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Significance of neutrophil CD11b in early diagnosis of neonatal sepsis

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ABSTRACT

Background: Sepsis necessitates additional diagnostic evaluations. In an effort to surmount the constraints of conventional laboratory diagnostic methods, there has been a recent emphasis on the development of novel markers for sepsis diagnosis. We aimed to study the neutrophil CD11b significance in early neonatal sepsis diagnosis and to determine its association with disease risk factors and prognostic impact of the disease. **Methods:** This case-control study was conducted on full-term neonates diagnosed with clinical sepsis based on the Töllner scoring system criteria. The study group comprised 50 newborns with clinical sepsis, while the control group included 40 newborns without sepsis. For all participants, complete blood counts, C-reactive protein (CRP) levels and D-dimer levels were measured. Blood cultures were also performed, and CD11b expression was assessed using flow cytometry. **Results:** The D-dimer, CRP, CD11b % and CD11b levels mean fluorescent intensity (MFI) were significantly elevated in the patient group compared to in the control group (p<0.05). Receiver operating characteristic analysis of CD11b % detected 76 % sensitivity, 67.5 % specificity, 72 % accuracy, and AUC was 0.759 at cutoff 66.5 (p<0.001). CD11b% was significantly greater in patients presenting with poor reflexes, cyanosis and seizures, and in patients associated with maternal risk factor (UTI) and neonatal risk factors (assisted ventilation, low APGAR score). **Conclusion**: CD11b may be a reliable, rapid and correct biomarker for the early neonatal sepsis recognition and significantly associated with poor risk and prognostic factors of neonatal sepsis.

Introduction

Neonatal sepsis is a life-threatening condition with an incidence ranging from one to five cases per 1000 live births [1]. It is crucial to diagnose and treat neonatal sepsis as soon as possible [2].

The clinical signs are nonspecific and indistinguishable from those caused by a wide neonatal non-infective disorders range for example neonatal encephalopathy, metabolic disorders, endocrine disorders and transient tachypnea of newborn representing a major challenge in diagnosis [3,4]

The most dependable method for diagnosing sepsis is blood culture. Although, the results take days to appear [5], and its diagnostic performance is unsatisfactory in certain situations, and it is frequently negative in pneumonia, meningitis, or even fatal cases generalized bacterial infections [4]. Thus, wide spectrum antibiotics are typically administered to all suspected neonates to avoid dangerous side effects [6]. This empiric

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antibiotic therapy led to unnecessarily high levels of antibiotic exposure, the establishment of drug-resistant bacteria, and substantial annual neonatal healthcare expenses [7].

A rapid test is required to accurately identify neonates who are truly infected. Neutrophil CD11b is a cell surface marker that is currently researchable and is believed to be beneficial in the sepsis diagnosis [8]. It functions as an Fc-receptor that is present on the nonactivated neutrophils surface in low concentration. It can be significantly upregulated upon the sepsis onset process when cells are exposed to bacterial infection or endotoxins [9]. A highly effective marker for the early-onset sepsis diagnosis has been reported, with higher expression in infected neonates than in non-infected neonates [10]. We aimed to study the neutrophil CD11b significance in early neonatal sepsis diagnosis and to determine its association with disease risk factors and prognostic impact of the disease.

Methods

The present study was performed during the period from January 2021 to January 2022. Neonates were selected from neonatal intensive care unit (NICU) (in Pediatric Department and laboratory work was done in Clinical Pathology Department, Menoufia University Hospital, Egypt. The research was approved by the Research Ethics Committee of Menoufia University Hospitals, Faculty of Medicine (IRB: 10/2020 CPATH5), and the parents of the recruited neonates provided informed written consent.

This study is a case-control study conducted on 90 full term neonates. Sample size was calculated at 80% power and 95% confidence interval (CI). Inclusion criteria included full term neonates and clinically suspected sepsis according to Tollner clinical sepsis score [11]. Exclusion criteria were preterm neonates, newborns with any congenital anomalies or congenital infection, neonates with other diseases such as hypoxic ischemic encephalopathy, birth injury, metabolic disorder or surgical problems.

Patients were categorized into two groups: the sepsis group (Group A, 50 patients) and the control group (Group B, 40 controls). Detailed medical history involving present history with emphasis on date of onset, personal history, precipitating factors, disease duration and course and sepsis presence or absence and prenatal symptoms suggestive, maternal and obstetric history were taken from all subjects. Clinical examination of the enrolled neonates was carried out including the need for incubation care, resuscitation need, gestational age assessment and sepsis clinical diagnosis.

Laboratory sepsis profile was done after withdrawal of 5 ml of blood, divided as follow: 1 ml of whole blood for complete blood count [Sysmex XN1000; Kobe, Japan], 2 ml of serum for estimation of D-dimer and 2 ml of serum for CRP, and chemistry profile involving aspartate transaminase, blood urea, alanine transaminase, and serum creatinine [ARCHITECT PLUS; Abbott Laboratories, Germany].

Blood cultures were performed using the BACTEC microbial detection system (Becton-Dickinson, Sparks, MD) to confirm the diagnosis of sepsis. In this process, 2 mL of whole blood was aseptically injected into blood culture bottles and incubated for up to 7 days. Sensor positive culture bottles were subjected to Gram staining and subcultured onto various media, including MacConkey agar, blood agar, and chocolate agar. These plates were then incubated at 37°C for 18-24 hours to facilitate organism growth. The identification of organisms was completed through Gram staining, culture on selective media, and biochemical tests, according to microbiology unit standard operating procedures.

Flowcytometric analysis: Surface CD11b was calculated by immunophenotyping, and Phycoerythrin(PE)-labeled mouse anti-human CD11b was utilized (Becton Drive BD Biosciences product, San Diego, California, USA). A Becton-Dickinson FACScan system was employed to conduct data analyses.

Whole peripheral blood samples were collected in EDTA and processed within 24 hours. A 10 μL sample of PE-conjugated anti-CD11b antibody was incubated with 50 μL of anticoagulated blood for 10 minutes at room temperature, followed by red cell lysis with ammonium chloride. Isotype controls (Mouse IgG2B PE-conjugated Antibody) were stained simultaneously. After incubation for an additional 15 minutes, samples were centrifuged at 400g for 5 minutes, washed twice with PBS, and resuspended in 500 μL of PBS. The supernatant was discarded. Flow cytometric analysis was performed using the Becton-Dickinson FACScan system, analyzing a

minimum of 10,000 events **(Figure 1)**. CD11b was measured as CD11b expression percentage (%) and CD11b Mean fluorescent intensity (MFI). In summary, while "CD11b %" often refers to whether and how many neutrophils have CD11b on their surface, "CD11b MFI " provides a numerical value representing the amount of CD11b per cell. MFI gives a more precise quantitative measure of CD11b levels than just expression percentages.

Statistical analysis

On an IBM compatible personal computer, SPSS statistical package version 28 (IBM Corp., Armonk, NY, US) was employed to collect, tabulate, and conduct statistical analyses of the data. The distribution's normality has been determined using the Kolmogorov-Smirnov test. Furthermore, to describe quantitative data, various measures were used including the range (both minimum and maximum), mean, standard deviation (SD), median, and interquartile range (IQR). For categorical variables, the chi-square test was used to compare different groups. The Student t-test was used to compare two groups for quantitative variables with a normal distribution, while the Mann-Whitney test was used for quantitative variables with a non-normal distribution. Additionally, Receiver Operator Characteristic (ROC) curves were used to determine the optimal cut-off of CD11b as a diagnostic biomarker of neonatal sepsis. Statistics were considered significant when the P value was < 0.05 and highly significant when the P-value was < 0.001.

Results

In this study, 90 neonates were recruited from NICU, Menoufia University Hospital. They were categorized into two groups: the sepsis group (Group A, n=50) and the control group (Group B, n=40). Group A included 25 male and 25 female with age ranged from 7 to 23 days. Group B included 20 male and 20 female with age ranged from 8 to 23 days.

Respiratory disorders represented the most common clinical presentation accounting for 70 % of cases subsequently, lethargy (56%), poor Moro and sucking reflexes (48%) and poor feeding (46%). Assisted ventilation (40%) and low birth weight (28%) were the common neonatal risk factors in septic neonates followed by low Apgar score<6 at 5m (18%) and umbilical catheterization (14%). Premature rupture of membrane (36%) represented the common maternal risk factor among the patient group followed by maternal fever (22%), maternal urinary tract infection (UTI) (16%) and meconium-stained amniotic fluid (14%) **(Figure 2)**.

Blood cultures were positive in 82% of all sepsis neonates. The different organisms identified by positive cultures were *staphylococcus aureus* (36.6%), *Klebsiella* (26.8%), *coagulase negative staphylococci* (24.4%), *Pseudomonas* (7.3%) and *E.coli* (4.9%).

Laboratory evaluation: Routine laboratory measures showed significant decrease in hemoglobin concentration in patients in relation to control whereas total leucocytic count (TLC), neutrophil count and SGOT detected a significant elevation in patients in relation to control group (p< 0.05) .

Regarding the studied measures: we detected out that CRP was significantly higher in patients contrasted to control group (mean ± SD of 54.9 ± 26.05 and 7.15 ± 5.84 respectively, p < 0.001) , D-dimer was significantly increased in patients contrasted to control group (mean ± SD of 1.69 ± 2.04 and 0.24 ± 0.09 respectively, p < 0.001), CD11b expression was significantly higher in patients compared to control group (mean ± SD of 74.8 ± 30.3 and 40.9 ± 35.3 respectively, p < 0.001) and CD11b MFI was significantly higher in patients contrasted to control group (mean ± SD of 4049.4 ± 2401.8 and 2663.3 ± 2239 respectively, p < 0.001) **(Table 1)**.

According to blood culture results in patients' group: CD11b expression was significantly higher in positive culture patients compared to negative culture patients (mean ± SD of 76.66 ± 28.8 and 67.11 ± 33.86 respectively, p = 0.017) and CD11b MFI was significantly higher in positive culture patients contrasted to negative culture patients (mean ± SD of 4303.6 ± 2486.9 and 2627 ± 1516.6 respectively, p = 0.018) **(Table 2)**.

The ROC curve analysis was utilized to detect the diagnostic CRP, D-dimer, CD11b % and CD11b MFI biomarkers performance **(Figure 3)**.

ROC analysis of CD11b% showed 76% sensitivity, 67.5% specificity, 72% accuracy, 74.5% PPV, 69.2% NPV, and AUC was 0.759. For CD11b MFI, it showed 82% sensitivity, 67% specificity, 76% accuracy, 75% PPV, 74% NPV, and AUC was 0.753. For CRP, it showed 98% sensitivity, 95% specificity, 97% accuracy, 96% PPV, 97% NPV, and AUC was 0.994. For D-dimer, it showed 92% sensitivity, 100% specificity, 96% accuracy, 100% PPV, 91% NPV, and AUC was 0.974.

The patients' group was divided into 2 groups according to CD11b% median and the relation between the number of patients associated with each maternal, neonatal risks factors and clinical presentations in each group was studied. **Figure 4** shows the statistically significant risk factors and clinical presentations for neonatal sepsis associated with high CD11b %.

When logistic regression analysis was applied to detect the neonatal sepsis risk factors, we found that decreasing hemoglobin, increasing D-dimer and increasing CD11b are independent risk factors that can predict neonatal sepsis (OR= 0.088P <0.001; OR = 27.479, *p* <0.001, and OR=4.486, *p* = 0.004 respectively) **(Table 3)**.

Table 1. Comparison between patients and controls regarding measures studied.

Variable	**Cases (No.=50)**	**Controls (No.=40)**	**Test of significance**	***p* value**
CRP (Mean ±SD)	54.9±26.05	7.15±5.84	U=8.124	<0.001**
D.dimer (Mean ±SD)	1.69±2.04	0.24±0.09	U=7.735	<0.001**
CD11b % (Mean ±SD)	74.8±30.3	40.9±35.3	U=4.212	<0.001**
CD11b MFI (Mean ±SD)	4049.4±2401.8	2663.3±2239	U=4.105	<0.001**

T: student t test, U: Mann-Whitney test, CRP: C reactive protein, MFI: mean fluorescent intensity, SD: standard deviation
**p* value of < 0.05: statistically significant. ***p* value of < 0.001: statistically highly significant.

Table 2. CD11b % and CD11b MFI results versus blood cultures results.

Variable	**Positive culture (No.=41)**	**Negative culture (No.=9)**	**Test of significance**	***P* value**
CD11b %			U=1.049	0.017*
(Mean ±SD)	76.66±28.8	67.11±33.86		
Range	6-99	7 -99		
Median(IQR)	89(74.5 – 97)	83(16 – 89)		
CD11b MFI			U=2.361	0.018*
(Mean ±SD)	4303.6±2486.9	2627±1516.6		
Range	1237 – 12355	1618 – 6537		
Median(IQR)	3583(2510.5 – 5744)	2091(1884 – 2729)		

T: student t test, U: Mann-Whitney test, MFI: mean fluorescent intensity, SD: standard deviation, IQR: inter quartile range
**p* value of < 0.05: statistically significant. ***p* value of < 0.001: statistically highly significant.

Table 3. Univariate and Multivariate regression analysis for variables significantly associated with increased risk of neonatal sepsis.

Predictors (Independent variables)	B coefficient	*p* value	Odds Ratio(OR)	95% CI	
				lower	upper
HB	0.219	0.044*	1.244	1.006	1.539
TLC	-0.181	0.011*	0.834	0.726	0.959
Neutrophil	-0.226	0.011*	0.798	0.670	0.949
D.dimer	-5.198	<0.001**	0.006	0.001	0.054
CRP	-0.655	0.063	0.520	0.621	1.036
CD11b %	-0.028	<0.00**	0.972	0.959	0.985
	Multivariate regression				
HB	-2.430	<0.001**	0.088	0.023	0.341
D.dimer	3.313	<0.001**	27.479	6.709	112.557
CRP	0.455	0.17	1.634	1.436	1.923
CD11b %	1.501	0.004*	4.486	1.619	12.432

HB: hemoglobin concentration, TLC: total leucocytic count, CRP: C reactive protein, CI: Confidence interval
*P value of < 0.05: statistically significant. **P value of < 0.001: statistically highly significant.
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Figure 1. Flow cytometry results of one of cases.

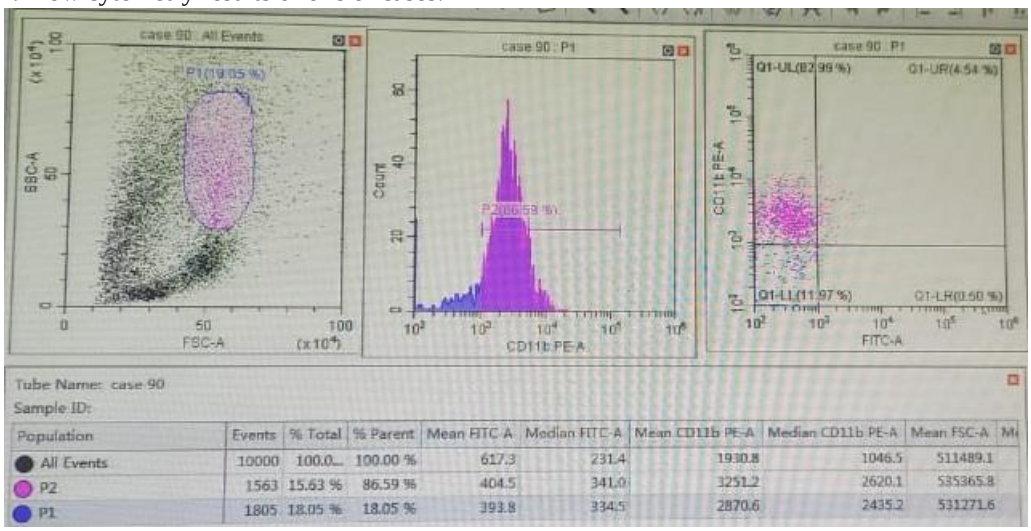


Figure 2. Relation between each maternal, neonatal risk factors and clinical presentations with level of CD11b. %.

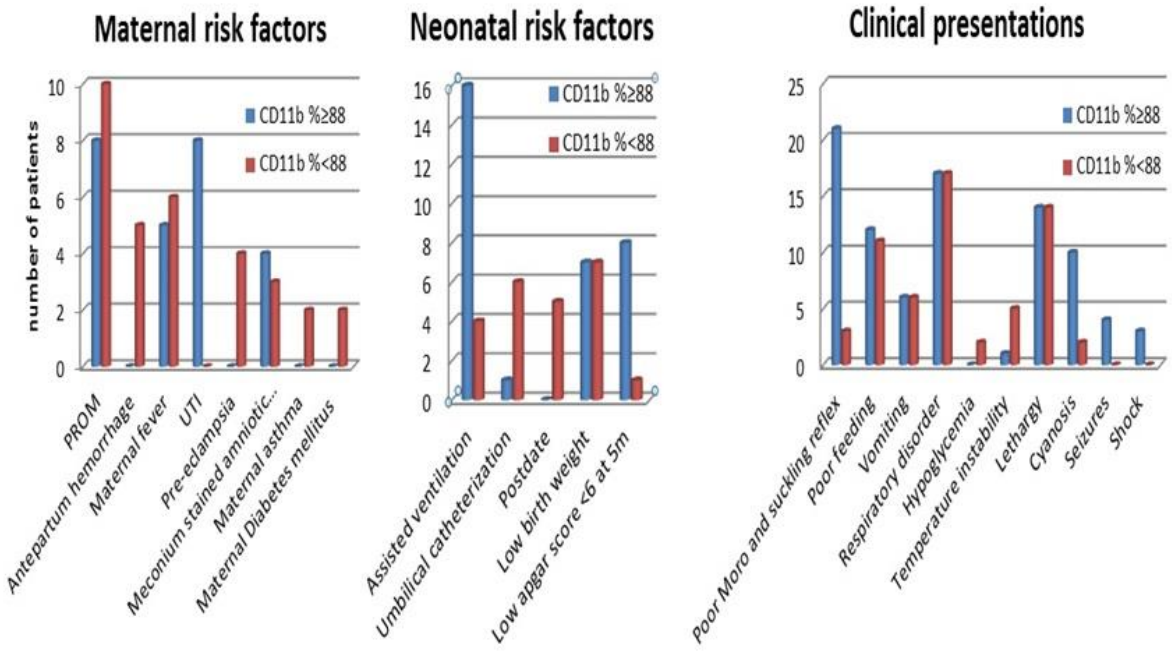


Figure 3. Receiver-operating characteristic curves of CRP, D-dimer, CD11b % and mean CD11b (MFI).

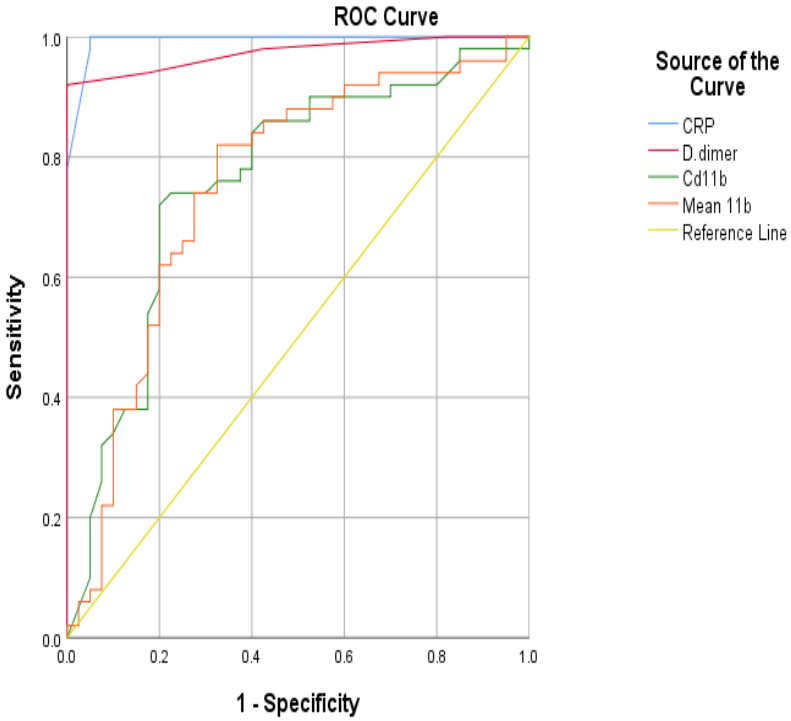
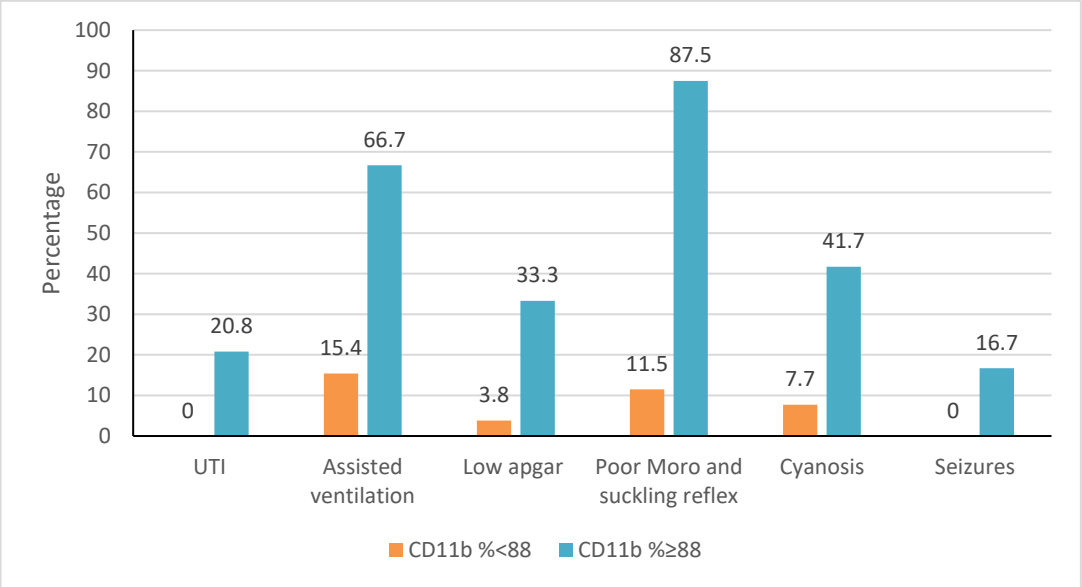


Figure 4. The significant risk factors and clinical presentations associated with high CD11b %.



Discussion

Neonatal sepsis is a systemic infection that is characterized by bacteremia through the first month of life. Neonatal sepsis is a significant issue due to the clinically nonspecific findings that occur through infection during this highly sensitive stage of life [12]. The traditional gold standard method for diagnosis, blood cultures, also exhibit a high frequency of false negative results [13]. The high morbidity and mortality rates of neonatal sepsis can be significantly reduced by prompt diagnosis and treatment. Furthermore, precise diagnosis aids in the prevention of needless antibiotic therapy, which has been associated with the accelerated gram-negative bacteria colonization and the drug-resistant strains emergence [14].

In the present study, a control group of 40 neonates without signs or symptoms of sepsis was included, while neonates with clinical sepsis (n = 50) were recruited. The clinical presentation varied between different cases, with respiratory disorders being the most common presentation (70%).

Regarding routine laboratory measures, the results indicated a significant difference between the control and patient groups. Hb concentration was lower in-patient group. TLC count, neutrophil count and SGOT were higher in-patient group in comparison to control group. Therefore, these parameters can help in neonatal sepsis diagnosis in resource-limited areas as suggested by **Shehab El-Din et al.** [15].

The most prevalent microorganism isolated from NICU sepsis cases was *Staphylococcus aureus* (36.6%), followed by *Klebsiella* (26.7%) and coagulase-negative *staphylococci* (24.4%) regarding blood culture results. In total, 82 % of all septic neonates had positive blood cultures. *Staphylococci* and *Klebsiella* were the most frequently isolated organisms from septic neonates, as found in other studies. These results are consistent with this [15,16].

D-dimers are fibrinogen fragments that are produced during fibrinolysis through the plasmin-mediated fibrin lysis. They can be used as microcirculatory failure indicator [17]. The present study revealed a significant rise in the serum D-dimer level in the patient groups in comparison to the control group. These results are in line with the findings of **Peker et al.** [18] and **Mautone et al** [19], who discovered elevated D-dimer levels in sepsis neonates. These findings are in contrast to those of **Brahmana et al.** [20], who discovered that septic neonates had low D-dimer levels. This discrepancy may be attributed to the neonates recruited gestational age, as the study involved preterm infants.

The host's immune response to bacterial infections is mediated by neutrophil cell-surface antigens, including CD11b. Sepsis pathophysiology is associated with changes in its expression on the cell surface. CD11b regulates leukocyte adhesion and migration, thereby mediating inflammation. Furthermore, it is involved in the complement

system, chemotaxis, cell-mediated cytotoxicity, and phagocytosis. In the present research, a significant difference in CD11b expression was found in sepsis patients comparable to control group. Many authors have shown CD11b upregulation through sepsis, as in this research [1, 9, 21- 23]. In the contrary, studies by **Zieba et al.** [24] In pre-term early onset neonatal sepsis neonates and in term infants with late onset neonatal sepsis, the levels of CD11b were significantly lower among septic neonates, as demonstrated by **Cui et al.** [25] These discrepancies can be partially accounted for by the reduced intracellular CD11b content amount and cell-surface biomarker expression immaturity in the immature neutrophils, which is influenced by gestational age [26].

This research demonstrated a highly significant difference in the CD11b expression percentage on neutrophils between culture-unproven sepsis and culture-proven sepsis. In patients with positive blood culture, percentage of expression was with a mean of 76.66±28.8, while in patients with negative blood culture was with a mean of 67.11±33.86.

It was utilized to detect the diagnostic CRP, D-dimer, CD11b % and CD11b MFI performance by the ROC curve analysis.

The specificity and sensitivity for CRP were 95% and 98% respectively with PPV of 96% and NPV of 97%.

The CRP test has a specificity of 53.49% and a sensitivity of 76.9% for diagnosing acute neonatal sepsis. According to **Hisamuddin et al.** [12], while CRP assays are useful for diagnosing neonatal sepsis, they are not accurate enough to be used as the sole diagnostic tool.

Regarding D-dimer, AUC is 0.974 (95% CI, 0.943 – 1) with 92 % sensitivity, 100% specificity with cutoff point > 0.48. **Zallocco et al**., [27] indicated that the AUC was found to be 0.729 (95% CI, 0.618–0.823), with a specificity of 78% (95% CI, 64–88%) and sensitivity of 68% (95%CI, 47– 85%).

The CD11b % specificity, sensitivity, and PPV in this study were 67.5%, 76%, and 74.54%, respectively. Similar findings for CD11b MFI were found with sensitivity, specificity, and PPV measuring 82%, 67% and 75% respectively. In neonatal sepsis, **Du et al.** [28] observed a significantly higher CD11b expression, with a specificity and sensitivity of 70% and 81%, respectively. It has been proposed that CD11b is a highly efficient marker for diagnosing early-onset infection in neonates through ROC analysis [22].

Some studies [28-31] oncurred with the diagnostic validity results of CD11b % and CD11b MFI, while others [32] rejected them.

ELMeneza et al. [33] determined that CD11b is a sensitive marker for sepsis in full-term neonates that could be incorporated into routine daily work. This was due to the significant neutrophils expressing CD11b upregulation in the sepsis and doubted sepsis groups compared to the healthy participants. Nevertheless, Turunen et al. [30] demonstrated that the CD11b role in neonatal infections is a topic of debate. They attributed their findings to the widespread sensitivity and specificity of the findings in studies that were influenced by other conditions, for example respiratory distress syndrome.

The observed data detected that CD11b expression was significantly higher in neonates presenting with poor moro and suckling reflexes, cyanosis and seizures. Also, a significant association was found with UTI as a maternal risk factor and assisted ventilation and low APGAR score as neonatal risk factors. These findings might reflect a poor prognostic role of CDb11 expression in neonatal sepsis.

Consistent with the aim of the study, multivariable logistic regression analysis was utilized to further explore the different sepsis variables correlation as a risk factor for neonatal sepsis. Both decreasing hemoglobin, increasing D-Dimer and increasing CD11b proved to be independent predictors of neonatal sepsis.

Current evidence suggests that CD11b may serve as a precise and rapid biomarker for the early detection and neonatal sepsis diagnosis, as well as a prognostic neonatal sepsis indicator. However, the study was limited by the lack of follow-up data, which would have provided a clearer assessment of CD11b's prognostic value. The clinical application of CD11b has the potential to lower the antibiotics over utilization in low-risk infants. In order to enhance the diagnostic value, additional extensive studies of a combination of biomarkers are required.

Conflicts of interest: None to be declared.

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