Can a Routine Blood Count Save Lives? Neutrophil-to-Lymphocyte Ratio

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Main Findings

- Despite variability, NLR shows promise as a **low-cost, accessible biomarker** for early diagnosis, especially in **late-onset sepsis**.
- **NLR is elevated in septic neonates** compared to controls, including both culture-positive and culture-negative cases.

Abstract

The neutrophil-to-lymphocyte ratio (NLR) is an emerging, low-cost biomarker for neonatal sepsis, offering potential advantages over conventional laboratory criteria and delayed blood cultures. This systematic review found consistently higher NLR values in septic neonates, though substantial heterogeneity across studies highlights the need for standardized definitions and prospective validation, particularly in late-onset sepsis.

Introduction

- Neonatal sepsis: major global health issue (1.3M cases, 203K deaths annually)[1].
- Classified as **early-onset (≤72h)** or **late-onset (≥72h)**[1].
- **Early diagnosis is critical** to reduce mortality[2].
- **Blood culture** remains the gold standard but is slow (up to 48h)[2].
- **Lab markers** (CRP, leukocyte counts, etc.) proposed but lack accuracy[3].
- **NLR** (neutrophil-to-lymphocyte ratio) from routine FBC is simple, low-cost, and emerging as a biomarker.
- Evidence suggests **NLR can detect sepsis early**, including in neonates[4].
- Prior reviews relied on reported NLR values;
- **This review calculates NLR directly** from raw counts for a more standardized assessment, with a focus on LOS.

Methods

- **Search Strategy:** Embase, Ovid, Cochrane (to March 2024); no date/language restrictions; manual reference checks; duplicates removed.
- The following **inclusion** and **exclusion** criteria was applied:

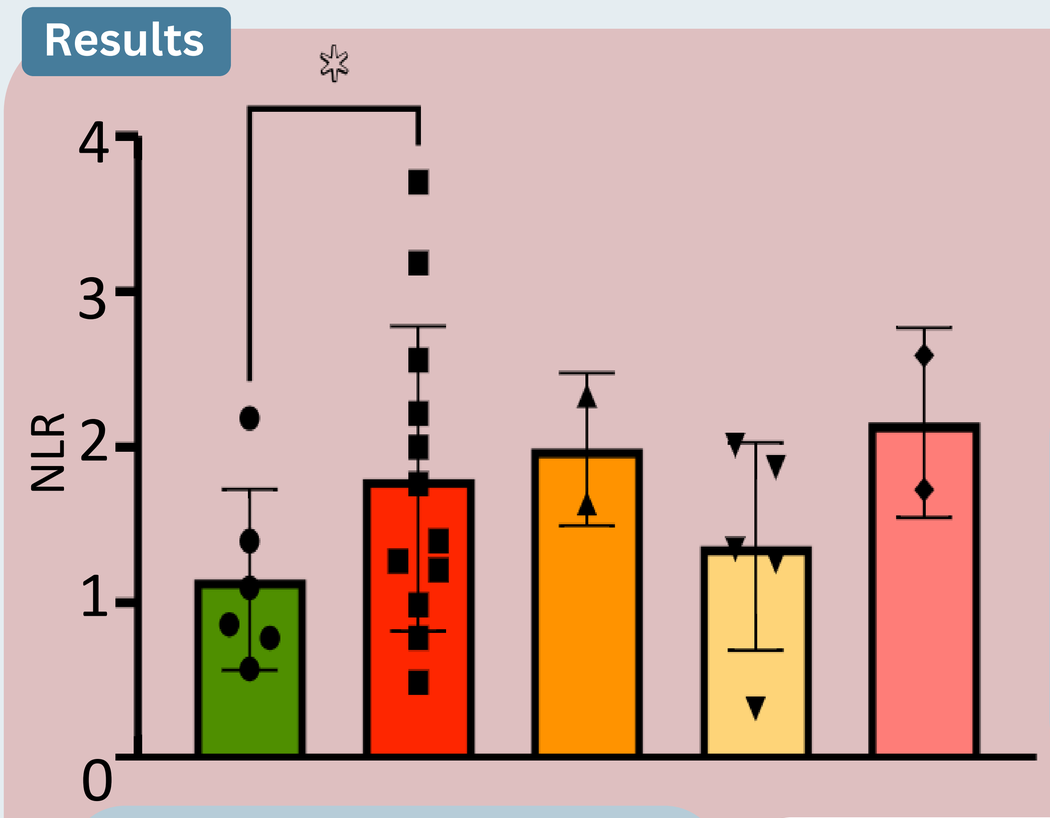
Inclusion criteria	Exclusion Criteria
Late onset sepsis (LOS)	Early Onset Sepsis (EOS) only
Studies in infant populations	Animal studies
Diagnostic parameters of sepsis	In vitro studies only
Reported relevant haematological markers, including lymphocytes, neutrophils, leukocytes, total leukocyte count (TLC), absolute neutrophil count (ANC), or white blood cell count (WBC)	Studies of infants with underlying genetic conditions Reviews and case studies Reported misdiagnosed cases of Misdiagnosed as sepsis, Analysis of maternal or cord-blood (only)

- **Study Types:** Observational (cohort, case-control, cross-sectional), case series (>10 patients), control arms of RCTs.
- **Quality Assessment:** QUADAS-2, JBI checklist, QUIPs, ROBIS → domains: selection, confounding, reporting, outcome, index test, reference standard.
- **Data Extraction:** Neutrophil & lymphocyte counts used to calculate NLR (mean/median with SD):

$$\frac{\text{Neutrophils}}{\text{Lymphocytes}} = \text{NLR}$$

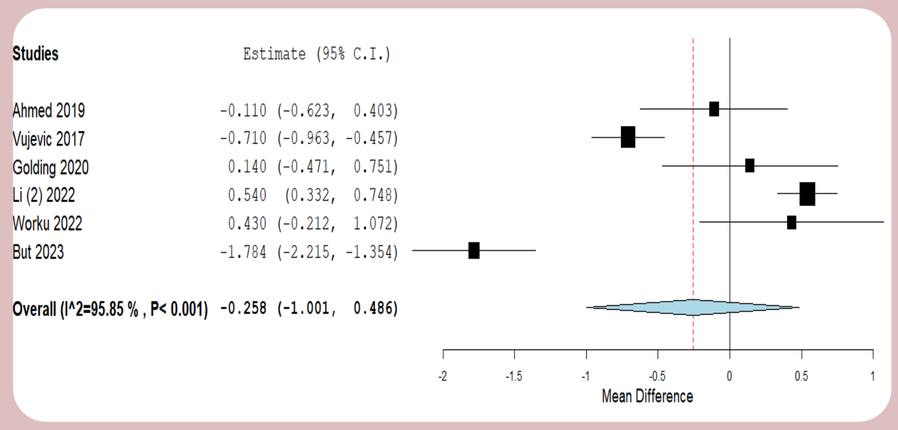
- **Analysis**: Forest plots (OpenMetaAnalyst), funnel plots (Excel). Sepsis definitions classified into 6 groups:
  1. Culture-positive
  2. Laboratory criteria
  3. SIRS
  4. Clinical evidence
  5. Töllner/HSS
  6. Undefined/suspected sepsis

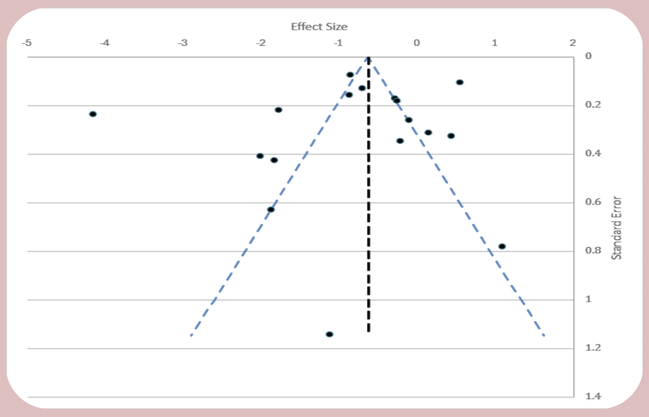
Results



- **NLR is consistently higher in septic neonates**
  - ➢ Significant difference especially in Sepsis Positive
- **Culture-negative sepsis still shows raised NLR**
  - ➢ Useful even when blood cultures fail
- **Heterogeneity in definitions can contribute to variability between groups**

- **Mixed results** observed: some studies show higher NLR in sepsis, others show no significant difference.
- **Confidence intervals overlap**, highlighting inconsistencies across individual studies.
- **Overall pooled effect**: Mean difference = −0.258 (95% CI −1.001 to 0.486), not statistically significant.
- **I^2 = 95.9% (P < 0.001)**, indicating **very high heterogeneity**, likely due to variations in study design, patient populations, and definitions of sepsis.



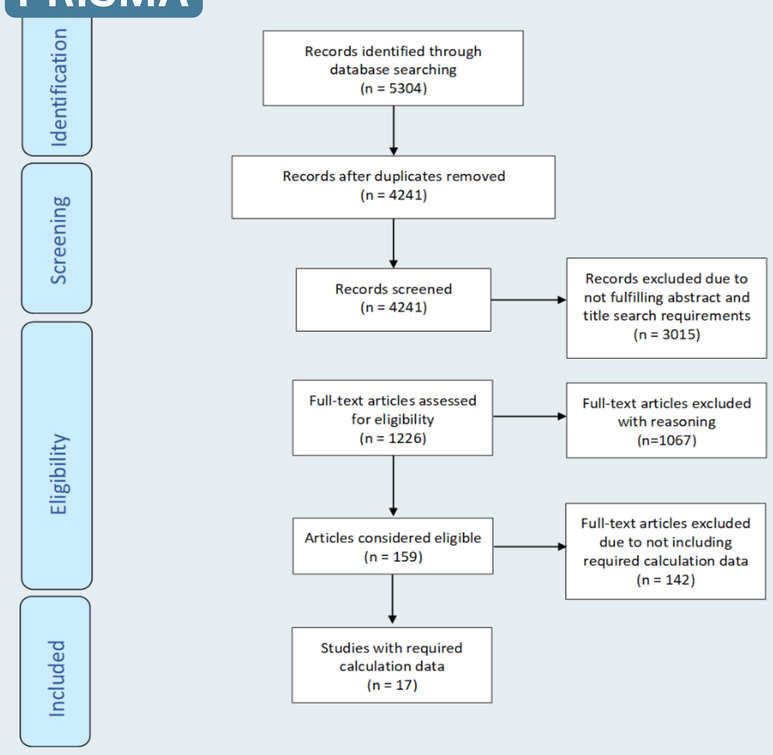


- **The funnel plot shows asymmetry**
  - ➢ suggests possible publication bias
- **Uneven scatter** of smaller studies
  - ➢ Forms asymmetrical funnel
- findings indicate that differences in **study design, patient populations, and sepsis definitions** may have influenced results and limit the reliability of pooled estimates.

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.

- **ROB indicative of data with potential for bias**
  - ➢ Several unknown information
  - ➢ Several high bias
  - ➢ Several with some concern

PRISMA



Conclusion

- **NLR is elevated in septic neonates**, supporting its role as a potential diagnostic biomarker.
- **Mixed results and high heterogeneity** (I^2 > 95%) reduce certainty of pooled findings.
- Variability reflects differences in **sepsis definitions, study designs, and patient populations**.
- **Future research** should focus on standardized criteria and prospective validation.

References

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2. Celik, I. H., Hanna, M., Canpolat, F. E., & Mohan Pammi. (2021). Diagnosis of Neonatal Sepsis: The Past, Present and Future. *Pediatric Research*, *91*(2), 337. https://doi.org/10.1038/S41390-021-01696-Z
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4. Wen, X., Zhang, Y., Xu, J., Song, C., Shang, Y., Yuan, S., & Zhang, J. (2024). The early predictive roles of NLR and NE% in in-hospital mortality of septic patients. *Heliyon*, *10*(4), e26563. https://doi.org/10.1016/J.HELIYON.2024.E26563

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