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Performance of the Hematological Scoring System for Early Diagnosis of Neonatal Sepsis in a Neonatal Intensive Care Unit of a Developing Country

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ABSTRACT:

— ***Objective:*** Neonatal sepsis is a common health problem in developing countries. Diagnosis of neonatal sepsis may be difficult as the early signs of sepsis may be subtle; hence, reliable identification of sepsis at an earlier stage is important. Thus, we aimed to assess the performance of the hematological scoring system (HSS) for early detection of neonatal sepsis in our Neonatal Intensive Care Unit (NICU).

— ***Patients and Methods:*** A cross-sectional study was conducted on 200 neonates admitted to NICU of Suez Canal University Hospital who were clinically suspected to have sepsis. Peripheral blood smears of all newborns have been collected and data were analyzed for neonatal sepsis using HSS, which included six hematological parameters that had an optimum sensitivity and NPV.

— ***Results:*** A total of 200 babies were evaluated for sepsis, 80 (40%) were proved to be septic by the positive blood cultures. Our study found that the highest sensitivity was recorded for platelet count and degenerative changes in PMN (100% each), while I:T ratio (>0.2) and I:M ratio recorded the highest specificity (96.7% each). Platelet count had the highest NPV (100%). White blood cell count had the highest PPV (90%) and the highest accuracy (92%) in identifying neonates with sepsis. Hematological scoring system ≥ 4 had a sensitivity of 95% and a specificity of 96.7%, PPV 26% and NPV 100%, respectively. ROC curve showed an area under curve (AUC) of 0.954 (95% CI 0.94-1.0).

— ***Conclusions:*** HSS can be used for diagnosis of neonatal sepsis; HSS ≥ 4 could be used for early diagnosis of neonatal sepsis in our NICU.

— ***Keywords:*** Early diagnosis, Hematological scoring system, Neonatal intensive care unit, Neonatal sepsis.

INTRODUCTION

Neonatal sepsis remains one of the leading causes of morbidity and mortality among term and preterm infants[1]. Although advances in neonatal care have improved survival and reduced complications in preterm infants, sepsis still contributes significantly to mortality and morbidity among very-low-birth-weight (VLBW) infants in Neonatal Intensive Care Units[2]. Every year, an estimated 4 million babies die in the neonatal period; 3/4 of these deaths occur in the first week of life, and almost all (99%) in low- and middle-income countries. Globally, 26% of neonatal deaths are estimated to be severe preterm infections[3].

The diagnosis of neonatal sepsis is difficult because clinical signs, particularly early in the course of disease, are hard to distinguish from other causes of neonatal disease[4]. Blood culture has been considered the gold standard for detecting bacterial sepsis; however, blood culture is time-consuming and the distribution of pathogens associated with neonatal sepsis is wide. Thus, for early diagnosis and treatment of the disease, it is meaningful to continue to analyze the clinical signs, pathogenic bacte-

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ria and antimicrobial resistance of neonatal sepsis[5]. Various investigators have evaluated some highly sensitive and specific inflammatory markers to diagnose neonatal sepsis (e.g. ELISA, haptoglobins, counter immune electrophoresis etc.); these markers are sensitive and specific, but are sophisticated, expensive and impractical for developing countries[6]. Various cheap but reliable laboratory tests have been evaluated for the diagnosis of neonatal sepsis[7]. The complete blood count (CBC) with various neutrophil parameters and C-reactive protein (CRP) are the most frequently used[8]. Early diagnosis of neonatal sepsis is still a great challenge. Hematologic scoring system (HSS) of Rodwell is preferable because it includes all the hematological parameters that should accurately predict the presence or absence of infection, reliably[9]. Several studies evaluated the hematologic scoring system (HSS) of Rodwell in Australia, in Dhaka, and in India, reporting that HSS was a simple, rapid, effective and reliable screening tool of sepsis[9-11]. Hence, it is important to assess the performance of this score in other populations; to decrease the widespread, prolonged use of unnecessary antibiotics and improve the outcome of the infants with sepsis, a reliable identification of sepsis at an earlier stage is paramount. Thus, the current study was designed to assess the performance of the hematological scoring system (HSS) for early detection of neonatal sepsis in our NICU.

PATIENTS AND METHODS

Patients

Neonates were enrolled in the study after fulfilling the following inclusion criteria: newborns aged 0 to 28 days, and newborn babies with clinical symptoms and sign of septicemia[12,13]. Exclusion criteria: major congenital anomaly, inborn errors of metabolism, neonates who received antibiotics and neonates who received blood transfusion. This study was approved by the Institutional Ethics Committee of Faculty of Medicine, Suez Canal University, and informed consent was obtained from the parents of the participants.

Methods

A cross-sectional study was conducted on 200 neonates who were suspected to have sepsis and admitted to Neonatal Intensive Care Unit (NICU) of Suez Canal University Hospital from January to June 2014.

Data Collection

All neonates in the study were subjected to the following: a detailed history for detection of maternal risk factors of sepsis (rupture of membranes> 18 hours, maternal urinary tract infection, maternal intrapartum fever >38°C, and chorioamnionitis), and infant risk factors like prematurity, low birth weight, asphyxia neonatorum, required resuscitation, invasive procedures (endotracheal intubation, ventilator, catheterization, infusion, central venous access). Clinical examination for assessment of gestational age using the New Ballard Score (14) and detection of clinical signs of sepsis included: (A) Respiratory system: tachypnea, severe apnea, increased ventilator support, oxygen desaturation; (B) Cardiovascular system: bradycardia, pallor, decreased perfusion, hypotension; (C) Metabolic change: hypothermia, hyperthermia, feeding intolerance, glucose instability, metabolic acidosis; (D) Neurologic changes: lethargy, hypotonia, decreased activity.

Complete blood count, peripheral blood smear, CRP level, and blood culture with antibiotic sensitivity were performed to all neonates. The reference values of the neonatal hematological parameters of Manroe et al[15] were used as the standard values.

Hematological scoring system: hematological parameters in HSS are total leucocyte count, platelet count, total PMN count, immature PMN, abnormal immature to mature neutrophil I:M PMN ratio, abnormal immature to total neutrophil I:T PMN ratio, and degenerative changes in PMN (toxic granules, cytoplasmic vacuoles, and Dohle bodies) in peripheral blood smear. The HSS assigns a score of one for each of the seven criteria found to be significantly associated with sepsis (Table 1) with one exception. Abnormal total count is assigned a score of 2 instead of 1. Sensitivity, specificity, positive and negative predictive values were evaluated for each of the seven criteria of HSS.

Statistical Analysis

All analyses were conducted using the SPSS for Windows statistical package, version 19.0. (SPSS Armonk, NY, USA). Non-parametric tests as Mann-Whitney U-test and Kruskal-Wallis test were applied to assess si-

Table 1. Hematological scoring system[8].

Criteria	Abnormality	Score
Total WBC count	≤5000/mm^3	1
	≥25,000 mm^{3}at birth	1
	≥30,000 mm^3 after 12-48 h	1
	≥21,000 mm^{3}day 2 onwards	1
Total PMN count	No mature PMN seen	2
	↓ or ↑	1
Immature PMN count	↑	1
I:T ratio (>0.2)	↑	1
I:M ratio	≥ 0.3	1
Degenerative changes in PMN	Toxic granules/ cytoplasmic vacuoles	1
Platelet count	≤ 150,000/ mm^3	1
Normal values: Total PMN count about 1800-5400; Immature PMN count about 600; Immature/total PMN: 0.120.		

I:M: abnormal immature to mature neutrophil; I:T: abnormal immature to total neutrophil; PMN =Polymorphonuclear; WBC: white blood cell.

Table 2. Demographic data of the studied neonates.

	Frequency (n=200)	%
Age in days {Mean ±SD} (Range)	4.6±4.0 (1-20)	——
Female	80	40%
Male	120	60%
Full-term	80	405
Pre-term	120	60%
Type of delivery		
Cesarean section	100	50%
Vaginal delivery	100	50%

gnificance of difference between data. x^2 test was used to compare observed data. The level of significance considered was 0.05. Sensitivity, specificity, negative predictive values, positive predictive value, and accuracy were used to compare the individual hematological findings. ROC curve was used to assess the accuracy and the cutoff point of the hematological scoring system in prediction of neonatal sepsis.

RESULTS

The mean age of the neonates was 4.6±4.0 days. Males were more represented than females (60% and 40%, respectively). Most of the neonates (60%) were preterm. 50% of them was delivered by cesarean section (Table 2).

According to the evaluation of the Hematologic Scoring System, we found that sepsis was unlikely (≤ 2) in 54 cases, sepsis was possible (3-4) in 66 cases and sepsis or infection was very likely (≥ 5) in 80 cases.

Table 3 shows performance of individual hematological findings among the investigated neonates. The highest sensitivity was recorded for platelet count and degenerative changes in PMN (100% each), while I:T ratio (>0.2) and I:M ratio recorded the highest specificity (96.7% each). Platelet count had the highest NPV (100%). White blood cell count had the highest PPV (90%) and the highest accuracy (92%). Cutoff value of Hematological Scoring System as an early diagnostic test for neonatal sepsis was 4 with sensitivity (95%), specificity (96.7%), PPV 26% and NPV 100%, and accuracy (95.5%) with area under the curve 0.954 (95% CI 0.94-1.0) (Table 4).

DISCUSSION

Bacterial sepsis is one of the most common challenges in newborn medicine. The lack of specificity of clinical and laboratory examination for detecting neonatal sepsis is a difficult problem to clinicians, because undiagnosed sepsis can lead to rapid deterioration and death, and because isolation of causative organism from blood samples can delay diagnosis, antibiotics are administrated to infants on the bases of non- specific findings[16]. In order to decrease the widespread and prolonged use of unnecessary antibiotics and improve the outcome of the infants with sepsis, reliable identification of sepsis at an earlier stage is paramount. Therefore, the current study was designed to assess the performance of the hematological scoring system (HSS) for early detection of neonatal sepsis in our NICU. We used the hematological scoring system (HSS) as a diagnostic tool formulated by Rodwell et al[8] in 1988 to establish early diagnosis of neonatal sepsis. The evaluation of this diagnostic tool

Table 3. Performance of individual hematological findings and CRP among the studied neonates.

	Sensitivity	Specificity	NPV	PPV	Accuracy
White blood cells count	90.0%	93.3%	93.3%	90.0%	92.0%
Platelet count	100.0%	56.7%	100.0%	60.6%	74.0%
Total PML count	97.5%	36.7%	95.7%	50.6%	61.0%
Immature PML	95.0%	66.7%	95.5%	65.5%	78.0%
I:T ratio (>0.2)	32.5%	96.7%	68.2%	86.7%	71.0%
I:M ratio	10.0%	96.7%	61.7%	66.7%	62.0%
Degenerative changes in PMN	100.0%	0.0%	—	40.0%	40.0%
CRP	69.0%	50.0%	45.0%	73.0%	67.0%

CRP: C reactive protein; I:M: abnormal immature to mature neutrophil, I:T: abnormal immature to total neutrophil; PMN=Polymorphonuclear.

Table 4. Hematologic Scoring System as a diagnostic test for neonatal sepsis; ROC curve Analysis.

Cut-off values	SN % (95% CI)	SP % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy (95% CI)	AUC (95% CI)
HSS	95% (88.4-100)	96.7% (59.5-98.3)	26% (22.2-27.2)	100% (85.3-99)	95.5% (78.8-98.4)	0.954 (0.94-1.0)

AUC: Area Under Curve; NPV: Negative Predictive Value; PPV: Positive Predictive Value; ROC curve: Receiver Operating Characteristic curve; SN: Sensitivity; SP: Specificity; 95% CI: 95% Confidence Interval; $p< 0.05$ is significant.

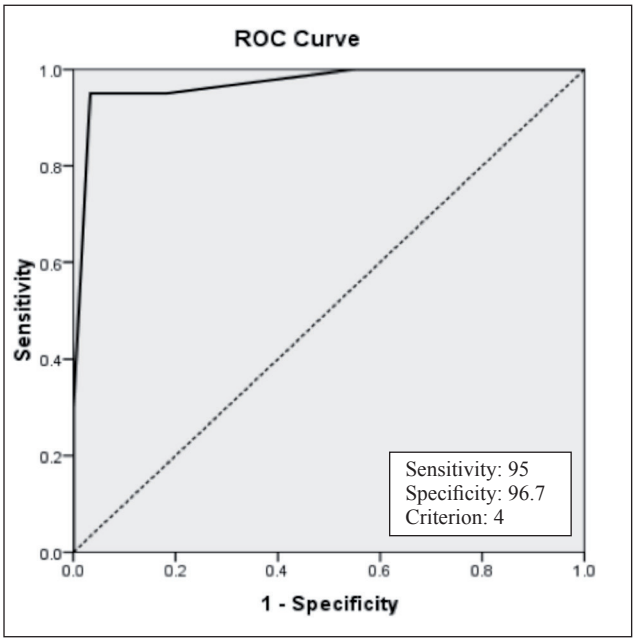

Figure 1. Receiver operating characteristic (ROC) curve of Hematologic Scoring System.

was investigated in several previous studies in different countries that found that HSS could be used in early diagnosis of neonatal sepsis. It is the first study in the Egyptian population to assess this score. In the present study total PMNs had high sensitivity and NPV and low specificity and PPV. Similar results were observed by Khair et al[10], Zaki et al[17], and Ghosh et al[18]. In this study the total PMNs count was associated with low positive predictive value and low specificity. Therefore, it should not be used in isolation as a predictor of sepsis. In our study immature PMNs reached high sensitivity and NPV, but low specificity and PPV. This result was in contrast to Ghosh et al[18] findings. The current work recorded that I/T ratio >0.2 had a low sensitivity and NPV, but high specificity and PPV, which is in contrast with the results of Rodwell et al[8]. We observed that I:M ratio (>0.30) was characterized by solid specificity only. Manroe et al[15] and Philip et al[19] observed that the sensitivity and PPV of I/M ratio (>0.3) were excellent. Rodwell et al[8] also used I/M ratio as a predictor of infection with high sensitivity, specificity, and NPV. Neonates with sepsis develop thrombocytopenia; this is thought to be due to increased platelet destruction, sequestration secondary to infections, failure in platelet production due to reduced megakaryocytes or damaging effects of endotoxin[20]. We found that thrombocytopenia was just associated to sensitivity. These results were against those of Shirin et al[21] and Khair et al[10]. This parameter could be used as an early but nonspecific marker for sepsis. We found that the highest sensitivity was recorded for platelet count and degenerative changes in PMN, while I:T ratio and I:M ratio recorded the highest specificity. Platelet count had the highest NPV. White blood cell count had the highest PPV and the highest accuracy. Narasimha and Harendrakumar[22] found that an abnormal immature to total neutrophil ratio (I:T), followed by an abnormal immature to mature neutrophil ratio (I:M), were the most sensitive indicators in the diagnosis of neonatal sepsis. The hematologic scoring system (HSS) should improve the efficiency of the CBC as a screening test for sepsis until a reliable diagnostic test is available. The HSS has practical advantages. Hematological score was calculated using the six hematological values, which had an optimum sensitivity and NPV[8]. In our series, we found that the cutoff value of HSS as an early diagnostic test for neonatal sepsis was 4, with elevated sensitivity, specificity, accuracy and area under the curve (0.954). These results are consistent with a previous study in Indonesia, which reported that HSS score of 4 had a good sensitivity, specificity, PPV and NPV. Another study in India found that HSS ≥ 4 could be used for early neonatal sepsis, because of high sensitivity and NPV[(4)]. Many studies evaluated the hematological scoring system for the early diagnosis of neonatal sepsis but revealed variable results, although mostly towards its utility[23].

CONCLUSION

Hematological Scoring System is useful test in the early diagnosis of neonatal sepsis, hematological scoring system ≥ 4 is accurate for early diagnosis of neonatal sepsis in our NICU.

Conflicts of Interest:
The authors declare no conflict of interest

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Authorship Contributors:
Nesrine M. Handoka designed the study, wrote the manuscript, and Hesham A. Fathy designed the study, and Shabaan G. Derbala collected and analyzed data. Basma B. Hasan performed laboratory analysis. All authors revised and approved the final manuscript.

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