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## Is jaundice a prognosis of leptospirosis?

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### ABSTRACT

**Objective:** To determine the incidence of leptospiral jaundice and find the correlation among human leptospiral cases with or without jaundice. **Methods:** Patients suspected for leptospirosis, attending Calcutta School of Tropical Medicine, Kolkata, India during 2002 to 2008 were evaluated as per modified Faine's criterion. **Results:** Out of 404 suspected cases, 214 were found positive for leptospirosis, 15 were jaundice positive but without leptospirosis and 175 cases had neither leptospirosis nor jaundice. Serum bilirubin and creatinine levels among leptospirosis patients were (1.89–42.70 mg/dL) and (0.60–6.40 mg/dL), respectively; serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were (99.00–410.00 U/L) and (57.00–887.00 U/L), respectively; IgM values by ELISA were (0.63–3.28 U/mL). **Conclusions:** There is no association between occurrence of jaundice and leptospirosis and it also does not confirm the expected 1:1 ratio of jaundice and leptospirosis ( $P < 0.005$ ).

## 1. Introduction

Leptospirosis is a widespread zoonosis caused by invasive spirochaetes belonging to the genus *Leptospira*<sup>[1]</sup>. The disease has anicteric phase of leptospiremia with flu-like illness that resolves into asymptomatic phase followed by convalescent leptospiruric immune stage<sup>[2]</sup>. However, the most distinctive form of severe leptospirosis develops during the anicteric phase, characterized by profound jaundice with hepatocellular necrosis, referred to as Weil's disease that occurs in approximately 10% of the patients<sup>[3]</sup>. The jaundice appears during days 5–9 of the anicteric stage and is the most intense 4–5 days later, continuing for about 1 month<sup>[1]</sup>. Sometimes many of the cases of infectious jaundice are treated as a case of viral hepatitis that might be due to *Leptospira* infection. Thus this disease is often not recognized, or is erroneously mistaken for other diseases with similar symptoms. As a consequence, this serious disease is often either left untreated or treated improperly. There have been very scanty reports on leptospirosis and its association with the occurrence of jaundice, if any, especially in our region. Thus the present study has been undertaken to determine the incidence of leptospiral jaundice and to find the correlation among human leptospiral cases with or without jaundice in order to ascertain whether jaundice is preindicative prognosis of

leptospirosis.

## 2. Materials and Methods

A total of 404 patients suspected for leptospirosis, attending Calcutta School of Tropical Medicine, Kolkata, India during 2002 to 2008 were selected for the study and evaluated as per modified Faine's criterion<sup>[4]</sup>. The design of the study was approved by the Institutional Ethical Committee Board of the school, and informed consent was obtained from the patients. Serum samples were obtained from each patient and tested for the *Leptospira biflexa* (*L. biflexa*) Patoc I leptospiral antibodies using IgM ELISA (Diagnostic Automation, Inc. California, USA) according to the manufacturer protocol. IgM levels were recorded from the given absorbance values at 450 nm. Hepatic dysfunction due to jaundice was defined with serum bilirubin ( $>1.5$  mg/dL) and elevated hepatic enzymes, hepatic encephalopathy. The normal range for the parameters of liver function test was as follows: total bilirubin: 0.2–1.0 mg/dL, serum glutamic-oxaloacetic transaminase (SGOT): 10–35 U/L, serum glutamic pyruvic transaminase (SGPT): 10–50 U/L, alkaline phosphatase: 80–306 U/L, total protein: 6.6–8.7 g/dL, albumin: 3.4–4.8 g/dL, globulin: 2.8–4.5 g/dL, albumin:globulin: 1.3–2<sup>[5]</sup>.

All the patients were screened for the presence of jaundice in both positive and negative leptospirosis cases and statistically compared using *t*-test in order to determine if any association of jaundice is present with the

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incidence of leptospirosis, and  $\chi^2$ -test to test the hypothesis that jaundice is indicative of leptospiral situation.

### 3. Results

Out of 404 suspected cases, 214 were found positive for leptospirosis and based on the incidence of jaundice associated leptospirosis, patients were categorized into four groups.

Group 1 consisted of leptospirosis positive jaundice positive cases. There were 84 such patients amongst which maximum number ( $n=53$ ) showed IgM levels within 1–2 U/mL. The IgM levels in the serum samples in response to the antigen *L. biflexa* Patoc I (serovar patoc I) were interpreted from the absorbance values and expressed in units/mL (U/mL), as shown in Figure 1.

Group 2 comprised leptospirosis positive jaundice negative cases. Amongst 130 patients, 41 had IgM values in the range of 1.2–1.6 U/mL while 44 cases showed IgM values within 0.5–1.5 U/mL.

Group 3 was composed of leptospirosis negative jaundice positive cases. A total of 15 cases depicted 0.08–0.90 U/mL as their IgM values.

Group 4 consisted of leptospirosis negative jaundice negative cases. There were 175 suspected cases who suffered from neither leptospirosis nor jaundice having their IgM values in the range of 0.03–1.09 U/mL.

Serum bilirubin levels among the patients ranged between 0.50 and 42.70 mg/dL. A total of 305 patients who were jaundice negative with leptospirosis positive or leptospirosis negative had bilirubin levels below 1 mg/dL within a range of 0.50–0.80 mg/dL. The SGOT values for leptospirosis

patients and jaundice patients ranged between 70.00–410.00 U/L and 99.00–110.00 U/L, respectively while the SGPT levels were 57.00–887.00 U/L and 57.00–100.00 U/L, respectively. Of the 214 leptospirosis cases, 17 (7.94%) and 41 (19.15%) had normal SGOT and SGPT values of 20–30 U/L and 30–53 U/L, respectively. Serum creatinine values among leptospirosis cases and jaundice cases ranged between 0.50 to 6.40 mg/dL and 0.60–2.00 mg/dL, respectively, while 42.05% leptospiral cases with or without jaundice patients had levels in the range of 0.6 and 1.2 mg/dL. The values of other biochemical findings were depicted in Table 1.

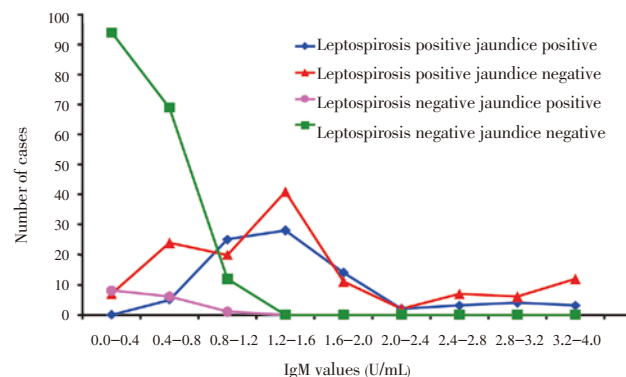


Figure 1. IgM values (U/mL) of patients by ELISA against the antigen *L. biflexa* Patoc I.

A significant difference between occurrence of jaundice and appearance of leptospirosis ( $P<0.005$ ) was found indicating no association between them. The 84 cases of jaundice out of a total 214 leptospirosis cases did not confirm the expected 1:1 ratio of jaundice and leptospirosis ( $P<0.005$ ).

Table 1  
Biochemical findings of leptospirosis suspected patients.

Biochemical findings	Leptospirosis positive jaundice positive ( $n=84$ )	Leptospirosis positive jaundice negative ( $n=130$ )	Leptospirosis negative jaundice positive ( $n=15$ )	Leptospirosis negative jaundice negative ( $n=175$ )
IgM (U/mL)	0.63–3.28	0.26–3.84	0.08–0.90	0.03–1.09
Bilirubin (mg/dL)	1.89–42.70	0.50–0.80	1.20–3.40	0.50–0.70
SGOT (U/L)	99.00–410.00	70.00–110.00	80.00–110.00	50.00–120.00
SGPT (U/L)	57.00–887.00	80.00–120.00	85.00–100.00	30.00–172.00
Alkaline phosphatase (U/L)	205.00–1180.00	175.00–820.00	420.00–530.00	127.00–750.00
Hb (g%)	4.60–9.32	6.70–9.80	8.00–8.50	9.00–11.00
Urea (mg/dL)	20.00–55.00	30.00–40.00	30.00–50.00	14.00–25.00
Creatinine (mg/dL)	0.60–6.40	0.50–0.80	1.00–2.00	0.50–0.80
Albumin (g/dL)	4.00–5.00	3.00–5.00	4.00–5.00	3.00–4.00
Globulin (g/dL)	3.00–4.00	2.50–4.00	3.00–4.00	2.00–3.00

### 4. Discussion

Leptospirosis is a major public health problem in tropical countries with potentially fatal systemic complications and multiorgan dysfunction, including hepatic and renal failure, with or without severe pulmonary haemorrhage syndrome[1]. In the present communication, the features of leptospirosis patients included the common clinical signs and symptoms as per modified Faine's criteria[4]. Leptospirosis at present is grossly underreported and is a diagnostic dilemma because of its protean clinical manifestations. Though the syndrome of icteric leptospirosis presenting with hepatic failure was first described over a century ago, it still poses a challenge to the diagnostic laboratory[1]. A serological survey work for leptospirosis on 42 patients with jaundice as a predominant

clinical symptom of which 10 (23.81%) were found to be positive for leptospirosis[6]. Among 400 clinically suspected leptospirosis patients, 20 (5%) had serological evidence of leptospirosis by LEPTO dipstick and microscopic agglutination test (MAT), of which fever and jaundice were the most common (16; 80%) clinical presentations[7]. This is in concordance with a study conducted in northern India[8] where 73.3% (63 out of 86) presented with jaundice, in contrast to the Kovai hospital, Coimbatore, where 35% of patients had jaundice[9], while among 13 positive against *Leptospira grippityphosa*, only 3 (13%) patients had jaundice during an outbreak in Germany[10]. Jaundice was observed in 44% patients most of whom also had renal failure as well as severe bleeding episodes in the form of adult respiratory distress syndrome[11]. In the present study, about 39.25% of leptospirosis was icteric compared with 60.75% of anicteric forms; while 7.89% suffered from jaundice only and 92.10%

had neither jaundice nor leptospirosis. The mean value of serum bilirubin levels among those with abnormal liver function was 14.61 mg/dL. As a result of the degradation of extravascular erythrocytes, most of the old wornout red blood cells in the circulatory system are phagocytosed in the spleen, bone marrow and liver<sup>[12]</sup>. Hence, the reticuloendothelial cells of these organs produce most of the bilirubin that is formed in the body. LipL46, a 46 kDa outer-membrane lipoprotein expressed during the dissemination stage of infection was found within the interstitium between hepatocyte epithelial cells, within splenic phagocytes, and invading the glomerular hilum of the kidney<sup>[13]</sup>. 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<sup>[12]</sup>. 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<sup>[12]</sup>. Our study highlighted that leptospirosis induced hepatic dysfunction is generally accompanied by hyperbilirubinaemia (up to 42.7 mg/dL) and elevated transaminases (SGOT and SGPT up to 410 and 887 U/L, respectively). The appearance of jaundice in leptospirosis caused by *Leptospira icterohaemorrhagiae* (*L. icterohaemorrhagiae*) in guinea pigs was the result of hepatocellular damage associated with a markedly increased production of bilirubin from the massive destruction of extravascular erythrocytes liberated by hemorrhagic diathesis<sup>[12]</sup>. Cases with high SGOT and SGPT levels (>200 U/mL, 2 cases) and very high bilirubin levels (>8 mg/dL, 2 cases) were also described from northern India<sup>[8]</sup>. Maroun *et al* described an increase in liver enzymes (up to five times normal) with a disproportionately high total bilirubin as a prognostic indicator in leptospirosis<sup>[14]</sup>. In humans, an elevation was observed in blood alkaline phosphatase activity (175–1180 U/L) in the icteric and anicteric cases of leptospirosis. A marked decrease in enzyme activity could be due to destruction of the same in capillary endothelium by the same injurious agent which causes disruption of the integrity of the capillary walls and allows the hemorrhagic phenomenon to develop<sup>[12]</sup>. Platelets in the current study presented a marked drop (15 000–28 000/mm<sup>3</sup>) in the leptospirosis infected group. Thrombocytopenia (platelets  $\leq 100 \times 10^9/L$ ) was significantly associated with clinical bleeding and the drop of platelets was attributed to the phenomenon of disseminated intravascular coagulation found in 10 (22%) of the 46 patients with severe leptospirosis<sup>[15]</sup>. The Hb values in all leptospirosis patients ranged between (4.6–9.8 g%) and in all jaundice patients with or without leptospirosis the Hb level was (5.2–8.5 g%). The onset of anemia may be due to erythrocyte loss through hemorrhages; bleeding manifestation included petechial hemorrhage, hematuria, hematemesis, and epistaxis. Anemia in leptospirosis caused by *L. icterohaemorrhagiae*, was attributed to tissue hemorrhages and a decreased production of erythrocytes rather than an increased destruction of those cells<sup>[12]</sup>.

Leptospirosis have some shared biochemical presentations with jaundice, including elevated serum bilirubin, hepatic enzymes, hepatic encephalopathy, thus from this view point leptospirosis cannot be distinguished from jaundice; however, it is apparent that the two forms may or may not be associated because leptospirosis is due to spirochaetal infection that can be detected by different serological methods such as ELISA, which are not applied to jaundice without leptospirosis. In our study, since out of 214

leptospirosis cases only 84 suffered from jaundice, it can be concluded that there is no association between occurrence of jaundice with the appearance of leptospirosis. Although the absence of jaundice does not eliminate the possibility of leptospirosis, and its presence could indicate hepatitis or other liver pathology rather than leptospirosis.

### Conflict of interest statement

We declare that we have no conflict of interest.

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