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Noninfectious Influencers of Early-Onset Sepsis Biomarkers

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Abstract

Diagnostic tests for sepsis aim to either detect the infectious agent (such as microbiological cultures) or detect host markers that commonly change in response to an infection (such as C-reactive protein). The latter category of tests has advantages compared to culture-based methods, including a quick turnaround time and in some cases lower requirements for blood samples. They also provide information on the immune response of the host, a critical determinant of clinical outcome. However, they do not always differentiate nonspecific host inflammation from true infection and can inadvertently lead to antibiotic overuse. Multiple noninfectious conditions unique to neonates in the first days after birth, can lead to inflammatory marker profiles that mimic those seen among infected infants. Our goal was to review noninfectious conditions and patient characteristics that alter host inflammatory markers commonly used for the diagnosis of early-onset sepsis. Recognizing these conditions can focus the use of biomarkers on patients most likely to benefit while avoiding scenarios that promote false positives. We highlight approaches that may improve biomarker performance and emphasize the need to use patient outcomes, in addition to conventional diagnostic performance analysis, to establish clinical utility.

INTRODUCTION:

Sepsis comprises of a systemic inflammatory response to infection with the production and release of inflammatory and immune mediators.[1] Neonatal sepsis is a major cause of morbidity and mortality[2] and early presentation can be nonspecific, making the diagnosis challenging. Diagnostic tests for sepsis either aim to detect the infectious agent (such

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Dr. Tiozzo conducted literature review, wrote the first draft of the manuscript, and reviewed, revised and approved the final manuscript.

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as microbiological cultures) or measure the levels of markers produced by the host responding to an infection (such as C-reactive protein, CRP; procalcitonin; interleukin 6, IL-6). The latter category of 'sepsis biomarkers' has many advantages compared to culture-based methods: they have a quick turnaround time, in some cases require smaller blood volumes, are less affected by antibiotic exposure, unaffected by contamination, and provide information about the host's immune response, a critical determinant of the final outcome.[3] However, host immune markers do not detect the actual pathogen or provide information on antimicrobial sensitivities. Importantly, they do not always distinguish between inflammation secondary to infection and a sterile inflammatory state, which will not benefit from antibiotic treatment. The performance of a biomarker also depends on its kinetics relative to the stage of the disease[4] and has been incorporated in implementation of procalcitonin use.[5] CRP rises later in the disease course, suggesting a limited role for CRP in antibiotic initiation decisions.[4] Despite this, single CRP values continue to be used in practice and drive both initiation and continuation of antibiotic therapy.[6, 7] When used in the absence of microbiologically confirmed infection and/or appropriate clinical context, these tests can increase antibiotic overuse,[8, 9] contribute to the adverse effects of antibiotic exposure[10, 11] and increase microbial resistance.[12]

Noninfectious inflammatory conditions associated with abnormal host inflammation markers such as malignancies and rheumatologic diseases are rare in neonates, while infection is relatively common. This may contribute to the difficulty in formulating an alternate explanation for an abnormal marker. However, multiple noninfectious conditions unique to the neonatal population can lead to inflammatory marker profiles that mimic those seen among infected infants, particularly in the first few days after birth.[13] The birth and early postnatal period are marked by physiological stress and complex adaptations in the newborn.[14] It is also the period when the most common indication for antibiotic administration in the Neonatal Intensive Care Unit (NICU) occurs - empiric antibiotic administration for suspected early-onset sepsis (EOS).[15] Our goal was to review noninfectious conditions and patient characteristics that alter host inflammatory markers commonly used for EOS diagnosis. To focus the scope of the review, we have limited the discussion predominantly to CRP, one of the most widely available sepsis biomarkers in clinical use, and included information on other biomarkers briefly and where available.

EOS evaluation:

Sepsis biomarkers, specifically CRP along with hematological markers, have been used for decades to assist with various aspects of EOS evaluation.[16] CRP is also part of some national guidelines for EOS evaluation, recommended for use in diagnosis and in determination of length of treatment.[17] However, routine use of CRP in EOS evaluations has several challenges: the reported sensitivity of CRP in EOS evaluations is variable;[18] among infants with maternal perinatal risk factors CRP use is associated with increased procedures and antibiotic use with limited information on improved patient outcomes;[8, 9, 19, 20] and its incremental contribution to decision making, beyond available clinical information, is debatable.[6] Many of these challenges stem from noninfectious conditions that can cause elevated CRP. Procalcitonin and IL-6 are promising but less widely used sepsis biomarkers. Although these biomarkers may perform better that CRP,[5] they are also influenced by

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noninfectious conditions and may involve similar challenges when implemented for routine use, as reported with CRP. Tables 1 and 2 summarize the noninfectious perinatal factors, patient characteristics, and conditions that are can influence common sepsis biomarkers used in EOS evaluation.

PERINATAL FACTORS AND PATIENT CHARACTERISTICS:

Birth injury:

Injury during the process of birth occurs at a rate of 1.9 per 1000 live births.[21] While these injuries are reported to increase CRP levels, many reports that highlight these associations do so without formal statistical analysis, making the attribution anecdotal rather than a true association.[18, 22–24] Other studies have refuted such associations after more formal analysis.[25, 26] In particular, Kaapa et al. reported results from a prospective study of 238 mother-infant dyads where they measured CRP levels at 24 and 72 hours after birth.[26] Signs of tissue trauma including cephalhematoma, fracture clavicle, and severity of bruising were documented. They noted a significant association of vaginal delivery and vacuum extraction with elevated CRP at 24 hours. However, they found no association between the presence or severity of tissue trauma and the level of CRP.

Delivery mode and labor:

Multiple studies report higher mean/median CRP levels among infants delivered by vaginal delivery (VD) and emergency cesarean delivery (CD) compared to elective CD.[27–30] The association is attributed to fetal ‘stress’ with labor,[31] and possibly with differences in mother-to-child colonization patterns.[32] Instrumental vaginal deliveries are also associated with a higher maximum CRP value and are attributed to labor duration, rather than tissue traumatization.[26, 27] Labor duration and VD are associated with higher total neutrophil levels, higher white count, and immature neutrophils that resolve after the first 24 hours.[33–35] Duration of labor is also associated with higher IL-6 levels.[36–39] Notably, delivery mode is not associated with differences in immature to total neutrophil count,[34, 35] or procalcitonin levels.[29.30]

Variation in peak levels by delivery mode can impact the proportion of infants who meet a set cut-off threshold for the diagnosis of sepsis. Overall, the proportion of uninfected infants with the highest CRP value above the 10 mg/L cut-off varies from 3–25% of the overall cohort depending on the study,[13, 19, 27, 29] and occurs more frequently in infants delivered by VD.[28, 30] In a cohort study of infants admitted to the NICU and ultimately managed as uninfected, the 75th quartile for the highest CRP value at 36 hours after birth was 13.7 mg/L compared to 2.74 mg/L among those delivered by CD.[30] Similarly, the 95th centile for CRP at 48 hours after birth in a cohort of uninfected term infants was 12.1 mg/L and 11.3 mg/L for infants delivered by VD and emergency CD respectively, compared to 6 mg/L for infants delivered by CD.[28]

Perinatal risk factors for infection:

Perinatal factors associated with the risk of EOS occur at a substantially higher incidence than actual invasive infection,[40] and can alter the inflammatory response in infants

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independently of actual infection. In a study of serial CRP values obtained among term infants ultimately diagnosed as uninfected, almost one-fourth infants with perinatal risk factors reported a CRP value at some point above the 10 mg/L cut-off.[19] Similarly, among 554 infants born to mothers with a diagnosis of chorioamnionitis, 22% were found to have a CRP value >10 mg/L and 28% had either an abnormal IT ratio or an elevated CRP at 12 hours of age.[9] While only 4 infants had culture-confirmed infection, an elevated 12 hour CRP led to both prolonged antibiotics administration and increased frequency of lumbar punctures. The lack of specificity when defining chorioamnionitis[41] and variation in the use of perinatal risk factors to identify at-risk infants,[42] can result in variable performance of inflammatory biomarkers.

Studies have described multiple perinatal factors that affect biomarker levels. Chiesa *et al.* enrolled infants without evidence of maternal intraamniotic infection and with an unremarkable early postnatal course to establish reference levels among uninfected infants.[29] After adjusting for gestational age, age at sampling, and infant sex, they noted a significant association of mean CRP value with duration of active labor (14.5% increase per hour), membrane rupture (0.4% increase per hour) and intrapartum antibiotic prophylaxis (increase by 28%) compared to infants without these factors. These factors were not associated with changes in procalcitonin level in this study; however, prolonged membrane rupture has been associated with higher procalcitonin levels in other studies.[43, 44] Other perinatal variables associated with elevated CRP levels, often reported as unadjusted associations, include maternal fever,[45] antenatal steroid administration,[29] maternal diagnosis of hypertension,[46] and low Apgar scores.[46] The level of procalcitonin has been variably associated with maternal antibiotic exposure with significantly lower values reported in one study[47] and no change in another study.[43] Maternal fever was associated with elevated maternal IL-6 levels and with elevated IL-6 in cord blood.[48]

Many of these factors are interrelated and only a few studies perform multivariable models to identify independent contributions. Study design and analytical approaches further limit interpretation of results. For example, while maternal antibiotic exposure was found to be associated with elevated CRP levels,[29] in a different study when the analysis was restricted to patients with an indication for intrapartum prophylaxis association was found only with incomplete prophylaxis.[28] Despite limitations, these studies confirm that multiple perinatal factors known to be associated with increased risk of infection are also associated with abnormal markers among uninfected infants, confounding the diagnostic performance of these biomarkers. Finally, the association of perinatal risk factors for infection with abnormal sepsis biomarkers cannot simply be attributed to undetected infection,[22] as many of these studies ensured an unremarkable course for study infants for multiple weeks after birth.[27–29, 49]

Gestational age:

Preterm gestation is associated with lower CRP,[13, 19, 27, 29, 50] and higher procalcitonin[29, 47] and IL-6 values.[46] The lower baseline level of CRP in preterm infants may alter diagnostic performance. In a cohort of 179 term and 353 preterm infants, CRP had a lower sensitivity of 53% among preterm infants compared to 86% in term infants for diagnosing culture-

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confirmed EOS.[13] After birth, the median CRP value increased for all gestational ages, with an earlier (27–36 hours) but lower peak value in preterm infants compared to term infants (56–70 hours).[13] Procalcitonin levels (adjusted for gender and age at sampling) among uninfected infants were negatively associated with gestational age: term infants had an estimated peak value of 2.9 ng/mL (0.4–18.7) at 24 hours while preterm infants (<37 weeks) had a peak value of 6.5 ng/mL (0.9–48.4) at 21–22 hours.[29] Neutrophil levels also vary by gestation age with higher peak values in term infants compared to moderately and late preterm infants and earlier peak levels compared to extremely preterm infants.[33]

Chronological age:

Many sepsis biomarkers increase immediately after birth, followed by a decline over 72–96 hours. This rise and fall is seen with CRP,[19, 29, 30, 50] procalcitonin,[29, 43, 44] IL-6,[51] and neutrophil counts.[33, 52] Accounting for age improves the diagnostic performance of hematologic markers,[53] and has been used with procalcitonin,[5] but has not been widely incorporated in the interpretation of CRP. Instead serial values are used to trend changes that incorporate information from both disease progression, if present, and physiological changes that occur in the first days after birth.[16] Such an approach is often aimed at discontinuing antibiotics rather than initiation.[17] However, single values are frequently used in practice despite poor performance.[6]

In light of the many perinatal and patient-related factors that affect baseline CRP levels, a single common threshold for all newborns may be inadequate. A dynamic threshold that accounts for gestational age and chronological age has been proposed as a means to improve performance, but is not yet widely available.[18]

HYPOXIC ISCHEMIC ENCEPHALOPATHY

Neonates diagnosed with hypoxic ischemic encephalopathy (HIE) are also at high risk for EOS. The incidence of culture-confirmed infection among infants enrolled in therapeutic hypothermia (TH) trials ranges from 3% to over 12%[54] and in database studies from 1–2%.[55, 56] No difference in the incidence of EOS is reported with the use of TH.[54] Sending cultures and initiating empiric antibiotics is therefore common among infants with HIE.[56] Stopping antibiotics once cultures are sterile is, however, more variable. In a study of more than 1,500 HIE cases, 16% infants were treated as culture-negative infection with 8 median days of antibiotics.[56] The hesitation to stop antibiotics when cultures are negative persists among neonatal providers,[57] and is heightened when managing children who are critically ill. Part of this hesitation comes from concerns about the reliability of blood cultures and part from a reliance on abnormal sepsis biomarkers instead.[58, 59] However, the reliability of biomarkers can also be affected by many factors in HIE, not related to infection, that result in systemic inflammation.

The pathophysiology of HIE, regardless of concomitant infection, includes an inflammatory cascade with microglial activation and migration, infiltration of peripheral macrophages into the brain, and the release of cytotoxic and pro-inflammatory cytokines such as IL-6 and IL-8 both locally in the neural circulation and in the systemic circulation.[60, 61] TH, alternately, is known to reduce neuroinflammation and can alter the dynamics of common

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sepsis biomarkers in the absence of proven infection.[62–64] An elevated CRP level >10 mg/L is reported in 55–68% of infants with HIE in the absence of culture-confirmed infection and is associated with severity of HIE.[65–67] Besides higher values, CRP levels were slower to peak, and remained high for a longer duration among patients undergoing TH compared to normothermic historic controls with HIE, independent of perinatal infection risk factors, severity of HIE and concomitant meconium aspiration.[58, 59, 67] Higher levels of procalcitonin and IL-6 levels are also reported in neonates and adults receiving TH.[63, 64, 68] The cut-off values proposed for IL-6 levels in sepsis diagnosis vary from <10 pg/mL to over 300 pg/mL.[69] Among 22 infants with HIE and without infection, IL-6 median levels were 198.2 pg/mL (IQR: 49.8–358.3) and 101.9 pg/mL (IQR: 24.9–562.9) on day 1 and 2, respectively.[63] These values suggest that reliance on abnormal inflammatory markers in infants with HIE will promote prolonged antibiotic administration in the majority. An appropriately obtained blood culture has a high detection rate for the vast majority of organisms between ≥4 CFU/mL,[70, 71] and it is unlikely that two-thirds of cases of HIE cases have actual bacteremia that was not detected in the blood culture. The wide center variation in prolonged antibiotic administration to infants suggests antibiotic overuse,[56] while there is no evidence to suggest that prolonged antibiotics based on inflammatory markers improve outcomes. In addition, infants with HIE have an increased risk of drug toxicity that can be compounded by unnecessary antibiotic exposure.[72]

In summary, the use of immune markers to guide antibiotic therapy in infants with HIE infants is fraught with challenges. Studies are urgently needed to establish the best antibiotic use practices in this population.

MECONIUM ASPIRATION SYNDROME:

Meconium stained amniotic fluid complicates approximately 10–20% of all pregnancies and meconium aspiration syndrome (MAS) occurs in 5–10% of these newborns.[73–76] The pathogenesis of MAS is multifactorial and involves airway obstruction, surfactant dysfunction, pulmonary hypertension, and alveolar inflammation with resultant hypoxia and hypercapnia.[77] Inflammation plays a central role in the pathogenesis of MAS, affecting both surfactant production and function, and pulmonary perfusion leading to local and ultimately systemic manifestations.[78] Pro-inflammatory cytokines (IL-8, IL-1B, IL-6, and TNF-a) are found in tracheal aspirates of patients affected by MAS as early as 6 hours after exposure and recapitulated in animal studies.[79–84] IL-8, found in meconium, plays a role in attracting neutrophils from the system circulation into alveoli spaces.[82] Inflammatory markers have been proposed as markers of disease severity and therapeutic response. Among 239 infants without culture-confirmed infection, severe MAS (requiring mechanical ventilation) in the first 2 days after birth was associated with a significantly higher CRP and immature to total neutrophil ratio and a lower WBC and ANC, compared to infants with less severe MAS (no mechanical ventilation).[85] Conversely, a decrease in inflammatory markers 96 hours after birth was associated with an improvement in respiratory parameters.[79]

The diagnosis of early-onset culture-negative infection is highly variable between units[2] and is often based on a combination of inflammatory markers and clinical symptoms.[7] The elevated inflammatory markers observed in MAS and the need for critical care in these

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infants can potentially lead to prolonged use. However, there is no established benefit from such use of antibiotics. Three trials conducted in low-middle-income settings have compared antibiotic administration in infants with MAS: two trials compared 7 days of antibiotics and one compared 3 days of empiric antibiotics with no antibiotics.[86–88] Individually and in a meta-analysis, no differences were observed in the incidence of proven infection, mortality, or duration of hospital admission.[89, 90]

Although no difference in the incidence of bacteremia is reported between infants born with and without meconium-stained amniotic fluid, the baseline rate of infection in some of these studies is high.[91] Therefore, we focus on sending appropriate microbiological tests and stopping antibiotics when they are negative rather than not initiating antibiotics at all. The association between inflammatory indices in the early phase of the disease and the severity of MAS raises the question whether the inflammatory markers should be more rigorously evaluated as predictors of the disease course, which can inform therapeutic planning, such as the decision to transport to a center with extracorporeal membrane oxygenation facilities.

SURGICAL CONDITIONS AFFECTING EARLY LIFE BIOMARKER LEVELS

Surgery is associated with metabolic stress and cytokine release that can raise many common inflammatory biomarkers.[92, 93] Surgical interventions soon after birth may involve major procedures such as correction of congenital anomalies or minor elective procedures such as circumcision. Inflammatory biomarker levels in response to circumcision during birth hospitalization have not been well described. In a study of 115 children aged 1–13 years undergoing circumcision with different modes of anesthesia, there was no difference in levels before and after the procedure.[94] It is unclear whether CRP and other inflammatory biomarkers are equally unaffected during neonatal circumcision.

In conditions that require major surgery soon after birth, evaluation for infection is often done, but antibiotics administered may target the ongoing risk of infection rather than EOS. A condition with baseline elevation of inflammatory markers is gastroschisis. Elevated CRP, I:T ratio, and IL-6 levels are reported both before and after surgery in infants with gastroschisis compared to control infants and infants with other anomalies such as omphalocoel.[95, 96] These high levels are thought to reflect inflammation that is intrinsic to gastroschisis and are not considered reliable markers for EOS.[96, 97] Nevertheless, clinical reports show that when obtained in gastroschisis patients, abnormal biomarker levels result in more invasive procedures such as lumbar punctures[95] and longer courses of antibiotics.[97] The more common use of inflammatory markers is to assess for postoperative infection. Studies vary in detecting changes in biomarker levels after neonatal surgery.[96, 98] The ability of a particular test to discriminate a postsurgical inflammatory response from infection is also variable.[99–101] In most cases higher cut-offs and close attention to the temporal relation with surgery are required for optimal test performance[98, 99, 101] As with many of the other conditions triggering sepsis evaluation after birth, it is unclear whether the use of biomarkers aids decision making and improves patient outcomes.

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DISCUSSION:

In summary, multiple noninfectious factors present among infants admitted to the NICU affect the median values of common sepsis biomarkers and the proportion of infants who meet the threshold for a 'positive' test. Beyond EOS evaluation, other investigators have also highlighted sensitivity issues when using CRP in late-onset infection evaluations. In a recent meta-analysis of 22 studies using a preset cutoff of 5–10 mg/L the pooled sensitivity was 0.62 (95%CI, 0.50–0.72).[102] The authors concluded that CRP would not contribute to improving sepsis diagnosis and may increase unnecessary medicalization. Along these lines, the deimplementation of routine CRP use in EOS evaluation significantly reduced antibiotic use without reported adverse effects in a single-center study.[103] One may say, at this point, why don't we just cut our losses with CRP and move on? And while that may be one approach, there remain unresolved issues. First, there *is* a gap in sepsis diagnosis that could be improved with a fast turnaround test. Second, the use of CRP is still quite prevalent.[74] Finally, many of the issues identified for CRP and other common biomarkers may also be relevant for the next novel inflammatory biomarker that is introduced into practice.

There are several ways to improve test performance. One is to recognize the noninfectious conditions that influence test results and incorporate them into the interpretation of sepsis biomarker results. For example, leukopenia in a growth-restricted infant delivered to a mother with preeclampsia prior to the onset of labor or rupture is likely not related to EOS and its use for antibiotic initiation during after birth could be avoided.[104] Another characteristic infrequently addressed is the changing pre-test probability of infection in different clinical scenarios. A biomarker is expected to be valuable when the pre-test probability of infection in the patient being tested is neither too high (almost all clinicians would treat regardless of test results) nor too low (no clinician would treat regardless of test results). Studies that include patients with extreme pre-test probabilities do not capture the information a clinician desires in real-world practice. A similar idea can be extended to the pre-test probability of inflammation in the absence of infection. Testing should be avoided in scenarios where the probability of sterile inflammation is too high for a biomarker to discriminate additional infection.

Another approach could be to incorporate adjusted receiver operator characteristic curves[105, 106] that account for covariates, such as gestational or chronological age, associated with the distribution of a biomarker value among uninfected infants. The traditional approach of using biomarkers for the diagnosis of sepsis with one cut-off point, regardless of patient age, characteristics or prior probability of infection of the patient, is potentially inadequate. Covariate adjustment, a cornerstone in bias reduction in association studies, is infrequently considered in the analysis of neonatal sepsis biomarker performance.[18] Variables that are associated with both biomarker value and the risk of infection, such as duration of membrane rupture and labor, qualify as confounders. Not accounting for these variables overestimates the performance of diagnostic markers.[105] In contrast, accounting for variables that are associated with the marker but not necessarily with EOS, such as delivery mode or sampling time, can improve the accuracy of the marker. While combining biomarkers may improve performance, accounting for covariate

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distribution in uninfected infants that influence individual markers and/or outcomes will still be required.

The end point for sepsis biomarker studies is often time to infection diagnosis and improved identification of infection cases.[107] Given the many concerns with the culture-based gold standard of infection diagnosis, it may be more relevant to focus on measures of patient outcome, such as mortality, and measures of morbidity, such as length of hospitalization and readmissions. Rigorous analysis is needed to understand which sepsis biomarkers change decision making beyond that provided by history and clinical exam, and whether incorporating the test into existing risk prediction models, such as the sepsis risk calculator, has incremental value with demonstrable health benefits.

A final thought is whether we have used all information that these common tests provide us with. Inflammation itself is recognized as a key mediator of multiple adverse outcomes among infants admitted to the NICU. Yet, the clinical focus when using common inflammatory biomarkers like CRP is primarily on antibiotic administration. A CRP value of >100 mg/L was reported in 4% of NICU admissions (258 infants); of the 106 infants identified in the first 3 days, most were of term gestation and 81% were considered not infected.[108] One wonders if such a heightened inflammatory response is not relevant to the health of these infants. Are there practices in neonatal care beyond antibiotics, that can be informed with these values? Does evidence of early inflammation impact ultimate outcomes and, if so, can that be manipulated in favor of the patient? Sepsis biomarkers provide information about the state of the host. Whether there is infection or not, an abnormal value may have health implications, as has been demonstrated in other settings.[109–111] Using these widely available markers to further our understanding of the newborn's immunological state may provide important avenues for improving outcomes.

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What does this article add to the existing literature?

1. Most reviews of neonatal sepsis biomarkers focus on detection of true positives and highlight the clinical utility in doing so. However, understanding the drivers of false positive test results is equally relevant in optimizing use.
2. We review common patient characteristics and non-infectious conditions that alter host inflammatory markers commonly used for neonatal sepsis diagnosis.
3. We discuss approaches that may improve biomarker performance and emphasize the need to use patient outcomes, in addition to conventional diagnostic performance analysis, to establish clinical utility.

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Table 1:

Perinatal factors and C-reactive protein, procalcitonin and interleukin-6 levels

Characteristic	Biomarker	Effect on biomarker	Reference
Vaginal delivery	CRP	Higher levels compared to cesarean deliveries, particularly those that were elective	[26, 27, 28, 29, 30, 39]
	PCT	No association	[29]
	IL-6	Higher levels compared to elective cesarean delivery	[38, 36]
		No effect; but significant effect of duration of labor	[37]
Duration of labor	CRP	Higher levels with longer duration of labor	[27, 28, 29]
	PCT	No association	[29]
	IL-6	Higher levels with longer duration of labor	[35, 37]
Rupture of membrane	CRP	Higher levels with longer duration of rupture	[29]
	PCT	Higher levels with longer duration of rupture	[43, 44]
Maternal fever or signs of infection	CRP	Higher levels	[45]
	PCT	No association	[43]
	IL-6	Higher levels	[48]
Maternal intrapartum antibiotic prophylaxis	CRP	Higher levels	[29]
	PCT	No association	[43]
		Lower levels	[47]
	IL-6	Higher levels	[46]
Maternal hypertensive disorder	CRP	Higher levels	[49]
	PCT	Higher levels	[46]
	IL-6	No association	[46]

CRP – C-reactive protein, IL-6 – interleukin-6

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Table 2:

Infant characteristics and C-reactive protein, procalcitonin and interleukin-6 levels

Characteristic	Biomarker	Effect on biomarker	Reference
Lower gestational age	CRP	Lower levels	[13, 19, 29, 46, 50]
	PCT	Higher levels	[29]
	IL-6	Higher levels	[49]
Increasing birth weight	CRP	Higher levels	[13, 29]
	PCT	Higher levels	[29]
Birth injury e.g. cephalhematoma and tissue trauma	CRP	No association	[26]
Hypoxic-ischemic encephalopathy	CRP	Higher levels	[65, 66, 67]
	PCT	Higher levels	[68]
	IL-6	Higher levels	[63]
Meconium aspiration	CRP	Higher levels	[79]
	PCT	Higher levels	[83]
	IL-6	Higher levels	[84]
Gastroschisis	CRP	Higher levels	[95, 96]
	IT ratio	Higher levels	[97]
	IL-6	Higher levels	[98]

CRP – C-reactive protein, IL-6 – interleukin-6

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