

Evaluation of Ema, Töllner and Rodwell scores in the diagnosis of neonatal sepsis

Yenidoğan sepsis tanısında Ema, Töllner ve Rodwell skorlarının değerlendirilmesi

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Abstract

Purpose: There are no specific signs, symptoms and rapid laboratory tests to definitively diagnose sepsis in the neonatal period. Therefore, in this study, we planned to investigate the clinical adequacy and reliability of EMA (European Medicines Agency), Töllner and Rodwell hematological scoring in the early diagnosis of neonatal sepsis.

Materials and methods: EMA, Töllner and Rodwell hematological scoring was performed on each patient. Complete blood count, peripheral smear, C-reactive protein, procalcitonin, blood gas and blood sugar values of newborn babies with suspected sepsis were recorded, blood culture, urine culture and cerebrospinal fluid examination and cultures taken when necessary were evaluated. Using statistical analysis, the 'Positive Expected Value and Negative Expected Values' ratios of the scores were obtained, and the performance results were examined.

Results: 95 newborns with a preliminary clinical diagnosis of sepsis were included in the study. These babies were divided into two groups: clinical (n:71) and proven sepsis (n:24) according to blood culture results. Positive and negative predictive values of scoring systems in definitive sepsis diagnosis; for EMA respectively; 21.5%, 56.3% for Töllner; it was determined as 31.3%, 77.8%, and 100%, 77.8% for Rodwell.

Conclusion: Our study showed that clinician opinion and standard laboratory tests are limited in the diagnosis of neonatal sepsis, and Rodwell hematological scoring is more prominent in recognizing proven sepsis compared to the other two scores.

Keywords: Sepsis, newborn, EMA, Töllner, Rodwell.

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Öz

Amaç: Yenidoğan döneminde sepsis tanısını kesin olarak saptayacak özgün belirti, bulgu ve hızlı laboratuvar testleri bulunmamaktadır. Bu nedenle bu çalışmada yenidoğan sepsisinin erken tanısında EMA (European Medicines Agency), Töllner ve Rodwell hematolojik skorlamalarının klinik yeterlilik ve güvenilirliğini araştırmayı planladık.

Yöntem: Her hastaya EMA, Töllner ve Rodwell hematolojik skorlaması yapıldı. Sepsis düşünülen yenidoğan bebeklerin tam kan sayımı, periferik yayma, C-reaktif protein, prokalsitonin, kan gazı ve kan şekeri değerleri kaydedildi, bebeklerden alınan kan kültürü, idrar kültürü ve gerekli hallerde alınmış beyin omurilik sıvı incelemesi ve kültürleri değerlendirildi. İstatistiksel analizler kullanılarak skorlamaların 'Pozitif Beklenen Değer ve Negatif Beklenen Değerler' oranları elde edildi, performans sonuçları incelendi.

Bulgular: Klinik sepsis ön tanısı alan 95 yenidoğan çalışmaya alındı. Bu bebekler kan kültürü sonuçlarına göre klinik (n:71) ve kanıtlanmış sepsis (n:24) olmak üzere iki gruba ayrıldı. Kesin sepsis tanısında skorlama sistemlerinin pozitif ve negatif prediktif değerleri; sırasıyla EMA için; %21,5, %56,3, Töllner için; %31,3, %77,8, Rodwell için ise %100, %77,8 saptandı.

Sonuç: Çalışmamız, yenidoğan sepsis tanısında klinisyen görüşünün ve standart laboratuvar testlerin sınırlı olduğunu, Rodwell hematolojik skorlamasının diğer iki skorlamaya göre kanıtlanmış sepsisi tanımda daha ön planda olduğunu göstermiştir.

Anahtar kelimeler: Sepsis, yenidoğan, EMA, Töllner, Rodwell.

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Introduction

Neonatal sepsis is a clinical syndrome in which systemic findings and signs of infection are seen in the first month of life and a specific pathogen is grown in blood culture [1-3]. Despite advances in maternal and neonatal care, neonatal sepsis continues to be a major factor in morbidity and mortality [4-6].

Signs and symptoms in the neonatal sepsis are generally non-specific. In early-onset neonatal sepsis, findings related to multiple organs or systems may occur, whereas in late and very late-onset neonatal sepsis, infection findings may be multisystemic or focal (such as meningitis, pneumonia, omphalitis, osteomyelitis, septic arthritis) [7]. Neonatal sepsis may affect many systems and present with many different findings such as moaning, withdrawal of auxiliary respiratory muscles, nasal wing respiration, apnea, cyanosis, tachypnea in the respiratory system; bradycardia/tachycardia, peripheral circulatory disorder, hypotension, increased capillary filling time in the cardiovascular system; feeding intolerance, failure to suck, vomiting, diarrhoea, abdominal distension, hepato-splenomegaly, jaundice in the digestive system; sclera, cutis marmoratus, pustules, abscesses, petechiae, pupura in the skin; and lethargy, hypotonicity, tendency to sleep, poor or high pitched crying, puffy fontanelle, irritability, convulsion, hypoactivity, temperature irregularities and failure to suck in the central nervous system [7-10].

Isolation of the specific pathogenic agent from the blood, which should be absolutely sterile, is the gold standart for definitely diagnosis of the neonatal sepsis [11]. In a blood culture taken with the correct methods, the growth time of the agent is within the first 48 hours in 90% of patients. While waiting for the culture result, there is no test with high sensitivity and specificity that can help to define the diagnosis of sepsis in a shorter time. Diagnosis is aided by the use of several inflammatory markers together [8].

In addition to the lack of specific signs, symptoms, findings and rapid laboratory tests for the diagnosis of neonatal sepsis, the possibility that findings suggestive of sepsis may be related to non-infectious causes that are common in the neonatal period makes the diagnosis of neonatal sepsis difficult. This situation makes timely diagnosis and initiation of treatment difficult in babies without sepsis or leads to unnecessary treatment [2].

Various combinations of inflammatory response factors, laboratory analysis, and physical examination findings have been used in the literature to create sepsis scores. In 1982, Töllner developed the first known scoring system for neonatal sepsis to define sepsis on the basis of both clinical and basic laboratory assessment [12]. Rodwell developed hematological sepsis scoring in 1988 [13]. The Pediatric Committee (PDCO) of the European Medicines Agency (EMA) proposed the EMA sepsis criteria for the standardisation of the diagnosis of neonatal sepsis in 2010 [14]. However, a specific scoring method with high sensitivity and reliability in recognizing neonatal sepsis has not yet been developed. Also, there are no reports evaluating EMA, Töllner and Rodwell scores together in the literature. Therefore, in this study, EMA, Töllner, and Rodwell scores were compared in proven and clinical sepsis cases and their predictive values in the early diagnosis of the neonatal sepsis were evaluated.

Materials and methods

A total of 95 neonates who were admitted to the neonatal intensive care unit of Pamukkale University Hospital between July 2021 and July 2023, who were diagnosed with clinical or proven sepsis, and for whom parental consent was obtained, were enrolled in this study.

Newborns who had significant congenital abnormalities, proven intrauterine infection, metabolic disease, history of chorioamnionitis, preterm rupture of membranes (>18 hours), history of maternal antibiotic use in the last

week of pregnancy (except for the last 4 hours prenatally), and antibiotic use in the last 1 week with a clinical diagnosis of sepsis were not included in the study.

Complete blood count, peripheral smear, C-reactive protein (CRP), procalcitonin, blood gas and blood glucose values routinely obtained from newborn babies with sepsis were recorded. Blood culture, urine culture and cerebrospinal fluid (CSF) examination and culture obtained when necessary were recorded.

EMA scoring, Rodwell hematological scoring, and Töllner scoring were performed in each patient included in the study.

All data were evaluated with SPSS 25.0 (IBM SPSS Statistics 25, IBM Corporation, Armonk, New York, United States). Continuous variables are expressed as mean \pm standard deviation. Categorical variables are expressed as numbers and percentages.

Spearman or Pearson correlation analyses were used to analyse relationships between continuous variables. When the assumptions for parametric tests were met, the significance test for the difference between two means and one-way analysis of variance were used to analyse differences between groups; when the assumptions for parametric tests were not met, Kruskal-Wallis analysis of variance and the Mann-Whitney U test were used.

Variations between categorical parameters were assessed by Chi-square analysis. ROC analysis method was used for analysing the performance and validity of the scores.

Youden Index value was used in determining the most appropriate cut-off point as a result of ROC analysis. As a result of the examinations made with the most appropriate cut-off points

obtained from Youden Index values, the performance results were analysed by obtaining the ratio of 'Positive Expected Value and Negative Expected Value' of the scoring.

This study was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee.

Results

A total of 95 neonates with clinical or proven sepsis admitted to the neonatal intensive care unit of Pamukkale University Hospital were involved in our study. Demographic and clinical data of these infants according to clinical sepsis and proven sepsis are presented in Table 1. Table 2' EMA, Table 3' Töllner and Table 4' Rodwell scores parameters are shown. Table 5, show the positive and negative predictive values of EMA, Töllner and Rodwell scores in proven sepsis, respectively.

When comparing the demographic and clinical data between both groups, a statistically significant difference was found in birth weight, Apgar scores, age at onset of infection, early (<3 days), late (3-30 days), very late (>30 days) sepsis and length of hospital stay, while there was no other statistically important difference. Significant differences were observed between both groups in terms of respiratory evaluation, metabolic acidosis and apnea data in the Töllner score, and degenerative changes in neutrophils in the Rodwell score, which are among the parameters of the EMA score.

The positive and negative predictive values of the scoring methods for the definite diagnosis of sepsis were 21.5%, 56.3%; 31.3%, 77.8% and 100%, 77.8% for EMA, Töllner, and Rodwell scoring, respectively.

Table 1. Comparison of demographic and clinical data between two groups

	Clinical sepsis	Proven sepsis	p value	z – x ²
Total Count (n)	71	24		
Birth weight				
Mean ± SD, (gram)	2570.18±934.24	1395.20±774.45	0.001*	z:4.715
Weight according to birth week				
AGA	55 (77.5%)	17 (70.8%)		
SGA	10 (14%)	5 (20.8%)	0.733	x ² :0.622
LGA	6 (8.5%)	2 (8.4%)		
Mean birth week ± SD	35.08±5.58	30.02±4.73	0.063	z:4.506
Gender				
Girl (percentage)	27 (38.0%)	7 (29.2%)		
Boy (percentage)	44 (62.0%)	17 (70.8%)	0.434	x ² :0.613
Birth type				
C/S	65 (91.5%)	24 (100%)		
SVD	6 (8.5%)	-	0.332	x ² :2.165
Apgar Score (median, min-max)				
1 th minute	8 (4-9)	9 (6-10)		
5 th minute	9 (5-9)	8 (1-10)	0.005*	z:3.415
Age at onset of infection (day)	7	17	0.001*	z:3.871
Respiratory support (percentage)	48 (67.6%)	18 (75.0%)	0.496	x ² :0.462
Respiratory support type (percentage)				
O ₂ in newborn incubator	4 (8.3%)	1 (5.6%)		
nCPAP	27 (56.3)	4 (22.2%)		
nIPPV	11 (22.9%)	9 (50%)	0.062	x ² :7.346
Intubated PTV	6 (12.5)	4 (22.2%)		
Inotrope support	4 (5.6%)	0 (44.4%)	0.569	x ² :1.412
RDS	31 (43.7%)	15 (62.5%)	0.110	x ² :2.549
PDA	8 (28.6%)	7 (38.9%)	0.304	x ² :6.022
GM-IVH	4 (10.5%)	5 (23.8%)	0.206	x ² :4.573
Sepsis				
Early	41 (57.7%)	2 (8.3%)	0.001*	
Late	29 (40.8%)	18 (75%)	0.027*	x ² :21.83
Hospital stay ± SD, days	30.33±25.22	55.50±36.30	0.001*	z:4.736

SD: standard deviation, AGA: appropriate for gestational age, SGA: small of gestational age, LGA: large of gestational age
 C/S: caesarean section, SVD: spontaneous vaginal delivery, nCPAP: nasal continuous positive airway pressure
 nIPPV: nasal intermittent positive pressure ventilation, PTV: patient triggered ventilation, RDS: respiratory distress syndrome
 PDA: patent ductus arteriosus, GM-IVH: germinal matrix intraventricular hemorrhage, z: mann whitney u, x²: Chi-squared test
 * p<0.05 statistically significant

Table 2. Evaluation of EMA score parameters

	Clinical sepsis	Proven sepsis	p value	x ²
Body temperature				
normal	58 (81.6%)	22 (91.6%)		
>38.5	12 (16.9%)	2 (8.3%)	0.486	x ² :1.444
<36.0	1 (1.40%)	0		
Cardiovascular system				
normal	50 (70.4%)	13 (54.1%)		
arrhythmia	16 (22.5%)	10 (41.6%)		
urine <1 ml/kg/h	3 (4.2%)	0	0.101	x ² :7.762
hypotension	2 (2.8%)	0		
impaired peripheral perfusion	0	1 (4.1%)		
Skin and subcutaneous lesions				
none	70 (98.5%)	24 (100%)	1.000	x ² :0.342
sclerem	1 (1.40%)	0		
Respiratory				
normal	21 (29.5%)	6 (25%)		
apnea	7 (9.8%)	10 (41.6%)	0.002*	x ² :14.563
tachypnea	29 (40.8%)	3 (12.5%)		
increased oxygen/ventilation support	14 (19.7%)	5 (20.8%)		
Gastrointestinal				
no findings	21 (29.5%)	6 (25%)		
feeding intolerance	17 (23.9%)	10 (41.6%)	0.165	x ² :5.094
decreased absorption	26 (36.6%)	4 (16.6%)		
abdominal distension	7 (9.8%)	4 (16.6%)		
Non-specific findings				
none	50 (70.4%)	16 (66.6%)		
irritability	8 (11.2%)	3 (12.5%)	0.429	x ² :2.768
lethargy	8 (11.2%)	1 (4.1%)		
hypotonicity	5 (7%)	4 (16.6%)		
Leukocyte count				
normal	60 (84.5%)	20 (83.3%)		
<4000	1 (1.40%)	1 (4.1%)	0.710	x ² :0.684
>20000	10 (14%)	3 (12.5%)		
Immature/Total neutrophil ratio				
<0.2	18 (25.3%)	4 (16.6%)	0.576	x ² :0.760
>0.2	53 (74.6%)	20 (83.3%)		
Platelet count				
>100000	64 (90.1%)	22 (91.6%)	1.000	x ² :0.490
<100000	7 (9.8%)	2 (8.3%)		
CRP				
<15 mg/dL	48 (67.6%)	20 (83.3%)	0.192	x ² :2.181
>15 mg/dL	23 (32.3%)	4 (16.6%)		
Base deficit				
<10 mEq/L	69 (97.1%)	21 (87.5%)	0.101	x ² :3.373
>10 mEq/L	2 (2.8%)	3 (12.5%)		
Serum lactate				
<2 mMol/L	17 (23.9%)	10 (41.6%)	0.119	x ² :2.769
>2 mMol/L	54 (76.1%)	14 (58.3%)		

CRP: c-reactive protein, x2: Chi-squared test; * p<0.05 statistically significant

Table 3. Evaluation of Töllner score parameters

	Clinical Sepsis	Proven Sepsis	p value	x ²
Change in skin color				
none	64 (90.1%)	20 (83.3%)	0.500	x ² :1.386
middle	4 (5.6%)	3 (12.5%)		
evident	2 (2.8%)	1 (4.1%)		
Peripheral circulatory disorder				
none	69 (97.1%)	23 (95.8%)	1.000	x ² :0.107
damaged	2 (2.8%)	1 (4.1%)		
Hypotonia				
none	66 (92.9%)	19 (78.2%)	0.078	x ² :5.093
middle	4 (5.6%)	5 (20.8%)		
evident	1 (1.40%)	0		
Bradycardia				
none	71 (100%)	24 (100%)	-	-
Apnea				
none	54 (76%)	10 (41.6%)	0.005*	x ² :9.650
yes	17 (23.9%)	14 (58.3%)		
RDS				
none	35 (49.2%)	13 (54.1%)	0.814	x ² :0.170
yes	36 (50.7%)	11 (45.8%)		
Hepatomegaly				
none	71 (100%)	23 (95.8%)	0.253	x ² :2.990
yes	-	1 (4.1%)		
GIS finding				
none	23 (32.3%)	6 (25%)	0.612	x ² :0.462
yes	48 (67.6%)	18 (75%)		
Leukocyte				
normal	50 (70.4%)	18 (75%)	0.586	x ² :1.067
leukocytosis	20 (28.1%)	5 (20.8%)		
leukopenia	1 (1.40%)	1 (4.1%)		
Shift left				
none	56 (78.8%)	16 (66.6%)	0.273	x ² :1.457
yes	15 (21.1%)	8 (33.3%)		
Thrombocytopenia				
none	60 (84.5%)	21(87.5%)	1.000	x ² :0.128
yes	11 (15.4%)	3 (12.5%)		
Metabolic acidosis				
none	28 (39.4%)	17 (70.8%)	0.003*	x ² :11.78
pH>7.2	42 (59.1%)	5 (20.8%)		
pH<7.2	1 (1.40%)	2 (8.3%)		

RDS: respiratory distress syndrome, GIS: gastrointestinal system, x²: Chi-squared test; * p<0.05 statistically significant

Table 4. Evaluation of Rodwell score parameters

	Clinical sepsis	Proven sepsis	p value	χ^2
Total leukocyte count				
normal <5000	67 (94.3%)	20 (83.3%)		
>25 000 at birth, 12-24	1 (1.4%)	1 (4.1%)	0.243	χ^2 :2.831
>30000 per hour, >21000 after 2 nd day	3 (4.2%)	3 (12.5%)		
Total neutrophil count				
normal	47 (66.1%)	16 (75%)	1.000	χ^2 :0.002
neutrophil count increased or decreased	24 (33.8%)	8 (25%)		
Immature Neutrophil count				
normal	17 (23.9%)	4 (16.6%)	0.576	χ^2 :0.552
increased	54 (76%)	20 (83.3%)		
I/T				
normal	18 (25.3%)	4 (16.6%)	0.576	χ^2 :0.760
increased	53 (74.6%)	20 (83.3%)		
I/M				
<0.3	18 (25.3%)	4 (16.6%)	0.090	χ^2 :3.712
>0.3	53 (74.6%)	20 (83.3%)		
Degenerative changes in neutrophils				
normal	68 (95.7%)	19 (79.1%)	0.023*	χ^2 :6.415
toxic granulation	3 (4.2%)	5 (20.8%)		
Platelet count				
<150 000	13 (18.3%)	3 (12.5%)	0.753	χ^2 :0.432
>150 000	58 (81.6%)	21 (87.5%)		

I/T: immature/total neutrophil ratio, I/M: immature/maturity neutrophil ratio, χ^2 : Chi-squared test; * $p < 0.05$ statistically significant

Table 5. Sensitivity, specificity, positive and negative predictive values of the EMA, Töllner and Rodwell score

		Clinical sepsis (n)	Proven sepsis (n)	Sensitivity	Specificity	PPV	NPV
EMA scoring	Positive	62	17	70.8%	12.7%	21.5%	56.3%
	Negative	9	7				
Töllner scoring	≥5 (possible sepsis)	22	10	41.7%	69%	31.3%	77.8%
	<5 (no sepsis)	49	14				
Rodwell scoring	≥5 (sepsis)	0	5	29.4%	100%	100%	77.8%
	<3 (no sepsis)	42	12				

Discussion

In this presented study, we found the positive and negative predictive values of the scoring methods in the diagnosis of proven sepsis to be 21.5%, 56.3%, 31.3%, 77.8%, and 100%, 77.8% for EMA, Töllner, and Rodwell, respectively. As can be seen from this study, Rodwell hematological scoring appears to be the most effective scoring method in definitive sepsis detection.

To demonstrate the importance of the Rodwell hematological scoring method in the detection of neonatal sepsis, a study was conducted in India in 2009 in which 12 patients with proven sepsis, 26 patients with clinical sepsis and 12 healthy infants were included. It was found that immature/total neutrophil ratio (I:T) and immature/maturity neutrophil ratio (I:M) were the highest sensitive parameters in defining neonates with sepsis [15]. A study was conducted in India in April-July 2011 to evaluate and emphasise the importance of the Rodwell hematological scoring method in the rapid detection of neonatal sepsis. A total of 110 infants with proven sepsis (n=42), clinical sepsis (n=22) and control group (n=46) were included in the study. Immature polymorphonuclear neutrophil (PMN) count was found to be the highest sensitive (96.87%) and I:M PMN ratio the most specific (97.22%) indicator. It has been shown that hematological sepsis scoring has a much higher sensitivity and specificity in premature than in term newborns [16]. In our study, we did not detect any differences in ratio of I:M and I:T and did not divide the groups into term and premature infants however, we noticed that the change in the direction of toxic granulation in neutrophils in the Rodwell hematological scoring method could be evaluated in favour of proven sepsis.

A multicentre prospective methodological study was conducted in Türkiye between October 2015 and November 2018 to evaluate the adequacy of EMA sepsis criteria in the definition of neonatal sepsis. A total of 245 infants over 34 weeks of age who met the EMA criteria or suspected sepsis were accepted into the trial. In 97 infants, EMA criteria were found to be positive, and 113 patients were diagnosed with proven sepsis. The sensitivity,

specificity, and accuracy of the EMA criteria for proven sepsis were 44.2%, 64.4%, and 55.1%, respectively [17]. In our study, we found the positive and negative predictive values of EMA scoring method in the diagnosis of definite sepsis to be 21.5% and 56.3%.

In a study published in Indonesia in 2022, which included forty-seven newborns, the positive predictive value of Töllner score in the diagnosis of neonatal sepsis was 91.7% and the negative predictive value was 87.5% [18]. In contrast to the high positive and negative predictive value according to Indonesia study, we found a positive predictive value of 31.3% and a negative predictive value of 77.8% for the Töllner score in our study.

To our knowledge, there is no any publication included a comparison of all three sepsis scoring methods including EMA, Töllner, and Rodwell used to diagnosis for the neonatal sepsis. Therefore, our study is the first study to comperison all three sepsis scoring methods. The primary limit of this research was the restricted number of patients and the lack of a healthy control group.

In conclusion, our study showed that clinical assessment and routine laboratory tests are limited in the definition of neonatal sepsis and that the Rodwell hematological score is more accurate in detecting proven sepsis than the other two scoring methods. It is urgently needed to find more sensitive and more specific scoring methods or biological parameters for earlier recognition of neonatal sepsis, which is an important cause of morbidity and mortality. For this, additional large-scale randomised controlled trials with long-term results are needed.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors' contributions to the article

O.M.A.O. and B.E. constructed the main idea and hypothesis of the study. Discussion section of the article written by M.T. O.M.A.O. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.