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ORIGINAL PAPER

The "MICE" scoring system in differentiating the identical twins leptospirosis and hantavirus infection

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Abstract

Purpose To develop a practical scoring system to assist clinicians in differentiating leptospirosis and hantavirus infections, whose epidemiological, clinical, and laboratory characteristics are literally like identical twins.

Methods The study population consisted of 162 patients admitted to hospital with a confirmed diagnosis of leptospirosis (LG group, $n=92$) and hantavirus infections (HG, group = 70) between January 2000 and January 2019. The two groups were compared in terms of demographic, clinical and laboratory features. Sensitivity, specificity, and positive and negative predictive values were determined from ROC analysis for findings of significance in the diagnosis of leptospirosis, and a scoring system for diagnosis was developed ("MICE" score). During the development of this scoring system, we were careful to employ parameters that would not affect one another statistically, to reflect the involvement of very different systems (such as the hematological, hepatic, renal, and musculoskeletal systems) due to the multisystemic effect of the disease in the organism, and to ensure that the system should be simple to apply and understand. Accordingly, five parameters, serum WBC, creatinine, creatine kinase, total bilirubin, and C-reactive protein, were employed in the "MICE" scoring system.

Results Three cut-off values were determined using ROC analysis for the five parameters included in the MICE system. Accordingly, scores of 0, 1, or 2 were given based on the values WBC (/μL): ≤ 7500, 7500–15,000, and > 15,000; total bilirubin (mg/dL): ≤ 3, 3–10, and > 10; CRP (mg/dL): ≤ 5, 5–15, and > 15; creatinine (mg/dL): ≤ 1.5, 1.5–3, and > 3; CK (U/L): ≤ 500, 500–1000, > 1000. AUC was calculated as 0.964 at ROC analysis, while the most noteworthy cut-off point was obtained when MICE score was ≥ 3, exhibiting 93.5% sensitivity, 92.9% specificity, PPV 94.5% and NPV 91.5%. A test score ≥ 3 was regarded as positive. In addition, our patients were evaluated using other current scoring systems in addition to "MICE," and our scoring system exhibited a greater diagnostic power in our subjects.

Conclusions Leptospirosis and hantavirus infections can be accurately predicted by the MICE scoring system. Early diagnosis and rational treatment will also help to lower the mortality rates in these diseases.

Keywords Leptospirosis · Hantavirus infection · Identical twins · MICE scoring system

Introduction

Vector-mediated zoonoses are increasingly important infections, and important problems still persist concerning their diagnosis. Factors such as the lack of gold standard diagnostic techniques, and problems with the sensitivity and specificity of tests and their time-consuming nature may result in delayed diagnosis and treatment, thus increasing the risk of mortality [1, 2].

Leptospirosis and hantavirus infections are some of the most common zoonotic diseases worldwide [2, 3]. They also merit their notoriety since they can proceed in the form of outbreaks and cause significant mortality [1, 2]. Mortality rates of 5–30% in cases of leptospirosis can exceed 70% in Weil's disease [4]. Mortality rates as high as 40%, closely dependent on the clinical form and subtype, have been reported in hantavirus cases [5]. These infections are also seen in Turkey, as well as in many other parts of the world, and particularly in our own region [5, 6]. With a climate and habitat ideally suited to rodent life, our region also provides

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suitable epidemiological conditions for both diseases, with abundant rainfall and occasional flooding disasters [6].

Hantavirus infection is the most commonly encountered disease in clinical practice, and perhaps exhibits the widest variety of symptoms [7]. It may be difficult to differentiate these two infections at first sight, since their epidemiological, clinical, and laboratory findings are very similar, and very different symptoms may also be seen simultaneously [8, 9]. In addition to hantavirus infections, the differential diagnosis of leptospirosis includes a wide group of diseases such as Dengue fever, rickettsiosis, influenza, typhoid fever [7–9]. However, other diseases apart from hantavirus also needing to be considered at differential diagnosis were excluded in our patients using clinical and/or laboratory methods. This study, therefore, examined cases diagnosed as leptospirosis or hantavirus infections and followed up by our clinic over a period approaching two decades.

The aim of this study was to perform differential diagnosis with hantavirus infections, which are the most difficult to differentiate from leptospirosis in clinical practice, and to assist physicians treating these diseases by revealing the distinguishing characteristics of the two conditions from initial evaluation. Very few studies have evaluated the data for the two diseases together. The present research is also the first from Turkey in this field [10, 11].

Methods

Study design and settings

This observational cohort study was performed retrospectively at our hospital and in compliance with the principles of the Helsinki Declaration. Hospital Ethical Committee approval (Protocol number: 2019/207) was granted before commencement. The study population consisted of 162 patients admitted to hospital with a diagnosis of leptospirosis (L-group: LG, 92 patients) and hantavirus infections (H-group: HG, 70 patients) between January 2000 and January 2019.

Inclusion and exclusion criteria

Cases diagnosed with proven/probable leptospirosis according to the CDC criteria or with hantavirus infection confirmed by serologic tests were included in the study.

Other diseases, such as Dengue fever, rickettsiosis, influenza, encephalitis, poliomyelitis, glandular fever, infectious mononucleosis, brucellosis, malaria, viral hepatitis, pneumonitis, HIV infection, and typhoid fever needing to be considered at differential diagnosis were excluded from the study. Pregnant women and subjects under the age of 18 were also excluded.

Diagnosis of leptospirosis and hantavirus infections

Serum specimens collected for diagnosis were sent to the National Reference and Research Laboratory under appropriate transport conditions and were tested on the day of arrival. The laboratory performed two tests recommended in routine diagnosis for hantavirus infections. The presence of hantavirus IgM and G antibodies was first investigated using the immunofluorescent assay (IFA) technique in a 1:100 serum dilution with hantavirus mosaic-1 (Euroimmun AG, Lübeck, Germany) kits for scanning purposes, in line with the manufacturer's instructions. Positivity was corroborated using the immunoblot test [Hanta Profile 1 EUROLINE (Euroimmun AG)]. All tests were conducted in line with the manufacturer's recommendations. Leptospirosis was confirmed by means of the microagglutination test (MAT) at the Microbiology Laboratory of the Etlik Central Veterinary Research Institute, Ankara, Turkey. In accordance with the criteria set out by the Centers for Disease Control and Prevention (CDC) in 2013, "confirmed cases" were defined as a leptospira agglutination titer of ≥ 800 by MAT in one or more serum specimens, or a fourfold or greater increase in *Leptospira* agglutination titers between acute- and convalescent-phase serum specimens investigated at the same laboratory. Leptospira agglutination titers of ≥ 200 but < 800 at MAT in one or more serum specimens, or detection of IgM antibodies (VIRION ALISA; Institut, Virion GmbH, Würzburg, Germany) against leptospira in an acute phase serum specimen were regarded as supportive findings. Cases with supportive findings or involvement in an exposure event (such as adventure trekking, triathlon, or flooding disasters) with known associated cases were regarded as 'probable' cases. On that basis, three quarters of our cases were in the 'probable' category.

Statistical analysis

All the studied variables were subjected to descriptive statistical analysis. Data elicited from measurement of normal distribution were analyzed using the Kolmogorov–Smirnov test. Data were analyzed using the Mann–Whitney *U* test. Data obtained by measurement are expressed as mean ± standard deviation, while those elicited by counting are expressed as numbers (%). Analysis was applied using the chi-square test. The area beneath the receiver operating characteristics (ROC) curve was applied to determine the capability of various laboratory values to identify patients with leptospirosis. Sensitivity, specificity, negative predictive values (NPVs), and positive predictive values (PPVs) were calculated for these markers on the basis of ROC curves. $p < 0.05$ was regarded as statistically significant.

MICE scoring system

Five parameters identified as exhibiting statistically significant variation were scored between 0 and 2 in terms of their contribution to diagnosis based on the area under the ROC curve (AUC) and odds ratio (OR) values. The "MICE" scoring system was obtained by subjecting the total score obtained to ROC analysis and determined criteria and cut-off points to be used in differentiating the two diseases. Care was taken in establishing this scoring system to select parameters that would not affect one another statistically, to reflect the involvement of very different systems (such as hemostatic, hepatic, renal, and musculoskeletal systems) due to the multisystemic effect of the disease in the organism, and that the system should be easy to apply and understand. Accordingly, serum WBC, creatinine, CK, total bilirubin and CRP values were used in the MICE scoring system. All parameters were divided into three cut-off values based on ROC analysis. These cut-off values were scored 0, 1 and 2 for each parameter and were subjected to calculation to establish MICE scores (Table 1).

Results

Demographic features

LG consisted of 92 cases diagnosed with leptospirosis, and HG of 70 cases of hantavirus. Sixty-five (70.7%) of the cases in LG were men and 27 (29.3%) were women, while 37 (52.9%) of the cases in HG were men and 33 (47.1%) were women ($p = 0.031$). Mean ages were 47.7 ± 17 in LG and 48.1 ± 15.7 in HG ($p = 0.884$). All factors such as living in regions where the disease is endemic, engagement in high-risk occupations and activities in terms of disease, and/or a history of contact with rodents were evaluated as history positivity. Accordingly, such history was present in 63/92 (68.4%) cases in LG and 40/70 (57.1%) in HG.

Table 1 Calculation table representing the basis of the "MICE" scoring system

Parameter	Value	Score
WBC (/μL)	≤ 7500	0
	7500–15,000	1
	> 15,000	2
Total bilirubin (mg/dL)	≤ 3	0
	3–10	1
	> 10	2
CRP (mg/dL)	≤ 5	0
	5–15	1
	> 15	2
Creatinine (mg/dL)	≤ 1.5	0
	1.5–3	1
	> 3	2
CK (U/L)	≤ 500	0
	500–1000	1
	> 1000	2

WBC white blood cell, *CRP* C-reactive protein, *CK* creatine kinase

Clinical findings

Fever, listlessness, nausea-vomiting, and myalgia were the most common symptoms in both groups. Nausea-vomiting was more prevalent in the leptospirosis patients (80.4% vs 58.6%, $p = 0.004$). Prevalences of arthralgia, conjunctival suffusion, impaired consciousness, jaundice, hemorrhage, and cough differed significantly between the two groups. Only conjunctival suffusion was significantly more prevalent in HG, the others being significantly more prevalent in LG. Abdominal pain/diarrhea was less common then the other symptoms, but was still observed in 41.8% of cases in LG and in 35.7% of those in HG.

Laboratory characteristics

In terms of laboratory results, significant differences were determined between the two groups' serum leukocyte count (WBC), erythrocyte sedimentation rate (ESR), hemoglobin (Hb), Blood urea nitrogen (BUN), creatinine, total and direct bilirubin, alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), creatine kinase (CK), myoglobin, sodium (Na), prothrombin time (PT), activated partial thromboplastin time (aPTT), C-reactive protein (CRP) and procalcitonin (PCT) values. Of these, only Na, aspartate transaminase (AST) and aPTT values were higher in HG, the other parameters all being higher in LG (both groups' epidemiological, clinical, and laboratory characteristics are shown in Table 2).

Time from onset of symptoms to hospitalization, dialysis requirements, and prognostic outcomes

Time elapsed from onset of symptoms to admission was 6.0 ± 3.2 days in LG, and 2.8 ± 1.9 days in HG ($p < 0.001$). Dialysis was required in 23.6% patients in LG, and in 7.1% in HG, the difference being statistically significant ($p = 0.019$). Intensive care support requirements were 9.6% in LG, and 2.9% in HG, and the difference was not statistically significant. Survival was 90.2% in LG, and 95.7% in HG. The difference was not significant.

Table 2 Demographic, clinical and laboratory characteristics of the leptospirosis and hantavirus infection cases

	Leptospirosis group (LG) $n=92$	Hantavirus group (HG) $n=70$	p
Female	29.3%	47.1%	**0.031**
Male	70.7%	52.9%	
Mean age	47.7 ± 17	48.1 ± 15.7	0.884
Epidemiological history	67.4%	57.1%	0.187
Fever	90.2%	87.1%	0.566
Nausea-vomiting	80.4%	58.6%	**0.004**
Arthralgia	56.5%	20%	**< 0.001**
Myalgia	62.0%	57.1%	0.647
Headache	47.3%	55.7%	0.449
Fatigue	87.3%	88.6%	1.000
Conjunctival hyperemia	20.7%	55.7%	**< 0.001**
Nuchal rigidity	1.1%	0%	1.000
Altered consciousness	16.4%	0%	**< 0.001**
Bleeding	26.1%	5.7%	**0.001**
Hypotension	34.8%	20%	0.489
Tachycardia	30.9%	30%	1.000
Icterus	36.4%	1.4%	**< 0.001**
Abdominal pain/diarrhea	41.8%	35.7%	0.609
Cough	22.2%	5.7%	**0.014**
Oliguria	27.3%	50%	0.262
Anuria	14.5%	40%	0.078
Dyspnea	27.3%	40%	0.461
Hepatomegaly	21.7%	0%	0.203
Splenomegaly	18.2%	0%	0.339
Requirement of dialysis	23.6%	7.1%	**0.019**
Survival	90.2%	95.7%	0.307
Intensive care requirement	9.6%	2.9%	0.135
WBC	11,081 ± 5430	3688 ± 5141	**< 0.001**
Hb	11.5 ± 2.3	13.9 ± 2.3	**< 0.001**
Platelets	51,653 ± 34,251	51,843 ± 30,750	0. 665
ESR	65.5 ± 37.2	14.9 ± 12.4	**< 0.001**
BUN	58.9 ± 35.3	18.9 ± 18.5	**< 0.001**
Creatinine	3.6 ± 2.5	1.0 ± 1.0	**< 0.001**
Total bilirubin	10.1 ± 10.7	0.5 ± 0.4	**< 0.001**
Direct bilirubin	8.1 ± 9.2	0.2 ± 0.2	**< 0.001**
ALP	144 ± 87.1	90 ± 69.4	**< 0.001**
GGT	125.9 ± 134.0	84 ± 100.6	**0.001**
AST	146 ± 163.0	313 ± 386.9	**< 0.001**
ALT	109 ± 132.9	135 ± 140.2	0.823
CK	1336 ± 2401.9	727 ± 1159.2	**0.042**
Myoglobin	679 ± 873.8	270 ± 558.4	**0.002**
Na	133 ± 5.1	136 ± 3.5	**0.001**
K	3.8 ± 0.7	3.8 ± 0.5	0.796
PT	13.9 ± 2.2	13.2 ± 1.9	**0.002**
PTT	31.6 ± 8.7	39.9 ± 9.3	**< 0.001**
INR	1.21 ± 0.4	1.14 ± 0.2	0.151
D-Dimer	5.93 ± 7.6	7.21 ± 9.4	0.995
CRP	19.0 ± 10.2	2.6 ± 3.1	**< 0.001**
PCT	10.3 ± 18.1	2.77 ± 7.8	**< 0.001**
Time from onset of symptoms to admission	6.0 ± 3.2	2.8 ± 1.9	**< 0.001**
Length of stay	12.2 ± 8	8.5 ± 5	**0.001**

Normal ranges of laboratory values: White blood cell (WBC): 4800–10,800/μL, Hemoglobin (Hb): 12–17 g/dL Platelet: 130,000–400,000/μL, Erythrocyte sedimentation rate (ESR):0–20 mm/h, Blood urea nitrogen (BUN): 6–20 mg/dL, Creatinine: 0.51–0.95 mg/dL, Total bilirubin: 0.3–1.2 mg/dL, Direct bilirubin: 0–0.2 mg/dL, Alkaline phosphatase (ALP): 30–120 U/L, Gamma glutamyl transferase (GGT): 0–55 U/L, Aspartate transaminase (AST): 0–35 U L, Alanine transaminase (ALT): 0–45 U/L, Creatine kinase (CK): 20–200 U/L, Myoglobin: 28–72 mg1 L, Sodium (Na): 136–146 mEq L, *K*: 2.5–5.1 mEq L, Prothrombin time (PT): 10–15 s, activated partial thromboplastin time (PTT): 22–35 s, International normalized ratio (INR): 0.85–1.15, D-dimer: 0–0.55 mg L, C-reactive protein (CRP): < 0.5 mg/dL, Procalcitonin (PCT): < 0.5: g/L

Bold values indicate significant values

Subtypes of causative agents

L. patoc patoc 1 was determined in 11 (30.5%) of the 36 serum specimens investigated in cases of leptospirosis, L. bratislava jez Bratislava in 7 (19.4%), L. pomona Pomona in 6 (16.6%), L. icterohemorragiae Wijnberg in 5 (13.8%), L. Hardjo Prajitno in 3 (8.3%), L. Hebdomadis Hebdomadis in 3 (8.3%), and L. canicola Hund Utrecht IV in 1 (2.7%). Subtype results were available for 20/70 (28.5%) of our cases with hantavirus infection, 17 (85%) being identified as subtype DOBV, 2 (10%) specimens could not be classified, and PUUV was determined in 1 (5%).

ROC analysis

WBC, AST, and total bilirubin values were the parameters exhibiting the highest sensitivity in the diagnosis of leptospirosis, while CRP, followed by total bilirubin and ESR, exhibited the highest specificity. The three parameters with the highest PPVs were total bilirubin followed by ESR and creatinine, while the three parameters with the highest NPVs were WBC, CRP and total bilirubin. All parameters subjected to ROC analysis and the results thereof are shown in detail in Table 3 and Fig. 1 (operating characteristics ROC curve analysis for calculation of the discriminative ability of laboratory markers for leptospirosis).

Table 3 Receiver operating characteristics (ROC) analysis for calculation of the discriminative ability of laboratory markers for leptospirosis

Parameter	Cut-off	AUC	AUC CI	Sensitivity	Specificity	PPV	NPV	*p*
WBC	> 3400	0.896	0.839–0.939	95.65	81.43	87.1	93.4	< 0.001
BUN	> 27	0.876	0.815–0.922	80.4	85.7	88.1	76.9	< 0.001
Creatinine	> 1.3	0.875	0.814–0.921	80.4	87.1	89.2	77.2	< 0.001
CK	> 441	0.598	0.515–0.677	80.4	35.0	71.1	50.0	= 0.037
Total Bilirubin	> 0.97	0.925	0.872–0.961	82.6	95.5	96.2	80.0	< 0.001
Myoglobin	> 199	0.709	0.593–0.808	57.1	81.8	80.0	60.0	= 0.001
Hb	≤ 12.4	0.799	0.729–0.858	70.7	80.0	82.3	67.5	< 0.001
ESR	> 33	0.882	0.821–0.928	76.7	92.5	93.2	74.7	< 0.001
CRP	> 9.5	0.954	0.903–0.983	79.4	96.8	84.2	92.6	< 0.001
PCT	> 1.04	0.808	0.703–0.889	70.2	71.0	78.6	61.1	< 0.001
Na	≤ 132	0.693	0.594–0.780	41.1	88.3	72.0	67.9	< 0.001
PT	> 13.3	0.642	0.561–0.717	64.7	70.0	72.4	62.0	= 0.002
aPTT	≤ 33.3	0.777	0.703–0.840	65.9	77.1	77.8	65.1	< 0.001
AST	≤ 199	0.674	0.596–0.745	83.7	45.7	67	68.1	< 0.001

WBC white blood cell, *BUN* blood urea nitrogen, *CK* creatine kinase, *Hb* hemoglobin, ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, *PCT* procalcitonin, *Na* sodium, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *AST* aspartate transaminase, *PPV* positive predictive value, *NPV* negative predictive value, *AUC* area underneath the ROC curve, *CI* confidence interval

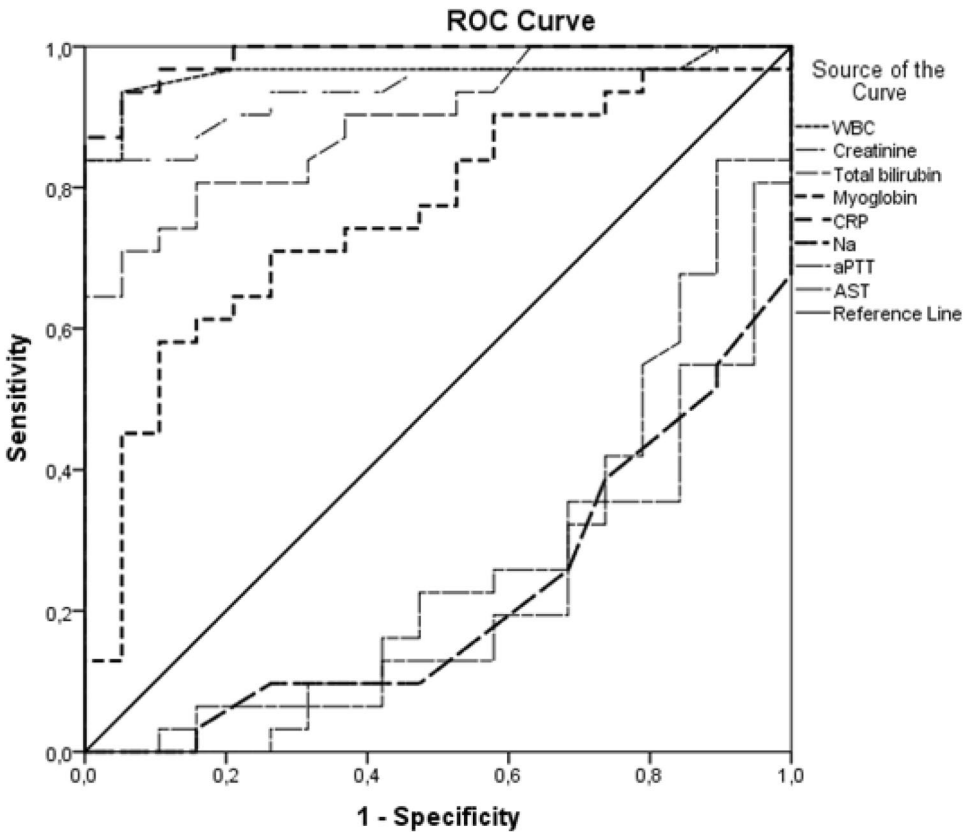

Fig. 1 Operating characteristics (ROC) curve analysis for calculation of the discriminative ability of laboratory markers for leptospirosis. *WBC* white blood cell, *CRP* C-reactive protein, *Na* sodium, *aPTT* activated partial thromboplastin time (aPTT), *AST* aspartate transaminase

MICE scoring system

Three cut-off values were determined for the five parameters included in the MICE scoring. Accordingly, scores of 1, 2, and 3 were given to WBC values (/μL) ≤ 7500, 7500–15,000, and > 15,000, respectively, to total bilirubin (mg/dL) ≤ 3, 3–10, and > 10, CRP (mg/dL): ≤ 5, 5–15, and > 15, creatinine (mg/dL) ≤ 1.5, 1.5–3, and > 3, and to CK (U/L) values ≤ 500, 500–1000, and > 1000. AUC was determined as 0.964 at ROC analysis, representing the most significant cut-off point

with 93.5% sensitivity, 92.9% specificity, 94.5% PPV and 91.5% NPV when MIC scores were ≥ 3. A test score ≥ 3 was regarded as test positivity. The contributions to diagnosis of other cut-off values are shown in Table 4. We also investigated other current scoring systems in the diagnosis of leptospirosis in our patients, and our scoring system exhibited a greater diagnostic power in our subjects (Table 4).

Discussion

Epidemiological history is of considerable importance in the diagnosis of zoonotic diseases. Various factors such as seasonal characteristics and habits, climatic features of the place of residence, and rodent fauna should be evaluated in the context of epidemiological history [4, 9–13]. Zoonoses are particularly prevalent in our region due to its abundant rainfall and habitat ideally suited to rodents. Occasional flood disasters resulting in increases in cases of leptospirosis are also observed [6]. The majority of cases followed up in our clinic consisted of individuals living in our province or in rural areas in neighboring provinces with similar climatic and geographic features and in close contact with nature for occupational reasons and/or due to their places of residence. Epidemiologically significant risk factors were observed in approximately 70% of cases in LG and 60% in HG.

As also reported in the previous literature, the majority of both leptospirosis and hantavirus infections involve young adult males, with a higher probability of encountering agents through occupation or hobbies [14, 15]. Unsurprisingly, the majority of our cases in both groups were men clustered in the 45–50 age group.

In agreement with the previous literature, the most common symptoms in our cases were fever, listlessness, nausea-vomiting, and myalgia [7, 8]. Nausea-vomiting was markedly more prevalent in our leptospirosis cases, and was observed in 4/5 patients. These symptoms have been reported in up to 60% of cases of leptospirosis [7]. Arthralgia, conjunctival suffusion, impaired consciousness, jaundice, bleeding, and cough were more common in our LG group, and are among the known signs and findings of leptospirosis [7, 8]. Although symptoms such as arthralgia and myalgia are more common in leptospirosis, they may still be seen in both infections [7, 8, 12]. Jaundice has been reported in up to 46.4% of cases of leptospirosis [4]. Weil's disease progresses with jaundice and is seen in only 5–10% of leptospirosis cases. Mortality is also very much higher in Weil's disease. Otherwise, jaundice is not expected in the majority of leptospirosis cases [8]. It is also not a particularly common finding in hantavirus infections [2, 16, 17]. Hemorrhage is an important cause of mortality in both disease groups, but is particularly significant in cases of leptospirosis. Hemorrhage in numerous organs may be observed in these patients [15–20]. Hemorrhage was present in approximately 1/3 of our cases in LG, but was much rarer in HG. Respiratory symptoms and pulmonary involvement may be seen in leptospirosis, and the course may be very severe in the form of leptospirosis-associated pulmonary hemorrhage syndrome (LPHS) and acute respiratory distress syndrome (ARDS) [7–9]. Symptoms such as respiratory difficulty and cough may be present in approximately 50% of hantavirus infections [7–9]. Although severe pulmonary syndrome was not observed in our cases, another study of ours including one group of our patients determined radiological findings of pulmonary involvement in 1/3 cases [21]. Cough reflecting the clinical manifestation was observed in approximately 1/5 cases in our study, but was much rarer in HG. Conjunctival suffusion is an important finding that can be seen in 4.5–55% of leptospirosis cases, and can also be observed in hantavirus infections [7, 8, 16, 22]. In our study, it was observed in approximately 1/5 of the cases in LG, and in half of those in HG. Clouded consciousness associated with aseptic meningitis may be seen in up to 25% of leptospirosis cases, and is a manifestation generally seen in the immune stage of the disease [7, 8]. However, this is very much rarer in hantavirus infections [22]. As far as this could be established retrospectively, consciousness problems were encountered in nearly 1/5 of our LG cases, but not at all in HG. Abdominal pain/diarrhea was observed at equal levels in the two groups. This may also be confused with acute abdomen that may sometimes be observed in both leptospirosis and hemorrhagic

Table 4 A comparison of the "MICE" and other current scoring systems in the diagnosis of leptospirosis in our patients

Score	Cut-off	AUC	AUC CI	Sensitivity	Specificity	PPV	NPV	*p*
MICE	≥ 2	0.964	0.922–0.987	97.8	70.0	81.1	96.1	< 0.001
	≥ 3	0.964	0.922–0.987	93.5	92.9	94.5	91.5	< 0.001
	≥ 4	0.964	0.922–0.987	79.4	95.7	96.1	77.9	< 0.001
	≥ 5	0.964	0.922–0.987	63.0	97.1	96.7	66.7	< 0.001
Thai-Lepto Score	> 4	0.820	0.752–0.876	75.0	84.3	86.2	72.0	< 0.001
Rajakse S. et al's model	> 14	0.828	0.761–0.883	77.2	88.6	89.9	74.7	< 0.001

AUC area underneath the ROC curve, *CI* confidence interval, *PPV* positive predictive value, *NPV* negative predictive value

fever with renal syndrome (HFRS) [2, 8, 16]. More recent studies have also emphasized that the two diseases produce very similar findings [10, 11]. Bakelants et al.'s study from Belgium involving five-year patient data was retrospective in nature and involved fewer patients than our study. Fever and lethargy were the most common symptoms in both diseases in that study, followed by myalgia and headache, while leptospirosis cases also experienced photo- or sonophobia. That study reported that nuchal rigidity and ocular lesions also suggested a diagnosis of leptospirosis [11]. Fever and fatigue were the most common symptoms in both groups in our research, while myalgia was relatively less common, and headache was observed in approximately half of cases. Conjunctival hyperemia was observed in 1/5 patients in LG, and in more than half of HG.

The diversity of clinical findings and their non-specific nature means that laboratory findings require particularly careful evaluation. Serum leukocyte levels in cases of leptospirosis are generally < 10,000/μL, but may also be as high as 26,000/μL. There are also studies reporting levels exceeding 11,000/μL in more than half of cases [23]. Previous studies have also reported that leukocytosis may also be present in hantavirus infections and is even associated with poor prognosis [5, 7]. The mean level in LG in this study was approximately 11,000/μL, but was significantly lower in HG. Hemoglobin levels have been reported to decrease below 11 gr/dL in 1/10–1/3 cases of leptospirosis, and this is a finding that can also be seen in hantavirus infections [2, 5, 15]. Hemoglobin levels were lower in LG than in HG, but this was not significant in either group. Thrombocytopenia is another important finding that can be seen in up to 71.5% of leptospirosis cases, while it appears almost inseparable from hantavirus infections [4, 15]. Mean platelet levels in our study were approximately 51,000 in LG and HG, and were similar between the two groups. One of the most important similarities between leptospirosis and hantavirus infections is the shared involvement of the kidney as the target organ [2, 8, 14]. Renal involvement seen in leptospirosis frequently assumes the form of a non-oliguric manifestation resulting in sodium and potassium loss, although oliguric cases with normal potassium levels can also be seen. Hyponatremia and hypokalemia resulting from an impaired sodium–potassium–chloride transport mechanism in the loop of Henle in particular have been reported in leptospirosis cases [8]. The oliguric phase is known to occur among the normal stages of the disease in HFRS [7, 20]. Blood sodium levels were significantly lower in LG compared to HG in this study. Oliguria was observed in approximately one in four cases in LG, and anuria in approximately one in six. As far as we could establish, these rates were higher in HG. This elevation is compatible with the previous literature [7, 20]. BUN and creatinine values increase in leptospirosis as a reflection of renal involvement, and were significantly more impaired in LG compared to HG in our study. To the extent that analysis was possible, dialysis requirements were seen in approximately one in four cases in LG, significantly more than in HG. Dialysis may be required at levels of 10–30% in cases of hantavirus infection, depending on the agent subtype [2]. Weil's disease accompanying icterus in cases of leptospirosis and capable of resulting in a high level of mortality is seen in 1/20–1/10 cases. Although the mechanism involved in icterus has not yet been fully explained, it has been suggested that anti-inflammatory activity increases as a result of apoptosis triggered in liver cells, thus giving rise to an increasing bacterial density in tissue [8, 12]. Parallel to this, it has also been reported that functional impairment in liver function tests such as AST and ALT, and a mild increase in ALP, may occur together with moderate liver enzyme elevation, without hepatic necrosis [8, 12]. Bilirubin elevation is not an expected finding in hantavirus infections, although a similar mild increase in liver function tests, ALP and GGT may be observed [2, 14]. The total bilirubin level in our LG cases was approximately 10 mg/dL, with a 90% direct bilirubin dominance. In HG, however, these values were within normal limits. Liver function tests were 2–3 times higher than normal in LG, while the increase in AST was significantly higher in LG than in HG. Similar elevations were also determined for ALP and GGT levels in favor of LG. CK elevation was present in more than half of the leptospirosis cases, and although this parameter is not specific, it has been described as an important marker in differentiating the disease from other febrile diseases [8]. CK was significantly higher in LG compared to HG in the present study. CRP and PCT are recommended markers for differentiating leptospirosis and febrile viral infections in particular, although CRP is reported to be more sensitive, while PCT is useful in determining severity [12]. CK, CRP and PCT elevation can also be seen in hantavirus infection, although not to the same extent as in leptospirosis, and these are reported to be associated with prognosis [2, 5]. In agreement with the literature, both parameters were significantly higher in LG in the present study. Bakelants et al. described abnormal liver function tests and increased total bilirubin as important findings in favor of leptospirosis, and serum CRP, lactate dehydrogenase (LDH) elevation, and leukocytosis with a left shift as important findings for hantavirus [11].

Mortality in leptospirosis is generally reported in cases of Weil's disease and LPHS, although LPHS is seldom seen in Turkey [3, 8, 24]. Within the restrictions imposed by the retrospective nature of the study, L.icterohemorrhagiae Wijnberg, important in terms of prognosis, was determined in 13.8% of our leptospirosis patients. The most commonly encountered serovars and subtypes, in descending order, were L.patoc patoc1, L.bratislava jez Bratislava, L.pomona Pomona, and L.icterohemorrhagiae Wijnberg. Prognosis of infections developing with various hantavirus subtypes

Table 5 Diagnostic score models of leptospirosis in literature and the "MICE" scoring system

Authors	Bhatia M et al. 2015 [25]	Jose LR et al. 2016 [26]	Bandara K et al. 2016 [27]	Rajapakse S et al. 2016 [28]	Sukmark T et al. 2018 [29]	Kaya S et al. 2019 (MICE score)
AUC (95% CI)	–	–	–	0.76	0.78 (0.68, 0.89)	**0.964**
Sensitivity (%)	–	89.39	100	80.3	73.5	**95.3**
Specificity (%)	–	58.82	–	60.2	73.7	**92.9**
PPV (%)	21	58.42	–	54	87.8	**94.5**
NPV (%)	–	89.55	–	84	58.3	**91.5**

AUC area underneath the ROC curve, *CI* confidence interval, *PPV* positive predictive value, *NPV* negative predictive value

All the values that belong to our study are mentioned in bold

varies considerably. PUUV has the lowest mortality rate at 1–2%, while mortality for DOBV can be as high as 15%, and as high as 40% in Sin Nombre (SNV), which causes HKPS. Cases of HKPS are not much seen in Turkey, and DOBV was a common subtype in our cases [2, 5, 9]. Mortality rates in our study were approximately 10% in LG, and approximately 5% in HG.

Various scoring systems have been developed in different studies for the differentiation of leptospirosis [25–29]. These exhibit strikingly different sensitivity, specificity, PPV and NPV values (Table 5). In our MICE coring system developed in this research, test positivity, a score of ≥ 3 on the test, emerged as differentiating leptospirosis from hantavirus infection with a probability exceeding 90%. When our patients were assessed according to two other current scoring systems in the literature, the "MICE" scoring system exhibited a higher capacity to differentiate leptospirosis from hantavirus infection based on AUC, sensitivity, specificity, PPV and NPV values. The "MICE" scoring system can be easily applied through routine blood tests and elicits rapid results, representing two further significant advantages of our system.

In conclusion, we think that the scoring system developed by the authors will be of considerable use to clinicians in differentiating leptospirosis and hantavirus infections, which are epidemiologically and clinically as closely alike as identical twins. Prompt rational treatment with early diagnosis will also reduce mortality associated with these diseases [8, 30].

Compliance with ethical standards

Conflict of interest The author declares that they have no competing interests.

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