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COMPARISON OF DIFFERENT SCORING SYSTEMS AS PREDICTORS OF THE SEVERITY OF LEPTOSPIROSIS

POREĐENJE RAZLIČITIH SKORING SISTEMA KAO PREDIKTORA TEŽINE KLINIČKE SLIKE OBOLELIH OD LEPTOSPIROZE

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Summary

Introduction. Leptospirosis is a zoonotic disease in which 10% of patients develop a severe form that leads to multiorgan dysfunction. Therefore, early identification of high-risk patients is crucial. Existing scoring systems, along with newer ones, can aid in this identification. The study aims to compare the effectiveness of various scoring systems as predictors of severe leptospirosis. **Material and Methods.** This retrospective study included 45 patients, divided into two groups: those with a mild form of the disease and those with a severe form requiring intensive treatment. Demographic, clinical and laboratory parameters were compared between the groups. The scoring systems were evaluated for their effectiveness as predictors of the severity of the clinical presentation. **Results.** Eleven patients (24.4%) developed a severe form of leptospirosis. These patients exhibited significantly higher levels of urea (p=0.001), creatinine (p=0.007), total (p=0.009) and direct bilirubin (p=0.006), and lower levels of hemoglobin (p=0.00) and hematocrit (p=0.00). The Sequential Organ Failure Assessment score emerged as the most statistically significant predictor of severe leptospirosis. **Conclusion.** While The Sequential Organ Failure Assessment score proved to be the best predictor of the severity of the clinical presentation, the QuickLepto score and the scoring system that includes three criteria – hypotension, oliguria and respiratory abnormalities – also have their practical significance. These symptoms are based on clinical criteria that can be assessed upon admission.

Key words: Leptospirosis; Systemic Inflammatory Response Syndrome; Organ Dysfunction Scores; Predictive Value of Tests; Severity of Illness Index; Early Diagnosis

Sažetak

Uvod. Leptospiroza je svetski rasprostranjena zoonoza koja se manifestuje različitom kliničkom slikom. Samo 10% obolelih razvija tešku formu bolesti koja dovodi do multiorganske disfunkcije zbog čega je rana identifikacija visokorizičnih pacijenata veoma važna. U tome nam mogu pomoći već postojeći, ali i noviji skoring sistemi. Stoga je cilj našeg rada bio da uporedimo efikasnost različitih skoring sistema kao prediktore teškog oblika leptospiroze. **Materijal i metode.** Retrospektivna studija je obuhvatila 45 pacijenata koji su podeljeni u dve grupe − na pacijente sa lakšim oblikom bolesti koji nisu zahtevali mere intenzivnog lečenja i na one sa teškim oblikom bolesti koji to jesu zahtevali. Upoređivani su demografski, klinički i laboratorijski parametri između ove dve grupe pacijenata. Međusobno su poređeni skoring sistemi kao prediktori težine kliničke slike obolelih od leptospiroze. **Rezultati.** Jedanaest pacijenata (24,4%) razvilo je težak klinički oblik bolesti. Kod pacijenata koji su razvili težak oblik bolesti značajno su više vrednosti uree (p = 0,001), kreatinina (p = 0,007), ukupnog (p = 0,009) i direktnog bilirubina (p = 0,006), odnosno značajno su niže vrednosti hemoglobina (p = 0,00) i hematokrita (p = 0,00). Kao statistički najznačajniji prediktor težine kliničke slike obolelih od leptospiroze pokazao se *The Sequential Organ Failure Assessment* skor. **Zaključak.** Iako se *The Sequential Organ Failure Assessment* skor pokazao kao najbolji prediktor težine kliničke slike obolelih od leptospiroze, *QuickLepto* skor i skoring sistem koji obuhvata tri kriterijuma – hipotenziju, oliguriju i respiratorne abnormalnosti imaju svoj praktični značaj s obzirom da su bazirani na kliničkim kriterijumima koji se mogu oceniti pri samom prijemu bolesnika na lečenje.

Ključne reči: leptospiroza; sindrom sistemskog inflamatornog odgovora; skorovi disfunkcije organa; prediktivna vrednost testova; indeks težine kliničke slike; rana dijagnoza

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Introduction

Leptospirosis is a systemic bacterial infection caused by a spirochete belonging to the genus *Leptospira* [1]. Literature indicates that 10% of patients with leptospirosis develop a severe form of the disease, characterized by high leptospiremia, multiorgan dysfunction, and a dramatic increase in mortality, akin to sep-

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Abbreviations

SIRS – Systemic Inflammatory Response Syndrome
SOFA score – Sequential Organ Failure Assessment score
SPiRO – Systolic blood Pressure, Respiratory auscultation abnormalities, Oliguria

sis [2]. Weil's syndrome is the most severe manifestation, accompanied by jaundice, azotemia, bleeding, anemia and impaired consciousness [3]. Mortality from this disease remains high, often due late diagnosis stemming from an atypical clinical presentation [4]. Early identification of high-risk patients is crucial for timely intervention, which can reduce complications and mortality [5]. Traditional scoring systems for assessing multiorgan dysfunction in sepsis, such as the SIRS criteria (Systemic Inflammatory Response Syndrome criteria) and the SOFA score (Sequential Organ Failure Assessment score), have not proven to be reliable predictors of outcomes in leptospirosis patients [6]. Consequently, researchers have developed new scoring systems such as the QuickLepto score and the SPiRO score (Systolic blood Pressure ≤100 mmHg, Respiratory auscultation abnormalities, Oliguria), to swiftly identify high-risk patients and expedite their referral to intensive care units [7,8]. The study aims to compare the effectiveness of these existing and new scoring systems as predictors of severe leptospirosis.

Material and Methods

This retrospective study included 45 patients diagnosed with leptospirosis and treated at the Clinic for Infectious Diseases of the University Clinical Center of Vojvodina in Novi Sad from January 2008 to August 2017. The study received approval from the Ethics Committee for Clinical Trials on Humans of the Clinical Center of Vojvodina (approval number 00-20/68).

Data were obtained from the patients' medical records, encompassing demographic (gender, age), epidemiological data, and clinical symptoms (myalgia, jaundice, oliguria, gastrointestinal complaints, changes in mental status, cough) observed at the time of admission. Clinical findings included tachycardia, tachypnea, and signs of hemorrhagic syndrome. Furthermore, data on the causative agent were collected.

Laboratory parameters monitored were complete blood count, hemoglobin, hematocrit, C-reactive protein (CRP), fibrinogen, procalcitonin, liver function indicators (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma–glutamyl transferase (GGT), alkaline phosphatase (ALP), total and direct bilirubin), renal function indicators (urea, creatinine, sodium, potassium and chloride), creatinine phosphokinase (CPK), and prothrombin time (PT) at hospital admission.

The diagnosis of leptospirosis was established on the basis of clinical, laboratory, and epidemiological data and confirmed by serological tests, including microscopic agglutination, ELISA test, and PCR diagnostics.

Patients were divided into two groups: those with a mild form of the disease who did not require intensive treatment and those with a severe clinical form who did. A severe form of the disease was defined as shock requiring vasoactive support, acute renal failure requiring hemodialysis, need for blood product transfusion, acute pulmonary failure requiring mechanical ventilatory support, admission to the intensive care unit, or death [7, 9].

Five scoring systems were used to predict severe leptospirosis: SIRS criteria, SOFA and qSOFA scores, SPiRO score, and QuickLepto score.

The SIRS diagnosis is based on the Centers for Disease Control and Prevention (CDC) criteria: body temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 respirations/min or PaCO2 <32 mmHg, leukocytes >12,000 cells/mm^3 or <4,000 cells/mm^3 or >10% immature forms of white blood cells [10]. Patients meeting two or more SIRS criteria were defined as having SIRS [11].

The SOFA score assesses the function of six organ systems (PaO_2/FiO_2, platelet count, bilirubin value, hypotension, Glasgow Coma Score, creatinine or diuresis value), with each system scored from 0 (no functional impairment) to 4 (severe functional impairment). Individual scores are summed to obtain a total score ranging from 0 to 24 [12]. The qSOFA score is a simplified version of the SOFA score, using blood pressure (SBP <100 mmHg), respiration rate (RR >22 respirations/min), and mental status (GCS <15) as criteria [13].

The SPiRO score, formulated by Smith and colleagues [7], includes three criteria: oliguria (urine output <500 ml in 24h), abnormal lung auscultation findings, and hypotension (SBP <100 mmHg). Each criterion scores 1 point, with a SPiRO score >1 indicating a severe form of the disease.

Galdino and colleagues [8] developed the QuickLepto score, which uses criteria including age (>40 years), mental status disorder, respiratory problems (cough, abnormal lung auscultation findings, or hemoptysis), mean arterial pressure <80 mmHg, and hematocrit <30%. Each criterion is scored 1 point, except for age, which scores 2 points.

Data processing and statistical analysis were performed using IBM SPSS Statistics version 23.0. The χ^2 test was used to determine the statistical significance of differences between categorical variables. The distribution and variance homogeneity of continuous variables were checked, revealing significant deviations from normal distribution and inhomogeneous variances. Therefore, mean values are presented as median and interquartile range, and the non-parametric Mann-Whitney test was used to compare two groups (mild and severe forms). ROC curves were constructed to assess the predictive significance of each scoring system in predicting severe diseases, and the area under the ROC curve was determined. A p-value <0.05 was considered statistically significant.

Results

During the observed period, 45 cases of leptospirosis were recorded at the University Clinical Center of Vojvodina. The vast majority of patients

Table 1. Age, comorbidities, clinical symptoms and causative agents (serological types of Leptospirosis) in patients with mild and severe forms of the disease
Tabela 1. *Godine života, komorbiditeti, klinički simptomi i uzročnici (seroloski tipovi Leptospiroze) kod bolesnika sa lakšim i težim oblikom bolesti*

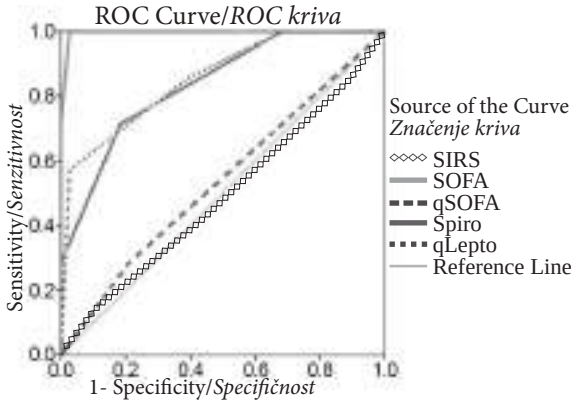
Parameter *Parametar*	Mild form/*Lakši oblik* n=34; n (%)	Severe form/*Teži oblik* n=11; n (%)	p value *p–vrednost*
Age/*Godine života*	49.0 (35.7-61.0)	54.0 (45.0-65.0)	0.285
Diabetes mellitus/*Dijabetes*	4 (57.1%)	3 (42.9%)	0.217
Hypertension/*Hipertenzija*	6 (17.6%)	3 (27.3%)	0.488
Other comorbidities/*Drugi komorbiditeti*	2 (66.7%)	1 (33.3%)	0.711
Hemorrhagic syndrome/*Hemoragijski sindrom*	13 (81.3%)	3 (18.8%)	0.509
Myalgia/*Bolovi u mišićima*	30 (78.9%)	8 (21.1%)	0.217
Jaundice/*Žutica*	20 (71.4%)	8 (28.6%)	0.408
Vomiting/*Povraćanje*	9 (75%)	3 (25%)	0.958
Diarrhea/*Dijareja*	4 (57.1%)	3 (42.9%)	0.217
Stomach pain/*Bol u stomaku*	3 (60%)	2 (40%)	0.391
Oliguria/*Oligurija*	**16 (64,0)**	**9 (36%)**	**0.044**
L. grippotyphosa	7 (100%)	0 (0%)	
L. icterohemorrhagica	3 (75%)	1 (25%)	
L. Bratislava	11 (73.3%)	4 (26.7%)	0.215
L. unspecified	11 (78.6%)	3 (21.4%)	
Other/*Drugi*	2 (40%)	3 (60%)	

Table 2. Presentation of laboratory parameters in patients with severe and mild forms of leptospirosis, and length of hospitalization and days until diagnosis
Tabela 2. *Prikaz laboratorijskih parametara kod pacijenata sa težim i lakšim oblikom leptospiroze kao i dužine hospitalizacije i dana do postavljanja dijagnoze*

Parameter *Parametar*	Mild form/*Lakši oblik* n=34; n (%)	Severe form/*Teži oblik* n=11; n (%)	p value *p–vrednost*
Leukocytes (x10^9)/*Leukociti*	9.05 (6.76-13.15)	11.11 (9.33-17.6)	0.162
Hemoglobin (g/L)/*Hemoglobin*	129.5 (118.0-136.25)	98.0 (90.0-119.0)	0.00
Hematocrit/*Hematokrit*	**0.37 (0.35-0.39)**	**0.29 (0.28-0.34)**	**0.00**
Platelets (x$10^{9)}$/*Trombociti*	**79.5 (38.4-203.5)**	**52.0 (32.0-374.0)**	**0.937**
CRP (mg/L)/*C-reaktivni protein*	158.,0 (83.82-193.85)	80.4 (13.6-142.0)	0.042
Fibrinogen (g/L)	6.18 (5.33-7.99)	4.68 (3.95-8.89)	0.297
PCT (ng/mL)	3.08 (0.67-8.04)	3.74 (1.36-28.55)	0.621
ALT (U/L)	70.5 (48.25-150.75)	82.0 (44.0-138.0)	0.741
AST (U/L)	59.0 (43.75-113.0)	105.0 (33.0-149.0)	0.468
GGT (U/L)	114 (65-238)	64.0 (43.0-103.0)	0.042
ALP (U/L)	97 (71.25-140.50)	132.0 (75.0-195.5)	0.189
LDH (U/L)	433 (237-619.25)	606.0 (292.5-850.5)	0.369
Total bilirubin (μmol/L)/*Ukupni bilirubin*	**55.55 (17.0-147.97)**	**204.6 (100.0-282.0)**	**0.009**
Direct bilirubin (μmol/L)/*Direktni bilirubin*	**30.35 (6.67-111.7)**	**170.0 (69.0-259.8)**	**0.006**
CPK (U/L)	321.0 (149.0-749.0)	410.0 (87.0-1798.0)	0.983
PT (sec)	1.020 (0.935-1.117)	1.030 (0.900-1.210)	0.751
Urea (mmol/L)	**10.35 (6.75-15.30)**	**23.90 (15.90-39.00)**	**0.001**
Creatinine (mmol/L)/*Kreatinin*	**126.0 (99.75-247.75)**	**353.0 (176.0-722.0)**	**0.007**
Sodium (mmol/L)/*Natrijum*	138.5 (135.75-142.0)	136.0 (133.0-141.0)	0.213
Potassium (mmol/L)/*Kalijum*	3.80 (3.49-4.17)	3.90 (3.20-4.20)	0.781
Chloride (mmol/L)/*Hlorid*	105.0 (101.0-110.0)	103.0 (95.0-110.0)	0.475
Days to diagnosis (day)/*Dani do postavljanja dijagnoze*	5.0 (4.0-8.0)	7.0 (5.0-8.25)	0.228
Length of hospitalization (day)/*Dužina hospitalizacije*	14.5 (11.0-21.0)	17.0 (8.0-25.0)	0.874

Table 3. Comparison of scoring systems as predictors of the severity of clinical presentation of patients with leptospirosis
Tabela 3. *Međusobno poređenje skoring sistema kao prediktore težine kliničke slike obolelih od leptospiroze*

	AUC ROC curve *AUC ROC kriva*	p value *p–vrednost*	95%CI *95%CI*	Optimal cut-off *Optimalni presek*	Sensitivity *Senzitivnost*	Specificity *Specifičnost*
SOFA	**0.996**	**<0.001**	0.914-1.000	>9	100%	97.37%
qSOFA	0.538	0.757	0.383-0.687	–	–	–
SIRS	0.509	0.940	0.356-0.661	–	–	–
SPiRO	**0.836**	**<0.001**	0.696-0.930	>1	71.43	81.58
QuickLepto	**0.855**	**<0.001**	0.718-0.942	>3	57.14	97.37



Graph 1. AUC ROC curves of observed scoring systems
Grafikon 1. *AUC ROC krive posmatranih skoring sistema*

were male (44/45, 97.8%), with only one female patient (1/45, 2.2%).

According to the criteria mentioned, 11 patients (24.4%) had a severe form of the disease, while 34 patients (75.6%) had a milder form. Hemodialysis was required in 6 patients (13.3%), blood transfusion in 8 patients (17.8%), intensive care unit treatment and mechanical ventilation support in 3 patients (6.7%), and vasoactive support in 1 patient (2.2%). There were 2 recorded deaths (4.4%).

A positive epidemiological survey was present in 9 out of 11 patients (81.8%) with a severe form of leptospirosis, and in 28 out of 34 patients (82.4%) with a milder form (p=0.968). Exposure factors were similar between groups, with fishing (16/34 patients (47.1%) with mild form and 5/11 patients (45.5%) with severe form) and swimming in stagnant water (8/34 patients (23.5%) with mild form and 2/11 patients (18.2%) with severe form) being the most common. Other risk factors, such as professional exposure in agriculture (2/34 mild form and 0/11 severe form) and animal husbandry (2/34 mild form and 1/11 severe form) were less prevalent. No statistically significant difference was found in the severity of the clinical picture concerning exposure (p=0.552).

Patients with severe leptospirosis were slightly older than those with a milder form, but this difference was not statistically significant (p=0.285). There was no statistically significant difference in comorbidities (diabetes mellitus, arterial hypertension and other comorbidities) between patients with mild and severe forms of leptospirosis **(Table 1).**

Analyzing clinical symptoms at admission, oliguria was more common in patients with severe leptospirosis (p=0.044), while the other symptoms did not show statistical significance **(Table 1).**

Although not statistically significant, the highest percentage of severe disease (3/5 patients, 60.0%) was caused by Leptospira Australis and Leptospira Harggio. Conversely, Leptospira grippotyphosa led to only a mild disease (7/7 patients, 100.0%) (**Table 1**).

Patients with severe leptospirosis had statistically significantly higher values of urea (p=0.001), creatinine (p=0.007), total bilirubin (p=0.009) and direct bilirubin (p=0.006), and statistically significantly lower values of hemoglobin (p=0.00) and hematocrit (p =0.00) compared to patients with mild leptospirosis (**Table 2)**.

There was no statistically significant difference in the length of hospitalization or the days from hospitalization to diagnosis between patients with mild and severe disease **(Table 2).**

To identify the best predictor of disease severity in leptospirosis, five different scoring systems (SOFA score, qSOFA score, SIRS, SPiRO score, and QuickLepto score) were compared **(Table 3).**

The SOFA score, SPiRO score, and QuickLepto score were statistically significant predictors of severe leptospirosis, whereas qSOFA and SIRS were not.

Comparing the AUC ROC values **(Graph 1)** between the SOFA, SPiRO, and QuickLepto scores showed that the SOFA score had the highest AUC ROC value, making it a statistically significantly better predictor than the SPiRO score (p=0.036). Although the SOFA score had a larger AUC ROC, the difference compared to the QuickLepto score was not statistically significant (p=0.074). Additionally, there was no statistically significant difference between the QuickLepto score and SPiRO scores (p=0.725).

Discussion

Leptospirosis is a globally prevalent zoonosis, posing significant challenges, particularly in underdeveloped countries [14]. While most patients exhibit asymptomatic or mild form, a minority experience severe immune responses, leading to cytokine storms and multiorgan dysfunction [2]. Given the similarities in pathophysiology and clinical mani-

festations with sepsis, the SIRS criteria and SOFA score (including qSOFA) are commonly used to predict the severity of leptospirosis. Recent studies have focused on developing new scoring systems to enable rapid diagnosis and prognosis of leptospirosis, and to determine the need for intensive care.

In our study, patients were categorized into two groups: those with mild forms (not requiring intensive care) and those with severe forms. Our findings indicated no statistically significant difference in age, comorbidities, length of hospitalization, and the causative Leptospira serotype between the groups. However, patients with severe forms had statistically significantly lower hemoglobin and hematocrit values and higher levels of urea, creatinine, direct and indirect bilirubin. Oliguria was also more common in severe cases. These observations are consistent with a study in Turkey [15], which found that SIRS positive patients (with severe leptospirosis) had statistically significantly higher leukocyte ($p=0.002$) and serum creatinine ($p<0.001$) levels, that vomiting ($p=0.046$) and abdominal pain were significantly more frequent ($p= 0.025$), and more frequent changes on chest X-ray ($p=0.003$). Different clinical manifestations of the disease may be a consequence of the different sample and different representation of serotypes, considering that different serotypes of Leptospira cause different clinical presentations [16].

Our results demonstrated that the SOFA score is a superior predictor of disease severity compared to the SIRS criteria and the qSOFA score ($p <0.001$). This aligns with other studies favoring the SOFA score over SIRS criteria [17–21] for predicting severe outcomes. On the other hand, some studies underscore the sensitivity of SIRS criteria [22, 23]. Our results are supported by the fact that, besides infection and sepsis, many non-infectious processes (e.g. pancreatitis, ischemia, multiple trauma, hemorrhagic shock) [25] can lead to systemic inflammatory response syndrome [24], making the SIRS criteria rather non-specific scoring system.

The SPiRO score, another recent scoring system, has shown promise as a predictor of severe leptospirosis. Smith and colleagues [7] conducted a study comparing the SPiRO score to the qSOFA score, finding that the SPiRO score was a statistically significantly better predictor of the severity of leptospirosis ($p=0.003$). The SPiRO score is also supported by numerous studies identifying hypotension, oliguria, and abnormal lung findings as predictors of severe leptospirosis [25–28]. Our research corroborates these findings, demonstrating that the SPiRO score is a statistically significantly superior tool for predicting severe clinical presentations compared to the qSOFA score. However, it did not outperform the SOFA score, which, based on our results, remains the best scoring system for predicting the severity clinical presentations of patients with leptospirosis.

The QuickLepto score is another emerging tool for predicting severe leptospirosis. Our findings indicated that the qLepto score is a better predictor than qSOFA score and SIRS criteria, though not statistically significantly different from the SOFA score ($p=0.074$) or SPiRO score ($p=0.725$). A similar study was conducted in March 2023 [8], comparing the newly developed LeptoScore and qLepto score with widely used scoring systems like SPiRO and qSOFA. Their results indicated that the SPiRO and qSOFA scores have low specificity and sensitivity for leptospirosis patients, making their performance inferior to LeptoScore and qLepto score.

While these studies suggest that SPiRO and qLepto scores are advantageous for predicting the severity of leptospirosis, our research found the SOFA score to be superior. The practical application of the SPiRO and qLepto scores remains noteworthy. Both scoring systems, particularly the SPiRO score, rely on clinical criteria that can be assessed upon patient admission. This is especially useful in rural areas where leptospirosis is more prevalent and laboratory diagnostics are limited. Furthermore, the availability of radiological methods and the expertise required for interpreting these findings are often lacking in such areas, making the SPiRO and qLepto scores highly valuable for quick and effective patient assessment.

A limitation of our study is its retrospective nature, leading to some missing patient information. Additionally, leptospirosis is not widespread in Serbia, resulting in a small sample size.

Currently, several scoring systems can predict the severity of leptospirosis quickly and easily based on criteria available during hospitalization. While different studies favor different systems, their use is crucial in managing and treating patients, particularly in resource-limited areas where the disease is prevalent.

Conclusion

Although the Sequential Organ Failure Assessment score proved to be the best predictor of leptospirosis severity, the **S**ystolic blood **P**ressure, **R**espiratory auscultation abnormalities, **O**liguria and the QuickLepto scores also have practical significance. These scores rely on clinical criteria that can be assessed upon admission, making them particularly useful in underdeveloped regions where leptospirosis is widespread.

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