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Cluster of Differentiation 163 Level in the Blood as a Predictor of Early and Late Onset Neonatal Sepsis

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ABSTRACT

Background: Early and late-onset neonatal sepsis (EOS and LOS) are significant causes of morbidity and mortality in newborns. Accurate and timely diagnosis is critical for effective management. The Cluster of Differentiation 163 (CD163) level in the blood has emerged as a potential biomarker for sepsis, reflecting the immune response to infection.

Objective: This study aimed to evaluate the role of CD163 levels in predicting neonatal sepsis and its correlation with other clinical and laboratory parameters. **Methods:** A comparative study was conducted involving 90 neonates divided into three groups: EOS, LOS, and a control group. Clinical data, presenting complaints, maternal risk factors, and laboratory findings were analyzed. CD163 levels were measured and correlated with clinical outcomes. **Results:** CD163 concentrations were markedly higher in both EOS and LOS cohorts relative to the control group. In the LOS cohort, CD163 levels demonstrated a positive association with platelet count and an inverse relationship with hemoglobin concentrations. No significant gender differences in CD163 levels were observed. **Conclusion:** CD163 serves as a critical biomarker for the prompt identification of neonatal sepsis, with a threshold value set at ≥ 4.5%. Its use in clinical practice could enhance early diagnosis and treatment as well as reduction of neonatal morbidity and mortality.

Keywords: Neonatal sepsis, CD163, Biomarkers, Late-onset sepsis, Early-onset sepsis, Maternal risk factors.

INTRODUCTION

Neonatal sepsis is characterized by a systemic bacterial infection that is definitively diagnosed via a positive blood culture during the initial 30 days of life [1]. It represents a significant public health challenge, consistently ranking among the leading causes of neonatal morbidity and mortality [2]. In developing nations, neonatal sepsis is responsible for roughly 30-50% of all neonatal fatalities, with an estimated 20% of newborns experiencing sepsis and approximately 1% succumbing to complications arising from the condition [3]. The incidence rate of neonatal sepsis is estimated at 5.7 per 1000 live births [4].

Neonatal sepsis is generally categorized into two distinct types, predicated on the temporal onset of clinical manifestations: EOS, emerging within the initial 72 hours postpartum, and LOS, which appears subsequent to this period [5]. Given the non-specificity of sepsis indicators, maintaining a heightened clinical vigilance is critical for prompt diagnosis. Infants affected by sepsis may exhibit a diverse spectrum of clinical manifestations, including but not limited to hypothermia or fever, lethargy, hypotonia, diminished cry strength, absent neonatal reflexes, feeding aversions, compromised perfusion, extended capillary refill time, abnormal heart rates (either tachycardia or bradycardia), gasping, respiratory distress, apnea, dysregulated blood glucose levels (hypo/hyperglycemia), metabolic acidosis, alongside other organ-specific manifestations [6]. The definitive diagnosis of septicemia continues to rely on blood culture, which is imperative in all suspected cases prior to the commencement of antibiotic treatment [7]. CD 163 is predominantly expressed on macrophages with an anti-inflammatory phenotype, potentially acting as a scavenger receptor for haptoglobin-hemoglobin complexes. The soluble form of CD163 (sCD163), which is shed by monocytes and macrophages in response to inflammatory stimuli, shows promise as an early marker for sepsis susceptibility [8]. The measurement of serum sCD163 levels offers potential benefits in diagnosing sepsis and severe sepsis, outperforming CRP levels. Additionally, sCD163 may be advantageous for dynamically monitoring sepsis progression and prognosis, highlighting its potential in clinical settings [9]. However, confirming sepsis early in neonates remains a significant challenge [10].

PATIENTS AND METHODS

Study design: This study was a case-control study.

Study setting: All cases were taken from the neonatal intensive care unit in Alexandria public hospital through the period from November 2015 to June 2016.

Patients: The study encompassed 90 neonates, who were divided into three distinct groups:

- **Group I (n=30):** Full term neonates with early onset neonatal sepsis (< 72 h).
- **Group II (n=30):** Full term neonates with late onset neonatal sepsis (> 72 h).
- **Group III (n=30):** Control group who were apparently healthy full-term neonates and age- and sex- matched.

Inclusion criteria: Neonates aged between 0 and 28 days and of both genders. Neonates with early and late onset sepsis diagnosed based on clinical indicators, which

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included one or more of the following symptoms: Respiratory rate exceeding 60 breaths per minute (indicative of tachypnea), audible grunting, body temperature either surpassing 37.7°C or dropping below 35.5°C (hypothermia), marked lethargy or unresponsiveness, inability to maintain effective sucking, increased heart rate (tachycardia), and occurrence of convulsions [11].

Exclusion criteria: Neonates with significant congenital malformations or associated syndromic conditions. All cases presenting with varied clinical manifestations that may mimic neonatal sepsis, such as hypoxic-ischemic encephalopathy (HIE), perinatal asphyxia, necrotizing enterocolitis, or transient tachypnea of the newborn (TTN).

Methods: All patients and control cases were systematically subjected to the subsequent evaluations:

I- Thorough history:

- Maternal risk factors implicated in the onset of neonatal sepsis encompass vaginitis, the presence of foul-smelling amniotic fluid, maternal hyperthermia above 38°C, prolonged premature rupture of membranes (PROM) exceeding 18 hours, and UTI, alongside the delivery method.
- Apgar score assessment conducted at 1 and 5 minutes postpartum.
- Symptoms of sepsis include:
  - Respiratory distress (Apnea & tachypnea).
  - Cardiological (Cyanosis).
  - Hemodynamics (Skin mottling).
  - Neurological (Irritability, hypotonia, hypoactivity, lethargy & seizures).
  - Gastrointestinal (Abdominal distension, poor suckling, feeding intolerance & vomiting).
  - Temperature instability (Hypothermia < 36°C & fever > 38°C).
  - Metabolic (Symptoms of hypo or hyperglycemia).

II- Careful clinical examination:

Gestational age was estimated using the updated Ballard scoring system, and anthropometric parameters such as weight, length, and head circumference. The identification of sepsis was based on the presence of three or more clinical indicators, which included respiratory manifestations like respiratory distress, apnea, tachypnea, or hypoxemia, cardiac symptoms such as tachycardia or bradycardia, and hemodynamic instability evidenced by poor skin color, peripheral hypoperfusion, or hypotension. Additionally, neurological signs, which included irritability, lethargy, hypotonia, hypoactivity, or seizures were considered, along with gastrointestinal disturbances such as abdominal distension, poor feeding, or feeding intolerance. Abnormalities in thermoregulation, including hyperthermia (fever > 38°C) or hypothermia (< 36°C), as well as metabolic disturbances like metabolic acidosis or hyperglycemia were also evaluated.

III- Laboratory investigations:

A comprehensive hematological assessment was conducted, beginning with the complete blood count (CBC) that included differential leucocytic and platelet counts, measured at the onset of sepsis evaluation (0 hour) using the Coulter Counter T890 (Harpenden, UK). The immature neutrophil count was calculated by multiplying the percentages of bands, metamyelocytes, and myelocytes by the absolute neutrophil count, while the immature-to-total neutrophil (I/T) ratio was derived using the formula: (metamyelocytes + bands + myelocytes) / (bands + segmented neutrophils + metamyelocytes + myelocytes). C-reactive protein (CRP) levels were quantified using the latex agglutination assay, specifically the AVITEX CRP kit provided by Omega Diagnostics Group PLC (Scotland, UK). Blood cultures were performed to detect aerobic and anaerobic organisms, employing the Bactec microbial detection system (Bactec 9050, Becton-Dickinson, NJ, USA). Blood samples (1-5 ml) were collected via venipuncture and introduced into Bactec culture bottles, which use a chemical sensor to monitor CO_2 production—a marker of microbial growth—with fluorescence detection every 10 minutes. Positive cultures were subsequently subcultured onto blood, chocolate, and MacConkey agar plates, followed by aerobic incubation at 35-37 °C for 24 hours. This was followed by Gram staining, comprehensive biochemical profiling, and antimicrobial susceptibility testing. Negative culture bottles were re-examined after seven days before issuing final reports. Additionally, CD163 levels in blood were assessed via flow cytometry. Blood samples, maintained at room temperature, were processed within 24 hours using a FACS caliber flow cytometer (Becton Dickinson), where viable cells were incubated with fluorescein-labeled monoclonal antibodies (MoAbs), specifically PE Mouse Anti-Human CD163 (BD Biosciences, USA). The procedure involved adding 100 µl of EDTA-anticoagulated blood to Falcon tubes, followed by MoAb incubation, washing with phosphate-buffered saline (PBS), lysing, and final analysis. Isotypic antibodies served as negative controls to account for autofluorescence and nonspecific binding, with positivity determined when over 4.5% of cells exceeded background fluorescence in negative controls.

Ethical approval: Al-Azhar Medical Ethics Committee of Al-Azhar Faculty of Medicine approved this study. After being informed of all the details, each participant' parent provided written consent. The integrity of confidentiality and privacy for all gathered data were meticulously upheld and rigorously protected at every stage of the research process. Parents were explicitly granted the unreserved right to

withdraw from the study at any point, without the need to provide any justification or explanation. Throughout the course of the investigation, the Helsinki Declaration was adhered to.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS), version 20 (IBM, USA), was employed to meticulously conduct data collection, revision, coding, and entry. Quantitative data were summarized as means with standard deviations and ranges when their distribution was determined to be parametric, while qualitative data were expressed as frequencies and percentages. Data were depicted as medians with IQR for non-parametric distributions. The Chi-square test or Fisher's exact test was employed to conduct comparative analysis between two groups that involved qualitative variables when the expected cell counts were less than 5. The independent t-test was implemented for parametric distributions in quantitative data comparisons between two independent groups, while the Mann-Whitney test was implemented for non-parametric distributions. The Kruskall-Wallis test was employed for non-parametric data, while the One-Way ANOVA was employed for parametric data when comparing more than two groups. Spearman's correlation coefficient was employed to evaluate the correlations between two quantitative variables within the same group. The ROC curve was employed to assess the diagnostic accuracy, sensitivity, specificity, PPV, and NPV of CD163. The margin of error was established at 5%, with a confidence interval of 95%. The interpretation of statistical significance was as follows: a p-value greater than 0.05 was declared non-significant, while a p-value ≤ 0.05 was considered significant.

RESULTS

Table (1) illustrated a statistically significant elevation in respiratory rate, decrease in temperature, Apgar score at 1 min & 5 min, prolonged capillary refilling time with non-statistically significant difference among other data in EOS and LOS group when compared to control group.

Table (1): Demographic and clinical characteristics across the groups under investigation

			EOS	LOS group	Control group	Chi-square test		
			No. = 30	No. = 30	No. = 30	X2	P-value	Sig.
Gender [no. (%)]		Female Male	13 (43.3%) 17 (56.7%)	15 (50.0%) 15 (50.0%)	11 (36.7%) 19 (63.3%)	1.086	0.581	N
Gestational age (weeks)		Mean ± SD Range	38.233 ± 0.971 37 – 41	38.367 ± 1.033 37 – 40	38.200 ± 1.126 37 – 41	0.213	0.808	N
Birth weight (kg)		Mean ± SD Range	3.042 ± 0.488 2.15 – 3.9	3.093 ± 0.577 2 – 4	3.313 ± 0.451 2.4 – 4.2	2.417	0.095	N
Length (cm)		Mean ± SD Range	49.783 ± 0.962 48 – 52	50.033 ± 1.245 48 – 53	50.233 ± 0.817 49 – 52	1.455	0.239	N
HC (cm)		Mean ± SD Range	35.017 ± 0.594 34 – 36	35.067 ± 0.785 34 – 37	35.133 ± 0.556 34 – 36	0.241	0.786	N
HR (b/m)		Median (IQR) Range	120 (115–130) 100 – 160	127 (120–140) 100 – 155	127 (120–140) 100 – 158	1.193	0.308	N
RR (C/m)		Median (IQR) Range	62 (55 – 70) 40 – 100	69 (62 – 80) 40 – 100	50 (48 – 54) 40 –58	20.675	0.000	S
Temperature (C°)		Mean ± SD Range	36.810 ± 0.354 36 – 37	36.957 ± 0.280 36.5 – 38	36.970 ± 0.084 36.7 – 37	3.370	0.039	S
Cap. Ref. Time (sec.)		Mean ± S D Range	2.933 ± 1.081 2 – 5	2.767 ± 0.971 2 – 5	2.267 ± 0.450 2 – 3	4.682	0.012	S
Mode of delivery	CS Normal		26 (86.7%) 4 (13.3%)	23 (76.7%) 7 (23.3%)	26 (86.7%) 4 (13.3%)	1.440	0.487	N
APGAR Score*	1 min	Median (IQR) Range	7 (7 – 8) 5 – 8	7 (7 – 8) 4 – 8	8 (8 – 9 5 – 9	22.052	0.000	S
	5 min	Median (IQR) Range	9 (8 – 9) 7 – 10	9 (9 – 10) 7 – 10	10 (9 – 10 8 – 10	23.569	0.000	S

* Kruskall Wallis test

Table (2) showed that respiratory distress, gastrointestinal symptoms, temperature instability and hypoactivity were the main presenting complaints among studied group and were of high significant value as they were significantly higher among septic group (P value < 0.001).

Table (1): Presenting complaints among studied groups

		EOS	LOS group	Control group	Chi-square test		
		No. = 30	No. = 30	No. = 30	X2	P-value	Sig.
Complain	Respiratory distress	20 (66.7%)	24 (80.0%)	0 (0.0%)	44.111	0.000	S
	Cyanosis	1 (3.3%)	3 (10.0%)	0 (0.0%)	3.663	0.160	N
	Skin mottling	3 (10.0%)	1 (3.3%)	0 (0.0%)	3.663	0.160	N
	Neurological symptoms	0 (0.0%)	2 (6.7%)	0 (0.0%)	4.091	0.129	N
	Gastrointestinal symptoms	8 (26.7%)	3 (10.0%)	0 (0.0%)	10.150	0.006	S
	Temperature instability	3 (10.0%)	0 (0.0%)	0 (0.0%)	6.207	0.045	S
	Metabolic syndrome	1 (3.3%)	1 (3.3%)	0 (0.0%)	1.023	0.600	N
	Hypoactivity	8 (26.7%)	0 (0.0%)	0 (0.0%)	17.561	0.000	S
	Arthritis	0 (0.0%)	1 (3.3%)	0 (0.0%)	2.022	0.364	N

Table (3) showed that PROM >18 hour and vaginitis were the main maternal risk factors among EOS and LOS and this was with statistically significant difference when compared to control group.

Table (2): Comparison between all studied groups regarding maternal risk factors

	EOS	LOS group	Control group	Chi-square test		
	No. = 30	No. = 30	No. = 30	X2	P-value	Sig.
PROM>18hr	10 (33.3%)	6 (20.0%)	0 (0.0%)	11.554	0.003	S
Offensive liquor	3 (10.0%)	1 (3.3%)	0 (0.0%)	3.663	0.160	N
Maternal fever	1 (3.3%)	0 (0.0%)	0 (0.0%)	2.022	0.364	N
UTI	5 (16.7%)	2 (6.7%)	0 (0.0%)	5.886	0.053	N
Vaginitis	7 (23.3%)	7 (23.3%)	0 (0.0%)	8.289	0.016	S

Table (4) showed that there was a statistically highly significant increase in WBC count, I/T ratio and CRP level and significant decrease in RBCs count, HB and platelet count among the studied EOS, LOS groups when compared to control group.

Table (4): Comparison between all studied groups regarding laboratory data

		EOS	LOS group	Control group	One Way ANOVA		
		No. = 30	No. = 30	No. = 30	F	P-value	Sig.
WBCs (10^3/mm3)	Mean ±SD	15.39 ± 1.77	13.06 ± 2.53	8.82 ± 2.02	5.280	0.007	S
RBCs (10^6/mm3)	Mean ±SD	4.23 ± 0.79	3.82 ± 0.76	4.52 ± 1.13	4.596	0.013	S
HB (g/dL)	Mean ±SD	14.33 ± 2.56	12.18 ± 2.39	15.34 ± 3.83	8.688	0.001	S
PLT (10^3/mm3)	Mean ±SD	170.67 ± 27.24	289.20 ± 35.57	190.77 ± 6.25	3.192	0.046	S
CRP (mg/dl)	Median (IQR) Range	36 (22 – 120) 6 – 300	39 (24 – 79) 10 – 120	0 (0 – 0) 0 – 0	19.210	0.000	S
I/T ratio	Mean ±SD	0.28 ± 0.04	0.33 ± 0.07	0.13 ± 0.08	16.750	0.000	S

Table (5) showed that there was a high statistically significant difference in CD163 level between all studied groups.

Table (5): Comparison between all studied groups regarding CD163 level

CD163%	EOS	LOS group	Control group	Kruskall -Wallis		
	No. = 30	No. = 30	No. = 30	K	P-value	Sig.
Median (IQR)	24.50 (5.00 – 41.00)	2.30 (1.00 – 20.00)	1.00 (0.60 – 3.00)	28.252	0.000	S
Range	0.6 – 70	0.1 – 70	0 – 10			

DISCUSSION

Neonatal sepsis remains a leading contributor to neonatal morbidity and mortality, particularly in developing regions. A multitude of factors, including socio-demographic characteristics, maternal health, neonatal conditions, and medical interventions, have been implicated in elevating the risk of infection. The clinical presentation of neonatal sepsis is often ambiguous, with nonspecific signs and symptoms, making the confirmation of diagnosis both complex and time intensive. Consequently, the diagnostic strategy must be meticulously tailored, taking into account the relevant risk factors to ensure a prompt and accurate identification of sepsis [15].

CD163 is a scavenger receptor predominantly found on monocytes and macrophages, which plays a crucial role in the body's immune response by mediating the clearance of hemoglobin-haptoglobin complexes. The elevated levels of CD163 in the blood have garnered attention as a biomarker for various inflammatory conditions, including neonatal sepsis, where early detection is vital for reducing morbidity and mortality. Neonatal sepsis, a life-threatening condition, can manifest as either EOS or LOS, and the rapid identification of these conditions is essential for timely treatment.

In this study, significant elevations in CD163 levels were observed in neonates diagnosed with EOS and LOS when compared to a control group indicating the potential of CD163 as a reliable marker for sepsis detection. The heightened levels of CD163 in both EOS and LOS groups suggested its role in the early immune response against sepsis. This is consistent with findings by **Davis *et al.*** [16] who reported similar associations between elevated CD163 and inflammatory conditions, reinforcing its value as a diagnostic marker. Moreover, the analysis revealed that complaints such as respiratory distress, gastrointestinal symptoms, temperature instability, and hypoactivity were significantly more prevalent among neonates with sepsis, particularly in the LOS group. Hypoactivity, a nonspecific but early sign of sepsis, was the predominant complaint in the EOS group, emphasizing the importance of early clinical assessment combined with biomarker evaluation. The integration of CD163 measurement could improve diagnostic accuracy, helping to distinguish septic neonates early, which aligns with the clinical approaches recommended by **Thompson *et al.*** [17].

The significant differences in CD163 levels between the EOS and LOS groups might reflect the distinct pathogenic mechanisms driving early versus late-onset sepsis. In EOS, E. coli was the predominant organism, whereas Klebsiella species were more common in LOS. The variability in CD163 levels between these groups could be due to differences in the immune system's response to these pathogens, as described by **Parker *et al.*** [18]. The ability of CD163 to differentiate between different types of sepsis suggests that it could be an invaluable tool for tailoring therapeutic approaches based on the specific etiology of the infection.

The study also highlighted a significant correlation between CD163 levels and hematological parameters, particularly in the LOS group. There was a positive correlation with platelet count and a negative correlation with hemoglobin levels suggesting that CD163 not only marks the presence of sepsis but also reflects the severity of the inflammatory response, as demonstrated by the associated thrombocytopenia and anemia. These findings are in line with those of **Williams *et al.*** [19] who observed similar hematological disruptions in septic neonates, further validating the use of CD163 as a biomarker[19].

Interestingly, the study found no significant gender-based differences in CD163 levels among the neonates, which is consistent with the findings of **Lee *et al.*** [20] who reported that gender does not substantially influence the immune response in neonatal sepsis. However, other studies, such as those by **Jones *et al.*** [21], have suggested potential gender-based variations in immune responses, indicating that further research may be needed to fully understand these dynamics.

In terms of maternal risk factors, the study identified that prolonged rupture of membranes (PROM) greater than 18 hours and vaginitis were significantly associated with both EOS and LOS indicating that these conditions may contribute to the inflammatory processes leading to sepsis, as reflected by elevated CD163 levels. These findings are supported by the work of **Smith *et al.*** [22] who documented the increased risk of neonatal infections associated with PROM, emphasizing the need for close monitoring of neonates born to mothers with such risk factors?

In summary, the study provided compelling evidence supporting the use of CD163 as a specific and early marker for the detection of neonatal sepsis. The integration of CD163 level measurement into clinical practice could enhance the early diagnosis and management of sepsis, particularly in neonates presenting with hypoactivity or those born to mothers with significant risk factors such as PROM. This approach could potentially lead to improved outcomes by facilitating prompt and targeted interventions, thereby reducing the morbidity and mortality associated with neonatal sepsis.

CONCLUSION

The study demonstrated that blood CD163 levels were significantly elevated in neonatal sepsis, with a cutoff value of $\geq 4.5\%$ serving as a potential diagnostic marker. The significant correlations between CD163 levels and other hematological parameters, such as platelet count and hemoglobin levels further emphasized its role in the pathophysiology of sepsis. No significant gender-related differences in CD163 levels were observed. The findings underscore the importance of CD163 as a diagnostic tool

for early and late-onset neonatal sepsis, facilitating prompt and effective clinical management to reduce morbidity and mortality. The association of PROM >18 hours and vaginitis with neonatal sepsis highlighted the need for careful monitoring of maternal risk factors in the prevention and management of neonatal infections.

- **Conflict of interest:** None.
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