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Review Article

Pilot Validation of Early Predictors for Neonatal Sepsis

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Abstract

Purpose: Pilot development of the system estimating the risk for sepsis in newborns and determining its discrimination power.

Methods: A retrospective observational single-center study. 124 newborns with sepsis are included; 34 of them died. Kullback's measure was used to estimate the information value of the examined clinical and laboratory variables. Disease outcome (whether survived or dead) was the response function. The discrimination power was determined using ROC-analysis.

Results: The information value of the examined clinical and laboratory variables in the newborns was analyzed as related to the risk for sepsis. Early neonatal sepsis predictors include platelet count, total protein content, body mass and neutrophil count. Discrimination power of the mentioned predictors was calculated.

Conclusion: Determination of the risk for sepsis in a newborn based on the estimation of platelet count, neutrophil count, total protein and body mass is of moderate value.

Keywords: *Newborns; Sepsis; Predictors; Information Value*

Introduction

One of the key issues in the fight against sepsis is its early recognition, that is, the detection of infection and significant predictors of organ dysfunction. Within the framework of the Sepsis-3 concept, an important role is played by the qSOFA assessment system, which is designed to identify patients with a high risk of sepsis and to immediately initiate therapy for those who need it [1]. As criteria for this prognostic scale, data are used on the level of systolic blood pressure, respiratory rate, and the state of metal status. This scale is a bedside test that does not require laboratory diagnosis but can only be used in adult patients. Currently, a number of authors rate this scale as excellent [2,3], although to a lesser extent this applies to countries with moderate health care funding [4].

At the beginning of 2018, L. J. Schlapbach., *et al*. pointed out the possibility of using for the early diagnosis of sepsis in the clinic not only special pediatric pSOFA or PELOD-2 scales, but also age-dependent pediatric qSOFA criteria adapted for pediatrics [5]. A recent work by C Peters., *et al*. demonstrated the appropriateness of using age-dependent pediatric qSOFA criteria (within the PELOD2 scale) to assess the risk of developing sepsis in children [6]. However, due to the anatomical and physiological characteristics of newborns, especially premature infants, the possibility of using the PELOD2 scale data as early predictors of neonatal sepsis seems to be very debatable. Signs and symptoms of neonatal sepsis are extremely non-specific [7]. They include fever or hypothermia, respiratory distress, including cyanosis and apnea, feeding difficulties, lethargy or irritability, hypotension, cramps, protruding fontanel, poor perfusion, bleeding problems, bloating, hepatomegaly, Gaussian-positive stool, unexplained jaundice or, more importantly, "just looking bad" [8]. Earlier, in the works of D. O. Ivanov., *et al*. as a predictor of early neonatal sepsis, a comprehensive assessment of a number of hematological and metabolic parameters (the number of leukocytes, neutrophils, platelets, total protein level) and, accordingly, the body weight of the child was proposed [9,10].

It is known that the doctor's knowledge of relevant predictors of the risk of the inverse course of the disease is essential for the choice of patient management tactics. In this regard, the goal of our work was the pilot development of a system for assessing the risk of developing sepsis in newborns and determining its discriminatory ability.

Materials and Methods

It is known that the doctor's knowledge of relevant predictors of the risk of the inverse course of the disease is essential for the choice of patient management tactics. In this regard, the goal of our work was the pilot development of a system for assessing the risk of developing sepsis in newborns and determining its discriminatory ability. According to the outcome of the disease, patients were divided into 2 groups. Group I included children with sepsis (91 patients). Group II included children whose sepsis was not established (32 patients).

On the first day of hospitalization, we monitored blood biochemical parameters (total protein, albumin, blood amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, blood glucose, electrolytes); monitoring of a general blood test (hemoglobin level, red blood cell count, platelet count, leukoformula). The information content, threshold values and diagnostic coefficients (DC) were calculated above the indicated clinical and laboratory parameters.

To assess the information content of the signs, the Kullback measure was used [11]. For the function from clique was taken the fact that the patient developed sepsis.

We divided this ordered series into intervals (2nd column). In the next two columns (3rd and 4th), data were placed on the frequency of the index falling from group A and B in each interval. Columns 5 and 6 were filled with relative frequency values in%, taking for 100% the sum of the particulars A and B, respectively, in all ranges. In order to minimize the influence of the choice of interval boundaries on the results, the average weighted (smoothed) particulars were determined in each interval by the method of calculating the weighted moving average. In this case, the frequency of this feature was taken into account in four neighboring ranges according to the formula:

$$y_3 = (y_1+2y_2+4y_3+2y_4+y_5)/10$$

To simplify further calculations, smooth percentages were surrounded around with a precision of up to 1, except for those whose magnitude is less than 5%. In these cases, they were rounded to the first decimal place. DK is the logarithm of the relations of smoothed particulars, multiplied by 10 and rounded up to an accuracy of 1.

The information content of the Ji-th range of the j-th attribute is equal to:

$$J(x^i_j) = DK(x^i_j)\ 1/2\ [P(x^i_j/A) - P(x^i_j/B)],$$

Where $DK(x^i_j)$ is the diagnostic coefficient of the i-th range of the j-th sign; $P(x^i_j/A)$ is the probability (smoothed frequency) of getting into the group of the Ai-th range of the j-th attribute.

To compile a diagnostic table, we calculated the information content of the sign x_j equal to the sum of the information content of its ranges.

$$J(x_j) = S_i J(x^i_j).$$

A clear boundary between the area where the diagnostic coefficients (DC) of group A and group B are concentrated are the intervals characterized by minimal information content.

Clinical and laboratory parameters in our study were not distributed abnormally (Shapiro - Wilk test), therefore non-parametric tests were used for statistical analysis. The significance of differences between the groups was checked using the Mann - Whitney test. The conclusions were considered reliable at a value of $p < 0.05$.

Results and Discussion

The characteristics of patients according to the studied clinical and laboratory parameters at the time of their admission to the intensive care unit are presented in table 1. To assess the information content of the studied clinical and laboratory parameters in the first days of intensive care of newborns with early sepsis, an analysis was carried out regarding the risk of sepsis using the Kullback measure (Table 2). The data table 2 indicate that the maximum informational value in children with early neonatal sepsis is the number of blood platelets, the level of total blood protein, body weight and the number of blood neutrophils.

Parameter name	Value	Confidence interval
Erythrocytes ($x10^{12}$/l)	4,86 + 0,73	3,4 - 5,8
Hemoglobin (g/l)	159,04 + 27,49	105 - 205
Leukocytes ($x10^{9}$/l)	11,95 + 5,78	4,1 - 39
Hematocrit (%)	31,89 + 12,19	31 - 55
Lymphocytes ($x10^{9}$/l)	3,42 + 1,25	0,59 - 6,41
Neutrophils ($x10^{9}$/l)	7,86 + 2,73	4,09 - 16,83
Platelets ($x10^{9}$/l)	279,2 + 60,12	210 - 480
Coagulation time (min)	4,53 + 2,04	1,3 - 10
Bilirubin (mmol/L)	125 + 82,17	9 - 408
Total protein (g/L)	53,19 + 6,72	38 - 68
Glucose (mmol/L)	3,59 + 2,37	0,9 - 18
ALT (IE/L)	39,05 + 10,32	28,4 - 50,6
AST (IE/l)	51,1 + 42,54	23,6 - 114,4
Creatinine (mmol/L)	70 + 29,69	49 - 91
K^{+} (mmol/l)	4,79 + 1,09	8,4 - 2,5
Na^{+} (mmol/l)	143,58 + 7,89	130 - 163
Body weight, (g)	1839 + 831,64	1001 - 2574

Table 1: *Clinical and laboratory variables in the examined new - borns on their admittance to the resuscitation unit.*

Index	Information coefficient*
Hematocrit	0,45
Glucose	0,5
Erythrocyte count	0,6
Hemoglobin content	0,8
Leukocyte count	0,7
Number of neutrophils	1,1
Lymphocyte count	0,6
Total protein	1,7
Platelet count	1,8
Body mass	1,49

Table 2: *Informativeness of clinical and laboratory parameters in children studied.*

Then we calculated the threshold diagnostic values of each of the selected clinical and laboratory indicators, depending on the sum of the diagnostic coefficients (Table 3-6). It is known that this indicator value is its level corresponding to the minimum positive value [9].

J	Z (J,1)	Z (J,2)	K (J)	K1 (J)	K2 (J)	K3 (J)	CK1 (J)	CK2 (J)	DK (J)	U (J)
1	150,0	198,0	24,0	0,0	0,545	0,000	0,259	0,050	7,145	0,747
2	198,0	246,0	5,0	0,0	0,114	0,000	0,205	0,150	1,347	**0,037**
3	246,0	294,0	8,0	1,0	0,182	0,500	0,180	0,300	–2,229	0,134
4	294,1	342,1	6,0	1,0	0,136	0,500	0,107	0,300	–4,485	0,433
5	342,1	390,0	1,0	0,0	0,023	0,000	0,055	0,100	–2,632	0,060

Table 3: *Estimating diagnostic coefficients as related to platelet count in the examined new-borns.*

The estimated diagnostic threshold for blood platelet counts was ≤ 198.0 10^{12}/L.

J	Z (J,1)	Z (J,2)	K (J)	K1 (J)	K2 (J)	K3 (J)	CK1 (J)	CK2 (J)	DK (J)	U (J)
1	1,0	10,6	19,0	2,0	0,760	0,286	0,304	0,114	4,249	0,403
2	10,6	20,3	0,0	0,0	0,000	0,000	0,152	0,057	4,249	0,202
4	29,9	39,5	0,0	0,0	0,000	0,000	0,016	0,100	7,959	0,027
5	39,5	49,1	0,0	2,0	0,000	0,286	0,036	0,200	7,447	0,611
6	49,1	58,8	4,0	3,0	0,160	0,429	0,076	0,229	4,782	0,321
7	58,8	68,4	1,0	0,0	0,040	0,000	0,056	0,086	1,849	0,222

Table 4: *Estimating the level of diagnostic coefficients as related to the level of total protein in those examined.*

The estimated diagnostic threshold for total blood protein was ≤ 29.9 g/L.

J	Z (J,1)	Z (J,2)	K (J)	K1 (J)	K2 (J)	K3 (J)	CK1 (J)	CK2 (J)	DK (J)	U (J)
1	833,0	1423,2	52,0	0,0	0,578	0,000	0,308	0,031	9,934	1,373
2	1423	2013,5	31,0	0,0	0,344	0,000	0,269	0,094	4,576	0,401
3	2013,7	2603,8	7,0	10,0	0,078	0,313	0,158	0,219	–1,419	**0,043**
4	2604	3194,3	0,0	10,0	0,000	0,313	0,050	0,256	–7,097	0,732
5	3194	3784,8	0,0	10,0	0,000	0,313	0,008	0,200	–14,10	1,355

Table 5: *Estimating the level of diagnostic coefficients as related to the body mass in the examined new-borns.*

The estimated diagnostic threshold for new-born body weight was ≤ 2013.7g.

J	Z (J,1)	Z (J,2)	K (J)	K1 (J)	K2 (J)	K3 (J)	CK1 (J)	CK2 (J)	DK (J)	U (J)
1	1,0	4,2	19,0	0,0	0,284	0,000	0,254	0,061	6,192	0,597
2	4,2	7,4	46,0	0,0	0,687	0,000	0,337	0,146	3,627	0,346
3	7,4	10,6	2,0	25,0	0,030	0,610	0,178	0,298	–2,241	0,134
4	10,6	13,8	0,0	10,0	0,000	0,244	0,075	0,232	–4,920	0,386
5	13,8	17,0	0,0	2,0	0,000	0,049	0,003	0,073	–13,894	0,488

Table 6: *Estimating the level of diagnostic coefficients as related to the neutrophil count in the examined new-borns.*

The threshold diagnostic value for the number of neutrophils in the blood of a new-born was ≥ 7.4 (x10^9/l).

Thus, we calculated the most informative signs of early neonatal sepsis and their threshold diagnostic values, which should be guided by. Then, the patients examined by us were distributed depending on the presence and absence of these signs (two or more signs) upon admission to the neonatal intensive care unit. 69 newborns had this symptom complex, and 54 newborns were absent. Next, we calculated the discriminatory ability of the indicators we identified by performing the ROC analysis (Figure 1). Thus, the diagnostic algorithm presented by us showed a low degree of discriminatory ability, which does not allow it to be used in clinical practice in this form. The most probable reason for this is the low sensitivity of the method of 41.3%.

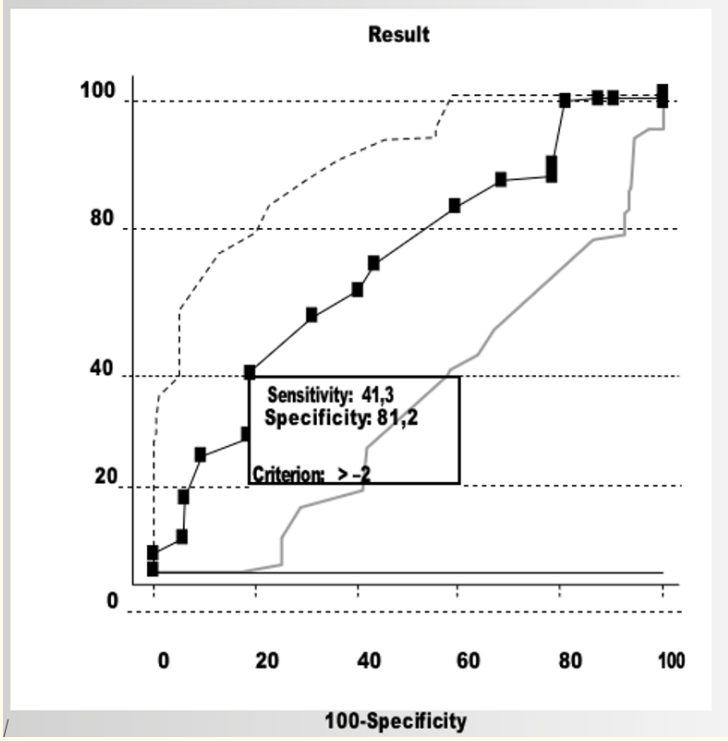

Figure 1: *ROC-analysis of the mentioned clinical and laboratory variables.*

It is known that the sensitivity of this approach can be increased by ranking the characteristics that we identified by points and by identifying the critical threshold value of the scoring of the newborn. In this regard, we, in order to identify more informative values of the identified clinical symptoms, it was decided to rank them by higher values of the diagnostic coefficient. In particular, the number of neutrophils is 10.6 x 10^9/l, platelets are 150.0 x 10^9/l, and body weight is 1423g. These values were observed in 26 newborns and were absent in 97 children. And we calculated the discriminatory ability of a system based on the above criteria (Figure 2).

The area under the ROC curve was 0.723 with a standard error of 0.054, 95% confidence interval 0.636 - 0.800. Thus, with the tightening of the threshold diagnostic criteria, we have a good discriminatory ability of the predictors of the development of sepsis of newborns that we have identified. But an increase in the sensitivity level of the test was accompanied by a decrease in its specificity from 81.2% to 62.5%.

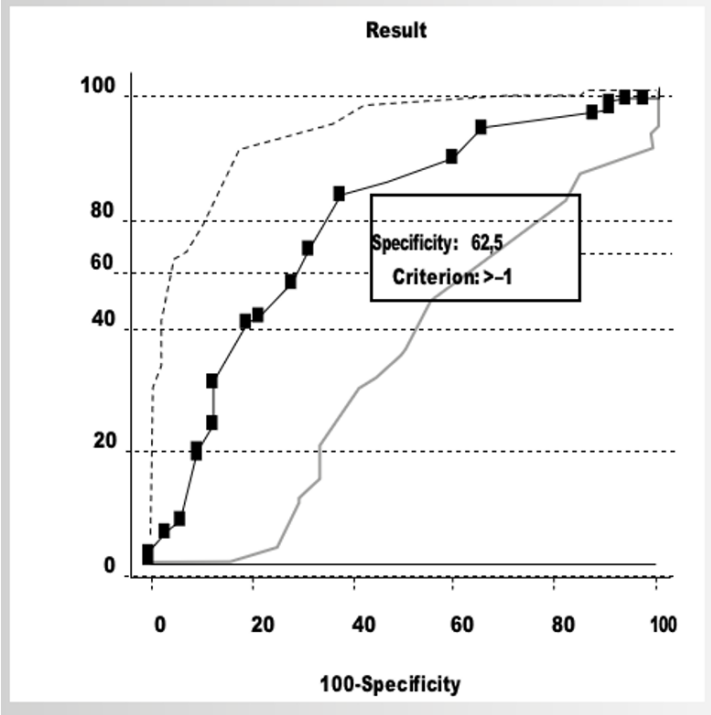

Figure 2: *ROC- analysis of the mentioned clinical and laboratory variables.*

Our work was of a retrospective nature; therefore, for a more justified identification of the risk factors for the development of sepsis of newborns, a prospective and larger study is necessary. At the same time, taking into account the practical lack of work on the early diagnosis of sepsis in newborns in the framework of the Sepsis-3 concept, its implementation seems quite reasonable.

Conclusion

Determination of the risk of sepsis in newborns based on the assessment of platelet count (≤ 150.0 × 10^9/L), neutrophils (≤ 10.6 × 10^9/L), total blood protein ≤ 29.9 g/L) and body weight (≤ 1423 g/l) has good diagnostic value (AUCROC - 0.723), but has a low specificity of 62.5%.

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