10.5152/turkjnephrol.2025.251024

Original Article

Turkish Journal of Nephrology

Leptospirosis-Associated Acute Kidney Injury—Still a Major Burden in Tropical Countries?

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ABSTRACT

Background: Leptospirosis is a common condition that affects people from the tropics. This disease is known to cause severe morbidity and mortality. Acute kidney injury (AKI) is commonly observed in leptospirosis patients. It was previously thought to occur only in severe forms of the disease, also known as Weil's disease. The current study was conducted to evaluate kidney involvement in leptospirosis in the era of early diagnosis and widespread antibiotic use.
Methods: A retrospective study was conducted over a period of 5 years, including all patients with a proven diagnosis of leptospirosis. The clinical characteristics and kidney involvement were noted in detail. Analysis was done to evaluate the frequency of complications and recovery characteristics of the patients with this disease.
Results: Acute kidney injury was common with leptospirosis and was present in 26.7% of patients; however, hypokalemia and other electrolyte abnormalities were seen only in 17.05% of the total patient population. There appears to be significant progression to chronic kidney disease (CKD) in patients with leptospirosis with 80% of patients who require dialysis during the AKI episode going on to varying stages of kidney failure in the future and 33.3% of patients requiring continuing KRT. Patients with AKI had an increased mortality compared to patients without AKI in leptospirosis.
Conclusion: Leptospirosis continues to be a significant contributor to mortality and morbidity even today. Abnormal electrolytes previously believed to be common in this disease, need not always be present. In view of a high rate of AKI to CKD transition, screening of all patients with AKI and leptospirosis may be recommended.
Keywords: Leptospirosis, acute kidney injury, progression to chronic kidney disease, hypokalemia, non-oliguric AKI

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Cite this article as: Elayaperumal I, Keeppallil KTJ, Jose N, Matcha J. Leptospirosis-associated AKI—still a major burden in tropical countries?. *Turk J Nephrol.* 2025;34(4):281-288.

INTRODUCTION

Leptospirosis is an important zoonotic disease that occurs worldwide and is more common in warm and humid environments. Humans with occupational exposure to animals such as sewage workers, veterinarians, or those in contact with contaminated water from infected animal urine during floods following heavy rainfall are at high risk for leptospirosis. Clinical manifestations vary from mild flu-like symptoms to acute severe illness with multiorgan dysfunction and associated mortality. A triad of fever, jaundice, and acute kidney injury (AKI) should raise the suspicion of leptospirosis.[1]

Acute kidney injury occurs in 40-87% of patients with leptospirosis. It can vary from mild pre-renal azotemia to severe dialysis requiring AKI in 10-60% of patients.[2] Acute interstitial nephritis is the most common kidney lesion observed in leptospirosis, with tubular dysfunction causing hypokalemia and hypomagnesemia. Acute kidney injury occurs either because of direct injury by the organism or indirectly via hypovolemia, hypotension, hyperbilirubinemia, endothelial injury, and rhabdomyolysis. Mortality from leptospirosis is high, occurring in up to 20% of patients, despite the widespread availability of antibiotics. Data on the risk factors

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for the development of AKI and mortality in leptospirosis are scarce. Hence, the current study aimed to identify the prevalence, clinical presentation, risk factors associated with the development of AKI, immediate outcomes of AKI, and impact of various clinical and laboratory features on mortality in the current era of widespread antibiotic therapy.

MATERIAL AND METHODS

This retrospective observational study was conducted at a single tertiary care center in South India. All consecutive patients who were found to have a positive ELISA for leptospirosis and were admitted between January 2015 and November 2020 were included in the study. Data were collected using the hospital's electronic system. The study was approved by Sri Ramachandra Institutional Ethics Committee (Approval No: IEC-NI/21/FEB/77/51 Date: 08.03.2021). Patients with incomplete data and pediatric patients were excluded from the study. In view of the retrospective nature of the study, informed consent was not mandated by the ethics committee of the institution.

A total of 258 adult patients were included in this study. Patients were divided into two groups: those with AKI (group) and those without AKI (non-AKI group), based on the KDIGO (Kidney Disease: Improving Global Outcomes) definition of AKI. Sixty-nine (26.7%) and 189 (73.3%) patients were included in the AKI and non-AKI groups, respectively.

Demographic factors such as age, sex, duration of hospital stay, clinical data such as the presence of fever, myalgias, jaundice, oliguria, bleeding diathesis, altered sensorium, and conjunctival suffusion and laboratory data such as complete blood count, presence of leucocytosis, thrombocytopenia, BUN, creatinine, electrolytes, liver function tests, coagulation profile, creatine phosphokinase (CPK), requirement of dialysis, kidney recovery, and patient survival were collected. The presence of comorbidities, such as diabetes and hypertension, was also noted.

Statistical Analysis

Data analysis was performed using SPSS version 17 (SPSS Inc.; Chicago, IL, USA). All categorical variables are expressed as numbers and percentages, and continuous variables are expressed as mean ± SD. Values between the AKI and non-AKI groups, survivors, and non-survivors were compared using Student's *t*-test or the Mann–Whitney test, as appropriate. The chi-square test was used to compare the categorical variables. Univariate Cox regression analyses were performed, with mortality as the outcome variable. All statistical tests were performed two-tailed, and a significance level of *P*-value of <.05 was considered statistically significant.

MAIN POINTS

- Leptospirosis is still associated with significant organ involvements such as the kidney, lung, and liver.
- All patients with kidney involvement need not follow that typically described, such as with hypokalemia and hypomagnesemia.
- Acute kidney injury is seen in 26.7% of patients and is associated with poor long-term recovery of kidney function.
- It can lead to chronic kidney disease and long term requirement for dialysis.

RESULTS

After screening the hospital online database over a period of 5 years, 258 patients who met the inclusion criteria were identified. The baseline characteristics are listed in Table 1. The mean age of the study population was 44 ± 16.67 years. More men were noted in this study. Diabetes mellitus was also observed in 25.2% of patients (Table 1).

The mean liver enzymes and creatinine-phosphokinase (CPK) were elevated. The mean sodium level was low, while the mean potassium level was normal (Table 1). The most common laboratory abnormality was metabolic acidosis (51.2%), followed by liver enzyme abnormalities (39.1%) (Figure 1). Hypokalemia was noted in 17.1% of the patients.

Almost all the patients (98.4%) had fever, as shown in Figure 2. The second most common symptom among patients was gastrointestinal (GI) disturbances, such as nausea, diarrhea, and vomiting. Myalgia was noted in 23.6% of the patients. Oliguria and conjunctival suffusion were rarely noted in 6.2% and 0.15% of patients, respectively.

The most common organ involved in leptospirosis was the kidney, which was observed in 41% of all patients (Figure 3). Shock, central nervous system, and lung involvement were observed in less than 20% of patients. Multi-organ involvement was noted in 12% of the patients.

Acute kidney injury was present in 26.7% of patients (Table 2). Proteinuria was noted in 18.2% of the patients. Only 5.8% of the patients required KRT (kidney replacement therapy). Among those who required KRT, complete recovery (i.e., return to baseline kidney function or normal kidney function) was seen only in 20%; 33.3% of patients with AKI who were on KRT, required persistent KRT, while the remaining patients had varying degrees of persistent kidney dysfunction. The mean duration of hospital stay due to leptospirosis was 1 week. Most patients recovered (93.8%), with mortality in only 6.2% of patients (Table 1).

The entire study cohort was divided into two groups, AKI and non-AKI, to facilitate comparison. The mean age of the patients in the AKI group was higher than that in the non-AKI group ((52.01 ± 15.01 years vs 41.33 years ±16.10, *P* < .001) (Table 3). Diabetes mellitus (n = 29,42%, P < .001) and hypertension (n = 21, 30.4%; *P* < .001) were significantly associated with AKI.

Table 1. Baseline Characteristics of the Study Population

Characteristics	Frequency (percentage) or mean (SD), N = 258
Age, years	44.19 (2SD 16.67)
Male: Female	163 (63.2%): 95 (36.8%)
Diabetes mellitus	65 (25.2%)
Hypertension	36 (14%)
Baseline laboratory data	
Hemoglobin (g/dL)	11.48 ± 2.41
Total leucocyte count (cells/cu.mm)	9954.84 ± 5777.13
Platelet count (×10^5/μL" or "Lakhs/μL" (should be standardized))	1.93 ± 1.26
SGOT (U/L)	119.60 ± 295.79
SGPT (U/L)	87.95 ± 251.24
Total bilirubin (mg/dL)	2.09 ± 3.44
CPK (mcg/L)	1014.20 ± 2223.22
Serum creatinine (mg/dL) (Admission)	1.35 ± 1.36
Serum creatinine (mg/dL) (Peak)	1.63 ± 1.73
Serum creatinine (mg/dL) (Discharge)	1.17 ± 1.11
Serum sodium (mEq/L)	133.87 ± 5.59
Serum potassium (mEq/L)	3.97 ± 0.66
Serum bicarbonate (mEq/L)	21.25 ± 4.00
Serum calcium (mg/dL)	8.22 ± 1.00
Serum magnesium (mg/dL)	1.79 ± 0.51
Prothrombin time (seconds)	14.85 ± 4.04
Activated partial thromboplastin time (seconds)	31.45 ± 10.96
International normalized ratio	1.25 ± 0.41
Outcome variables	
Recovered from leptospirosis	242 (93.8%)
Duration of hospital stay, days	7.43 (2SD6.94)
Death from leptospirosis	16 (6.2%)

SD, standart deviation.

Leucocytosis (n = 35, 50.7%; $P < .009$), hyperbilirubinemia (n = 22, 31.8%; $P < .005$), coagulation profile abnormalities, proteinuria, hypotension, and bleeding diathesis were more common in the AKI group. The AKI group had a greater number of patients with rhabdomyolysis than the non-AKI group ($P < .01$). Patients with multi-organ dysfunction (n = 17, 24.6%, $P < .001$), requiring mechanical ventilation (n = 13, 18.8%, $P < .001$), and inotropic support (n = 21, 30.4%, $P < .001$) seemed to develop AKI more frequently than patients without these conditions. Central nervous system involvement was more common in the AKI group (n = 9, 13%; $P < .005$). Hospital stay was more prolonged in patients with AKI than without AKI (10.32 ± 10.17 vs. 6.37± 4.93 days, $P < .001$). Mortality was more common among patients with AKI (n = 13, 18.8%; $P < .001$) (Figure 4).

DISCUSSION

Leptospirosis is a common condition that affects people from endemic regions. These regions are generally hot and humid, such as sub-Saharan Africa, India, Malaysia, the Caribbean, and South-east Asia.[3] Disease morbidity due to leptospirosis is very high resulting in 102,000 years lived with living with disability and 2.8 million years of life lost due to the disease.[4] Kidney involvement in leptospirosis is seen in 10-60% of patients.[2] Kidney disease occurs in various forms in leptospirosis, ranging from acute tubular necrosis to tubule-interstitial nephritis, and later progression to chronic kidney disease (CKD). The current study shows the type of renal involvement and current mortality rate in leptospirosis in an endemic region.

Clinical Characteristics of Leptospirosis

As in this study and worldwide, males have been more affected by this disease than females. The reasons contributing to this appear to be exposure-related (at workplaces such as walking through paddy fields or sewer water) and behavioral (associated with perceived severity of the disease).[5] This is also the same reason why the age group most affected by this disease is 10-39 years.[6] In this study, the mean age of patients affected by leptospirosis was 44.19 years. Fever was the most common manifestation of leptospirosis observed in this study. This is a common finding corroborated by several other cohorts worldwide where leptospirosis is endemic. Fever is usually accompanied by severe myalgia, back and calf pain. This was also a common finding in this cohort of patients, where myalgia was noted in 23.6% of the patients. In other cohorts, bleeding manifestations were commonly recorded in leptospirosis[7] however, in this study, bleeding manifestations were uncommon in only 2.7% of patients. Abnormal platelet counts were observed in 25.2% of patients, while abnormal bleeding tests were noted in 7% of patients. The reason for this is not certain; it may be due to an early presentation to the hospital and early initiation of treatment. Jaundice was noted in 6.9% of the patients and was associated with multi-organ involvement. In other studies, liver involvement generally varied widely between less than 20% and >80%.[8]

Kidney Involvement in Leptospirosis

The most common organ affected in this study was the kidney, which was affected to varying degrees in 39% of the patients. In leptospirosis from the tropics, the kidney is the primary organ affected, with involvement varying from between 40% and 60% of cases.[9] In known leptospirosis data, the triad of fever and liver and kidney involvement points to a diagnosis of leptospirosis. The Leptospira outer membrane protein (OMP) triggers inflammation and injury via TLR receptor (toll-like receptor) proteins.[10] This results in tubulointerstitial involvement during the early stages, which can later progress to interstitial fibrosis. Other indirect kidney insults, such as hypovolemia, hypoxemia, and

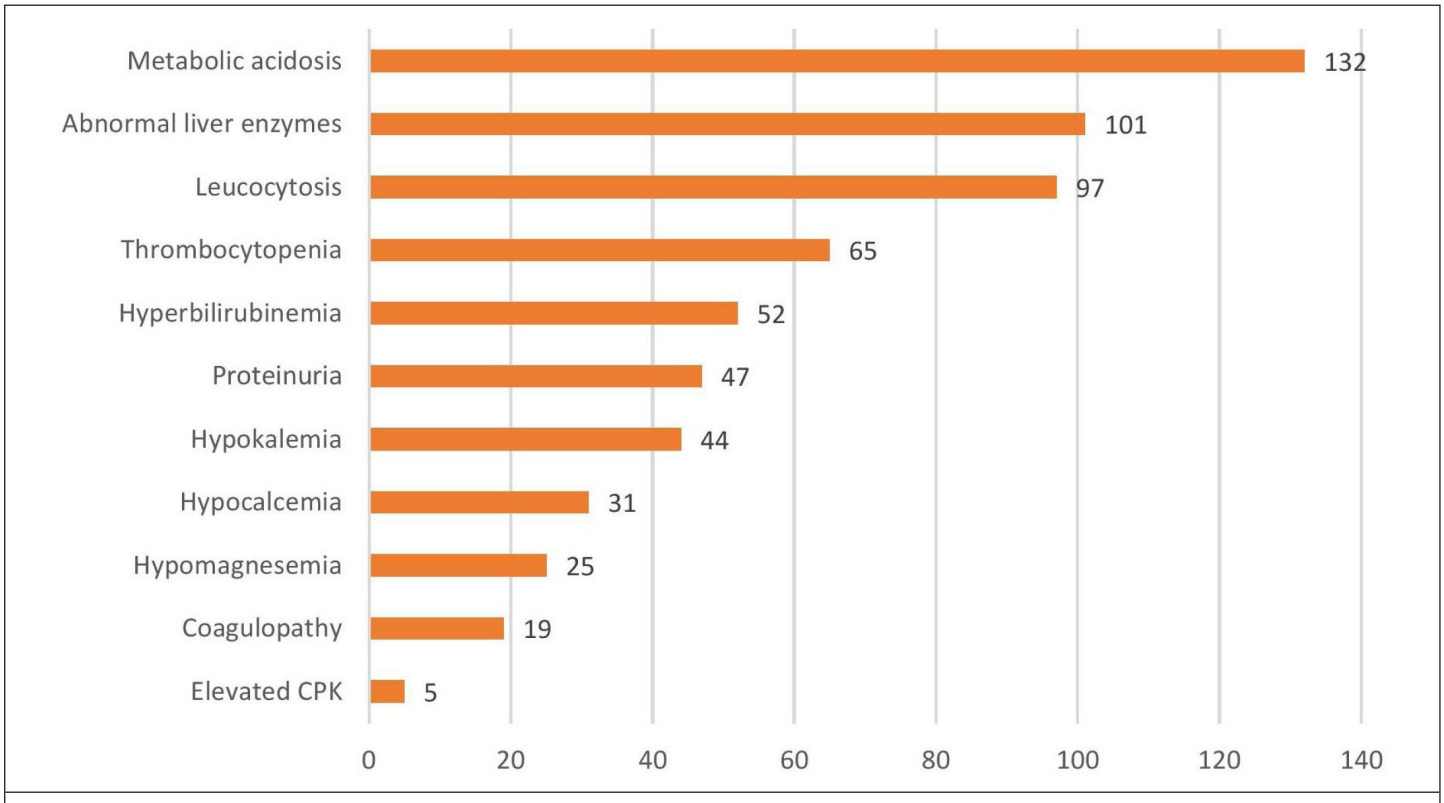

Figure 1. The frequency abnormal laboratory values in leptospirosis.

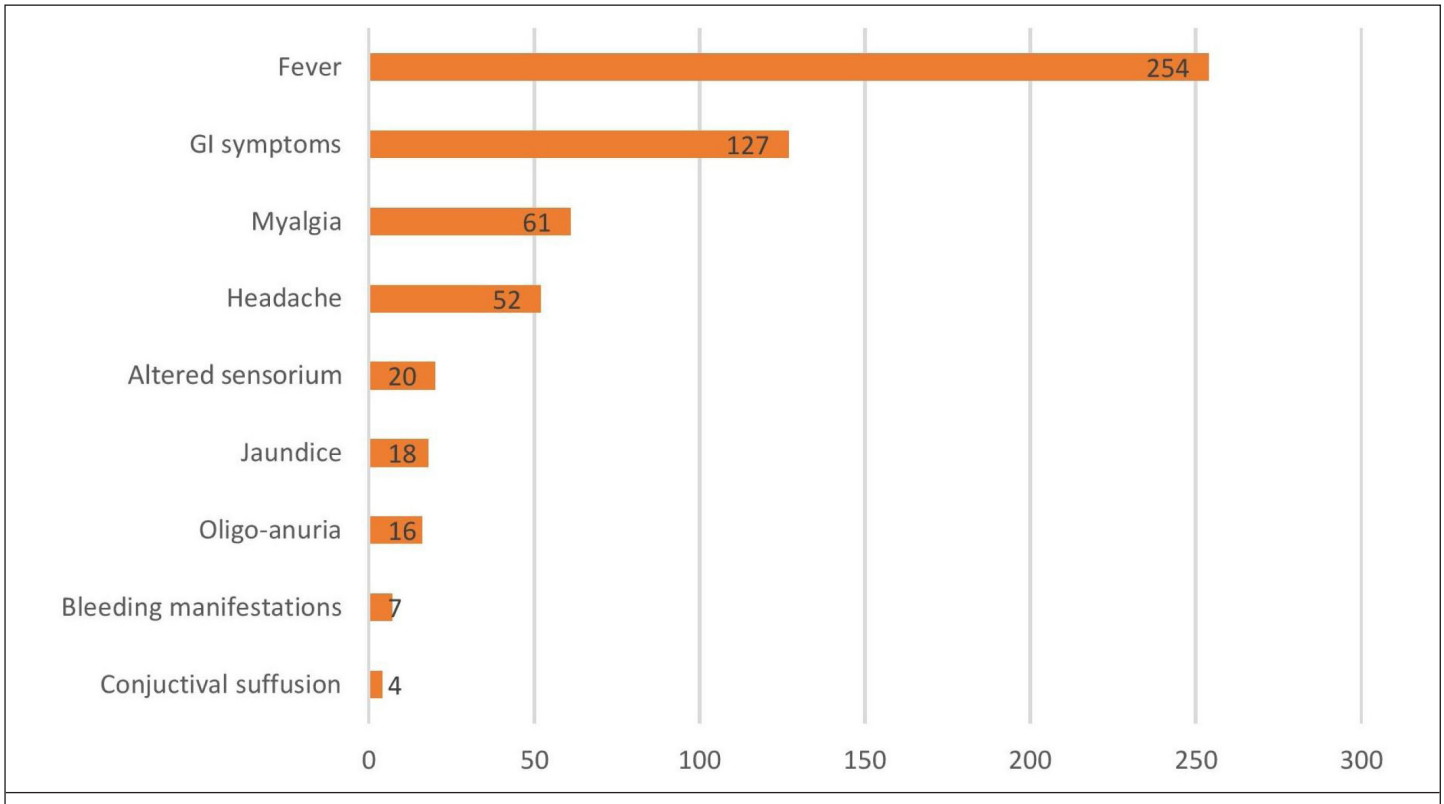

Figure 2. The frequency of clinical characteristics in leptospirosis.

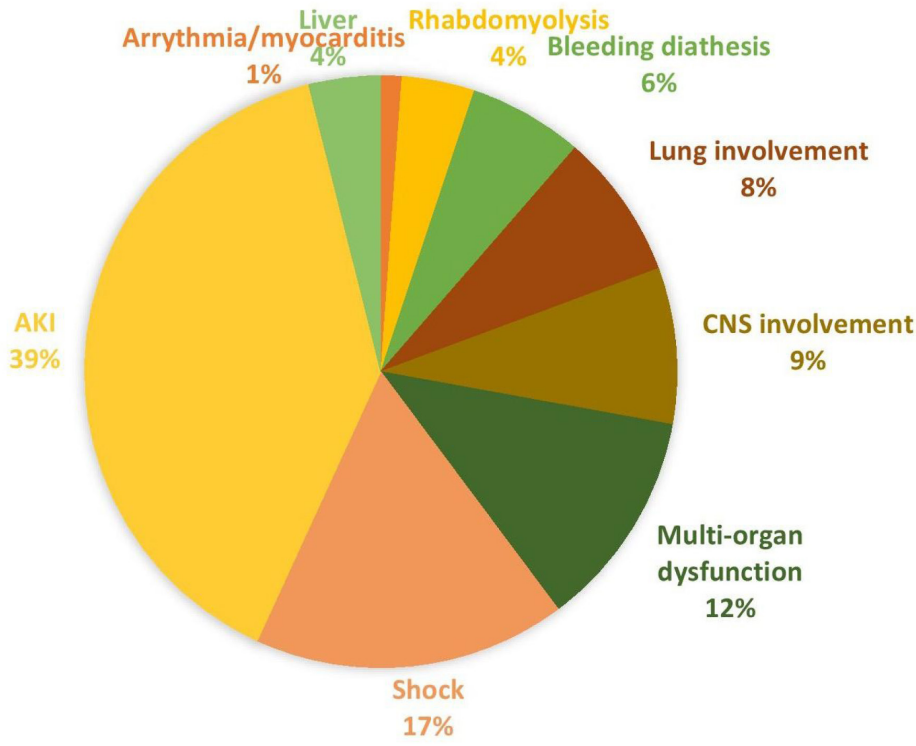

Figure 3. The frequency of organ involvement in leptospirosis.

rhabdomyolysis, also contribute to AKI.[11] The pathognomonic type of kidney involvement in leptospirosis is a non-oliguric AKI with hypokalemia.[12] In fact, certain serovars of leptospirosis are known to cause polyuria due to their effect on the NKCC2 (Na^+-K^+-Cl^- co-transporter) channel in the TAL (thick ascending limb) segment of the loop of Henle.[13] In keeping with data from abroad, in this study, oligo-anuria was uncommon, seen in only 6.2% of patients, and hypokalemia was noted in 17.08% of patients. Among those with AKI only a small proportion—5.8%, required KRT. About one-third of patients who required KRT remained dialysis-dependent after the infection was cleared. This is probably due to interstitial fibrosis and inflammatory pathways triggered by Leptospira. Originally, it was thought that only Weil's disease would have severe AKI requiring dialysis; however, this study adds to the growing body of evidence that even anicteric leptospirosis (a milder form of leptospirosis without major end-organ involvement) can often trigger severe AKI[14] since very few patients in this cohort had jaundice.

Table 2. Characteristics of Kidney Involvement in Leptospirosis

Variables	Frequency (percentage)
AKI present	69 (26.7%)
Stage of AKI	
AKI stage 1	30 (11.6%)
AKI stage 2	21 (8.1%)
AKI stage 3	18 (7.0%)
Proteinuria more than 1+ urine analysis	47 (18.2%)
Kidney replacement therapy (KRT)	
KRT required	15 (5.8%)
SLED	4 (1.6%)
CRRT	1 (0.4%)
IHD	10 (3.9%)
Kidney recovery after AKI	
No recovery	12 (80%)
Recovered	3 (20%)
Persistent KRT required	5 (33.3%)

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; KRT, Kidney replacement therapy; SLED, sustained low-efficiency dialysis.

Hypokalemia was previously thought to occur commonly in leptospirosis, often seen in 35-70% of patients with AKI;[15] however, in this cohort, it was observed in only 17% of patients with leptospirosis. Other electrolyte abnormalities known to occur in leptospirosis include hyponatremia, hypomagnesemia, hypophosphatemia, hypocupremia, hypozincemia, and hypocalcemia.[16] This is usually due to the increased urinary excretion of these compounds. Some of these also occur due to diarrheal illness, which may be part of leptospirosis. In the current study, other electrolytes were also found to be low in keeping with worldwide data; however, the frequency of these manifestations appears to be low (12% and 9.6% for hypocalcemia and hypomagnesemia, respectively).

Table 3. Association between Various Clinical and Laboratory Variables and Acute Kidney Injury

Parameters	AKI		*P*
	AKI GROUP (n, %) (69, ...%)	Non- AKI GROUP (n,%) (189, ...%)	
Age (years)	52.01 ± 15.78	41.33 ± 16.10	<.001
Age			.076
<65 years	55 (79.7%)	167 (88.3%)	
>65 years	14 (20.3%)	22 (11.6%)	
Gender			<.001
Male	60 (86.9%)	103 (54.4%)	
Female	9 (13.0%)	86 (45.5%)	
Diabetes mellitus	29 (42%)	36 (19%)	<.001
Hypertension	21 (30.4%)	15 (7.9%)	<.001
Fever	68 (98.5%)	186 (98.4%)	1.000
Jaundice	6 (8.6%)	12 (6.3%)	.5803
Conjunctival suffusion	3 (75.0%)	1 (25.0%)	.0583
Hemoglobin (g/dL)	10.67 ± 2.73	11.77 ± 2.21	<.001
Total leucocyte counts (/cu.mm)	13042.03 ± 7083.44	8827.78 ± 4764.58	<.00
Leukocytosis	35 (50.7%)	62 (32.8%)	.009
Platelet count (Lacs/cu.mm)	1.77 ± 1.46	1.99 ± 1.18	.052
Thrombocytopenia	23 (33.3%)	42 (24.8%)	.069
Hyperbilirubinemia	22 (31.8%)	30 (15.8%)	.005
Creatine phosphokinase	978.26 ± 1976.88	1051.77 ± 2501.82	.518
S. Creatinine (mg/dL) (Admission)	2.79 ± 1.97	0.83 ± 0.31	<.001
S. Creatinine (mg/dL) (Peak)	3.70 ± 2.26	0.87 ± 0.30	<.001
S. Creatinine (mg/dL) (Discharge)	2.34 ± 1.59	0.75 ± 0.27	<.001
Hypokalemia	15 (21.7%)	29 (15.3%)	.227
Metabolic acidosis	46 (66.6%)	86 (45.5%)	.003
PT (s)	15.77 ± 4.01	14.52 ± 4.01	<.001
aPTT (s)	35.16 ± 14.59	30.10 ± 8.96	<.001
INR	1.36 ± 0.45	1.22 ± 0.38	<.001
Coagulopathy	12 (17.4%)	7 (3.7%)	<.001
Proteinuria	35 (50.7%)	12 (6.3%)	<.001
Hypotension	21 (30.4%)	9 (4.7%)	<.001
Bleeding diathesis	9 (13%)	2 (1.05%)	<.001
Arrhythmias/myocarditis	1 (1.4%)	1 (0.5%)	.464
Rhabdomyolysis	5 (7.2%)	2 (1.05%)	.016
MODS	17 (24.6%)	4 (2.1%)	<.001
Mechanical ventilation	13 (18.8%)	6 (3.1%)	<.001
Inotropic support	21 (30.4%)	7 (3.7%)	<.001
Pulmonary manifestations	4 (0.5%)	10 (5.3%)	1.000
CNS involvement	9 (13%)	6 (3.1%)	.005
Length of hospital stay (days)	10.32 ± 10.17	6.37 ± 4.93	<.001
Mortality	13 (18.8%)	18 (9.5%)	<.001

AKI, acute kidney injury. PT, Prothrombin time, APTT, activated prothrombin time, INR, International normalised ratio, MODS, Multi-organ dysfunction syndrome, CNS, Central nervous system

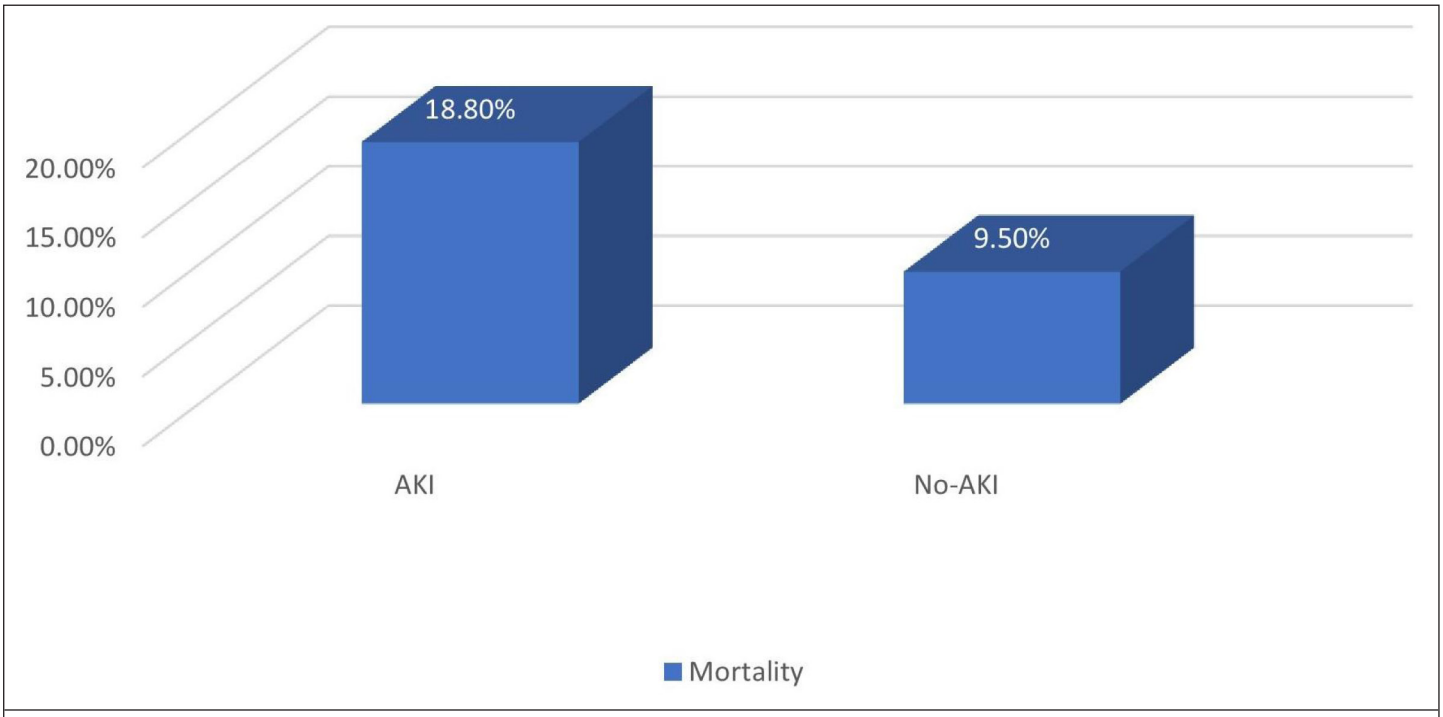

Figure 4. Comparison of mortality in patients with acute kidney injury vs. those without acute kidney injury.

Table 3 showed the association between various clinical risk factors and AKI development. As with other infections that trigger AKI, more severe disease in terms of multi-organ dysfunction, requirement of mechanical ventilation and inotropic support, and severe coagulopathy were significantly associated with the development of AKI. Pre-existing comorbidities such as diabetes seem to influence the development of AKI. One difference from other studies on AKI[17] is that myoglobinuria was not significantly associated with the development of AKI. The mean CPK level was also not very high in this cohort. Acute kidney injury is associated with increased mortality in most infections. Early KRT is believed to decrease mortality in patients with leptospirosis. This could not be proven in this cohort, because the timing of initiation was not recorded in most patient files. Figure 4 showed the difference in mortality between patients with AKI and those without AKI.

Kidney recovery is uncommon in patients with leptospirosis. Multiple studies have delineated pathogenic mechanisms that link the loss of nephrons due to AKI or trigger transcription molecules such as STAT-3 and profibrotic molecules to signal maladaptive repair within the kidney, leading to progression to CKD among those who survive AKI.[2]

The strength of this study was that it is one of the largest single-center studies on the epidemiology and clinical characteristics of leptospirosis in the Indian subcontinent. All significant factors associated with AKI were identified. The limitations of this study were its retrospective nature and single-center design.

Severe kidney involvement in leptospirosis occurs even in the absence of liver injury. Acute kidney injury is frequently non-oliguric. Hypokalemia may be seen even without overt AKI in leptospirosis and may not be as common in AKI as was previously believed. Kidney recovery was observed in only 20% of the patients with leptospirosis and AKI. Acute kidney injury is significantly associated with leptospirosis-related mortality.

Data Availability Statement: Research data supporting this publication is available within this manuscript.

Ethics Committee Approval: Ethical committee approval was received from Sri Ramachandra Institutional Ethics Committee (Approval No: IEC-NI/21/FEB/77/51 Date: 08.03.2021).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – I.E., K.J., J.M.; Design – I.E., K.J., N.J.; Supervision – I.E., J.M.; Resources – N.J., K.J.; Materials – K.J., N.J.; Data Collection and/or Processing – K.J., N.J., I.E.; Analysis and/or Interpretation – N.J., I.E., J.M.; Literature Search – N.J., K.J., I.E.; Writing Manuscript – I.E., N.J.; Critical Review – I.E., N.K., J.M.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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