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ORIGINAL PAPER

THE RISK FACTORS OF SEVERE LEPTOSPIROSIS IN THE TRANSCARPATHIAN REGION OF UKRAINE – SEARCH FOR „RED FLAGS"

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Abstract

Introduction. Leptospirosis is a re-emerging illness with a wide spectrum of clinical manifestations, from asymptomatic or moderate to severe and lethal results. Leptospirosis can be adequately treated if detected early; however, comparable clinical presentations with various other febrile illnesses or co-infections, as well as laboratory diagnosis problems can result in misdiagnosis, leading to severe illness. Identifying clinical predictors for the severe form of the disease is critical to reduce the disease complications and mortality.
The objective of the study was to establish the risk factors for mortality in patients with leptospirosis.
Materials and methods. A retrospective study of 102 medical records of patients diagnosed with leptospirosis in the period from 2009 to 2019 was conducted. Quantitative variables in the presence of normal distribution were compared using a paired Student's t-test, and in the case of an abnormal distribution, the Mann–Whitney U test was used. The criterion χ^2 was used for qualitative variables. A two-step cluster analysis was also performed.

Résumé

Facteurs de risque de leptospirose sévère dans la région transcarpatique de l'Ukraine – recherche «drapeau rouge»

Introduction. La leptospirose est une maladie ré-émergente à spectre large de manifestations cliniques, allant des résultats asymptomatiques ou modérés aux résultats graves et mortels. La leptospirose peut être traitée de manière adéquate si elle est détectée tôt ; cependant, des présentations cliniques comparables avec diverses autres maladies fébriles ou co-infections, ainsi que des problèmes de diagnostic en laboratoire, peuvent conduire à un diagnostic erroné, entraînant une maladie grave. L'identification des prédicteurs cliniques de la forme grave de la maladie est essentielle pour réduire les complications et la létalité de la maladie.
L'objectif de l'étude a été d'établir les facteurs de risque de létalité dans la leptospirose.
Matériaux et méthodes. Pour déterminer les facteurs de risque de létalité, une étude rétrospective de 102 dossiers médicaux de patients atteints de

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Results. The following factors associated with death from leptospirosis have been identified: oliguria (OR, 13.5; 95% confidence interval [CI], 2.56-71.12), serum creatinine and urea levels, direct and total bilirubin, platelets, and white blood cells count.
Conclusions. These „red flag" laboratory and clinical characteristics will aid medical personnel in rapidly identifying a patient at risk of death, which is critical in determining the severity of the condition and the need for early intensive care and therapy adjustment.

Keywords: leptospirosis, mortality, predictors, risk factors.

Abbreviations list
ALT – alanine transaminase
AST – aspartate aminotransferase
CFR – case fatality rate
CI – confidence interval
CK – creatinine kinase
DALY – disability-adjusted life year
MAT – microscopic agglutination test
OR – odds ratio
WBC – white blood cells

Résultats. Les facteurs suivants associés au décès par leptospirose ont été identifiés : oligurie (OR, 13,5 ; intervalle de confiance [IC] à 95 %, 2,56-71,12), taux sériques de créatinine et d'urée, bilirubine directe et totale, plaquettes et numération leucocytaire.
Conclusions. Ces caractéristiques cliniques et de laboratoire de type « drapeau rouge» aideront le personnel médical à identifier rapidement un patient à risque de décès, ce qui est essentiel pour déterminer la gravité de l'état et la nécessité de soins intensifs précoces et d'un ajustement thérapeutique.

Mots-clés: la leptospirose, mortalité, prédicteurs, facteurs de risque

Introduction

Leptospirosis is a major threat to the public health and one of the most important and widely distributed zoonoses in the world[1,2]. Every year, nearly one million people are diagnosed with leptospirosis, with 58,000 of them dying[3]. This disease causes an annual loss of 2.9 million disability-adjusted life years (DALY)[4].

In the Transcarpathian region of Ukraine, leptospirosis is a significant public health concern. The incidence rate in this region is more than three times higher than the relative incidence in Ukraine and the case fatality ratio (CFR) in leptospirosis in Transcarpathia averages 12.5%, while the national level is 9.8%[5,6].

The symptom spectrum is extremely broad, and leptospirosis shares clinical signs with many other acute febrile diseases (i.e. flu). Severe manifestations occur in 10–15% of human infections and are typified as Weil's syndrome (a triad of jaundice, haemorrhage, and acute renal failure), which has a 15–20% case fatality rate and severe pulmonary haemorrhage syndrome (SPHS), which may present as acute respiratory distress and has been linked to case fatality rates more than 50% in several studies[7].

The early detection of severe or potentially severe cases of leptospirosis may be useful in reducing mortality, which is still quite high in this disease[8,9]. The identification of prognostic factors that lead to severe course and death from leptospirosis is important, to establish the need for hospitalization in the intensive care unit and the use of more aggressive therapeutic measures[8,9].

The presentation of leptospirosis appears to be distinct in different geographical areas around the world[10]. This is especially true because different geographical locations may have different Leptospira species and serovars, socioeconomic factors, and environmental factors. Variations in the intrinsic virulence among serovars and species have been proposed to explain some of the differences in disease severity between mild and severe forms of leptospirosis[11].

The factors that cause severe forms to appear have not been identified[12,13].

The objective of the study was to determine the risk and prognostic factors associated with severe forms of leptospirosis in laboratory-confirmed cases from the Transcarpathian region of Ukraine.

Materials and methods

Study design

A retrospective case-control study was conducted in the Transcarpathian Regional Clinical Infectious Diseases Hospital, Uzhhorod, Ukraine. The study protocol included a review of 102 medical records of patients who were hospitalized

Table 1. Analysis of demographic and clinical variables.

Characteristic	*Survivors n = 76 (%)*	*Non-Survivors n = 26 (%)*	*OR (95% CI)*	*P-value*
		Demographic		
Age (Years)[a]	49 (36 – 61)	50 (44 – 58)	-	0.761
Gender (Male)	72 (73.6%)	20 (76.9%)	0.6 (0.15 – 2.80)	0.730
		Symptomatology		
Fever ≥38 °C	64 (84.2%)	32 (61.5%)	0.3 (0.07 – 1.23)	0.121
Myalgia	58 (76.3%)	20 (76.9%)	1.0 (0.23 – 4.59)	1.000
Jaundice	62 (81.5%)	26 (100%)	1.4 (1.17 – 1.71)	0.169
Arthralgia	4 (5.2%)	0 (0%)	0.7 (0.62 – 0.86)	1.000
Oliguria	22 (28.9%)	22 (84.6%)	13.5 (2.56 – 71.12)	0.001
Nausea	18 (23.6%)	10 (38.4%)	2.0 (0.52 – 7.72)	0.309
Vomiting	20 (26.3%)	8 (30.7%)	1.2 (0.31 – 4.95)	0.73
Headache	10 (13.1%)	0 (0%)	0.71 (0.59 – 0.86)	0.311
Abdominal pain	4 (5.2%)	4 (15.3%)	3.27 (0.41 – 26.01)	0.266

a – IQR (Interquartile Range)

between 2009 and 2019. Leptospirosis was determined according to the criteria of the World Health Organization[14]. Each case was confirmed in the Especially Dangerous Infections (EDIs) of the State Institution Transcarpathian Region, Centre for Disease Control and Prevention of the Ministry of Health of Ukraine, where a microscopic agglutination test (MAT) was conducted. The study did not include individuals who did not have laboratory confirmation of the diagnosis. A standardized questionnaire was used to collect the following information: age, gender, clinical symptoms (fever ≥38 °, myalgia, jaundice, arthralgia, oliguria, nausea, vomiting, headache, abdominal pain). Urine production of fewer than 400 ml per day was defined as oliguria.

Statistical analysis

Statistical data were processed using IBM SPSS Statistics 23 software. Quantitative variables in the presence of normal distribution were compared using a paired Student's t-test, and in the case of an abnormal distribution, the Mann–Whitney U test was used. Qualitative variables were compared through the χ^2 test. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated. The value of p <0.05 was considered significant. A two-step cluster analysis was also performed. The prognostic importance was used and a cut-off level of 0.4 was set.

Results

Among the 102 leptospirosis patients included in the study, 76 patients (74.5%) survived and 26 (25.5%) died. Demographic data such as age, gender, and clinical signs associated with severe leptospirosis, are shown in Table 1.

Most patients with severe leptospirosis (n = 26, 100%) indicated that they had jaundice, a total of 22 patients had oliguria (84.6%). A total of 20 patients complained of myalgia symptoms (76.9%), and 16 patients had fever (61.5%). A total of 10 patients had nausea (38.4%), while 4 patients with leptospirosis reported abdominal symptoms (15.3%).

The chi-square test showed a significant association between oliguria (p = 0.001) with lethality and severe leptospirosis. Oliguria was the strongest risk factor with an estimated odds ratio of 13.5.

As shown in Table 2, patients who died from leptospirosis had higher serum creatinine levels compared with those who survived, namely 475.70±120.95

Table 2. Analysis of laboratory values between survivors and non-survivors among patients with leptospirosis.

Characteristic	*Survivors n = 76 Mean ± SD or (%)*	*Non-survivors n = 26 Mean ± SD or (%)*	*P-value*
ALT (UI/L)	117.55 ± 125.19	111.57 ± 87.20	0.953
Erythrocyte Sedimentation Rate (mm/hr)	39.24 ± 17.36	45.31 ± 17.40	0.163
Creatinine (mmol/L)	190.97 ± 56.26	475.70 ± 120.95	0.001
Urea (mmol/L)	13.05 ± 9.56	30.20 ± 12.33	0.001
Total bilirubin (mmol/L)	182.50 ± 87.20	363.00 ± 110.23	0.001
Direct bilirubin (mmol/L)	108.85 ± 120.50	248.86 ± 95.23	0.001
Platelets (10^9/L)	120.57 ± 121.57	45.67 ± 43.57	0.005
WBC count (10^9/L)	14.03 ± 7.47	30.8 ±12.5	0.003
Granulocytes (%)	89.90 ± 8.57	92.55 ± 7.89	0.255

Table 3. Cluster analysis of lethality predictors in leptospirosis.

Characteristic	*Cluster 1*	*Cluster 2*	*Cluster 3*	***Predictor importance***
	Mean	*Mean*	*Mean*	
Non-Survivors (%)	0	0	95.7	1.00
Male	100	0	82.6	0.88
Creatinine (mmol/L)	165.91	211.85	479.63	0.51
Urea (mmol/L)	11.33	12.46	28.87	0.48
Direct bilirubin (mmol/L)	120.21	71.01	242.23	0.29
Total bilirubin (mmol/L)	191.90	130.86	345.66	0.22
Platelets (10^9/L)	125.72	101.50	46.83	0.10
Age (y)	44.88	52.12	52.83	0.08
Granulocytes (%)	86.95	89.51	90.94	0.05
Erythrocyte Sedimentation Rate (mm/hr)	40.90	36.92	43.87	0.02
ALT (IU/L)	120.86	112.92	112.7	0.02

mmol/L versus 190.97±56.26 mmol/L, respectively (p = 0.001). Statistically significant changes were also found in the levels of laboratory parameters such as urea (p = 0.001), total bilirubin (p = 0.001), direct bilirubin (p = 0.001) platelet level (p = 0.005) and white blood cells (WBC) count (p = 0.003). Alanine aminotransferase (ALT), erythrocyte sedimentation rate, and granulocyte percentage in the blood were not associated with leptospirosis lethality (p > 0.05).

A cluster analysis of probable predictors was also performed. Three clusters were formed, the size of each cluster is shown in Figure 1.

The first and second clusters were formed from surviving patients (the first cluster was formed only from male patients and the second only from female patients). The third cluster consisted of most patients who did not survive. As can be seen from Table 3, the most important factors associated with leptospirosis lethality are gender (male), serum creatinine, and urea.

Discussion

This study was carried out to determine the predictive factors for lethality and severe leptospirosis in the Transcarpathian region. The findings suggest that oliguria is a risk factor for severe leptospirosis. This sign can be recognized after hospitalization, and early identification and control of diuresis can alert the treating physician to the possibility that the patient will develop severe leptospirosis. As a result, aggressive treatment should start immediately.

The kidney is one of the main targets of Leptospira, with kidney damage occurring in 20–85% of patients[15]. Renal failure, especially in oliguric forms of leptospirosis, is a well-established predictor of death and it is also associated with more frequent pulmonary involvement[16,17]. Histologically, there are spirochetes in the renal tubules, interstitial nephritis, and glomerular damage with tubular necrosis[18]. The cause is unknown, but is thought to be a mix of

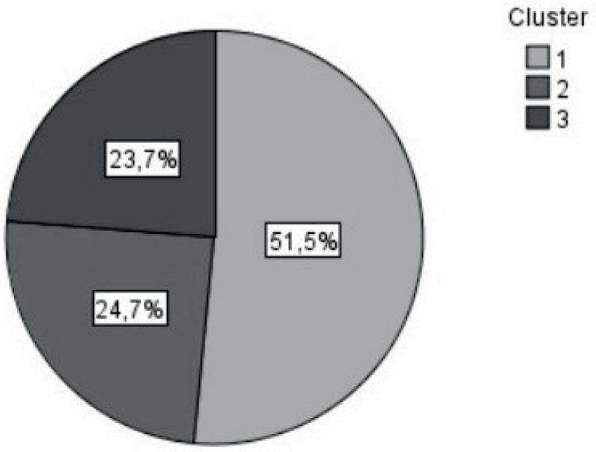

Figure 1. Cluster sizes of patients with leptospirosis. The first (51.5%) and second (24.7%) clusters were formed from surviving patients (the first cluster was formed only from male patients and the second only from female patients). The third (23.7%) cluster consisted of most patients who did not survive.

direct toxic injury, immune-mediated responses, and circulatory collapse[19].

The results of our study suggest that risk stratification for patients with leptospirosis should not be relied on the presence of icterus. Jaundice occurs because of damage to the vessels of the hepatic capillaries without hepatocellular necrosis. There are retrospective studies that confirm[20,21], or deny[9,10] the role of jaundice as a predictor of death in this infectious disease.

Myalgia is a symptom of leptospirosis and is often described as affecting the back and legs[22]. In most studies, myalgia was not a factor associated with lethality in leptospirosis[9,23]. Histologically, there is focal necrosis of muscle fibres, with a slight increase in creatinine kinase (CK) as a result[24]. A study by Dupont et al. in France found that CK levels were higher in non-survived patients with leptospirosis[8].

Headache is a common symptom of leptospirosis, and it is frequently described as severe and connected with vomiting. Patients may have impaired consciousness in the early stages, followed by meningitis symptoms in one-quarter of cases during the immunological phase[17]. In our study the headache wasn`t a common presentation.

In our study, patients who died had higher total and direct bilirubin levels than those who recovered. Several scientific articles have proven the importance of hyperbilirubinemia as a predictor of lethality and severe leptospirosis[8-10]. In leptospirosis, liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are moderately increased, suggesting that liver impairment is generally mild and resolves with time[17]. The role of liver aminotransferases as a factor of disease severity or lethality needs to be further researched, as there is evidence that confirms[25] or refutes[9,26] the role of these biochemical parameters in patients with leptospirosis. An AST/ALT ratio > 3 may indicate a poorer prognosis[27].

Thrombocytopenia, which is frequent in leptospirosis, is another key risk factor for a severe course of the disease and lethality[28]. Thrombocytopenia in leptospirosis may be caused by specific Leptospira strains that directly activate platelets, according to one theory[29]. Thrombocytopenia in the acute phase of the disease may play a role in haemorrhagic disorders. In many studies, thrombocytopenia has been identified as one of the most common causes of severe course and death[8,10,30,31]. Uraemia may also be a factor in the acute phase of the disease that causes bleeding. The pathophysiology of bleeding in uraemia is complex, nevertheless alterations in platelet–platelet and platelet–vessel wall interaction play a crucial role. Uremic toxins present in the bloodstream contribute to platelet dysfunction[32].

Increased levels of creatinine and urine in the blood indicate kidney damage and the possibility of acute kidney failure, one of the most common and decisive predictors of death in leptospirosis[30]. Jaundice (Weil's syndrome) is the clinical syndrome most closely associated with the risk of death, so the presence of renal failure in leptospirosis patients should receive special attention[31].

The age, which did not differ between the two groups in our study ($p > 0.05$), but did in certain studies[8,10], is one of the demographic variables that can be discussed; however, patients who died from leptospirosis were older than those who recovered. Most studies[8-10], including our, have found that although gender is not a significant factor in leptospirosis lethality, men have a higher incidence of the disease than women.

Conclusions

In our study, oliguria, serum creatinine and urea levels, as well as levels of direct and total bilirubin, platelets, and WBC count were found as important predictors of lethality in leptospirosis. These „red flag" laboratory and clinical characteristics will aid medical personnel in rapidly identifying a patient at risk of death, which is critical in determining the severity of the condition and the need for early intensive care and therapy adjustment.

Author Contributions:

Conceptualization, P.P., and G.V.; methodology, I.V, and G.V.; software, P.P.; validation P.P.; formal analysis, I.V, and G.V.; investigation, P.P., I.V, and G.V.; resources, P.P.; data curation, P.P.; writing–original draft preparation, P.P., I.V, and G.V.; writing–review and editing, I.V and G.V.; visualization, P.P..; supervision, P.P..; project administration, P.P.. All authors have read and agreed with the final version of this article.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study „

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