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Leptospirosis in southern Coastal Karnataka, India: Analysis of clinical and laboratory characteristics

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Abstract

The current study analyses the clinical, haematological and biochemical characteristics in patients diagnosed with leptospirosis. This study was retrospective of a period of two years from March 2021 to February 2023. A total of 138 patients clinically suspected of leptospirosis with positive *Leptospira* IgM ELISA results were included in the study. The clinical presentation, complications, treatment, outcome, haematological parameters like haemoglobin, leucocyte count, platelet count, prothrombin time, biochemical parameters like total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea and serum creatinine were studied. Males were majority (n=99, 71.7%) and average age was 47.5 ± 13.3 years with maximum number of cases (n=68, 49.2%) noted in age group of 41 to 60 years. Fourteen patients (10.1%) succumbed to leptospirosis. Fever (n=115, 83.3%), vomiting (n=56, 40.6%), malaise (n=49, 35.5%), decreased urine output (n=40, 29.0%), and abdominal pain (n=37, 26.8%) were common complaints. The common complication was acute kidney injury (n=87, 63.0%). Majority of cases showed deranged haematological and biochemical parameters with leucocytosis (n=65, 47.1%), significant neutrophilia (n=95, 68.8%), thrombocytopenia (n=109, 80.0%), raised ESR (n=121, 87.7%), raised prothrombin time (n=27, 19.6%), hyperbilirubinemia (n=103, 74.6%), raised AST (n=108, 78.3%), raised ALT (n=86, 62.3%), hyperuremia (n=92, 66.7%), and raised creatinine (n=98, 71.0%). AST was significantly *(p=0.011)* higher in deceased patients compared to patients who recovered. Most of the patients received doxycycline antibiotic therapy (n=134, 97.1%). Febrile illness with deranged haematological, renal and liver function tests should raise a suspicion of leptospirosis in endemic regions. Prompt supportive treatment along with antibiotic therapy with doxycycline has favourable outcomes. Significantly elevated AST levels were associated with mortality.

Introduction

Leptospirosis is a neglected worldwide zoonotic disease, caused by the thin spiral bacteria *Leptospira* species. There are more than 300 pathogenic serovars which have been identified, till date (1). Rodents are important reservoirs, but other

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animals like cattle and other ruminants, dogs, small terrestrial mammals and even bats can also be reservoirs and transmitters (2). The mode of transmission is by exposure to environmental surface water that is contaminated with the urine of infected animals. Infection occurs through damaged skin or mucosa (3). Clinical presentation can range from a mild anicteric febrile illness to a potentially fatal Weil's disease or hepatorenal-haemorrhagic syndrome. Mild anicteric febrile illness or acute leptospirosis is characterized by clinical features like fever, chills, headache, severe myalgia, conjunctival suffusion, abdominal pain, anorexia, nausea, vomiting, and malaise. Icterohaemorrhagic form occurs in 5-10% of the patients. It often progresses rapidly with a case–fatality rate of 5 to 15%. High-grade fever, jaundice and raised liver enzymes, petechiae and purpura, conjunctival haemorrhage, gastrointestinal haemorrhage, pulmonary haemorrhage, raised serum urea and creatinine characterize this syndrome. Pulmonary haemorrhage and acute kidney injury are the common causes of death in severe leptospirosis (3, 4). Defect in primary or secondary haemostatic mechanisms causes bleeding in leptospirosis. There will be enhanced coagulation or activation of fibrinolysis which leads to decrease in coagulation proteins (5).

Leptospirosis is a global health problem. The incidence rate ranges from 0.1–1/100,000 per year in temperate climates to 10–100/100,000 in tropical countries. Approximately one million cases are reported annually, with a total fatality of 60,000 (6). The data regarding true incidence of leptospirosis in India is lacking but the disease is endemic in Southern parts namely in Kerala, Tamil Nadu, Maharashtra, Karnataka, Gujarat and Andaman-Nicobar Islands (7). In the nearing country Srilanka too only estimates of annual caseload is available amounting to 10,423 and cumulative incidence of leptospirosis requiring hospitalisation between 2008-2015 was 52.12/1,00,000 people per year (8). The non-specific nature of symptoms and challenges in clinical and microbiological diagnosis contributes to increased morbidity and mortality. Administration of antibiotics seems to be effective when initiated up to the fourth day after the onset of symptoms. Costa E et al (9) have shown that penicillin therapy after 4 days of symptomatic disease did not provide better clinical outcome in patients with leptospirosis and acute kidney injury. Hence, early identification of leptospirosis is necessary (3, 9).

Hence, this study aimed to evaluate the clinical, haematological and biochemical characteristics of patients diagnosed with leptospirosis and to explore any parameters helping in identifying patient's with risk of mortality.

Materials and methods

Study setting and duration: This study was done at a tertiary care hospital in coastal Karnataka. Retrospective data of a period of 2 years from March 2021 to February 2023 was recorded. The study was approved by the institutional ethics committee.

Inclusion criteria: Data from the in-patient case records of patients with a clinical suspicion of leptospirosis and a positive *Leptospira* IgM ELISA (Enzyme-linked Immunosorbent Assay) test were included in the study.

Exclusion criteria: Patients less than 18 years of age, patients with known history of haematological abnormalities, chronic kidney disease, chronic liver disease and patients with co-infections of other febrile illness evidenced by positive reports of malaria by quantitative buffy coat examination, viral hepatitis by serological tests, typhoid by Widal test or culture, dengue NS1 and IgM ELISA, tuberculosis by sputum smear microscopy, HIV serology, blood culture for bacterial or fungal organism were excluded from the study.

Data collection: The following details were collected by reviewing the medical records of the patient. Clinical details namely; duration of illness, presenting symptoms, length of hospital stay, complications like pulmonary involvement based on imaging studies showing parenchymal

infiltrates/pleural effusion, documented pulmonary haemorrhage or requirement of mechanical ventilation; hepatic, renal, cardiac, central nervous system complications, antibiotic treatment and outcome. Multiorgan dysfunction syndrome (MODS) was considered when two or more organ systems were involved and was mentioned in case records. Demographic data namely age, sex was also collected. Haematological parameters namely haemoglobin, total and differential leucocyte count, platelet count, prothrombin time, biochemical parameters namely liver function tests which included Total bilirubin, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and renal function tests (blood urea, serum creatinine) were recorded.

Statistical analysis: The collected clinical and laboratory data were analysed statistically with SPSS 23 and data was expressed in frequency, percentage, median and inter-quartile range (IQR). The haematological and biochemical parameters were compared and analyzed by performing Mann-Whitney U test; in between patients who recovered and deceased cases.

Results

A total of 138 cases of *Leptospira* IgM-positive cases were included from March 2021 to February 2023. Records showed that among the 138; 5 patients were positive for leptospirosis by ELISA (Panbio, Abbot) as well as PCR. PCR was done using Truenat (Malbio diagnostics). Male patients were 99 (71.7%) and female patients 39 (28.3%). Average age of the patients was 47.5+/-13.3 years with a minimum of 19 years and maximum of 91 years. Maximum numbers of cases were aged between 41 and 60 years (49.2%) as shown in Table 1.

Clinical characteristics

The predominant complaints when presenting to the hospital were fever in 115 (83.3%) cases, vomiting in 56 (40.6%), malaise in 49 (35.5%), decreased urine output in 40 (29.0%) and abdominal pain in 37 (26.8%), followed by other symptoms as shown in Table 2. Acute kidney injury was the most common complication noted with 87 cases (63.0%) and multi organ dysfunction was documented in 61 cases (44.2%). Details of the complications noted are shown in Table 3. Intensive care unit (ICU) admission was required for 19 (13.8%) patients and remaining patients were managed in the wards. Mortality among the cases was 10.1% (14 cases), 84.8% had a good outcome with improved and discharged, whereas 7 patients left against medical advice. The mean duration of hospital stay was 9.4 days.

All 138 patients received antibiotics and supportive treatment. Most of the patients received multiple antibiotics. 134 (97.1%) were treated with doxycycline, 71 (51.4%) patients received ceftriaxone, and 46 (33.3%) received piperacillin-tazobactam. However, empirical and targeted antibiotic therapy could not be identified from the case records.

Haematological and biochemical characteristics

On analysis of haematological parameters, gross derangements were found. The results showed average haemoglobin 11.6 gm/dl, leucocytosis was seen in 65 cases (47.1%), thrombocytopenia in 109 cases (80.0%), raised erythrocyte sedimentation rate (ESR) in 121 (87.7%). Differential white blood cell analysis showed predominantly neutrophils in 95 cases (68.8%) with a mean differential neutrophil count of 82.5%. The prothrombin time was increased in 27 (19.6%), especially in cases with complications. The liver function tests (LFTs), mainly serum total bilirubin in 103 cases (74.6%), AST in 108 cases (78.3%), and ALT in 86 cases (62.3%) were deranged and were raised in majority of cases as shown in Table 4. Similarly, renal function parameters namely blood urea and serum creatinine showed increased levels in 92 (66.7%) and 98 (71.0%) cases respectively. The hematological and biochemical characteristics are shown in table 4. The haematological and biochemical parameters were compared between patients who recovered and patients who died. There was no significant difference in any of the

parameters except AST which was deranged significantly in deceased cases. The median (IQR) of AST in recovered cases were 66.7 U/L (38.0 - 108.3) and in deceased cases were 126 U/L (63.85 - 163.8) respectively with a *p value of 0.011*.

Table 1. Age-wise distribution of patients with leptospirosis (N=138)

Age in years	Number (%)
18-20	2 (1.4%)
21-40	46 (33.3%)
41-60	68 (49.2%)
61-80	20 (14.5%)
81-100	2 (1.4%)

Table 2. Presenting complaints of patients with leptospirosis (N=138)

Presenting complaints	Number (%)
Fever	115 (83.3)
Vomiting	56 (40.6)
Myalgia	49 (35.5)
Decreased urine output	40 (29.0)
Abdominal pain	37 (26.8)
Diarrhea	27 (19.6)
Yellowish discoloration of the eyes	23 (16.7)
Breathlessness	21 (15.2)
Headache	17 (12.3)
Cough	14 (10.1)
Edema, abdominal distension	11 (8.0)
Altered sensorium	8 (5.8)

(Note: More than one complaint was recorded in most patients.)

Discussion

Leptospirosis is a disease of worldwide concern especially in the regions between the Tropic of Cancer and Tropic of Capricon. In India, leptospirosis is commonly seen in the coastal areas, and rainfall is an important risk factor. The most common serovar identified in India is icterohaemorrhagiae. The disease has a high morbidity and mortality rate, especially in developing countries (10).

In this study, the majority of patients were males (71.7%). These findings are similar to the results of study conducted by Amela Becirovic et al (11) in which out of the 160 patients enrolled in the study 118 (73.8%) were male and 42 were female (26.3%). Majority of the patients in this study were in the age group of 41-60 years (49.2%). Another study conducted in coastal India also showed similar results. Out of 202 leptospirosis patients, 82 were in the age group of 41-60 years (40.6%) and majority 142 (70.3%) were males (12).

Male adults experience more exposure due to the outdoor nature of their occupation. Though occupation history was not analysed in this study, majority of the population in the coastal areas of India are engaged in farming. In India traditional farming practices continue where farmers do not wear any protective gear resulting in high chances of skin abrasions during work. Collection of water in and around the houses and proximity to sewers were important risk factors seen in a study at Kodagu (13).

Table 3. Complications seen in patients with leptospirosis (N=138)

Complications	Number (%)
Acute kidney injury	87 (63.0)
Multi-organ dysfunction	61 (44.2)
Hepatic dysfunction	42 (30.4)
Sepsis	39 (28.3)
Radiological parenchymal infiltrates/ pleural effusion	13 (9.4)
Mechanical ventilation	11 (8.0)
Meningitis	6 (4.3)
Myocarditis	6 (4.3)
Hemorrhagic signs	6 (4.3)
Pulmonary haemorrhage	3 (2.2)

(Note: More than one complication was recorded in some patients.)

Table 4. Haematological and biochemical parameters in patients with leptospirosis (N=138)

Parameter (normal range)	Median	Interquartile range (IQR)	Cases in which deranged n (%)
Leucocyte count (4000-11000 cells/mm^3)	9,900	6,800-14,377.5	65 (47.1%)
Platelet count (1,50,000-4,10,000 cells/mm^3)	56,500	27,750-1,39,750	109 (80.0%)
Erythrocyte sedimentation rate (0-20 mm/hour)	80	39.3-90	121 (87.7%)
Prothrombin time (11-15 seconds)	13.7	13.7-14.5	27 (19.6%)
Serum total bilirubin (0-0.4 mg/dL)	2.75	1.31-6.57	103 (74.6%)
Aspartate aminotransferase (AST) (14-36 U/L)	66.1	39.5-122.2	108 (78.3%)
Alanine aminotransferase (ALT) (<50 U/L in male, <35 U/L in female)	54.8	35.5-89.0	86 (62.3%)
Blood urea (16.6-48.5 mg/dL)	66.5	39.7-133.3	92 (66.7%)
Serum creatinine (0.7-1.4 mg/dL)	2.6	1.3-4.9	98 (71.0%)

The common presenting clinical features among the patients included fever, vomiting, myalgia, reduced urine output, abdominal pain, diarrhoea, breathlessness and jaundice which were consistent with findings of the study by Holla R et al (12). A study by Kembhavi RS et al (14) in Maharashtra showed fever in 90.7%, headache in 63.2%, myalgia in 59.1%, breathlessness in 19.4%, conjunctivitis in 16.4%, jaundice in 7.8% and anuria /oliguria in 6.1%.

In terms of disease outcome, in the present study group 84.8% showed improvement after treatment but 10.1% succumbed to the disease and 5.1% refused continuation of treatment thus making the outcome unknown. In this study, 19 patients (13.8%) required ICU admission and among them mortality was seen in 11 patients (57.9%). The study centre being a tertiary care hospital; critical cases are often referred. So, the severity of the disease at presentation could be the reason for a mortality rate of 10.1% seen despite appropriate treatment. Case fatality varies in different studies. Holla R et al (12) study showed 3.5% mortality; Al Hariri YK et al (15) showed 6.48% mortality, whereas Sharp TM et al (16) showed mortality as high as 15%. The case fatality rate in study by Wang HK et al (17) was 19% and among them 55% succumbed due to acute respiratory distress syndrome and pulmonary haemorrhage.

Complications after acute kidney injury, myocardial involvement or pulmonary haemorrhage are usual causes of death. Organ and tissue damage are due to both direct tissue damage and immune-mediated mechanisms. Multi-system

complications were seen. Acute kidney injury and multi organ dysfunction syndrome were the most common followed by sepsis and hepatic dysfunction. The hepatic involvement includes acute liver injury, which further leads to liver failure. This presents as an altered sensorium in later stages. Daher et al (4) noted similar complications in their study, with 87% having acute kidney injury.

The respiratory complications may be due to haemorrhage into the lung parenchyma or pleura or pleural effusion. This upon worsening necessitates the use of mechanical ventilation. In this study, 11 (8.0%) patients required mechanical ventilation. Myocarditis was seen in 4.3%. Shah K et al (18) studied the cardiac complications in leptospirosis, and they found myocarditis in 96% of the 24 patients who had died of leptospirosis. A CNS bleed was seen in one patient in this study. Atypical complications like CNS involvement manifesting as intracranial bleeding and thrombosis, ocular manifestations, gastrointestinal like pancreatitis and cholecystitis are seen in some cases of leptospirosis (19).

Microscopic agglutination test (MAT) is the gold standard for diagnosis of leptospirosis. But MAT requires live *Leptospira*, is labour intensive and requires well experienced staff and equipped laboratory. IgM antibodies can be detected 4 to 5 days after the onset of symptoms and can persist for 5 months. Since early identification of the disease is important to prevent progression to severe forms and widespread availability; most clinicians rely on *Leptospira* IgM ELSIA which provides results in 2 to 4 hours. Rosa MI et al (20) did a systematic review and meta-analysis of 52 studies on diagnostic tests for leptospirosis and showed that IgM ELISA had a sensitivity and specificity of 0.86 and 0.8 respectively in all phases of the disease whereas in acute phase it increased to 0.90 and 0.91 respectively. In this study, 5 patients were positive by PCR also. PCR was documented in low numbers as the diagnostic test was introduced during the last 2 months of the study. But utility of PCR is maximum during the first week of illness alone after which sensitivity decreases (21).

Upon biochemical evaluation there was derangement in liver function tests. In this study 74.6%, 78.3% and 62.3% showed an increase in total bilirubin, AST and ALT respectively. Deranged liver function test is a consistent feature in various studies on leptospirosis (10, 12, 22). In a study conducted by Praveen V et al (22), 93% of patients had raised AST and ALT. Chang M et al (23) have shown that disproportional elevated AST as a useful marker in predicting poor outcomes in leptospirosis. This study too demonstrated that AST levels have statistically significant difference between the patients who recovered and deceased cases. Hence, this finding emphasises AST as a potential prognostic marker in leptospirosis.

Leptospirosis caused a derangement in hematological parameters also. There was thrombocytopenia, leucocytosis and a gross increase in neutrophils as seen in other bacterial infections. The ESR levels and prothrombin time were also increased. The findings in this study were in concurrence with other studies (3, 12, 24). Viruses are the common causes of acute febrile illness. The presence of leucocytosis differentiates leptospirosis from viral causes (10).

Haemorrhage is one of underlying pathology resulting in life threatening complications in patients with leptospirosis. The prothrombin time, which gives a reflection of the bleeding or clotting profile, was elevated in this study, thus providing an insight to the hemorrhage seen in the infection. The most powerful mechanism for invasion is interaction with fibrinogen and thrombin. This decreases the formation of fibrin clot and along with secreted proteases helps in dissemination of leptospirosis in host body (1).

The most common antibiotic used in the study setting was doxycycline. Some patients received multiple antibiotics. The sequence of events in each patient which led to the administration of various antibiotics could not be ascertained. But, predominance of doxycycline indicates that it is the

most opted antibiotic for the treatment of leptospirosis in this hospital. In cases with complications additional specific interventions hemodialysis and mechanical ventilation were used. In an open, randomized, controlled trial of penicillin, doxycycline, cefotaxime for patients with severe leptospirosis they found no significant differences between the antibiotics regarding mortality. They also said that as rickettsial infections can also have similar presentations, doxycycline is a better drug option for treatment of both infections rather than penicillins (9, 25).

Conclusion

This study provides an insight into clinical, haematological and biochemical characteristics of leptospirosis. The findings emphasise that a patient with acute febrile illness having leucocytosis, neutrophilia, thrombocytopenia, deranged liver function tests, or deranged renal function tests should be suspected of leptospirosis in endemic regions. The leading cause of morbidity was due to acute kidney injury.

Significantly elevated AST levels were associated with mortality. Therefore, AST is a potential prognostic marker in leptospirosis. Prompt initiation of doxycycline antibiotic therapy combined with aggressive supportive care is essential for favourable outcomes, though severe complications like acute kidney injury and markedly elevated AST portend higher mortality.

Limitations: The study design being retrospective had its inherent limitations in data collection. Occupation and specific exposure risks, important in leptospirosis, were not analysed. The confirmation of clinically suspected cases was by *Leptospira* IgM ELISA test which was available at the study hospital. As this was a retrospective data collection, MAT was not performed. In this study the laboratory parameters recorded at the time of admission was considered. A prospective study design with a case and control group is suggested to evaluate the laboratory parameters at different stages of the disease to note any marker which predicts a severe course of the disease, to identify such patients for early intervention.

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Conflict of Interests

The authors declare no conflicts of interest.

Ethical Approval

The study was approved by the Institutional Ethics Committee of Nitte (Deemed to be University), KS Hegde Medical Academy under the No. INST.EC/EC/029/2023.

Artificial Intelligence Statement

The authors confirm that there was no use of AI-assisted technology for assisting in the writing of the manuscript.

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