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LEPTOSPIRAL-ACUTE KIDNEY INJURY; AN ALARMING PICTURE IN GENERAL PRACTICE: A SYSTEMATIC REVIEW

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SUMMARY

Leptospirosis is most widespread zoonotic infection prevalent in hot and humid regions of the world. Severe form of disease is accompanied by several fatal complications. Kidney involvement is most dreaded complication of leptospirosis varies from urine sedimentations to severe acute kidney injury (AKI). Leptospiral AKI (LAKI) is most common and fatal intricacy of leptospirosis with incidence varying from 40-60% and a mortality rate of about 22%. LAKI leads to higher mortality rate and longer hospital stay as compared to those without acute kidney injury. Currently there is no such systemic review that describes association of acute kidney injury with leptospirosis and its impact on mortality and hospital stay. We systematically reviewed 35 research publications showing association of leptospirosis with acute kidney injury. Predictors of leptospiral acute kidney injury and mortality associated with leptospiral AKI were also observed. Most of the participants were male, rural residents and belong to leptospirosis risk groups. Mean hospital stay was 4-15 days and longer hospitalization was found in patients with severe form of acute kidney injury, multi organ failure and wrong diagnosis. Similarly mortality rate was around 19% which is also validated with previous findings. High mortality rate was found in severe acute kidney injury with multi organ failure. Other findings with LAKI were hypokalemia, oliguria and thrombocytopenia.

Leptospirosis with acute kidney injury is severe form of disease that causes high mortality and increases hospitalization Moreover LAKI is also burdening overwhelmed health services so vigilant and proactive approach is needed to manage such patients for their better quality of life.

KEYWORDS: Acute kidney injury, Leptospirosis, Weil`s Disease, Acute renal failure.

INTRODUCTION

Leptospirosis is most widespread zoonotic disease endemic in warm and humid climate. It is not only confined in tropical regions but also widespread in developed and developing countries of the world.[1] Its 100,000 incidence is 0.1-1 in temperate regions, ≥10 in tropical countries, 0.1-2 in developing and developed countries and ≥ 100 in areas of outbreak. [2] Leptospirosis and its high mortality (10%) is also one of the most significant health problems in developed and developing countries even in regions with well-organized health system e.g. USA and Europe. [3] Risk factors associated to leptospirosis are given in table 1.

Genus *Leptospira (L.)*, perpetrator of leptospirosis, comprises more than 300 serovars. The clinical manifestations of leptospirosis range from mild (90%) anicteric infection to severe (10%) icteric *Weil`s* disease, as depicted in figure 1. Multiple organ dysfunction (MOD) may be encountered in leptospiral disease course. The mortality rate among patients with *Weil`s* disease is 10%.[4]

Table 1: Risk groups having high incidence of leptospirosis [3]

Environmental risk factors	Individual/personnel risk factors
Wild and peridomiciliary mammals	Occupation of endemic territories
Floods and other natural disasters	Veterinary practitioners
High reproduction rats in rodents	Agriculture workers
Development of tourism	Slaughterhouse workers
Military invasion	Cleaners and sewers of tunnel
Rise of urban population	Fishermen
Infective waste disposal	Soldiers
Unusual climatic events (heavy rains)	Water games
Hot and humid environment	Contact with fresh water

Kidney is one of the principle target organs of *Leptospira* and the signs of renal impairment may observe in 26.3% to 100% of patients. [5] Acute kidney injury is a prominent feature of leptospirosis induced kidney disturbances. The overall incidence of acute kidney injury (AKI) in leptospirosis is 40-60% in patients having age > 18 years and 17-79% in children of age 4-

17 years. [6] Leptospiral AKI causes high mortality and increase in hospitalization. Mortality rate due to leptospiral AKI (LAKI) is around 22%. [4] Hospital stay of patients due to LAKI is higher (sometimes >3 folds) than those having leptospirosis with no AKI. [7]

Currently there is no systemic review that summarizes studies conducted on association of leptospirosis with acute kidney injury and its impact on hospitalization and mortality. The purpose of current review is to advocate neglected tropical infection leptospirosis, its burden due to leptospiral acute kidney injury and impact of LAKI on mortality and hospital stay.

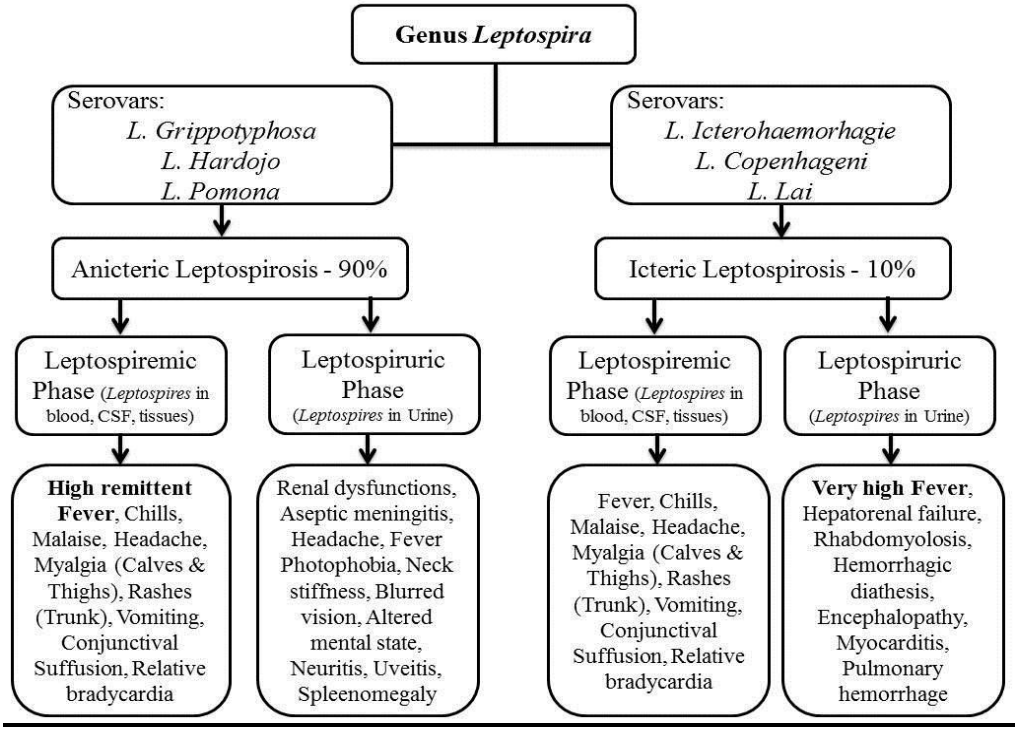

Figure 1: Clinical manifestations of anicteric leptospirosis and and Weil`s disease. [5]

Methodology

We searched articles from databases like PubMed/MEDLINE online database, GoogleScholar, Sciencedirect, EBASE, *SCI* Expanded and Cochrane Library for 1990 – 2014. Following terms were searched: Leptospirosis, leptospiral nephropathy, leptospirosis induced nephropathies, leptospirosis induced kidney damage, Weil`s disease and kidney, icteric and anicteric leptospirosis, leptospirosis and acute kidney injury, leptospirosis associated renal damage, prognosis of leptospirosis, leptospira and kidney dysfunction, multiorgan involvement in leptospirosis, multiorgan failure and leptospirosis , leptospirosis and chronic kidney disease, retrospective and prospective study with leptospirosis and acute

kidney injury, leptospirosis in children, and predictors of leptospirosis induced AKI. Figure 2 shows inclusion/exclusion criteria and methodology adopted for review process.

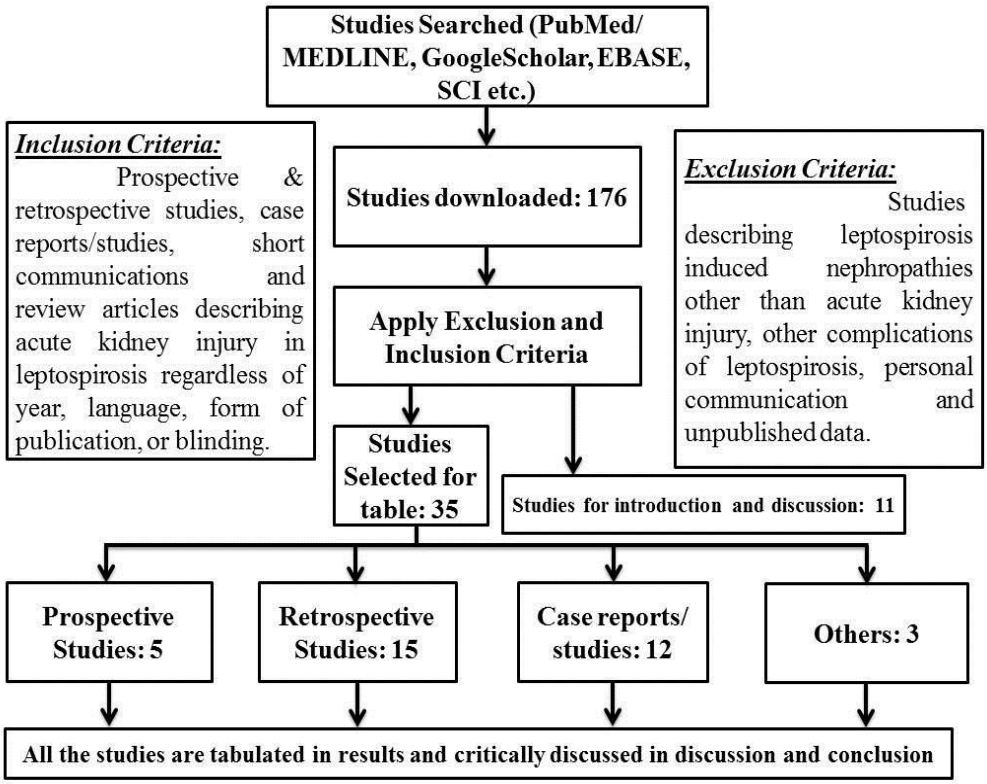

Figure 2: Inclusion and Exclusion criteria and methodology process for systemic review

Leptospiral Acute Kidney Injury (LAKI)

Vary from mild proteinuria to AKI, nephropathies are prominent features of both anicteric self-limited infection and severe icteric *Weil`s* disease.[1] Leptospiral nephropathies include abnormal sediment (50%-80%), proteinuria (50%-80%), acute renal failure (50%-80%), hemolytic uremic syndrome (<10%), hemolysis (<10%), disseminated intravascular coagulation (<10%) and jaundice (50%-80%). The spectrum of leptospiral renal histopathologies includes membranoproliferative glomerulonephritis (<10%), necrotizing glomerulitis (<10%), vasculitis (<10%), acute interstitial nephritis (10%-24%) and acute tubular necrosis (25%-50%).[8]

Leptospirosis induced AKI is usually hypokalemic (45-74%), non-oliguric (41-45%) and presents with high serum levels of creatinine and urea. Hypokalemia is among most common laboratory findings of LAKI requiring IV potassium replacement in 80% of patients. Severe hypomagnesemia (causing myalgia and lethargy) requiring Mg replacement therapy is also a characteristic acute leptospirosis. [9] Kidney injury in patients with hyperbilirubinemia

represents a severe form that is frequently accompanied by oliguria-anuria. The investigators also found that morbidity and mortality were lower in those with nonoliguric AKI than in those with oliguric AKI. [4, 10, 11] *Leptospires* can cause renal injury by three ways as shown in figure 3.

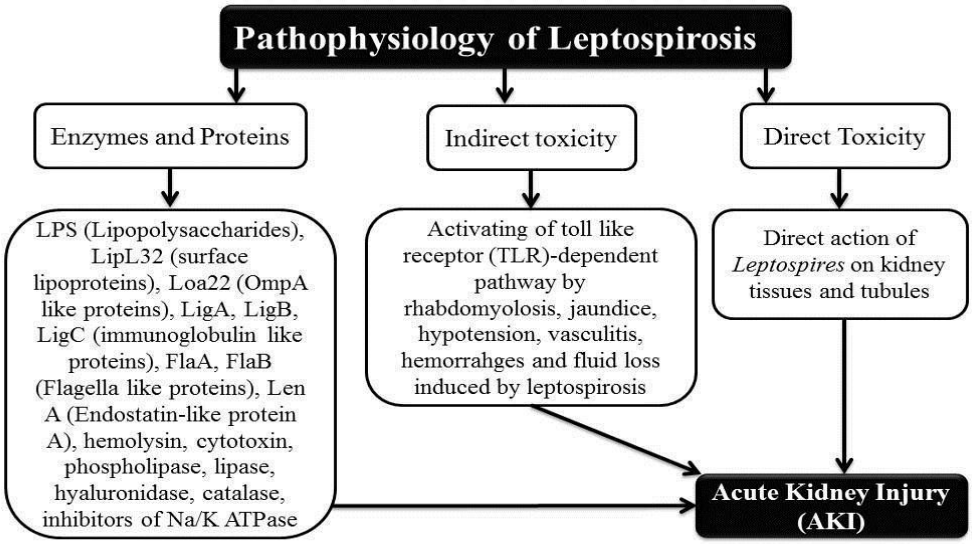

Figure 3: Pathophysiology of Leptospirosis induced Acute Kidney Injury (LAKI). [5, 10, 11]

RESULTS

Total 35 (Retrospective 16: Prospective: 5, Case reports & others: 14) studies showing leptospiral AKI (LAKI) were reviewed. Among total participants in reviewed studies, 1307 patients [male: 911 (70%); female: 396 (30%)] had LAKI. Higher incidence of leptospirosis and LAKI was observed in rural areas. 70-85% cases in studied population were from risk groups a given in table 1. Participants also had pulmonary failure, multiple organ dysfunction, thrombocytopenia, jaundice, meningitis, rhabdomyolosis and myocarditis in association with acute kidney injury (AKI). The mean days of hospitalization were 4-15 days. The longer hospitalization (70 days & 42 days) was due to multiple organ failure and wrong diagnosis respectively. Mortality rate among participants was 19.05% (249). Higher mortality rate was found in patients having LAKI as well as pulmonary involvement (ventilator support) while lower mortality rate was observed in patients under critical care or those had vigilant monitoring.

Table 2: Summary of studies describing association of acute kidney injury (AKI) during leptospirosis

Authors	Study type and duration of study	Patient demographics	Patient presentation in Hospital	Mortality (%)	Hospital Stay
Bartakke & Muench, 2014[12]	Case Report (2014)	N: 1 (M: 1), Age: 58 Years	Leptospirosis with pulmonary hemorrhage and acute kidney injury	None	42 days
Pichel et al., 2013[13]	Instructive Case (2013)	N: 1 (M: 1), Age: 14 Years	Leptospirosis with acute kidney injury and pulmonary hemorrhage	None	9 days
Cavoli et al., 2013[14]	Clinical Report (2010)	N:1 (Male: 1), Age: 74 Years	Weil`s disease with jaundice, oliguric ARF, hypotension, alveolar hemorrhage and thrombocytopenia	None	18 days
Taylor & Karamadoukis, 2013[15]	Case Report (2013)	N: 1, (Male: 1), 67 years	Leptospirosis with marked icterus AKI and cardiorespiratory failure	None	30 days
Dassanayak et al, 2012[16]	Prospective Observational Study (2007-2008)	N: 10 (M: 7, F: 3), Mean age: 39±10 Years	Confirmed leptospirosis patients with AKI and myocarditis	None	*NR*
Gancheva, 2012[17]	Retro. (1976-1984) plus Prosp. Study (1985-2012)	N: 59 (M: 53, F: 6), Mean ages: 37±18 Years	Leptospirosis with ARF and at least two other major organ failures	None	*NR*
Daher et al., 2012[18]	Retrospective	N: 45 (M: 37, F: 8), Mean age: 45±15 Years	Confirmed leptospirosis patients presented in ICU with kidney and lung involvement	20 (44.4%)	*NR*
Patil et al., 2012[19]	Retrospective study (2010, July-Dec)	N: 23 (M: 21, F: 2), Ages: 18-60 Years	Mild to severe leptospirosis patients with oliguric and non-oliguric AKI	1 (4.34 %)	Mean days: 16±7
Choi et al., 2011[20]	Case Report (2011)	N: 1 (Male: 1), 58 Years	Leptospirosis with Rhabdomyolosis and AKI without jaundice	None	9
Bourquin et al., 2011[21]	Case Report (2011)	N:1 (M: 1), Age: 65 Years	Leptospirosis with multi organ failure	None	70 days
Silva Júnior et al., 2011[22]	Retrospective (1985-2008)	N: 242 (M: 32, F: 10), Mean age: 37±16 Years	Confirmed diagnosis of leptospirosis having AKI	37 (15.2%)	Mean days: 10±7
Spichler et al., 2011[23]	Prospective Study (2008-2009)	N: 22 (M: 19, F: 3), Mean age: 41±16 Years	Mild and severe leptospirosis with acute renal failure and pulmonary involvement	None	Patients were not hospitalized
Morales et	Case Study	N: 3 (M: 3),	Children presented with	None	Median

al., 2011[24]	(2011)	Ages: 4-6 Years	leptospirosis and renal failure		days: 8
Daher et al., 2009[25]	Retrospective Study (1985-2006)	N: 196 (M: 156, F: 40), Ages: 22-57 Years	Confirmed leptospirosis with oliguric and non-oliguric AKI	27 (14%)	Mean days: 11±8 (1-42)
Hurst et al., 2009[7]	Retrospective (1992-2004)	N: 18 (M:16, F: 2) Mean age: 27.1±9.3 Years	Laboratory confirmed leptospirosis patients having evidence of AKI on admission	None	Mean days: 19±10
Mohammad et al., 2008[26]	Case Report	N: 1 (M: 1), Age: 41 Years	ARF, liver derangements and thrombocytopenia due to leptospirosis and dengue co-infection	None	5 days
Spichler et al., 2008a[9]	Case Report (2008)	N: 1 (F: 1), Age: 15 Years	Severe hypomagnisemia with non-oliguric ARF caused by leptospirosis	None	6 days
Spichler et al., 2008b[27]	Retrospective Study (2004-2006)	N: 102 (M: 86, F: 16), Ages: 19-58 Years	Leptospirosis with combined presentation of renal and pulmonary involvement	18 (18%)	*NR*
Daher et al., 2008[28]	Retrospective (2003-2006)	N: 17 (M: 12, F: 5), Mean age: 45±15.6 Years	Patients presented with leptospirosis ICU of hospital	6 (35.2%)	Mean days: 11.5±10.3
Santana et al., 2006[29]	Letter to Editor (2006)	N: 1, (M: 1), Age: 51 Years	Leptospirosis with jaundice, severe respiratory and renal failure	None	18 days
de Souza et al., 2006[30]	Case Report (2006)	N: 1 (M: 1), Age: 1.75 Years	Leptospirosis with ARF and meningitis without jaundice	None	4 Days
Chawla et al., 2004[31]	Retrospective Study (2002-2003)	N: 60 (M: 48, F: 12), Ages: 12-60 Years	Confirmed leptospirosis patients with multiorgan dysfunction syndromes and ventilator support	31 (52%)	Mean 8 days
Cetin et al., 2004[32]	Retrospective/ Clinical Study (1998-2005)	N: 16 (M: 16), Age: 40±17 Years	Leptospirosis with ARF and Jaundice	4 (25%)	Mean days: 15±9
Covic et al., 2003[1]	Retrospective (1997-2001)	N: 58 (M: 53, F: 5), Mean age: 44±13 Years	Leptospirosis with acute renal failure (ARF)	15 (26%)	Mean days: 11.1±9.8
Peces, 2003[33]	Retrospective (1977-1991)	N: 24 (M: 23, F: 1), Ages: 16-71 Years	ARF with severe leptospirosis associated with multi organ involvement	2 (8.3%)	*NR*
Cengiz et al., 2002[34]	Retrospective Study (1991-1998)	N: 27 (M: 20, F: 7), Mean age: 42±12	Leptospirosis patients with ARF	2 (7.4%)	21-35 days

		Years			
Niwattayakul et al., 2002[35]	Retrospective Study (1999-2000)	N: 148 (M: 107, F, 41), Ages: 8-76 Years	Leptospirosis with ARF	2 (1.35%)	*NR*
Rojas et al., 2001[36]	Case Report (2001)	N: 1 (M: 1), Age: 14 Years	Leptospirosis with jaundice, acute renal failure and thrombocytopenia	None	35 days
Yang et al., 2001[37]	Retrospective Study (1996-1999)	N: 12 (M: 9, F: 3), Mean age: 56.3±13.3 Years	Severe leptospirosis with ARF and Multi organ dysfunction (MOD)	4 (33.4%)	*NR*
Daher & Nogueira, 2000[38]	Prospective Study 1996 – 1998	N: 35 (M: 30, F: 5), Mean age: 35±10 Years	Confirmed leptospirosis patients with ARF and Jaundice on admission	1 (2.85%)	Mean days: 11.5±5.5
Coursin et al., 2000[39]	Brief Case Report (2000)	N: 1 (M: 1), Age: 63 Years	Leptospirosis with rhabdomyolosis and MOF	None	30 days
Seguro et al., 1999[40]	Retrospective Study (1986-1987)	N: 56 (M: 55, F, 1), Ages: 11-46 Years	Leptospirosis with ARF	10 (17.8%)	*NR*
Daher et al., 1999[41]	Retrospective Study (1925-1996)	N: 110 (M: 86, F: 24), Mean age: 40±17 Years	Leptospirosis with ARF	24 (21.8%)	1-23 days
Gerding et al., 1997[42]	Correspondence 1997	N: 2 (M: 2), Age: 71 & 47 Years	Leptospirosis cases with ARF	None	21 & 50 days
Abdulkader et al., 1993[43]	Prospective Study	N: 10 (M: 9, F: 1), Mean age: 31±7 Years	Weil`s Syndrome with ARF, jaundice and thrombocytopenia	None	*NR*

NR: not reported, M: male, F: female, N: patients having leptospirosis and AKI/ARF among study population, ARF: acute renal failure, AKI: acute kidney injury
Note: Patient`s ages are represented as Mean±SD or range of age of patients from minimum to maximum; days of hospitalization are represented as Mean±SD, range of days of hospitalization, median days of hospitalization

Many countries are doing efforts to enlighten the association of leptospirosis with AKI. Most of the studies included in this review are from Brazil (39%), India (10%), USA (8%) and UK (6%). The studies of other countries included in this review are given in figure 4.

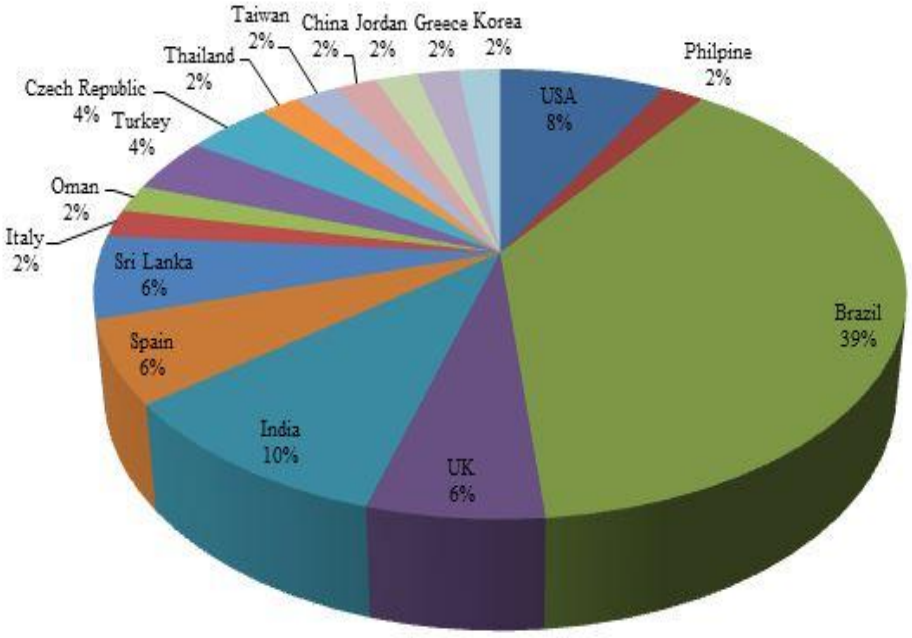

Figure 4: Percentages of studies conducted in different countries included in review.

Brazil has done a lot of work to highlight the association of leptospirosis with AKI. Very useful findings e.g. predictors of LAKI, LAKI classification according to RIFLE and AKIN criteria, pattern of mortality in LAKI, predictors of mortality in LAKI and management of LAKI patients are well discussed and advocated by Brazil. Other tropical countries having endemic potential of leptospirosis should focus this neglected infection that leads to acute kidney injury and most common cause of mortality.

DISCUSSION

Leptospirosis is a neglected zoonotic infection accompanied by fatal complications. Lack of disease knowledge and its intricacies result in increased morbidity and mortality. The most common manifestations of Weil's disease are acute kidney injury (79%), jaundice (70%), thrombocytopenia (50-65%), elevated transaminases (56%), meningitis (23%) and hemorrhage (11.6%). [36] Renal involvement is most dreaded complication of leptospirosis and is commonest cause of death. Depending on the affected organ system case fatality rate during leptospirosis varies from 3-54%. [17]

Leptospirosis induced AKI is a severe form of disease causing death in one third of patients. [1] Majority of patients studied in review had age >40 years. Prevalence and incidence of leptospirosis were high in male, risk groups (table 1) and rural residents. Data showed the participants having multiple organ failure, especially pulmonary involvement, had higher

mortality and hospital stay e.g. patients in ICU. On the other hand patients having only LAKI without any other organ involvement also had longer hospital stay due to wrong diagnosis of disease. The average mortality rate in reviewed studies (19%) was almost similar to overall mortality (22%) due to leptospirosis induced AKI.

In vitro examination reveals outer membrane proteins (OMPs) are major pathogenic factors of LAKI. [37] Main histological findings are acute interstitial nephritis (AIN) and acute tubular necrosis (ATN). [6] Prognosis of LAKI is usually favorable but underlying diseases, associated infections, old age, olig-anuria, diarrhea, hyperkalemia, hyperbilirubinemia, hypotension (Niwattayakul et al., 2002) hypertension, WBCs > 12,900/mm3, repolarization abnormalities on ECG, , hemoptysis, metabolic acidosis, thrombocytopenia[16] and pulmonary complications (dyspnea, alveolar infiltrates) are bad prognostic factors with mortality ranging from 12% to 35 %. Patients with these risk factors should be treated in ICU. [14]

Currently AKI is not considered as single disease but a spectrum of diseases that can be defined by RIFLE and AKIN criteria. Silva Júnior *et al.*, 2011[22] studied incidence of AKI in leptospirosis by using AKIN and RIFLE criteria e.g. RIFLE-R (17 %), RIFLE-I (26%), RIFLE-F (57%) or AKIN-1 (19%), AKIN-2 (25%), AKIN-3 (56%). Severity of disease can be assessed by APACHE II and SOFA scoring system. Staging of AKI by these methods may help to predict mortality e.g. mortality rate 58% in RIFLE-F and AKIN-3 stage. APACHE-II/SOFA score is also high in severe form of acute kidney injury. [18]

Various predictors of leptospiral acute kidney injury are well studied among them oliguria, jaundice and arrhythmia are strong predictors. [16 Age > 40 years, crackles, hyponatremia, high serum creatinine, elevated direct bilirubin and elevated activated prothrombin time are predictors of oliguric AKI. [22]

There is no evidence of chronic sequel after discharge, recovery of symptoms have been reported in 96% after discharge. [23] Leptospirosis might not be associated with development and progression of chronic kidney disease (CKD). [44]

Mortality due to LAKI is 22% and this incidence is validated in reviewed studies as shown in table 2. The mortality rate of leptospirosis ICU patients is high, where patients have at least two organ system failures. [31] Risk factors associated with mortality due to LAKI are well studied. Oliguria, metabolic acidosis, sepsis, hypovolaemia, use of vasopressors, mechanical

ventilation, high APACHEII/SOFA score [28], multiple organ dysfunctions, acute respiratory distress syndrome, acidosis, alcohol use [31], age > 40 years, platelet count < 70,000/µL, creatinine > 3 mg/dL [27], cardiac arrhythmia, pulmonary rales [41], pulmonary crackles, syncope, agitation, high pulse rate, need of dialysis and headache[22] are some predictors of mortality in leptospirosis induced AKI. Oliguric-AKI is a strong predictor of death as compared to non-oliguria-AKI with mortality rate 27% vs 8% respectively.[25] Worse classification of RIFLE and AKIN criteria e.g. RIFLE-I (OR: 3.3), RIFLE-F (OR: 11.6) AKIN-2 (OR: 3.4) and AKIN-3 (OR: 12.4) is significantly associated with mortality in leptospirosis. Mortality rate is high (58%) in RIFLE-F stage. [18] Gender as a predictor of mortality is still under debate. In one study mortality rate in female was observed higher as compared to male. It might be due to high incidence of oliguria in female. More studies are needed to evaluate role of gender as a predictor of leptospiral mortality. [41]

There is no specific treatment for leptospiral AKI but it can be symptomatically managed. Intravenous Penicillin (6 million IU/day for 8 days) is the gold standard treatment for leptospirosis. But penicillin does not provide additional improvements in renal function, need for dialysis and mortality. Elevation of protein in urine may increase with penicillin in patients with LAKI. [38] Weil`s disease associated with multiorgan failure (MOF) can also be treated with plasma exchange followed by high volume-hemofiltration but it can cause severe cytomegalovirus (CMV) colitis. [21] Plasma exchange, in combination of fresh frozen plasma and human albumin solution, can be a promising treatment of sepsis caused by leptospirosis and immune-complex mediated organ injury. Hemodialysis and renal biopsy can be considered in patients with leptospiral AKI. [7] Initiation of dialysis in patients with RIFLE-F and AKIN-3 should always be considered. [22] In high-risk and short term exposure chemoprophylaxis with doxycycline is effective. Doxycycline cannot prevent leptospirosis in endemic regions but may be valuable for reduction of morbidity and mortality during outbreaks. [45]

Duration of hospitalization and mortality may increase due to late diagnosis, unusual clinical presentations, unusual biochemistry and lack of disease knowledge. [12 Patients with fever, pulmonary infiltrates, renal failure, thrombocytopenia and rhabdomyolosis should be suspected for leptospirosis despite the absence of jaundice or meningitis, especially in patients with risk factors described in table 1. [46] In such patients leptospirosis should be evaluated with other highly suspected infections. High suspicion, early diagnosis and

intensive therapy (antibiotics, plasma exchange and dialysis) may be helpful in reducing morbidity and mortality of patients with severe leptospirosis and multi organ failure e.g. renal and respiratory failure. [29] Brazil has valuable contribution to provide useful findings to evaluate role of leptospirosis and acute kidney injury. Warm and humid tropical countries, having high incidence leptospirosis should focus to evaluate pattern of LAKI and should take adequate measures to control leptospirosis induced burden of AKI and death.

We are currently working on association of tropical infections with acute kidney injury and chronic kidney disease. Preliminary findings of our studies have been presented and published in reputable conference proceedings. [47, 48]

CONCLUSION

Leptospirosis induced AKI (LAKI) is severe disease and most common cause of death. Negligence to leptospiral AKI is additionally burdening overwhelmed health services. Therefore more prospective studies are required to evaluate leptospirosis association with AKI and CKD. Tropical countries, having endemic potential of disease, should conduct epidemiological and clinical studies to evaluate and eradicate fatal renal complications of leptospirosis. Secondly high suspicion in risk groups, prompt diagnosis, and understanding of renal injury during disease course, individualized therapy and follow-up of patients having leptospiral AKI can be the gold standard strategies to reduce the increasing burden on health system. Involvement of nephrologist in such cases may aid infectious disease specialists in reducing workload and in improvement of quality of life (QOL) of patient.

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CONFLICT OF INTEREST

None

AUTHOR`S DISCLOSURE

Authors have nothing to disclose.

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