The pattern of systemic inflammatory markers response in neonatal sepsis

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Abstract

Background: Early diagnosis of sepsis is a clinical challenge as the clinical symptoms are subtle, late, and nonspecific. Minimum of 48 hours is required for the earliest result of blood culture, and it can be negative despite clinical signs of sepsis. Delaying the treatment leads to an increase in mortality. Thus, it is crucial to diagnose neonatal sepsis early to initiate treatment as early as possible.
Aims: To assess the pattern of systemic peripheral inflammatory response markers as early predictors for the diagnosis of sepsis in neonates.
Patients and methods: This was a case-control study conducted on one hundred cases suspected to have with neonatal sepsis (NS), in addition to other fifty neonates with no suspicion of having NS. All the subjects underwent thorough history taking, complete clinical evaluations, and laboratory investigations for a systemic inflammatory response.
Results: The overall patients' mean ages were (14.12 ±7.12 days), 70% were male and 30% were females. When compared to the control group we found elevated immature to total neutrophil (IT) ratio, CRP, ESR, TLC, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) to have significant diagnostic value for NS, in addition to hematological indices and scores.
Conclusion: The IT ratio is the best single index for NS diagnosis having a comparable significance as CRP and ESR, however, the IT ratio was superior to WBC count in the sensitivity, specificity, the positive predictive value, and the negative predictive value.
Keywords: Inflammatory markers, IT ratio, Neonatal sepsis.

Introduction

Sepsis is a clinical condition secondary to a dis-regulated systemic inflammatory reaction secondary to infection and characterized by a systemic inflammatory condition**(Plunkett and Tong, 2015).**It is one of the most common cause of morbidity and mortality in children, globally affecting (almost 60% of children below 5 years **(Labuda et al., 2019).**

Early diagnosis of sepsis is a challenge as the clinical symptoms are subtle, late, and non-specific. Blood culture is still the gold standard for the diagnosis of sepsis, but a minimum of 48 hours is required for the earliest result, and it can be negative despite clinical signs of sepsis. Delaying the treatment leads to an increase in mortality. Thus, there is an urgent need for early diagnosis of sepsis so that timely and proper use of antibiotics can be started leading to better outcomes **(Gros et al., 2012).**

C-reactive protein (CRP) an acute-phase protein; is a rapid indicator of inflammation and tissue necrosis in response to bacterial infection **(Sproston and Ashworth, 2018).** Albumin

likewise is a potent prognostic marker for the outcomes in an infection-related disease. Thus, we assumed that the CRP to albumin ratio could be used as a predictive marker for disease activity **(Kim et al., 2015)**, and therefore the Glasgow prognostic score (GPS), can be used as a reflectionof the systemic inflammatory response, depending on the combination of serum albumin and CRP levels **(Lu et al., 2018).**

Systemic inflammatory response (SIR) scores as a neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) have diagnostic value in many diseases with inflammatory response and the ratio of these two cell types offers a measure to detect inflammation **(Liu et al., 2020).**We aimed to assess the pattern of systemic peripheral inflammatory response markers as early predictors in the diagnosis of sepsis in neonates, and to evaluate the sensitivity and specificity of these markers.

Patients and methods

This was a case-control study conducted on 100 cases admitted to the neonatal intensive care unit (NICU), suspected clinically to have neonatal sepsis (NS).

Setting: NICU of Pediatric department Qena University Hospital and Qena general hospital, and Clinical and Chemical Pathology Department, Qena, Egypt.

The inclusion criteria: any neonate with the following signs or symptoms according to (Arani et al., 2013):

1. Respiratory symptoms (tachypnea, apnea, respiratory distress, respiratory retraction).
2. Digestive symptoms (vomiting, poor feeding, abdominal distention).
3. Cardiovascular symptoms (cyanosis, hypotension, weak pulse rate).
4. Neurological symptoms (seizure, lethargy, poor neonatal reflexes).
5. Cutaneous symptoms (fever, hypothermia, skin molting).
6. Unexplained metabolic acidosis.

The exclusion criteria: neonates with congenital and chromosomal anomalies.

All NS cases enrolled in the study were subjected to full history taking, clinical examination, and laboratory tests.

Ethical approval:

The study protocol was approved by the Ethical Committee of Faculty of Medicine, South Valley University, and written informed consent was obtained from all patients' relatives.

Blood sampling for Laboratory investigations:

5ml venous blood sample was collected under aseptic conditions and divided into 2 tubes; EDTA tube first for complete blood count, and later for ESR estimation, and plain tube to obtain serum samples by centrifugation of the clotted blood at 3000x g for 10 min at room temperature and allocated for CRP and albumin assay.

1. **Complete blood count:** using automated cell counter Celtac α (Nihon Kohden- Rosbach-Germany).
2. **Erythrocyte Sedimentation Rate (ESR):** by Wintrobe method (3-13 mm/h).
3. **C-reactive protein:** (2-6mg/L), by semi-quantitative latex agglutination assay, Spinreact (Spain).
4. **Serum Albumin:** (3.5-5.5 g/dl) by respons® 920 automated analyzer DiaSys (diagnostic systems –Holzheim-Germany).
5. **Calculation of inflammatory scores and indices** as immature to total neutrophil (I:T) ratio, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), neutrophil

platelet score, MPV/platelets, WBCs/MPV, systemic immune-inflammation index (SII) (Platelet count × neutrophil count/lymphocyte count), prognostic index (PI) which depends on CRP and WBCs values, prognostic nutritional index (PNI), CRP/albumin ratio, modified Glasgow Prognostic Score (mGPS).

Statistical analysis: Data verified, coded, and analyzed using Statistical Package for Social Sciences (SPSS) 26 (IBM-Inc., Chicago-IL-USA). Data normality tested by Shapiro-Wilk's test. Descriptive statistics: means, standard deviations, ranges, medians, and percentages calculated. Chi-square test used to compare the difference in the frequencies among different groups, and an independent t-test used for continuous variables. Spearman correlation is used to test the correlation between variables. $P < 0.05$ was considered statistically significant.

Results:

Table 1. Demographic data of the study population

Variable	suspected NS Cases (no=100)	Control (no=50)	P-value
Age (days)	4.12 ± 7.12	8.7 ± 4.2	0.703
Gestational age (weeks)	35.14± 2.4	35.28 ± 2.6	0.924
Weight (kg)	2.278±0.69	2.37 ± 0.73	0.967
Disease duration (days)	8.20 ± 5.1	4.76 ± 2.2	**0.031**
Sex NO (%)			
• Male	70(70%)	27(54%)	**0.04**
• Female	30(30%)	23(46%)	
Age NO (%)			
• ≤72 hr.	8(8%)	17(34%)	**0.001**
• >72 hr.	92(92%)	33(66%)	
Gestational age NO (%)			
• Preterm	64(64%)	27(54%)	0.16
• Term	36(64%)	23(46%)	
Weight (kg)NO (%)			
• ≤2.5	70(70%)	27(54%)	**0.04**
• >2.5	30(30%)	23(46%)	
Mode of delivery NO (%)			
• CS	86(86%)	38(76%)	0.09
• N	14(14%)	12(24%)	

This table shows that the suspected neonatal sepsis group was (70 males& 30 females) with a mean age (14.12 ±71.2 days), 8(8%) ≤72 hr. of age and 92(92%) >72 hr. of age, gestational age (35.14± 2.4 weeks), and their mean body weight was (2.2776 ±.69 kg). Fifty normal neonates were selected as a control group (27 males & 23 females) with a mean age of 8.7±4.2 days, 17 (34%) ≤72 hr. and 33(66%) >72hr. of age, gestational age (35.28± 2.6 weeks), and their body weight were (2.37 ± 0.73 kg).

Table 2. Vital signs of the studied NS cases and control

Variable	suspected NS Cases (n=100)	Control (n=50)	P-value
Temp.	37.2±0.5	36.90±0.4	**0.003**
HR	120.±17	118±20	**0.035**
RR	54.5± 7.7	45.5±6.9	0.748

This table shows that the suspected NS group had tachycardia (>90 beats/min); tachypnea (>20 breaths/min), significantly higher body temperature and heart rate.

Table 3. Distribution of cases according to the types of NS

Types of sepsis	No. (%)	P-value
Early onset sepsis	44(44%)	**0.001**
Late-onset sepsis	56(56%)	

This table shows that Early-onset sepsis represented 44% while late-onset sepsis represented 56%.

Table 4. CBC parameters and ratios of the study population

Variable	suspected NS Cases (no=100)	Control (no=50)	P-value
Hb(g/dl)	12.09±3.3	13.61±2.7	0.061
RBCs (100^6 Cells/µL)	3.88± 0.9	4.6± 0.8	0.07
MCHC (g/dL)	32.9.±1.4	31.7±1.1	**0.02**
RDW (%)	15.3± 2.2	15.3±1.6	**0.006**
Platelets (10^3/mm^3)	209.42±105	259.8±100	**0.001**
MPV (fL)	10.74± 2.2	9.63± 1.4	0.201
PCT (%)	0.1763±0.12	0.2371±0.08	**0.002**
PDW (%)	16.2.±3.01	13.2±2.4	0.140
MPV/platelet	0.1245± 1.6	0.05±0.02	**0.001**
WBCs/MPV	1.57±0.8	0.9461±0.3	**0.001**
WBCs	16.27± 8.4	8.93±3.1	**0.001**
Monocytes	1.04± 0.67	0.70±0.38	**0.003**
Neutrophils	9.05±7.54	3.98±2.23	**0.001**
Immature neutrophils	2.5±0.5	0.65± 0.4	**0.001**
Lymphocyte	5.31±2.9	3.67±1.39	**0.001**
I/T ratio	0.26±0.07	0.159±0.01	**0.001**
NLR	2.69± 3.3	1.20±0.8	**0.001**
MLR	0.236±.17	0.22±0.15	0.713
LMR	7.21± 0.3	6.48± 3.2	0.281
PLR	53.78± 26.1	78.350± 36.2	**0.041**

This table shows that the suspected NS cases had significantly higher mean corpuscular hemoglobin concentration (MCHC), & red blood cell distribution width (RDW).Also cases had significantly lower mean platelet count and platelet crit (PCT), and significantly higher mean platelet volume (MPV), platelet distribution width (PDW), the mean of MPV/ platelet ratio, and mean WBCs/MPV ratio, and a significantly higher count of WBCs, monocytes, neutrophils, immature neutrophils, and lymphocytes. Regarding WBCs ratios Cases had significantly higher I/T ratio, NLR, and PLR.

Table 5. Acute-phase inflammatory response markers

Variable	suspected NS Cases (no=100)	Control (no=50)	P-value
ESR (mm/h)	23.8± 10.6	8.66±5.1	**0.001**
CRP (mg/L)	49.14±33	8.40± 4.1	**0.001**
Albumin (g/dl)	3.06±0.6	3.88±4.8	0.171
CRP/albumin ratio	16.94± 11.1	2.2±0.4	**0.001**

This table shows that neonates with suspected sepsis had significantly higher ESR, CRP, and CRP/albumin ratios.

Table 6. Hematological scores and indices

Variable	SuspectedNS Cases (no=100)		Control (no=50)		*P*-value
	No.	%	No.	%	
Prognostic index (PI)					
• **0**	4	4	29	58	**0.001**
• **1**	28	28	17	34	
• **2**	68	68	4	8	
mGPS					
• **0**	2	2	32	64	**0.001**
• **1**	28	28	15	30	
• **2**	70	70	3	6	
Prognostic nutritional index (PNI)					
• **<45=0**	98	98	43	86	**0.005**
• **>45=1**	2	2	7	14	
Neutrophil platelets score					
• **0**	58	58	41	82	**0.02**
• **1**	32	32	9	18	
• **2**	10	10	0	0	
SII	693.14± 1365.9		300.66± 195.14		**0.023**

This table shows that cases had statistically higher inflammatory indices including the prognostic index (PI), modified Glasgow prognostic score (mGPS), a prognostic nutritional index, neutrophil

platelet score, and the systemic immune-inflammation index.

Table 7. ROC curve analysis among septic and control groups

Test	AUC	Cut off	Sensitivity	Specificity
PLT	0.689	≤162	54	92
WBCs	0.790	>9.9	82	66
IT ratio	**0.920**	**>0.179**	**90**	**80**
ESR	**0.918**	**>11**	**86**	**84**
CRP	**0.915**	**>12**	**76**	**96**
Albumin	0.846	≤3.26	72	88
Test	**PPV**	**NPV**	**Accuracy**	**P-value**
PLT	93.1	50	73	<0.001
WBCs	82.8	64.7	74	<0.001
IT ratio	**90**	**80**	**85**	<0.001
ESR	**91.5**	**75**	**85**	<0.001
CRP	**97.4**	**66.7**	**86**	<0.001
Albumin	92.3	61.1	**80**	<0.001

The ROC curve showed that IT ratio was more superior followed by ESR and CRP, as the IT ratio produced (AUROC 0.920, 90% sensitivity, 80% specificity). The ESR produced (AUROC of 0.918, 86% sensitivity, 84% specificity). The CRP produced (AUROC 0.915, 76% sensitivity, 96% specificity). For accurate diagnosis of NS, we can use IT ratio, ESR, and CRP at the cutoff value of 0.179, 11, and 12 respectively.Table VII, figure 1.

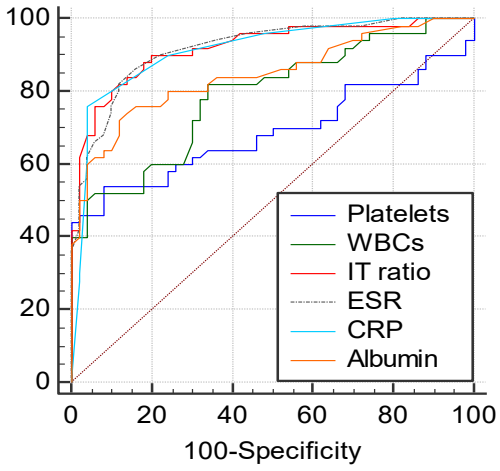

Fig.1.Comparison of ROC curves of different tests

Discussion

Neonates are at great risk of infection because of their weakly immature immune systems. Neonatal sepsis is the prevalent cause of neonatal mortality and morbidity resulting in 30-50% of global neonatal deaths in developing countries **(Manandhar and Basnet, 2020).**

Earlier diagnosis of sepsis permits proper management and a little likelihood of sepsis. The clinical signs and symptoms of NS are subtle and nonspecific, making its early diagnosis hard **(Medhat et al., 2016).**

Blood culture is yet the gold standard for the diagnosis of sepsis, but a minimum of 48 hours is wanted for the earliest result, and it can be negative despite clinical signs of sepsis. Delaying the treatment leads to an increase in mortality. Thus, there is a crucial need for early diagnosis for better outcomes **(Gros et al., 2012).**

Our study showed how the currently available and cost-effective markers implement in NS, so we present a large series of CBC, in addition to ESR, CRP, and albumin. We also used hematological inflammatory and immune scores and indices as the combination of many markers always exceeding the use of a single one.

In this study; septicemia was often observed in males more than females in agreement with the results of **(Shobowale et al., 2017).** Also, NS was found in preterm neonates far more than term neonates. This was in agreement with **(Çelik et al., 2016).**

In this study, we found that MCHC and RDW in the sepsis group significantly higher than the control group (P= 0.02 and 0.006 respectively). This was in line with **(Mousa et al., 2019).**

Also, we found a significant decrease in the platelet count in the sepsis group when compared to the control group. This finding goes in line with **(Choudhary et al., 2018; Nasser et al., 2020).** Also, the NS group had significantly higher MPV/ platelets and WBCs/MPV ratios.

In this study, the sepsis group showed significantly higher TLC than the control group, this was in agreement with **(Arcagok and Karabulut, 2019).** Also, the sepsis group had a much higher IT ratio than the control group, this finding was in concordance with the findings of **(Çelik et al., 2016; Saboohi et al., 2019; Arcagok and Karabulut, 2019; Nasser et al., 2020).**

In this study, we found that the NS group had significantly higher neutrophil counts and NLR. This was in line with **(Omran et al., 2018; Ozdemir et al., 2018; Can et al., 2018; Nasser et al., 2020).** Also, we found that the sepsis group had a significantly higher monocytic count.

In our study, we found that the NS group had a significantly higher lymphocytic count; and a significantly lower platelet lymphocyte ratio (PLR) than the control group. On the contrary, **(Arcagok and Karabulut, 2019)** found that the control group had a significantly higher lymphocytic count and a significantly lower PLR.

In this study, we found that CRP was significantly higher in neonates with sepsis. This was in line with **(Hisamuddin et al., 2015; Çelik et al., 2016; Mousa et al., 2019; Arcagok and Karabulut, 2019; Nasser et al., 2020).** We also found a significant correlation between the CRP/ Albumin ratio and the presence of NS, moreover, mGPS found to be significantly associated with NS. This goes in line with the findings of **(Yang et al., 2016; Abdelaal et al., 2019).**

In the present study, the sensitivity, specificity, positive predictive value, and negative predictive value of laboratory parameters were evaluated. An elevated IT ratio with a cut-off value of > 0.179 was found to be the most reliable indicator of sepsis in our study and also in various other studies like those done by **(Khair et al., 2010; Makkar et al., 2013; Khurram et al., 2016; Bhalodia et al., 2017; Dey et al., 2020).**

In the present study, TLC with a cut-off value of > 9.9 (103 /mm3) has a sensitivity of 82% which is comparable to the finding of **(Makkar et al., 2013),** yet lower than that found by **(Dey et al., 2020)** (97.56%), and in contrast with **(Elsayed et al., 2021)** who found low sensitivity of 46% .

We found the TLC has a specificity of 66% which is lower than that reported by **(Khurram et al., 2016; Bhalodia et al., 2017; Elsayed et al., 2021)** and higher than that reported by **(Dey et al., 2020),** also we found that the TLC to has a PPV of 82.8% and NPV of 64.7%, these findings are in line with **(Makkar et al., 2013).**

In our study, platelet count with a cut-off value of ≤162 (103 /mm3) showed a sensitivity of (54%), a specificity of (92%) and PPV (93.1%), NPV (50%). These results were nearly similar to the results reported by **(Khair et al., 2010; Khurram et al., 2016; Bhalodia et al., 2017; Elsayed et al., 2021).**

In our study, CRP with a cut-off value of >12 (mg/L) have a sensitivity of (76%), a specificity of (96%) and PPV (97.4%), NPV (66.7%). This goes in line with the findings of **(Celik et al., 2010; Aydemir et al., 2018; Rashwan et al.; Kumar et al.; Eschborn and Weitkamp, 2019).**

Also, we found serum albumin level with a cut-off value of ≤3.26 g/dl to have 72% sensitivity and 88% specificity in diagnosing NS; these results go in line with **(Yang et al., 2016; El-Lahony et al., 2018).**

In our study, we found that the prognostic index (PI) had a significant value in diagnosing NS. This finding goes in line with **(Caldas et al., 2008; Chacha et al., 2014)** as they found that combining WBCs and CRP increases the diagnostic power for NS.

Also, we found that the neutrophil platelet score and the systemic immune-inflammation index correlated significantly with other inflammatory indices and scores in the NS group.

Conclusion

Several inflammatory-immune indices and scores are utilizing CBC parameters, serum albumin and CRP (mean MPV/platelet ratio, mean WBCs/ MPV ratio, prognostic index, modified Glasgow prognostic score (mGPS), prognostic nutritional index, neutrophil platelet score, and the systemic immune-inflammation index) they are easily performed, readily available, and cost-free to diagnose NS; the search for the ideal marker is still on. The use of the combination of these scores and indices was found to increase the diagnostic power .

In our study, we found that the IT ratio to be the best single index for NS diagnosis having a comparable significance as CRP and ESR, however, the IT ratio was superior to WBC count, albumin and platelet count in the sensitivity, specificity, the positive, and the negative predictive values .

Recommendation

Larger, prospective studies are wanted to elucidate the true diagnostic and prognostic values of laboratory tests in diagnosing neonatal sepsis.

Conflict of Interest:

The authors of the study have no conflict of interest related to this publication.

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