The predictive score for early-onset neonatal sepsis

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The aim of the present study was to analyze complete blood count (CBC) and C-reactive protein (CRP) levels to create the predictive score for diagnosis of early-onset neonatal sepsis (EONS).

All neonates treated for suspected EONS between January 2004 and December 2006 were evaluated from their case record. A diagnosis of EONS was made if either clinical findings consistent with sepsis developed within 72 hours of life, or if positive cultures were obtained.

Evaluations for EONS were performed in 341 neonates, and 199/341 (58.4%) developed EONS. Total white blood count, immature/total ratio, immature/mature ratio, and CRP levels were found to be independent predictors of EONS, and the predictive score for EONS was created. An increase in the predictive score for EONS was directly correlated with the possibility of EONS.

Receiver operating characteristic (ROC) curve analysis determined a cut-off value of a predictive score for EONS >0.503, with sensitivity of 73% and specificity of 89%. Correct prediction of EONS was found in 78% of all neonates, 80% for positive and 75% for negative outcome (p<0.0001).

In conclusion, for its high sensitivity and prediction rates, the predictive score for EONS is useful in diagnostic evaluation of neonates suspected for EONS.

Key words: neonatal sepsis, early-onset, predictive score, diagnosis.

Neonatal sepsis may be classified according to the time of onset of the disease, as early-onset (EONS) and late-onset (LONS) neonatal sepsis. EONS occurs from birth to 72 hours of life and is associated with transplacental infection or an ascending infection from the cervix caused by microorganisms colonizing the maternal genitourinary tract or birth canal¹². It may have subtle, diverse and non-specific clinical signs. Therefore, early diagnosis and treatment of the neonate with suspected sepsis are essential to prevent severe and life-threatening complications³.

The incidence of neonatal sepsis in developed countries is 3.5-4.3/1,000 live births, with EONS representing 58% of the cases. Developing countries have both the highest incidence and the highest mortality rates⁴,⁵. It is a major cause of fatality during the first month of life, contributing to 13-15% of all neonatal deaths⁶.

Despite the development of medicine, new antibiotics and other means of treatment, EONS remains an important problem in perinatal medicine. Accurate and timely diagnosis of EONS remains challenging to the clinician and the laboratory. A definitive diagnosis based on the culture of blood, cerebrospinal fluid (CSF) or urine is usually reached only after a delay of a day or two, yet rapid progression of untreated infection may greatly increase morbidity or mortality⁷,⁸. Moreover, clinical signs of EONS manifest themselves in the absence of a positive culture. This is particularly common in probable EONS with obstetric risk factors where receipt of antenatal maternal antibiotics is common⁹.

Thus, over the last decade, a variety of laboratory tests have been developed to enhance the early and accurate identification and treatment of neonates with suspected sepsis¹⁰,¹¹. As yet, no international consensus regarding screening of EONS has been made¹².

The aim of the present study was to analyze complete blood cell count (CBC) and C-reactive...
protein (CRP) levels to create the predictive score for diagnosis of EONS.

**Material and Methods**

**Subject Population**

The study was conducted at the Department of Neonatology, Clinic for Gynecology and Obstetrics, University Clinical Center, Tuzla, over a three-year period from January 1, 2004 to December 31, 2006. Subjects were identified prospectively. Relevant data of the neonates during this period were obtained retrospectively from their case records. The clinical characteristics of the analyzed population and characteristics of delivery are shown in Table I.

In very low gestational age neonates, who are routinely admitted to a neonatal intensive care unit (NICU), the neonate can be evaluated and treated with little additional cost. In contrast, older neonates are unlikely to be admitted to the NICU, and there is economic pressure to discharge them sooner rather than later, particularly with vaginal deliveries. The clinician’s dilemma is: “Which neonate needs antibiotic treatment?” Thus, neonates were included in the study if they: a) were gestational age >33 weeks; b) were from single pregnancies; and c) were ever evaluated for EONS during the birth hospitalization. A neonate was considered to have been evaluated for EONS if culture (from a normally sterile site) and laboratory studies (CBC and CRP) were obtained in the first 72 hours of life. Some of them were asymptomatic and were evaluated for sepsis because of maternal intrapartum sepsis risk factors (prolonged rupture of membranes, maternal urinary tract infection, maternal intrapartum fever >38°C, chorioamnionitis, and excessive vaginal discharge) according to the Centers for Disease Control and Prevention. Neonates were excluded if they: a) were critically ill and received antibiotic treatment before blood sampling; b) had a major congenital anomaly; c) had inborn errors of metabolism, hemolytic jaundice or respiratory distress syndrome (due to surfactant deficiency); d) underwent the first evaluation after 72 hours of life; and e) were born outside the clinic.

Clinical signs consistent with EONS included: poor feeding, feeding intolerance, lethargy, irritability, temperature instability, poor respiratory effort (apnea, need for supplement oxygen, need for ventilation), tachypnea, tachycardia/bradycardia, hypotension, abnormal glucose homeostasis, metabolic acidosis, nonphysiologic jaundice, abdominal distention, and necrotizing enterocolitis.

Gender, gestational age, birth weight, Apgar score, and delivery characteristics were recorded for each neonate.

**Subject Classification**

Patient classification was based on culture results or clinical factors (results of physical examinations or laboratory studies). A proven EONS was defined as an infection confirmed by a positive culture from a normally sterile site. Cultures were obtained using a standard clinical pathway. Bacteria recovered in cultures were considered to be pathogenic unless they were normal skin or upper respiratory flora, all other laboratory studies were normal, and the neonate either had no clinical signs of infection.

<table>
<thead>
<tr>
<th>Neonatal characteristics</th>
<th>Male/Female</th>
<th>163/178</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (number)</td>
<td>Male/Female</td>
<td>163/178</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>X±SD</td>
<td>38.6±1.4</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>X±SD</td>
<td>3167.0±721.3</td>
</tr>
<tr>
<td>Apgar score 1 st minute</td>
<td>X±SD</td>
<td>8.4±1.5</td>
</tr>
<tr>
<td>Apgar score 5 th minute</td>
<td>X±SD</td>
<td>8.58±1.2</td>
</tr>
<tr>
<td>Delivery characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous vaginal delivery</td>
<td>n (%)</td>
<td>86 (25.2%)</td>
</tr>
<tr>
<td>Induced vaginal labor</td>
<td>n (%)</td>
<td>146 (42.8%)</td>
</tr>
<tr>
<td>Elective cesarean section</td>
<td>n (%)</td>
<td>71 (20.8%)</td>
</tr>
<tr>
<td>Urgent cesarean section</td>
<td>n (%)</td>
<td>38 (11.1%)</td>
</tr>
<tr>
<td>Duration of labor (h)</td>
<td>X±SD</td>
<td>4.8±3.4</td>
</tr>
<tr>
<td>Duration of rupture of membranes (h)</td>
<td>Median (range)</td>
<td>24 (0-96)</td>
</tr>
</tbody>
</table>
or such signs resolved without antimicrobial therapy. A probable EONS was determined if: clinical or laboratory studies were consistent with this diagnosis but cultures were negative. No EONS (who served as control group) indicated there were no clinical or laboratory study results attributable to sepsis.

**Statistical Analysis**

Statistical analyses were preformed using SPSS version 10 for Windows. The Kolmogorov-Smirnov test was used to test for normality; statistics determined to be normal are displayed as mean ± standard deviation, while those determined to be nonparametric are shown as median and range. Student t-test was used to compare categorical variables. CBC and CRP levels were tested by multiple regression analysis, and according to weight factors, their regression coefficients were calculated. Receiver operating characteristic (ROC) analysis was used to determine the cut-off value of the predictive score for EONS. The area under the ROC curve was calculated using the method of Hanley and McNeil¹⁵. The predictive score levels were tested by logistic regression analysis to calculate likelihood of EONS.

A two-sided p value <0.05 was considered significant.

**Results**

During the study period, there were 12,298 live births in the Clinic for Gynecology and Obstetrics in Tuzla. Evaluations for EONS were performed at the age of 72 hours or less in 341 neonates, and 199 (58.4%) of them developed EONS, with an incidence of 16.2 per 1,000 live births. Fifty-two of 199 neonates (26.1%) had culture-proven EONS. The rates of gram-positive and gram-negative isolates were almost equal (51.9% vs 48.1%), and the rate of infection was higher among males (54.3%) than females (45.7%).

The mean of total white blood cell (WBC) count, immature/total (I/T) ratio and immature/mature (I/M) ratio, and serum CRP levels were significantly different between neonates with and without EONS (Table II).

In multivariable regression model, total WBC count, I/T ratio, I/M ratio and CRP levels were found to be independent predictors of EONS (Table III). According to weight factors of predictors from the described analysis, the predictive score for EONS was created (Formula 1).

The mean predictive score for EONS was significantly higher in neonates with EONS than in healthy neonates (0.71±0.32 vs 0.36±0.12, p<0.001) (Fig. 1). An increase in predictive score for EONS was directly correlated with possibility of EONS, while values larger than one in almost 100% suggested the presence of EONS (Fig. 2).

Receiver operating characteristic (ROC) analysis was made according to the mean predictive score values in the analyzed neonates, and the best results were determined for a cut-off value of more than 0.503, with area under the curve of 0.867±0.019 (p<0.0001), and sensitivity of 73% and specificity of 89% (Fig. 3). Logistic regression analysis of predictive score for EONS was significant with p<0.0001. Correct prediction of EONS was found in 78% of all neonates, 80% for positive outcome and

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Early-onset neonatal sepsis (EONS)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total WBC count (x10⁹/L)</td>
<td>YES</td>
<td>22.5±9.5</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>20.5±5.1</td>
</tr>
<tr>
<td>I/T ratio</td>
<td>median (range)</td>
<td>0.09 (0-0.48)</td>
</tr>
<tr>
<td>I/M ratio</td>
<td>median (range)</td>
<td>0.10 (0-0.92)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>median (range)</td>
<td>20.6 (4.4-197.8)</td>
</tr>
</tbody>
</table>

75% for negative outcome [odds ratio (OR): 4562.18; 95% confidence interval (CI): 675.54-30810.36].

Discussion

Early-onset neonatal sepsis (EONS) is one of the most common diagnostic challenges in neonatal medicine today. Although culture results are the “gold” standard for diagnosis, among the studies, positive cultures ranged from 8-73%. The isolation of microorganism depends on skin disinfection, sample volume and sampling site. Similar to Arshad et al. [17], we found that 26.1% of neonates had positive cultures.

Ideally, a screening test that is considered reliable and diagnostic must have a high level of sensitivity and specificity in identifying what it is measuring. In other words, a test used to diagnose EONS must always indicate abnormal results in those neonates who have EONS (sensitivity) and indicate normal results in neonates who are not infected (specificity). Thus, the idea of predictive models based on initial laboratory data is worth trying and seems to be of practical value in evaluation of neonates for EONS. Using multivariable
regression model, we found WBC, I/T ratio, I/M ratio, and CRP levels to be independent predictors of EONS, but this was not found for other hematological parameters. According to weight factors of predictors from the described analysis, the predictive score for EONS was created. Song et al. [19] emphasized superior performance of multivariable regression models in correctly predicting health outcomes. In the present study, an increase of predictive score for EONS was directly correlated with possibility of EONS, while values larger than one in almost 100% suggested the presence of EONS.

Receiver operating characteristic curve analysis determined a cut-off value of predictive score for EONS of more than 0.503, with sensitivity of 73% and specificity of 89%. The ROC curve provides a comprehensive picture of the ability of the test to make the distinction being examined over all decision thresholds. Qualitatively, the closest the curve is to the upper left corner, the higher the overall accuracy of the test20. In the current study, the predictive score for EONS with high area under the curve (0.867) showed good accuracy in the diagnosis of EONS.

On the other side, traditional descriptors (sensitivity, specificity, positive and negative predictive values) may not accurately represent test performance, because they are heavily influenced by the prevalence of disease in the sample population. Logistic regression analysis allows us to estimate the relationship between one dichotomous dependent variable and one or more independent variables21. Logistic regression analysis of predictive score for EONS was significant with p<0.0001. We found correct prediction of EONS in 78% of all neonates, 80% for positive and 75% for negative outcome. Thus, using the constructed predictive score for EONS for levels >0.503 with accuracy of 80% and high OR, we can predict that a neonate had EONS. Huptertan et al.22 reported the importance of designing prognostic models using their own database, because there is a low accuracy of models from other regions.

Although EONS may have subtle, diverse and non-specific early clinical signs and can easily be confused with other noninfective causes, management of symptomatic neonates is not controversial, as all need evaluation for infection and early treatment. There is the problem, however, with asymptomatic neonates and maternal intrapartum risk factors. Do they really need diagnostic evaluation for infection? In our study, 115/199 (57.8%) newborns with EONS (proven or probable) were asymptomatic at delivery, and 27.8% of them developed symptoms within 24 hours of life. Almost all of them (85.2%) had abnormal predictive score for EONS. It is true that almost all of these neonates would have developed symptoms suggestive of infection at some time after delivery, and be treated with antibiotics, but the consequences of the short delay in evaluation and treatment are not fully known.

In conclusion, for infection, a neonate is more likely to suffer if infection is underdiagnosed and not treated than if the infection is overdiagnosed and the neonate is treated unnecessarily. While awaiting culture results, for its high sensitivity and prediction rates, the predictive score for EONS is useful in evaluation of neonates suspected for EONS. It is a cheap and cost-effective method in developing countries. Of course, validation of the designed predictive model, using larger databases, is necessary to improve its accuracy.

REFERENCES


