

Utility of C-Reactive Protein and Complete Blood Count Values as Primary Screening Markers for Sepsis in Preterm Neonates: Retrospective Study from United Arab Emirates

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Abstract

Objective: To assess the diagnostic utility of CRP and CBC parameters taken on admission for early screening of neonatal sepsis in a single center from the United Arab Emirates (UAE).

Methods: A retrospective chart review was conducted to retrieve the data of all preterm infants who were admitted to Latifa Hospital in Dubai through the period from January to December 2014. Data of 471 infants (257 males, 214 females) were retrieved and analyzed.

Results: For culture-proven sepsis, CRP had a sensitivity of 60%, specificity of 90%, positive predictive value (PPV) of 19%, and negative predictive value (NPV) of 98%. For clinical sepsis, CRP had an overall sensitivity of 48.6%, overall specificity of 94%, and overall PPV and NPV values of 53.9% and 92.7%, respectively. The total leucocytic count (TLC) and absolute neutrophil count (ANC) showed an overall sensitivity of 15% and 10% for culture-proven neonatal sepsis, respectively. On the contrary, specificity numbers for TLC and ANC were decent for both culture-proven and clinical sepsis. For culture-proven sepsis, a low platelet count had a sensitivity of 55%, with a specificity of 84.5%. For clinical sepsis, low platelet count had a sensitivity of 42.9%, a specificity of 87%, and PPV and NPV values of 32.2% and 91.4% for overall neonatal sepsis. The in-hospital mortality rate was 7.6%.

Conclusion: None of the primary sepsis screening investigations has adequate sensitivity for early detection of neonatal sepsis. At the same time, CRP only exhibits decent specificity in neonates with suspected sepsis.

Keywords: Preterm; Neonatal Sepsis; C-Reactive Protein; Complete Blood Count

Introduction

Neonatal sepsis is a prevalent disorder affecting neonates and exerting a substantial burden on the patients and healthcare system. The condition is universally defined as infection-mediated hemodynamic changes that lead to severe morbidities and a high risk of mortality, which occurs during the first 28 days of life [1]. Classically, neonatal sepsis is classified according to its onset into early-, happening within 72 hours from birth, and late-onset sepsis, emerging with the 3rd to 28th day of delivery [2]. According to recent epidemiological figures, the global incidence of neonatal sepsis is nearly 2800 new cases per 100,000 live births, with a notably higher incidence in low

and middle-income countries (almost 3900 new cases per 100,000 live births) [3]. In the Gulf region, it was estimated that the incidence of late-onset sepsis is nearly 1160 per 100,000 live births [4]. Various risk factors are implicated in the development of neonatal sepsis, including fetal (such as prematurity and fetal distress) and maternal (such as chorioamnionitis and local bacterial colonization) factors [5]. In particular, premature infants are 3-10 times at higher risk of developing neonatal sepsis due to low birth weight, higher risk of perinatal infections, and suboptimal levels of maternal IgG [1]. The causative organisms of neonatal sepsis vary depending on the type of sepsis and characteristics of the local settings, with group B streptococcal (GBS) and coagulase-negative staphylococci (CONS) account for the majority of early- and late-onset sepsis, respectively [6,7]. Neonatal sepsis is a leading cause of neonatal mortality, particularly in preterm infants, with a reported mortality rate of 17.6% [3]. Besides, neonatal sepsis is an independent risk factor for long-term complications, such as cognitive impairment and visual and hearing defects [8].

Despite neonatal sepsis imposing a high risk of serious complications, its diagnosis is still challenging. The early signs of sepsis in affected neonates are vague and nonspecific [9]. Besides, many routine laboratory findings yield low diagnostic performance for the early detection of neonatal sepsis [10]. Although blood culture is considered the gold standard tool for diagnosing neonatal sepsis, some patients can present with negative culture due to several factors, such as maternal antibiotic use [8]. On the other hand, the use of cerebrospinal fluid (CSF) and urine cultures is controversial and yielded low diagnostic accuracy in the early stage of sepsis [11]. Thus, it is imperative to develop new, simple, and readily available markers with high diagnostic accuracy for early screening of neonatal sepsis.

Recently, several investigators assessed the diagnostic value of C-reactive protein (CRP) in the early screening of neonatal sepsis. Previous reports showed that a high CRP level was a sensitive biomarker for detecting neonatal sepsis within 24 - 28 hours from disease onset [12]. Besides, CRP was found to have a predictive utility in assessing the response to treatment [13]. The diagnostic performance of complete blood count (CBC) parameters was also evaluated for screening of neonatal sepsis, with wide controversies in the reported results [1]. Moreover, not only are there existing controversies pertaining to clinical and laboratory diagnosis of neonatal sepsis among term infants, the scenario is even more unclear when it comes to preterm neonates.

Aim of the Study

Thus, we performed the present retrospective study to assess the diagnostic utility of CRP and CBC parameters taken upon admission for early screening of neonatal sepsis in premature neonates in a single center from the United Arab Emirates (UAE).

Materials and Methods

The current retrospective study gained ethical clearance from the Dubai Scientific Research Ethics Committee, UAE and was planned per the recommendations of the STROBE guidelines [14]. We confirm that none of the study's procedures violated the main principles of the Declaration of Helsinki [15]. The need for written informed consent was waived owing to the retrospective nature of the study.

Study design and patients

A retrospective chart review was conducted to retrieve the data of all preterm infants who were admitted to the neonatal ICU unit of Latifa Hospital in Dubai through the period from January to December 2014. Infants were included in the present study if their gestational age was less than 37 weeks. Data were retrieved only if complete records of CRP level, CBC parameters, blood cultures and clinical condition of the included neonates were available at the time of data collection. Initially, a total of 510 preterm infants were screened. Of them, data of 471 infants (257 males, 214 females) were retrieved and analyzed.

Data collection

Data of eligible patients were collected using an online electronic form and included the following: age, gender, nationality, birth weight, maternal characteristics (such as parity, GBS status, history of chorioamnionitis, and the mode of delivery), signs and symptoms of sepsis, CBC values at admission, CRP value at admission, blood culture findings, antibiotics received and duration of treatment, need for ventilation/surfactant, ICU stay, mortality. At our institution, the CRP is mainly measured using immunochemical assay (Nycocard Reader II™, Immunochemical assay), with a positive CRP value defined as > 10 mg/L. The CBC values were obtained using UniCelDxH 800 Coulter Cellular Analysis System™, in which low total leucocytic count (TLC < 5000/mm³), low absolute neutrophil count (ANC < 1500/mm³), and low platelet counts (< 150000/mm³) were considered abnormal. Culture positive sepsis was defined as positive blood and/or CSF and/or urine culture along with signs and symptoms attributable to sepsis. Clinical sepsis was defined as presence of symptoms and signs related to neonatal sepsis in absence of any other identifiable cause of the existing symptomatology and positive blood/body fluid cultures.

Study's outcomes

The primary outcome of the present study was the diagnostic performance of CRP in predicting clinical and culture-proven sepsis in preterm neonates. The secondary outcomes included the diagnostic performance of CBC values in predicting clinical and culture-proven sepsis in preterm neonates and the predictors of mortality in preterm infants with culture-proven sepsis.

Statistical analysis

The statistical software SPSS (IBM SPSS™ Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) was used for data processing and analysis. According to the normality of data distribution, the central tendency and variability of the numerical data were presented in the form of mean ±standard deviations (SD) or median with interquartile range (IQR). Frequency counts and percentages summarized categorical variables. The diagnostic performance of CRP and CBC values were assessed in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The hypothesis of significant association between mortality and other variables was tested using the Mann-Whitney test and the Chi-square test, with Fisher exact correction when needed. P-value <0.05 was regarded as statistically significant.

Results

The study was performed on 471 preterm neonates who fulfilled the inclusion criteria, with a male to female ratio of 1.2: 1. One-hundred and sixty-three (36.6%) infants were born between 28 and 32+6 weeks, and 241 (51.2%) were born between 33 and 36 + 6 weeks gestational age. The vast majority of infants (76.9%) were born via lower segment Caesarean section. A total of 251 babies (53.3%) were born with low birth weight (1.5 - 2.49 kg), 81 babies (17.2%) with very low birth weight (1 - 1.49 kg), and 74 babies (15.7%) with extremely low birth weight (< 1 kg). During hospitalization in NICU, 37.4% of the sample under study (176 babies) required intubation and full mechanical ventilation, and 31.8% (150 babies) required non-invasive ventilation. Besides, 32.5% of the patients under study required the administration of surfactant during hospitalization (Table 1).

Variables, No. (%)	Infants (= 471)
Males	257 (55%)
Gestational age	
Less than 28 weeks	69 (14.2%)
28 - 32+6 weeks	163 (36.6%)
33 - 36+6 weeks	241 (51.2%)

Mode of delivery	
NVD	109 (23.1%)
LSCS	362 (76.9%)
Birth weight	
Normal	58 (12.3%)
Low Birth Weight	251 (53.3%)
Very Low Birth Weight	81 (17.2%)
Extreme Low Birthweight	74 (15.7%)
Not Available	7 (1.5%)
Ventilation	
Invasive	176 (37.4%)
Non Invasive	150 (31.8%)
Not Ventilated	145 (30.8%)
Surfactant requirement	
Given Surfactant	153 (32.5%)
Not Given Surfactant	316 (67.1%)
Not Available	2 (0.4%)

Table 1: Demographics of neonatal data.

In terms of maternal data, 55.8% of the mothers were in the age ranging between 30 and 39 years. Fifty-seven mothers (12.1%) of the sample under investigation had premature rupture of membranes more than 18 hours before delivery. Of them, 13 mothers (2.8%) were reported to have chorioamnionitis associated with fever. Fifty-one (10.8%) mothers tested positive for GBS in the high vaginal swab, and 41 (8.7%) mothers tested positive for GBS in urine culture. On the other hand, high vaginal swaband/or urine culture showed mixed growth in 158 mothers (33.5%). Overall, 79 of the mothers in the sample (16.8%) were treated with antibiotics adequately before delivery (at least 4 hours before delivery), and 24 mothers (5.1%) were treated inadequately with antibiotics (started antibiotics less than 4 hours before delivery) (Table 2).

Variables, No. (%)	Mothers (= 471)
Age	
> 40 Years	24 (5.1%)
30 - 39 Years	263 (55.8%)
20 - 29 Years	164 (34.8%)
< 20 Years	7 (1.5%)
Not Available	13 (2.8%)
PROM	
> 18 Hours Before delivery	57 (12.1%)
< 18 Hours Before delivery	392 (83.2%)
Not Available	22 (4.7%)
Maternal ante/intrapartum antibiotic therapy	
Adequate	79 (16.8%)
Inadequate	24 (5.1%)
Not Required	314 (66.7%)
No Available information	54 (11.5%)

Table 2: Demographics of maternal data.

Within the patients under study, there were two episodes of early culture positive neonatal sepsis (0.42%) and 14 episodes of early clinical sepsis (2.97%), in comparison to 18 late positive blood cultures (3.82%) and 56 episodes of late clinical sepsis (11.9%) (Figure 1).

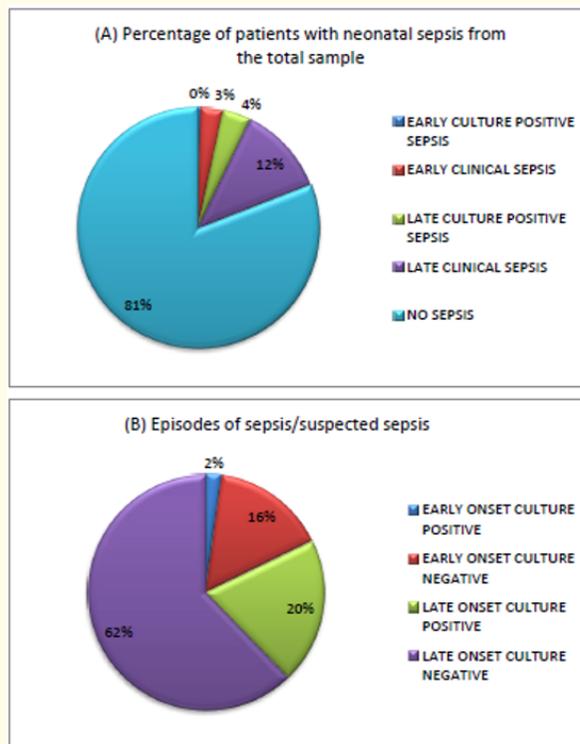


Figure 1: Frequency of (A) Infants with neonatal sepsis, and (B) Episodes of sepsis.

CRP had a sensitivity of 50% for early neonatal sepsis, 61% for late neonatal sepsis, and overall sensitivity of 60% for culture-proven sepsis. The CRP had a specificity of 95% for early neonatal sepsis, 52% for late neonatal sepsis, and overall specificity of 90%. The PPV and NPV were 4% and 99.7% for early neonatal sepsis, 27.5% and 82% for late neonatal sepsis, and 19% and 98% for overall neonatal sepsis. For clinical sepsis, CRP had an overall sensitivity of 48.6%, overall specificity of 94%, and overall PPV and NPV values of 53.9% and 92.7%, respectively (Table 3).

			CRP	TLC	ANC	PLT
Culture - proven sepsis	Early Sepsis	Sensitivity	50%	-	-	50%
		Specificity	95%	92%	84.4%	86.9%
		PPV	4%	-	-	1.6%
		NPV	99.7%	99.5%	99.5%	99.8%
	Late Sepsis	Sensitivity	61%	37.5%	11%	55.5%
		Specificity	52%	95%	90%	65.6%
		PPV	27.5%	50%	25%	32.2%
		NPV	82%	79.5%	77.4%	83.3%
	Total	Sensitivity	60%	15%	10%	55%
		Specificity	90%	92%	85%	84.5%
		PPV	19%	6.8%	2.4%	11.7%
		NPV	98.3%	96.7%	96.2%	98%

Clinical Sepsis	Early Sepsis	Sensitivity	42.8%	7.1%	14.2%	35.7%
		Specificity	96.3%	92%	84.4%	87.7%
		PPV	26%	2.6%	2.7%	8%
		NPV	98.2%	97%	97%	97.8%
	Late Sepsis	Sensitivity	50%	8.9%	7.4%	44.6%
		Specificity	47.8%	95.6%	88%	73.6%
		PPV	70%	83.3%	57.1%	80.6%
		NPV	28.2%	30.1%	30%	35.4%
	Total	Sensitivity	48.6%	8.6%	8.8%	42.9%
		Specificity	94%	92%	84.6%	87%
		PPV	53.9%	13.6%	7.4%	32.2%
		NPV	92.7%	87.5%	86.9%	91.4%

Table 3: Profile of CRP, TLC, ANC and platelet in screening for culture positive and clinical early onset/late onset neonatal sepsis.

TLC and ANC showed an overall sensitivity of 15% and 10% for culture-proven neonatal sepsis, respectively. For clinical sepsis, sensitivity was 8.6% and 8.8% for TLC and ANC, respectively. On the contrary, specificity numbers for TLC and ANC were decent for both culture-proven and clinical sepsis; 92% and 85%, respectively, for culture-proven and 92% and 84.6%, respectively, for clinical sepsis.

For culture-proven sepsis, low platelet count had a sensitivity of 55%, with a specificity of 84.5%, and PPV and NPV values of 11.7% and 98% for overall neonatal sepsis. For clinical sepsis, low platelet count had a sensitivity of 42.9%, a specificity of 87%, and PPV and NPV values of 32.2% and 91.4% for overall neonatal sepsis.

In the present study, the in-hospital mortality rate was 7.6% (36 patients), primarily due to congenital anomalies not compatible with life, extreme prematurity and prematurity-related complications, sepsis, and suspected inherited metabolic diseases.

Discussion

Neonatal sepsis still represents a diagnostic dilemma for ICU healthcare professionals due to the nonspecific early symptoms and the lack of well-validated markers for early screening. In the present study, we aimed to assess the diagnostic utility of CRP and CBC parameters taken at birth for early screening of neonatal sepsis. Overall, we found that the CRP had low sensitivity and high specificity for the detection of early and late neonatal sepsis in preterms. On the other hand, the CBC parameters had limited sensitivity and high specificity for the detection of early and late sepsis in premature neonates.

CRP is a widely used laboratory marker for elevated inflammatory status in a wide range of clinical conditions, including sepsis. The release of this pentameric protein is induced by elevated levels of proinflammatory cytokines [16]. In neonates, the normal CRP level is below 1 mg/dL in the neonatal period [17]. Several investigators assessed the diagnostic value of CRP in the early screening of neonatal sepsis. Previous reports showed that a high CRP level was a sensitive biomarker for detecting neonatal sepsis within 24 - 48 hours from disease onset [12]. Besides, CRP was found to have a predictive utility in assessing the response to treatment [13]. It was also suggested that CRP > 10 mg/L is an indicator of sepsis in high-risk groups, such as preterms. We considered that CRP of > 10 mg/L as a cut point to be considered in this study [18]. We found that in culture-proven sepsis, CRP has a sensitivity of 50% in early sepsis, 61% in late sepsis, and 60% overall sensitivity (early plus late), with a specificity of 95% in early neonatal sepsis, 53% in late sepsis, and overall specificity of 90% (early plus late). That is much lower sensitivity, with approximately similar specificity compared to other studies, such as Baptista-González HA., *et al.* [19], who found that CRP has a sensitivity of 91% and specificity of 93% for diagnosing culture-proven neonatal sepsis. Therefore, they accepted that CRP could be used systematically to diagnose neonatal sepsis, being a simple procedure and accessible for use in newborns suspected of having sepsis. Mannan MA., *et al.* [20], also proved a similar concept, with 93% sensitivity for culture-proven sepsis but a much lower specificity of 36.11%.

Due to the previously mentioned limitations regarding the positive blood cultures in neonatal sepsis, we further studied the sensitivity, specificity, positive and negative predictive values for primary screening tests concerning clinical (culture-negative) sepsis, which is relatively unclear entity. We found that CRP has sensitivity and specificity of 42.8% and 96.3% in early neonatal sepsis, 50%, and 47.8% for late sepsis, and 48.6% and 94% for overall clinical sepsis (early plus late), respectively, with positive and negative predictive values of 26% and 98.2% in early neonatal sepsis, 70% and 28.2% in late sepsis, 53.9% and 92.7% in overall clinical sepsis, respectively, in comparison to the sensitivity of 78.6%, specificity of 62.5%, and positive predictive value of 88% found in the study done by Mannan MA., *et al* [20].

A full blood count is another essential part of primary sepsis screening. In this study, low TLC ($< 5000/\text{mm}^3$), low ANC ($< 1500/\text{mm}^3$), and low platelet counts ($< 150000/\text{mm}^3$) were considered abnormal. For early neonatal sepsis, low platelet count had the best sensitivity and negative predictive values for both culture-proven and clinical sepsis. On the other hand, the CBC parameters had limited sensitivity and high specificity for detecting early and late neonatal sepsis. Such findings run in parallel with two large multicenter studies that have evaluated the diagnostic value of CBC parameters in early-onset neonatal sepsis. These studies found that low TLC, ANC and relative neutropenia had low predictive utilities for the detection of neonatal sepsis. In addition, another large multicenter study showed that low platelet count had inadequate performance to predict late-onset sepsis [21,22].

Limitations of the Study

The present study has some limitations. Most importantly the retrospective nature of the study, with the only source of our information was limited to patient records, which led limitation or unavailability of some data. The inherent limitations of a retrospective study in terms of misclassification and recording bias may be present as well. Another limitation is that the number of culture-proven episodes of sepsis in the sample under study was very limited, especially for early-onset sepsis. This resulted in the calculated sensitivity and positive predicted values for some investigations becoming 0%, and this was mainly due to the limited number of episodes. Thus, a larger number of patients with more episodes of sepsis may be helpful for more accurate results. However, one cannot deny the paucity of data on preterm neonatal sepsis from the middle eastern geographic location, and hence on the positive side, our study does contribute to this aspect.

Conclusion

In conclusion, our findings suggested that none of the primary sepsis screening investigations has adequate sensitivity for early detection of neonatal sepsis in preterm infants. At the same time, CRP only exhibits decent specificity in neonates with suspected sepsis. Thus, diagnosing neonatal sepsis needs a combination of clinical Suspicion coupled with experience and serial readings of primary sepsis screening laboratory investigations. Further randomized controlled trials are required to find a reliable single marker for early detection of neonatal sepsis in high-risk infants.

Bibliography

1. Özmeral Odabaşı I and Neonatal Sepsis. "SiSli Etfal Hastan Tip Bul". *The Medical Bulletin of Sisli Etfal Hospital* 54 (2020): 142.
2. Glaser MA., *et al.* "Neonatal Sepsis: A Review of Pathophysiology and Current Management Strategies". *Advances in Neonatal Care* 21 (2021): 49-60.
3. Fleischmann C., *et al.* "Global incidence and mortality of neonatal sepsis: A systematic review and meta-analysis". *Archives of Disease in Childhood* (2021): 1-8.
4. Hammoud MS., *et al.* "Late-onset neonatal sepsis in Arab states in the Gulf region: two-year prospective study (2017).
5. Shane AL., *et al.* "Neonatal sepsis". *Lancet* 390 (2017): 1770-1780.

6. Stoll BJ, *et al.* "Early onset neonatal sepsis: The burden of group B streptococcal and E. coli disease continues". *Pediatrics* 127 (2011): 817-826.
7. Dong Y and Speer CP. "Late-onset neonatal sepsis: Recent developments". *Archives of Disease in Childhood. Fetal and Neonatal* 100 (2015): F257-263.
8. Singh M., *et al.* "Neonatal Sepsis". Stat Pearls Publishing (2021).
9. Aggarwal R., *et al.* "Sepsis in the newborn". *Indian Journal of Pediatrics* 68 (2001): 1143-1147.
10. Gerdes JS. "Diagnosis and management of bacterial infections in the neonate". *Pediatric Clinics of North America* 51 (2004): 939-959.
11. Neto MT. "Group B streptococcal disease in Portuguese infants younger than 90 days". *Pediatric Clinics of North America* (2008): 93.
12. Hengst JM. "The role of C-reactive protein in the evaluation and management of infants with suspected sepsis". *Advances in Neonatal Care* 3 (2003): 3-13.
13. Franz AR., *et al.* "Reduction of unnecessary antibiotic therapy in newborn infants using interleukin-8 and C-reactive protein as markers of bacterial infections". *Pediatrics* 104 (1999): 447-453.
14. Von Elm E., *et al.* "The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies". *International Journal of Surgery* (2014).
15. JAVA. Declaration of Helsinki World Medical Association Declaration of Helsinki". *The Bulletin of the World Health Organization* 79 (2013): 373-374.
16. Ismail AQT and Gandhi A. "Using CRP in neonatal practice". *Journal of Maternal-Fetal and Neonatal Medicine* 28 (2015): 3-6.
17. Celik IH., *et al.* "What are the cut-off levels for IL-6 and CRP in neonatal sepsis?" *Journal of Clinical Laboratory Analysis* 24 (2010): 407-412.
18. Philip AG and Mills PC. "Use of C-reactive protein in minimizing antibiotic exposure: experience with infants initially admitted to a well-baby nursery". *Pediatrics* (2000): 106.
19. Chan DKL and Ho LY. "Usefulness of C-Reactive Protein in the Diagnosis of Neonatal Sepsis". *Singapore Medical Journal* 38 (1997): 252-255.
20. Mannan MA., *et al.* "Utility of C-reactive protein and hematological parameters in the detection of neonatal sepsis". *Mymensingh Medical Journal* 19 (2010): 259-263.
21. Hornik CP, *et al.* "Use of the complete blood cell count in late-onset neonatal sepsis". *The Pediatric Infectious Disease Journal* 31 (2012): 803-807.
22. Newman TB., *et al.* "Interpreting complete blood counts soon after birth in newborns at risk for sepsis". *Pediatrics* 126 (2010): 903-909.

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