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Liver Involvement in Leptospirosis

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Abstract: Liver involvement is a common feature of leptospirosis. It is variable from mild to severe hepatic dysfunction. Objective: to analyze liver involvement and to assess its prognostic value in leptospirosis. Materials and methods: We performed analysis of 100 consecutive leptospirosis cases treated in Clinic of Infectious Diseases at University Hospital – Pleven (1976-2015)(90 male, mean age 37±18 years, lethal outcome in 13%), followed by comparative analysis of group with liver involvement (n_1=71) versus group without liver involvement (n_2=29). Results: Fever (100%), hepatomegaly (92%), myalgia (86%), vomiting (84%), splenomegaly (74%), oliguria (69%), jaundice (63%), hypotension (49%), abdominal pain (41%), and hemorrhagic diathesis (37%) were the characteristic manifestations. Headache, myalgia, abdominal pain, oliguria, hemorrhagic diathesis, myocarditis, acute respiratory failure and pancreatitis had had a significantly higher prevalence in the group with liver involvement. Increased levels of total bilirubin (mean 157.8±71.5 μmol/L) with prevalent direct fraction, ASAT (mean 112±18 IU/L), ALAT (mean 96±78 IU/L), hypoproteinemia and hypoalbuminemia were the main laboratory parameters that expressed hepatic dysfunction. Conclusion: The most affected liver functions are bilirubin metabolism and protein synthesis. Liver involvement in leptospirosis is important factor for severity, in combination with acute renal failure has severe course and requires early diagnosis and prompt intensive treatment.

Keywords: Acute Renal Failure, Hepatic Dysfunction, Leptospirosis, Liver Involvement

1. Introduction

Leptospirosis is a globally distributed zoonosis caused by pathogenic Leptospira. The disease has protean clinical manifestations and variable severity. Severe disease is estimated to occur in 5-15% of all human infections, typically presenting as Weil's disease – a triad of jaundice, renal failure, and hemorrhage [1]. In the city of Salvador, Brazil, acute renal failure (ARF) is recognized as the major cause of death [2]. A recent systematic review estimated that there are 1.03 (95% CI 0.43–1.75) million cases of leptospirosis worldwide each year and 58,900 deaths (95% CI 23,800–95,900) [3, 4], which corresponds to an estimated 2.9 million disability-adjusted life years per annum, including 2.8 million years of life lost due to premature death [5].

Leptospirosis has a broad geographical distribution, occurring in both rural and urban areas of tropical, subtropical and temperate regions. The disease outbreaks in developed countries are usually associated with occupational exposure, tourism or sporting events. Developing countries carry the major burden of the disease, with half a million cases reported yearly and a mortality rate ranging from 5 to 10% [6].

In Bulgaria, which is located in South-Eastern Europe, the climate is temperate. In the country, leptospirosis is a reportable disease since 1952, when a database and official registration was initiated. A mean annual incidence rate of 0.9 to 3.1 per 100 000 was reported during the period 1953-1968 followed by decreasing to 0.1 per 100 000 population within next ten years. Since 1976, a mean annual incidence of 0.37 per 100 000 was reported [7], decreasing to 0.18/100 000 population (2006-2009) [8].

The clinical presentation of leptospirosis is biphasic, with the acute or septicemic phase lasting about a week, followed by the immune phase, characterized by antibody production and excretion of leptospires in the urine. Most of the complications of leptospirosis are associated with localization of leptospires within the tissues during the immune phase and thus occur during the second week of the illness [1]. Leptospirosis has been described as a zoonosis of protean manifestations. The spectrum of symptoms is

extremely broad. The great majority of infections caused by leptospires are either subclinical or of very mild severity, and patients will probably not seek medical attention. The classical syndrome of Weil's disease (including major triad of acute renal failure, jaundice and hemorrhagic diathesis) represents only the most severe presentation. Due to variable clinical manifestations and different severity, the disease provokes diagnostic difficulties (especially in the early phase), followed by delayed adequate treatment. This worsens the prognosis of disease. From this view point, the increased awareness for leptospirosis and good knowledge of clinical and laboratory manifestations of organs involvement in this disease are crucial for successful management of cases of leptospirosis [1, 7, 9].

Liver involvement is a common feature of leptospirosis. It is variable from mild to severe hepatic dysfunction. The jaundice (when is presented), appears within initial five to nine days of the clinical onset and lasts to one month. It has been observed in leptospirosis independent on causative serovar Leptospira but *L. icterohaemorrhagiae* is the most common causative agent of icteric leptospirosis [1]. According to Vijayachari P et al (2008), a small proportion of patients develop severe icteric illness with renal failure. Jaundice occurs between the fourth and sixth day but may occur as early as the second day or as late as the second to third week. The liver is often enlarged and tender. Jaundice is due to hepatocellular necrosis, intrahepatic cholestasis and increased bilirubin load from absorption of tissue hemorrhage. Marked elevations of bilirubin with mildly elevated transaminases are some characteristic features. Death rarely occurs due to hepatic failure [10].

The lesions in the liver histopathological findings revealed disorientation of the hepatic cords and disorganization of hepatocytes with some degree of dissociation along with fatty infiltration and hyperplasia of Kupffer cells. A high content of bilirubin in the blood is produced by the reticuloendothelial cells of the body phagocytosing red blood cells at such a rapid rate that the parenchymal cells of the liver cannot effectively excrete all the bilirubin brought to them. The bilirubin in the blood stream increases and jaundice occurs [11]. In contrast to markedly increased bilirubin level, hepatic enzymes are slightly elevated [1, 11-15].

The mortality predictors for leptospirosis published by different authors are quite variable. While some indicators are repeatedly cited as predictors of mortality, the significance of others is questionable. Evidences for hepatic dysfunction are prominent during the clinical course of leptospirosis. However, many of these are not reported as predictors of mortality [16]. Some host-related factors are independently associated with severity: history of chronic hypertension, hyperamylasemia, history of chronic alcoholism etc. [11, 12, 17].

The aim of this study was to focus on liver involvement in leptospirosis, to analyze clinical features and laboratory parameters, and to assess the significance of liver involvement as prognostic factor.

2. Materials and Methods

We performed retrospective study of all consecutive leptospirosis cases treated after written informed consent in Clinic of Infectious Diseases at University Hospital – Pleven (1976-2015) (n=100, lethal outcome in 13%). A retrospective database for patients presenting with leptospirosis (1976-1984) was initiated and continued prospectively to the December 31st 2015. Subjects were screened by microscopic agglutination test (MAT) for leptospirosis (in the National Reference Laboratory at National Center of Infectious and Parasitic Diseases – Sofia). A positive diagnosis was confirmed if an initial titer of ≥100 for MAT was observed.

The following items were included in the database, for each patient: demographic data, clinical symptoms, laboratory parameters on admission and outcome.

After analysis of data for whole series, the patients were divided in group with liver involvement (total serum bilirubin level >21.4 μmol/L) and control group without liver involvement (total serum bilirubin level <21.4 μmol/L). Comparative analysis of the group with liver involvement (n_1=71 cases) versus control group (n_2=29 cases) was performed. The data were analyzed using the Statgraphics *Plus* Version 2.1. Package. We used t-test and χ^2 test (for parametric and non-parametric distributions, respectively); $p<0.05$ was considered to be significant.

Severity of cases was complexly assessed as mild, moderate and severe according to the following definitions [7]:

Mild form of leptospirosis had been defined at mild to moderate intoxication, anicteric or mild icteric, without hemorrhagic diathesis, without involvement of respiratory, cardiac and central nervous system (CNS), with mild renal dysfunction without ARF.

Moderate form of leptospirosis had been defined at markedly demonstrated intoxication, moderate jaundice, skin hemorrhages, transitory cardiovascular abnormalities without myocardial dysfunction, ARF improving without dialysis.

Severe leptospirosis had been defined at severe intoxication, intensive jaundice with severe hepatic dysfunction, skin hemorrhages and visceral bleeding, toxic myocarditis, severe ARF requiring dialysis, common respiratory and CNS-involvement.

Except mentioned above analysis, odds ratio (OR), sensitivity, specificity and positive prognostic value of criteria for severity (see mentioned above definitions) were evaluated.

The outcome of leptospirosis cases was analyzed. We used φ-coefficient by modified Pearson's test (interpreted by three-grade score as follows: weak correlation at $\varphi<0.3$, moderate $0.31<\varphi<0.7$ and strong – $\varphi\geq0.7$) about correlation of the lethal outcome with a presence of lung edema, brain edema, metabolic acidosis, myocarditis, ARF, visceral bleeding, jaundice and age (>45 years old).

3. Results

The distribution of cases according to mentioned above

definitions in the whole series was as follows: mild, moderate and severe cases were 27, 39 and 34, respectively. Comparing the groups with and without liver involvement, the distribution of cases according to severity is shown on Figure 1.

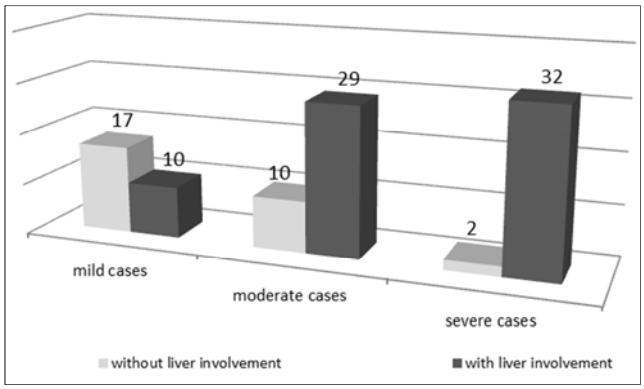

Figure 1. *Distribution of leptospirosis cases in Pleven region, Bulgaria (1976-2015) according to severity.*

Fever (100%), hepatomegaly (92%), myalgia (86%), nausea and vomiting (84%), splenomegaly (74%), oliguria (69%), headache (67%), jaundice (63%), hypotension (49%), abdominal pain (41%), and hemorrhagic diathesis (37%) were the characteristic clinical manifestations. The prevalence of most frequent symptoms and syndromes in the whole series and in the group with liver involvement versus the control group are shown on Table 1. Headache, myalgia, abdominal pain, oliguria, hemorrhagic diathesis, myocarditis, acute respiratory failure and pancreatitis had had a significantly higher prevalence in the group with liver involvement.

Comparative analysis of laboratory investigations had found significant differences in blood count, liver biochemical parameters (except prothrombin index), blood urea nitrogen (BUN) and serum creatinine. These parameters were more abnormal in the group with liver involvement. For the whole series, increased levels of total serum bilirubin (mean 157.8 ± 71.5 μmol/L) with prevalence of the direct fraction, ASAT (mean 112 ± 18 IU/L) and ALAT (mean 96 ±78 IU/L), hypoproteinemia and hypoalbuminemia were the major laboratory criteria of hepatic dysfunction. These parameters were significantly different in the compared groups (Table 2). Comparing of laboratory parameters in different according to severity cases of leptospirosis, we had found significant alterations in levels of serum bilirubin and ASAT in severe forms. It was not valid for ALAT, alkaline phosphatase and gamma glutamyl transferase (GGT).

Table 1. *Clinical findings in patients with leptospirosis in Pleven region, Bulgaria (1976-2015).*

Symptoms and syndromes	Whole series (n=100) %	Group with liver involvement (n_1=71) %	Group without liver involvement (n_2=29) %	p
Fever	100	100	100	=0
Hepatomegaly	92	94	86	n.s.
Conjunctival suffusions	87	86	90	n.s.
Myalgia	86	82	97	<0.01
Nausea and vomiting	84	83	86	n.s.
Splenomegaly	74	77	66	n.s.
Oligo/anuria	69	65	38	<0.01
Headache	67	58	90	<0.0005
Tachycardia	54	56	48	n.s.
Hypotension	49	51	45	n.s.
Abdominal pain	41	49	21	<0.0025
Hemorrhagic syndrome	37	51	3	<0.0005
Myocarditis	21	30	0	<0.0005
Meningitis	21	20	24	n.s.
Diarrhea	15	15	14	n.s.
Acute respiratory failure	14	20	0	<0.0005
Pancreatitis	7	10	0	<0.005

Note: n.s. – non significant

Ultrasound sonography, performed at thirty eight cases, had confirmed the frequent involvement of the liver. Enlarged liver (in 92%) and steatosis (in 84%) had found at the investigated patients. There were not found signs for intra- and extra hepatic cholestasis.

Treatment of the liver dysfunction was a part of the management of leptospirosis and was carrying out by infusions of glucose, dextrose and electrolytes according to the diuresis and the levels of blood glucose and electrolytes. Corticoids were administered in 50% of the cases. Hepatoprotective therapy was performed by L-ornitine and ademetionine (in 11% and 6%, respectively), and silimarin orally in 72% of the cases.

Assessment of the major criteria for severe course [7] revealed significant sensitivity of strong adynamia and increased levels of serum creatinine and blood urea nitrogen (BUN). The liver involvement, hemorrhagic syndrome and CNS involvement were criteria with significant specificity (respectively to 100%). All of assessed criteria had positive prognostic value above 50% (Table 3).

The outcome of treated patients was as follows: 87% of cases survived and were discharged after mean hospital treatment 15 ± 7 days (from 1 to 46 days) and 13% were with lethal outcome after mean hospital treatment 4 ± 2 days

(from 1 to 10 days). The mean hospital treatment of the patients with liver involvement was thirteen days versus twelve days of the control group (p>0.05). Thirteen of the patients were with lethal outcome (all in group with liver involvement).

The clinical onset of leptospirosis in deceased patients was meanly five days before admission in hospital. All of them had fever, muscular pains, oligo/anuria, two had epistaxis and hemorrhagic rash before admission. Ten deceased patients had co-morbidity including hypertonic disease and chronic alcohol abuse (respectively three cases), past myocardial infarction, stomach ulcer, past tuberculosis (respectively two), podagra and calculous cholecystitis (respectively one). Six of patients with lethal outcome were admitted in other clinical wards (surgery, internal) with diagnosis such as acute pancreatitis, obstructive jaundice and sepsis. They were transferred to Clinic of Infectious disease later.

All patients with unfavorable outcome had, besides ARF, at least two other major organ failures. Other abnormalities seen in deceased patients were altered consciousness, multi- site hemorrhagic diathesis (in nine). The major factors leading to death were lung edema and brain edema (OR 25.00 and 17.29, respectively) due to severe ARF.

Table 2. *Laboratory findings in patients with leptospirosis in Pleven region, Bulgaria (1976-2015).*

Laboratory parameter	**Reference value**	**Whole series – mean ± SD (min-max)**	**Group with liver involvement – mean ± SD (min-max)**	**Group without liver involvement – mean ± SD (min-max)**	**p**
Leucocytes (cells x 10^9/L)	4.0-11.0	13.5 ± 6.5 (2.9-32)	14.3 ± 6.7 (2.9-32)	11.3 ± 5.5 (5.2-26.6)	<0.025
Platelets (cells x 10^9/L)	150-400	146 ± 104 (8-445)	127 ±106 (8-445)	197 ±79 (91-408)	<0.0005
Total bilirubin (μmol/L)	3.4-21	157.8 ± 71.5 (3.1-801)	204.8 ± 172.9 (31.8-801)	12.5 ± 4.7 (3.1-19)	<0.0005
Total bilirubin – *Mild form*			67.6 ± 31.3 (31.8-132)		
Total bilirubin – *Moderate form*			150.6 ± 90) (32.4-368.5)		
Total bilirubin – *Severe form*			296.9 ± 205.8 (35-801)		
Direct bilirubin (μmol/L)	0.8-8.5	139 ± 31.7 (2.5-564)	156.1 ± 130.3 (7.3-564)	5.5 ± 1.3 (2.5-7.2)	<0.0005
ASAT (IU/L)	≤37	112 ± 18 (6-625)	131 ± 130 (6-625)	58 ± 37 (23-151)	<0.0005
ASAT – *Mild form*			99 ± 62 (6-320)		
ASAT – *Moderate form*			84 ± 70 (7-330)		
ASAT – *Severe form*			190 ± 167 (32-625)		
ALAT (IU/L)	≤40	96 ± 78 (11-382)	105 ± 80 (11-382)	72 ± 67 (14-287)	<0.025
ALAT – *Mild form*			114 ± 82 (15-264)		
ALAT – *Moderate form*			74 ± 45 (12-171)		
ALAT – *Severe form*			178 ± 156 (32-625)		
Alkaline phosphatase (IU/L)	50-260	313 ± 237 (37-1431)	334 ± 255 (37-1431)	233 ± 123 (51-461)	<0.005
GGT (IU/L)	15-28	168 ± 58 (16-568)	178 ± 158 (16-568)	124 ± 65 (22-556)	<0.01
Total protein (g/L)	58-80	64.5 ± 9.2 (47.8-87)	62.3 ± 9 (48-87)	70.3 ± 7.4 (47.8-80.5)	<0.0005
Albumins (g/L)	35-55	36.2 ± 7.8 (18.5-51)	33.7 ± 7 (18.5-51)	43.4 ± 5.1 (31.1-51)	<0.0005
Fibrinogen (g/L)	2.0-4.5	6.8 ± 2.4 (1.4-12)	7.2 ± 2.4 (1.4-12)	5.7 ± 2.0 (2.3-10.8)	<0.0025
Prothrombin index (%)	80-110	86 ±18 (24-114)	87 ± 19 (24-114)	85 ± 14 (60-101)	n.s.
Urea (mmol/L)	1.7-8.3	22.5 ± 16.9 (2.8-98.6)	27.2 ± 17.4 (2.8-98.6)	10.3 ± 6.2 (4.9-27.8)	<0.0005
Creatinine (μmol/L)	44.2-134	280 ± 197 (56-818)	325 ± 203 (56-818)	164 ± 116 (86-537)	<0.0005

Note: n.s. – non significant

Using modified Pearson's test, we established strong correlation between lethal outcome and lung edema (odds ratio/ OR 25.00; φ = 0.66), brain edema (OR 17.29; φ = 0.53) and decompensated metabolic acidosis (OR 8.80; φ = 0.95). Moderate correlation had been established with myocarditis (OR 11.00; φ = 0.43), ARF (OR 2.20; φ = 0.42), visceral bleeding (OR 1.43; φ = 0.38) and age above 45 years (OR 11.00; φ = 0.43). The correlation between lethal outcome and presence of jaundice was weak (OR 1.15; φ = 0.03).

Pathomorphological investigations were performed in seven deceased cases. Macroscopically, severe lung edema, brain edema leading to cerebellar inclination, multi-site bleeding, enlarged congestive liver were established in all of autopsied, pancreatitis in five, peritonitis in one. The histological investigations had demonstrated gastrointestinal and myocardial hemorrhages, focal myocardial necrosis, destruction of liver architectonic, severe tubular necrosis of kidneys in all investigated cases.

Table 3. *Criteria for severe course of leptospirosis.*

Criteria for severe course	t (Student) p	OR	Sensitivity (%)	Specificity (%)	Positive prognostic value (%)
Adynamia	<0.05	12.21	78.95	0	61.22
Anuria	<0.05	22	53.19	50	83.33
Hemorrhagic syndrome	<0.05	34	38.64	100	100
CNS involvement	<0.05	6.5	18.18	100	100
Liver involvement	*<0.025*	*60.67*	*43.75*	*100*	*100*
Increased BUN	<0.05	68.88	75	0	78.95
Increased creatinine	<0.0025	232	66.67	0	90.91

4. Discussion

The discussion of the results mentioned above requires analysis of global and local information about leptospirosis. Liver involvement, as a part of involvement of the reticuloendothelial system (manifested by hepatomegaly and splenomegaly), is one of the leading processes in the pathogenesis of leptospirosis. In our study, hepatomegaly had found in 92%. The prevalence of hepatomegaly that had found in other studies varies from 25% [18] to 76% [19]. The splenomegaly also is common – in our study it was recorded in 74% of all cases. According to Tappero et al (2000), hepatosplenomegaly had found in more than 25% of icteric cases of leptospirosis [20].

Jaundice has been observed in leptospirosis independent on causative serovar Leptospira but *L. icterohaemorrhagiae* is the most common causative agent of icteric leptospirosis. As a result of the degradation of extravascular erythrocytes, most of the old worn-out red blood cells in the circulatory system are phagocytosed in the spleen, bone marrow and liver. Hence, the reticuloendothelial cells of these organs produce most of the bilirubin that is formed in the body at such a rapid rate that the parenchymal cells of the liver cannot effectively excrete all the bilirubin brought to them. The bilirubin increases in the blood stream and jaundice appears [21]. Other authorities consider that the jaundice is due to hepatic damage, centrilobular cholestasis and microcirculatory disorders [22]. In our study, we had found jaundice in 63% of all cases but according to Covic A et al. (2003) 93% of their cases were icteric [19]. Yang CW et al. (2001) had observed jaundice in 83% [18], Daher et al (2010) in 94.5% [15], whereas DebMandal et al (2011) – in 39% of leptospirosis cases [11]. In our study, increased serum bilirubin levels had found at admission in 71% of cases (up to 150 μmol/L in 37%). There is a correlation between hyperbilirubinemia and severity of the disease (p<0.05). This correlates with other study with leptospirosis patients, where bilirubinemia was higher in severe cases and jaundice was demonstrated to be a predictive factor of severity in leptospirosis according to multivariate analysis (p = 0.005, OR = 10.1, CI = 1.79 – 56.8) [23]. The dynamic of bilirubin levels showed increasing in first seven days after admission followed by gradually decreasing. According to some studies, the serum bilirubin level is less than 200 μmol/L in acute phase and rises to peak levels in 85% of cases [20]. In two of our cases maximal total bilirubin level was 1273 and 1128 μmol/L, respectively (the second patient succumbed).

There is not discrepancy in attitudes concerning elevations of aminotransferases activity. ASAT and ALAT levels seldom are more than 200 IU/L [1, 20]. In our study, ASAT was increased in 72% of cases (mean 112 ± 18 IU/L) and in 56% ASAT was to 200 U/L. There was positive correlation between ASAT levels and severity (p<0.05). According to Chang et al (2005), disproportional exaggerated ASAT is a useful prognostic parameter in late leptospirosis [24]. According to Daher et al (2010), ASAT and ALAT levels were higher than 40 IU/L in 82.4 and 72.1% of the patients, respectively [15]. In our study, ALAT was increased at admission in 74% of cases (mean 96 ± 78 IU/L), and in 64% ALAT activity was to 200 IU/L. There was no correlation between ALAT levels and severity. The parallel investigation of ASAT and ALAT revealed a prevalence of ASAT at admission of cases but later investigations showed prevalence of ALAT. It could be due to damage of hepatocytes requiring hepatoprotective treatment.

The parallel analysis of serum bilirubin levels and aminotransferases activity is important in diagnostic aspect. All studies consider discrepancy between markedly elevated bilirubin levels and slightly elevated aminotransferases in icteric cases of leptospirosis [1, 11, 13-15]. Maroun et al (2011) described an increase in liver enzymes (up to five times normal) with a disproportionately high total bilirubin as a prognostic indicator in leptospirosis [25]. But it is interesting to compare these parameters in anicteric cases. In our study, there were 29 cases with normal serum bilirubin

and increased aminotransferases activity. This fact has important diagnostic significance especially in early phase of disease. If a patient has fever, strong muscular pains (especially in calf muscles), conjunctival suffusions, hepatosplenomegaly, mild to moderate aminotransferases activity with normal bilirubin level, leptospirosis is a possible diagnosis before appearing of jaundice, oliguria and hemorrhagic syndrome.

Concerning enzymes alkaline phosphatase and GGT, considered as markers of cholestasis, our investigations had found slightly to moderately increased alkaline phosphatase levels in 46% of cases (mean 313 ± 237 IU/L), without correlation with severity. The presence of moderately increased alkaline phosphatase is evidence for cholestatic component of jaundice in leptospirosis [1, 11, 13, 14]. GGT as typical microsomal enzyme is a sensitive marker of hepatobiliary damage, especially at cholestasis. In our study, GGT was increased in 95% of cases (mean 168 ± 58 IU/L).

The protein synthesis is an important aspect of the liver function. There are renal and hepatic involvements in leptospirosis and elucidation of alterations in protein metabolism (and their connections with renal and liver damage) is important. We had found hypoproteinemia in 25% of all cases (mean 64.5 ± 9.2 g/L) and hypoalbuminemia in 49% (mean 36.2 ± 7.8 g/L). That data had confirmed altered protein synthetic function of the liver and the role of increased protein losses with urine, and increased protein catabolism. We consider that altered protein metabolism in leptospirosis has complex genesis [7].

Fibrinogen is important for evaluation of liver function. In our study, the fibrinogen level had increased in 82% of all cases (mean 6.8 ± 2.4 g/L; maximally to 12.0 g/L). The increased fibrinogen level is important for diagnosis and distinguishes leptospirosis and viral hepatitis. Prothrombin index is marker for activity of clothing factors (2^{nd}, 5^{th}, 7^{th} and 10^{th}). It had been slightly decreased in 29% of all cases (mean 86%) and had not correlated with severity of liver dysfunction [26]. We had not observed cases with manifested acute liver failure in difference of the studies of Asauljuk et al (1985) – in 19% (1985) [27], and Covic A et al (2003) – in 72% [19].

Ultrasound sonography, performed at thirty eight cases, had confirmed the frequent involvement of the liver. Enlarged liver (in 92%) and steatosis (in 84%) had found at the investigated patients. There were not found signs for intra- and extra hepatic cholestasis. Kaul et al (2005) described ultrasound sonography findings at leptospirosis case such as enlarged liver with hyperechogenic structure, without cholestasis but they concerned that these findings are not disease-specific [28].

Assessment of the major criteria for severe course [7] revealed significant sensitivity of strong adynamia and increased levels of serum creatinine and blood urea nitrogen (BUN). The liver involvement, hemorrhagic syndrome and CNS involvement are criteria with significant specificity (respectively to 100%). The liver involvement has positive prognostic value for severe course in 100%. It is in accordance with the study of Abgueguen et al (2008), in which the clinical jaundice is the second independent variable significantly predictive of development of severe leptospirosis ($p < 0.05$) [23].

Analysis of outcome in our series revealed strong correlation between death and lung edema and brain edema, whereas the correlation between the presence of jaundice and lethal outcome was weak. Vijayachari P et al (2008) also had concluded that death rarely occurs due to hepatic failure [10]. According to study of Panaphut et al (2002), the levels of ASAT and total bilirubin were significantly higher, but serum albumin was significantly lower in no survivors than in survivors [29]. According to Ko et al (1999), total serum bilirubin, an indicator of hepatic dysfunction, was not a significant predictor of death in univariate or multivariate analyses. The presence of the three strongest predictors in multivariate analyses (altered mental status, oliguria, and age >36 years) had in 82% (18 deaths among 22 cases) positive predictive value for death from leptospirosis [30].

5. Conclusion

This study recruited all leptospirosis cases treated in our Clinic of Infectious Diseases during forty years. We had focused on liver involvement in leptospirosis and had assessed its significance for severe course of the disease. It was found that the most affected liver functions are bilirubin metabolism and protein synthesis. Liver involvement in leptospirosis is important factor for severity, in combination with ARF has severe course and requires early diagnosis and prompt intensive treatment with multidisciplinary approach.

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