CLINICAL PROFILE AND OUTCOMES OF LABORATORY-CONFIRMED AND SERONEGATIVE LEPTOSPIROSIS IN A TERTIARY CARE HOSPITAL IN COASTAL SOUTH INDIA

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ABSTRACT

Background

Leptospirosis is a widespread zoonotic infection and an important cause of acute febrile illness in tropical and subtropical regions. Early diagnosis remains challenging because laboratory confirmation may be delayed or unavailable, and a substantial proportion of patients with clinically suspected leptospirosis remain seronegative despite presenting with characteristic clinical manifestations. Understanding the differences in clinical presentation, complications, management requirements, and outcomes between laboratory-confirmed and seronegative cases is essential for improving patient care and reducing disease-related morbidity and mortality.

Aim

To compare the clinical profile, complications, management, and outcomes of laboratory-confirmed and seronegative leptospirosis among patients admitted to a tertiary care hospital in coastal South India.

Objectives

1. To evaluate and compare the demographic characteristics, clinical features, laboratory parameters, and complications among patients with laboratory-confirmed and seronegative leptospirosis.
2. To assess and compare treatment requirements, intensive care utilization, and clinical outcomes, including mortality, among laboratory-confirmed and seronegative leptospirosis patients.

Methods

A hospital-based comparative observational study was conducted among patients admitted with clinically suspected leptospirosis to a tertiary care hospital in coastal South India. A total of 164 patients were included in the study. Based on laboratory investigations, patients were classified into laboratory-confirmed leptospirosis (n=90) and seronegative leptospirosis (n=74) groups. Demographic characteristics, clinical manifestations, laboratory parameters, complications, treatment requirements, intensive care utilization, and outcomes were recorded and compared between the two groups. Continuous variables were expressed as mean ± standard deviation and compared using the independent t-test, while categorical variables were expressed as frequencies and percentages and analyzed using the Chi-square test or Fisher's exact test. A p value of <0.05 was considered statistically significant.

Results

The mean age of the study population was 51.68 ± 13.40 years, and males constituted 80.0% of the patients. The demographic characteristics were comparable between the two groups. Comorbidities were more frequent among laboratory-confirmed patients (55.6% vs. 40.5%, p=0.061). Thrombocytopenia (89.9% vs. 87.5%, p=0.802) and acute kidney injury (80.2% vs. 84.5%, p=0.535) were the most common complications in both groups. Laboratory-confirmed patients demonstrated higher rates of shock (48.7% vs. 36.9%, p=0.178), non-invasive ventilation (18.3% vs. 11.3%, p=0.333), mechanical ventilation (15.1% vs. 9.7%, p=0.439), and mortality (28.3% vs. 17.0%, p=0.250). The mean duration of ICU stay was significantly longer among laboratory-confirmed patients compared to seronegative patients (4.48 ± 4.54 days vs. 2.96 ± 2.94 days, p=0.028). Ward stay duration was comparable between the groups (7.04 ± 4.17 days vs. 6.95 ± 3.32 days, p=0.885).

Conclusion

Laboratory-confirmed leptospirosis was associated with a greater severity of illness, reflected by higher frequencies of complications, increased need for intensive care and ventilatory support, longer ICU stays, and higher mortality compared to seronegative leptospirosis. However, the substantial overlap in clinical presentation between the two groups emphasizes that seronegative status does not exclude severe disease. In endemic regions, clinicians should maintain a high index of suspicion and initiate early management based on clinical assessment, irrespective of initial laboratory confirmation, to improve patient outcomes.

Keywords

Leptospirosis; Seronegative leptospirosis; Acute kidney injury; Thrombocytopenia; Intensive care unit; Mortality.

How to cite this article: Pratheeksha Rai G, Suresh G. Clinical Profile and Outcomes of Laboratory-Confirmed and Seronegative Leptospirosis in a Tertiary Care Hospital in Coastal South India. Int J Drug Deliv Technol. 2026;16(64s):528-538. DOI: 10.25258/ijddt.16.64s.52

INTRODUCTION

Leptospirosis is a globally important zoonotic disease caused by pathogenic spirochetes belonging to the genus Leptospira. The disease is transmitted to humans through direct contact with infected animals or indirect exposure to environments contaminated with the urine of infected reservoir hosts, particularly rodents, cattle, pigs, and dogs. Human infection commonly occurs through exposure to contaminated water or soil via abrasions in the skin or through mucous membranes. Owing to its wide spectrum of clinical manifestations, ranging from a mild self-limiting febrile illness to severe multiorgan dysfunction, leptospirosis remains a significant public health challenge, especially in tropical and subtropical regions.[1]

Leptospirosis is recognized as one of the most widespread yet neglected zoonotic diseases worldwide. The burden of the disease is substantial, with an estimated 1.03 million cases and approximately 58,900 deaths occurring annually. The highest incidence rates are reported from South and Southeast Asia, Oceania, Latin America, and sub-Saharan Africa, where warm climatic conditions, heavy rainfall, flooding, inadequate sanitation, rapid urbanization, and occupational exposure create favourable conditions for disease transmission.[2] Climate change and the increasing frequency of extreme weather events have further contributed to the emergence and re-emergence of leptospirosis in endemic regions.[3]

India is among the countries with the highest burden of leptospirosis due to its tropical climate, extensive agricultural activities, recurrent monsoon-associated flooding, and large rural population engaged in occupations involving frequent contact with contaminated water and animals. The disease is endemic in several states, including Tamil Nadu, Kerala, Karnataka, Maharashtra, Gujarat, and the Andaman and Nicobar Islands. Recurrent outbreaks have been documented in coastal regions of South India, particularly during and following the monsoon season. [4] Tamil Nadu has consistently reported a high number of leptospirosis cases, and the disease remains an important cause of acute febrile illness requiring hospitalization in tertiary care centres across the state. [5]

The clinical presentation of leptospirosis is highly variable and nonspecific, making early diagnosis challenging. Patients commonly present with fever, headache, myalgia, conjunctival suffusion, jaundice, vomiting, and abdominal pain. Severe disease, often referred to as Weil's disease, may manifest with acute kidney injury, hepatic dysfunction, pulmonary haemorrhage, myocarditis, shock, meningitis, and multiorgan failure. The overlap of clinical features with other endemic tropical infections such as dengue, malaria, scrub typhus, enteric fever, and viral hepatitis frequently leads to diagnostic uncertainty and delayed treatment. [6]

Laboratory confirmation of leptospirosis relies on serological tests such as immunoglobulin M enzyme-linked immunosorbent assay (IgM ELISA) and the microscopic agglutination test (MAT), as well as molecular methods including polymerase chain reaction (PCR). However, the sensitivity of these diagnostic modalities varies according to the stage of illness. During the early phase of infection, antibody titres may remain undetectable, resulting in false-negative serological results despite strong clinical suspicion. Consequently, a significant proportion of patients with clinically compatible illness remain seronegative, posing diagnostic and therapeutic challenges in routine clinical practice. [7]

Comparative evaluation of laboratory-confirmed and seronegative leptospirosis is essential to improve understanding of the disease spectrum, identify distinguishing clinical and laboratory characteristics, and optimize management strategies. Data comparing these two groups remain limited, particularly in the Indian context and in coastal regions where the disease burden is high. Understanding the similarities and differences in presentation, complications, and outcomes among laboratory-confirmed and seronegative cases may facilitate early recognition, timely initiation of therapy, and improved patient outcomes.

Therefore, the present study aims to assess the clinical profile, laboratory characteristics, complications, and outcomes of patients with laboratory-confirmed and seronegative leptospirosis admitted to a tertiary care hospital in coastal South India.

AIM

To compare the clinical profile, complications, management, and outcomes of laboratory-confirmed and seronegative leptospirosis among patients admitted to a tertiary care hospital in coastal South India.

OBJECTIVES

1. To evaluate and compare the demographic characteristics, clinical features, laboratory parameters, and complications among patients with laboratory-confirmed and seronegative leptospirosis.
2. To assess and compare treatment requirements, intensive care utilization, and clinical outcomes, including mortality,

among laboratory-confirmed and seronegative leptospirosis patients.

METHODOLOGY

Study Design

Hospital-based retrospective observational analytical study.

Study Setting

Department of General Medicine and Intensive Care Unit of a tertiary care teaching hospital in coastal South India.

Study Duration

All eligible patients admitted during the study period will be included. The study duration shall be specified according to the period of data collection from hospital records.

Study Population

Adult patients admitted with a clinical diagnosis of leptospirosis.

Sample Size

A total of **164 patients** with clinically suspected leptospirosis were included in the study.

Study Groups

- **Group 1:** Laboratory-confirmed leptospirosis (positive IgM ELISA)
- **Group 2:** Seronegative leptospirosis (negative or non-reactive IgM ELISA with compatible clinical features)

Inclusion Criteria

- Patients aged ≥18 years.
- Patients admitted with clinical suspicion of leptospirosis.
- Patients with available serological test results and complete clinical records.

Exclusion Criteria

- Patients with incomplete medical records.
- Patients with alternative confirmed diagnoses explaining the clinical presentation.
- Patients with missing outcome data.

Data Collection

Data were extracted from hospital case records using a predesigned data collection proforma. The following variables were collected:

- Demographic characteristics (age and sex)
- Clinical manifestations
- Comorbidities
- Serological status (IgM ELISA)
- Complications including thrombocytopenia, acute kidney injury, myocarditis, shock, coagulopathy, and acute respiratory distress syndrome
- Requirement for dialysis, non-invasive ventilation, invasive mechanical ventilation, and platelet transfusion
- Duration of ICU stay and ward stay
- Clinical outcome (discharge, death, or discharge against medical advice)

Statistical Analysis: Data will be entered into Microsoft Excel and analysed using SPSS version 26.0. Categorical variables will be expressed as frequency and percentage. Continuous variables will be expressed as mean ± standard deviation or median with interquartile range depending on data distribution. Independent Student's t-test will be used to compare normally distributed continuous variables. Mann–Whitney U test will be used for non-normally distributed continuous variables. Chi-square test or Fisher's exact test will be used to compare categorical variables. A p-value <0.05 will be considered statistically significant.

RESULTS

A total of 164 patients admitted with a clinical diagnosis of leptospirosis were included in the study. Based on laboratory testing, 90 patients (54.9%) were classified as laboratory-confirmed leptospirosis, while 74 patients (45.1%) were categorized as seronegative leptospirosis.

Table 1. Comparison of demographic characteristics between laboratory-confirmed and seronegative leptospirosis patients

Variable	Laboratory-confirmed (n=90)	Seronegative (n=74)	Total (n=164)	p value
Age (years), Mean ± SD	51.17 ± 14.27	52.30 ± 12.34	51.68 ± 13.40	0.592
Male sex, n (%)	71 (81.6)	57 (78.1)	128 (80.0)	0.692
Female sex, n (%)	16 (18.4)	16 (21.9)	32 (20.0)	
Age group, n (%)				0.396
<30 years	10 (11.5)	5 (6.8)	15 (9.4)	
30–45 years	14 (16.1)	19 (26.0)	33 (20.6)	
46–60 years	37 (42.5)	29 (39.7)	66 (41.3)	
>60 years	26 (29.9)	20 (27.4)	46 (28.7)	

Interpretation:

The mean age of patients was comparable between the two groups, with laboratory-confirmed cases having a mean age of 51.17 ± 14.27 years and seronegative cases having a mean age of 52.30 ± 12.34 years (p=0.592). Males predominated in both groups, accounting for over three-fourths of the study population. The majority of patients belonged to the 46–60 years age group. No statistically significant differences were observed in age distribution or sex between the two groups, indicating comparable baseline demographic characteristics.

Table 2. Comparison of comorbidity profile between laboratory-confirmed and seronegative leptospirosis patients

Variable	Laboratory-confirmed (n=90)	Seronegative (n=74)	Total (n=164)	p value
Presence of comorbidity, n (%)	50 (55.6)	30 (40.5)	80 (48.8)	0.061
No comorbidity, n (%)	40 (44.4)	44 (59.5)	84 (51.2)	

Interpretation:
Comorbid illnesses were observed in nearly half of the study population. A higher proportion of laboratory-confirmed patients had associated comorbidities compared with seronegative patients (55.6% vs. 40.5%); however, this difference did not reach statistical significance (p=0.061). This finding suggests a trend toward increased disease burden among laboratory-confirmed cases.

Table 3. Comparison of major complications between laboratory-confirmed and seronegative leptospirosis patients

Complication	Laboratory-confirmed (n=90)	Seronegative (n=74)	p value
Thrombocytopenia, n (%)	80 (89.9)	63 (87.5)	0.802
Acute kidney injury, n (%)	69 (80.2)	60 (84.5)	0.535
Myocarditis, n (%)	26 (29.9)	19 (26.8)	0.725
Shock, n (%)	38 (48.7)	24 (36.9)	0.178

Interpretation:
Thrombocytopenia and acute kidney injury were the most common complications observed in both groups. Acute kidney injury affected more than four-fifths of the patients, while thrombocytopenia was present in approximately 90% of cases. Myocarditis and shock occurred less frequently. Although laboratory-confirmed patients demonstrated a higher frequency of shock, no statistically significant differences were observed in complication rates between the two groups.

Table 4. Comparison of respiratory support requirements between laboratory-confirmed and seronegative leptospirosis patients

Variable	Laboratory-confirmed (n=90)	Seronegative (n=74)	p value
Non-invasive ventilation required, n (%)	13 (18.3)	7 (11.3)	0.333
Mechanical ventilation required, n (%)	11 (15.1)	6 (9.7)	0.439

Interpretation:
Respiratory support requirements were numerically higher among laboratory-confirmed leptospirosis patients. Non-invasive ventilation was required in 18.3% of confirmed cases compared with 11.3% of seronegative cases, while mechanical ventilation was required in 15.1% and 9.7% of patients, respectively. However, these differences were not statistically significant.

Table 5. Comparison of intensive care utilization between laboratory-confirmed and seronegative leptospirosis patients

Variable	Laboratory-confirmed (n=90)	Seronegative (n=74)	p value
ICU stay (days), Mean ± SD	4.48 ± 4.54	2.96 ± 2.94	0.028*
Ward stay (days), Mean ± SD	7.04 ± 4.17	6.95 ± 3.32	0.885

Interpretation:
Laboratory-confirmed leptospirosis patients had a significantly longer ICU stay compared with seronegative patients (4.48 ± 4.54 vs. 2.96 ± 2.94 days, p=0.028). However, the duration of ward stay was similar between the groups (p=0.885). These findings suggest that laboratory-confirmed patients may require more intensive monitoring and critical care support.

Table 6. Comparison of mortality outcomes between laboratory-confirmed and seronegative leptospirosis patients

Outcome	Laboratory-confirmed (n=90)	Seronegative (n=74)	p value
Mortality, n (%)	17 (28.3)	8 (17.0)	0.250
Survival, n (%)	43 (71.7)	39 (83.0)	

Interpretation:
The mortality rate was higher among laboratory-confirmed leptospirosis patients than among seronegative patients (28.3% vs. 17.0%). Although this difference was not statistically significant

(p=0.250), the trend suggests greater disease severity among laboratory-confirmed cases.

Table 7. Overall comparison of clinical severity indicators between laboratory-confirmed and seronegative leptospirosis patients

Severity indicator	Laboratory-confirmed (n=90)	Seronegative (n=74)	p value
Acute kidney injury, n (%)	69 (80.2)	60 (84.5)	0.535
Shock, n (%)	38 (48.7)	24 (36.9)	0.178
Mechanical ventilation, n (%)	11 (15.1)	6 (9.7)	0.439
ICU stay (days), Mean ± SD	4.48 ± 4.54	2.96 ± 2.94	0.028 *
Mortality, n (%)	17 (28.3)	8 (17.0)	0.250

Interpretation:

Laboratory-confirmed leptospirosis patients consistently demonstrated more severe clinical profiles, including higher rates of shock, increased need for mechanical ventilation, longer ICU stays, and higher mortality. Among these indicators, only ICU stay duration showed a statistically significant difference. These findings suggest that laboratory confirmation may identify patients with more severe disease manifestations and greater healthcare resource utilization.

Summary of key findings

Laboratory-confirmed leptospirosis constituted 54.9% of the study population. Both groups were comparable in terms of age and sex distribution. Thrombocytopenia and acute kidney injury were the most frequent complications in both groups. Laboratory-confirmed patients showed a trend toward increased shock, respiratory support requirements, and mortality. ICU stay was significantly longer among laboratory-confirmed patients. Overall ward stay was similar between the groups. Laboratory-confirmed leptospirosis was associated with greater clinical severity and higher intensive care utilization.

DISCUSSION

The present study compared the clinical profile, complications, management requirements, and outcomes between laboratory-confirmed and seronegative leptospirosis patients admitted to a tertiary care hospital in coastal South India. A total of 164 clinically suspected cases were analysed, of whom 54.9% were laboratory-confirmed. The findings demonstrate that although both groups shared similar demographic characteristics and clinical manifestations, laboratory-confirmed cases exhibited a trend toward greater disease severity, increased intensive care utilization, and higher mortality.

The demographic profile of the present study showed that middle-aged adults constituted the majority of cases, with a mean age of approximately 52 years, and males represented nearly 80% of the study population. Similar observations have been consistently reported in studies from tropical regions, where leptospirosis predominantly affects economically productive age groups engaged in occupations involving environmental exposure to contaminated water and soil. Male predominance has been attributed to greater occupational exposure among agricultural workers, sewage workers, and individuals involved in outdoor activities. [8–10]

The comparable age and sex distribution observed between laboratory-confirmed and seronegative patients suggests that clinical suspicion of leptospirosis remains high among all patients presenting with acute febrile illness in endemic regions, regardless of serological status. Seronegative cases may represent patients in the early phase of infection before antibody development, infections caused by different serovars with variable serological responses, or patients with alternative infectious etiologies presenting with similar clinical features. [9,11]

Comorbid conditions were observed in nearly half of the study population, with a higher proportion among laboratory-confirmed cases. Although the difference was not statistically significant, the presence of underlying illnesses may predispose patients to more severe disease manifestations. Previous studies have demonstrated that advanced age, diabetes mellitus, hypertension, chronic liver disease, and pre-existing renal dysfunction are associated with increased severity and adverse outcomes in leptospirosis. [12,13]

Among complications, thrombocytopenia and acute kidney injury (AKI) were the most frequent findings in both groups. Thrombocytopenia was observed in approximately 90% of patients, highlighting its importance as a key laboratory marker in severe leptospirosis. The pathogenesis of thrombocytopenia is multifactorial and includes direct endothelial injury, platelet consumption, immune-mediated destruction, and disseminated intravascular coagulation. Similar high rates of thrombocytopenia have been reported in severe leptospirosis cohorts from India and Southeast Asia, where platelet counts have also been shown to correlate with disease severity and mortality.[10,12]

Acute kidney injury was present in more than 80% of patients in both groups, emphasizing the substantial renal burden associated with leptospirosis in hospitalized patients. Leptospiral AKI is characterized by acute tubulointerstitial nephritis, tubular dysfunction, hypokalemia, and

non-oliguric renal failure during the early stages. The high prevalence of AKI in the present study likely reflects delayed presentation and referral of severe cases to tertiary care centers. Previous studies have identified AKI as one of the most important predictors of intensive care requirement, prolonged hospitalization, and mortality in leptospirosis. [13,14]

Myocarditis and shock were also commonly encountered complications, with a higher proportion observed among laboratory-confirmed patients. Cardiovascular involvement in leptospirosis ranges from electrocardiographic abnormalities to fulminant myocarditis and circulatory collapse. The higher occurrence of shock among confirmed cases in the present study supports earlier evidence suggesting that laboratory-confirmed disease is often associated with higher bacterial burden and more severe systemic inflammation. [11,14]

Respiratory support requirements, including non-invasive ventilation and mechanical ventilation, were numerically greater among laboratory-confirmed patients, although statistical significance was not achieved. Pulmonary involvement in leptospirosis can vary from mild respiratory symptoms to severe pulmonary hemorrhage syndrome and acute respiratory distress syndrome (ARDS), both of which are associated with high mortality rates. The requirement for ventilatory support is widely recognized as a marker of severe disease and multiorgan dysfunction. [12,15]

A major finding of the present study was the significantly longer ICU stay among laboratory-confirmed patients compared with seronegative patients. This observation indicates increased healthcare resource utilization and reflects the greater severity of illness among seropositive individuals. Previous studies have shown that severe leptospirosis frequently necessitates prolonged intensive care management due to complications such as AKI, shock, respiratory failure, and multiorgan dysfunction syndrome. [13,15]

Although mortality was higher among laboratory-confirmed patients (28.3%) compared with seronegative patients (17.0%), the difference was not statistically significant. Nevertheless, the observed mortality rates highlight the substantial burden of severe leptospirosis in tertiary care settings. Similar studies have reported mortality rates ranging from 10% to 40%, particularly among patients with pulmonary hemorrhage, shock, severe AKI, and multiorgan failure. Delayed diagnosis, limited access to intensive care facilities, and delayed initiation of antimicrobial therapy have been identified as major contributors to adverse outcomes. [12,16]

Overall, the present study demonstrates that laboratory-confirmed leptospirosis is associated with more severe disease manifestations, longer ICU stays, greater need for organ support, and higher mortality. However, the substantial overlap in clinical presentation between laboratory-confirmed and seronegative cases reinforces the importance of maintaining a high index of suspicion in endemic areas. Early recognition and prompt initiation of treatment should be prioritized irrespective of initial serological results to improve patient outcomes.

CONCLUSION

The present study demonstrated that laboratory-confirmed and seronegative leptospirosis patients shared similar demographic characteristics and clinical profiles, highlighting the diagnostic challenges associated with this disease in endemic regions. Thrombocytopenia and acute kidney injury were the most frequent complications observed in both groups, underscoring the multisystem nature of leptospirosis. Although laboratory-confirmed patients exhibited higher rates of shock, ventilatory support requirements, and mortality, these differences were not statistically significant. The duration of intensive care unit stay was significantly longer among laboratory-confirmed patients, indicating greater disease severity and increased healthcare resource utilization. However, overall ward stay duration was comparable between the groups. Importantly, the occurrence of severe complications and adverse outcomes among seronegative patients emphasizes that negative serological tests do not exclude clinically significant leptospirosis, particularly during the early phase of illness. Therefore, in endemic settings such as coastal South India, prompt clinical recognition and early initiation of appropriate treatment should be prioritized irrespective of initial laboratory status. A high index of clinical suspicion, combined with timely supportive care and close monitoring for complications, remains essential for reducing morbidity and mortality associated with leptospirosis.

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