ITR, PLT
#8	Guney Varal 2020 [31]	Turkey	Retro	BC+/CS	76	40/36	15.0	29.0	No CS	40	22/18	15.0	28.0	6.50	NLR
#9	Guney Varal 2023 [32]	Turkey	Pro	BC+	64	36/28		28.0	No SUS	44	24/20		29.0	7.00	PLT, MPV
#10	Hanaganahalli 2018 [28]	India	Retro	BC+/CS	64	41/23	7.4	39.6	No CS	71	46/25	3.6	39.8	8.00	MPV
#11	Kumar 2015 [19]	India	Pro	BC+/CS	101	58/43			No CS	96	52/44			5.50	WCC

				Cases					Controls						
No	**Study Author and Year**	**Setting**	**Design**	**Definition**	**No**	**Sex (M/F)**	**Age[a] (Days)**	**GA[a] (Weeks)**	**Definition**	**No**	**Sex (M/F)**	**Age[a] (Days)**	**GA[a] (Weeks)**	**Applicability Score**	**Biomarkers**
#12	Leibovitch 2024 [20]	Israel	Retro	BC+	63	34/29		31.1	No SUS	63	28/35		31.7	6.00	MPV
#13	Madani 2019 [29]	Iran	Pro	BC+/CS	20	10/10	7.5		No SUS	20	12/8	2.6		5.00	MPV
#14	Mahmoud 2022 [21]	Egypt	Pro	BC+/CS	80		2.3	38.7	No SUS	80		2.0	38.8	7.00	NLR, PLR
#15	Manucha 2002 [33]	India	Pro	BC+	21				No SUS	40				4.00	WCC, NEUT, ITR, PLT
#16	Nesargi 2020 [22]	India	Pro	BC+/CS	84	44/40	7.0	37.0	No CS/LS	160	88/72	3.0	38.0	7.00	MNV, MNC, MNS
#17	Panda 2021 [30]	India	Retro	BC+/CS	41	27/14		34.2	No CS	52	25/27		33.8	6.00	NLR
#18	Panda 2022 [34]	India	Pro	BC+/CS	43	23/40		33.3	No CS	54	24/30		34.2	7.00	PLT, MPV
#19	Schrama 2008 [23]	NL	Pro	BC+/CS	24	8/16		31.0	No CS	55	27/28		30.1	6.00	ITR
#20	Tosson 2024 [24]	Egypt	Pro	BC+/CS	45	25/20	15.0	38.1	No CS/LS	45	25/20	13.0	38.3	6.50	ITR, MPV
#21	Vardar 2023 [25]	Turkey	Retro	BC+	77	38/39		28.0	No SUS	77	39/38		28.0	5.50	NLR
#22	Yang 2016 [35]	China	Retro	BC+/CS	60	31/29	17.9	34.3	No CS	60	35/25	18.4	37.5	5.00	WCC
#23	Zaki 2009 [36]	Egypt	Pro	BC+/CS	58	32/26	8.7	39.3	No SUS	30	16/14	8.8	36.9	6.50	WCC, NEUT, ITR, PLT
#24	Zhang 2021 [26]	China	Pro	BC+/CS	74	45/29		38.0	No SUS	50	25/25		38.0	5.50	NLR, PLR

Table 2: Meta-analysis results for parameters of the complete blood count investigated in this review. Abbreviations: WCC – white cell count ($x10^9$/L); NEUT – neutrophil count ($x10^9$/L); ITR – immature to total neutrophil ratio; NLR – neutrophil to lymphocyte ratio; MNV – mean neutrophil volume (au); PLT – platelet count($x10^9$/L); MPV – mean platelet volume (fL). [a]median (IQR).

Biomarker	Number of Studies	Case Values[a]	Control Values[a]	Optimal Threshold	Sensitivity[a]	Specificity[a]	AUC	I2
WCC	8	15.55 (11.19 - 16.54)	10.89 (9.02 - 12.76)	> 10.50	55.06% (38.06% - 70.95%)	83.33% (73.44% - 90.03%)	0.786	0.29
NEUT	5	6.90 (6.90 - 7.76)	6.51 (4.90 - 6.51)	> 4.13	67.16% (46.77% - 82.64%)	75.93% (63.21% - 85.27%)	0.783	<0.01
ITR	8	0.30 (0.18 - 0.33)	0.10 (0.09 - 0.11)	> 0.20	66.33% (58.55% - 73.31%)	85.41% (74.95% - 91.97%)	0.773	<0.01
NLR	4	3.20 (2.10 - 4.16)	1.40 (0.70 - 2.34)	> 3.17	69.14% (63.30% - 74.42%)	72.63% (54.80% - 85.31%)	0.685	0.03
MNV	3	180.30 (161.60 - 180.30)	146.90 (146.90 - 150.00)	> 157.90	76.64% (27.51% - 96.59%)	90.88% (70.18% - 97.69%)	0.925	0.85
PLT	6	187.15 (109.00 - 220.00)	285.19 (251.00 - 289.00)	< 278	66.45% (45.69% - 82.34%)	81.41% (66.52% - 90.62%)	0.815	0.52
MPV	6	9.70 (9.56 - 9.97)	8.90 (8.88 - 9.22)	> 11.60	67.72% (58.68% - 75.60%)	73.71% (55.82% - 86.15%)	0.735	0.39
ITR > 0.20	5	0.33 (0.30 - 0.33)	0.10 (0.09 - 0.10)	> 0.20	72.46% (60.73% - 81.73%)	85.25% (64.44% - 94.86%)	0.816	<0.01
PLT < 150	4	187.15 (187.15 - 220.00)	251.00 (251.00 - 285.19)	< 150	51.24% (38.08% - 64.23%)	82.01% (62.16% - 92.67%)	0.653	<0.01