Review

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Abstract: Leptospirosis is a re-emerging zoonotic disease that has had an unprecedented impact on most health systems in the world. The spectrum of symptoms is variable and usually ranges from asymptomatic cases to severe manifestations involving multiple organ dysfunction accompanied by jaundice, hemorrhage, meningitis, and acute kidney injury that requires the need for intensive care assistance. Although early antibiotic treatment is usually effective, in severe cases it may require renal replacement therapy, invasive mechanical ventilation, vasoactive support, and invasive hemodynamic monitoring, increasing the risk of death. In Latin America, the real burden of acute kidney injury in this condition is unknown and may be underestimated due to the rapid progression of the disease, similar to other vector zoonoses, and the low coverage of diagnostic tests in primary care, especially in rural regions. Therefore, below, we review the clinical aspects and describe the scientific, clinical, and therapeutic evidence of acute kidney injury attributed to *Leptospira spp.* and its relevance in patients with severe leptospirosis in Latin America.

Keywords: leptospirosis; acute kidney injury; renal replacement therapy; zoonotic disease; antibiotic; death

1. Introduction

Leptospirosis is a re-emerging tropical zoonotic disease with worldwide distribution, caused by spirochetes of the genus *Leptospira spp.* [1]. According to estimates by the Pan American Health Organization (PAHO), leptospirosis is an endemic disease in Latin America and there have been an estimated 10 702 cases annually [2]. However, little is known about the actual current burden, which becomes a threat to public health in the region. The incidence is expected to increase in the coming decades as a consequence of exposure in vulnerable areas, peri-urban growth of marginal neighborhoods, and limited access to basic services (insufficient garbage collection, absence of drinking water and sewage) recurrent in our region [3].

The spectrum of symptoms is variable and usually ranges from asymptomatic cases to fatal manifestations [4]. Although early antibiotic treatment is usually effective, late presentation during the immune phase of the disease often causes serious complications [5]. These occur in 5-10% of cases and present as Weil's disease, which involves multiple organ dysfunction accompanied by jaundice,

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hemorrhage, meningitis, and acute kidney injury (AKI) requiring intensive care assistance [1,6]. In addition, there may be pulmonary involvement and it is described as severe pulmonary hemorrhage syndrome that reaches a fatality rate greater than 50% [7]. The prognosis depends on early diagnosis, severity, and timely intensive treatment [8]. However, the presentation is usually different in different geographical areas of the world and is explained by the variations in intrinsic virulence between serovars and existing species [4].

In the initial clinical phase, the symptoms and signs may be nonspecific due to their similarity to other tropical diseases such as Dengue, Zika, Chikungunya, Malaria, etc. [6]. Therefore, early diagnosis of leptospirosis is essential to attenuate disease progression and obtain better outcomes [9]. In clinical practice, the use of IgM through ELISA and the microscopic agglutination test are useful diagnostic tools for screening the disease [10]. However, the definitive diagnosis is made by detecting Leptospira in culture samples [6]. Polymerase chain reaction (PCR) tests remain important; however, they are expensive and difficult to apply in a primary healthcare setting in our region [10].

The presence of AKI is an early manifestation of severe leptospirosis and its incidence ranges from 10 to 60% of total cases [1]. This can occur due to the direct action of the etiological agent, dehydration, rhabdomyolysis, and hemodynamic alterations [11]. *Leptospira spp.* enters the host through the skin or mucous membranes, spreads hematogenous, and then reaches target organs, such as the liver, lungs, and, mainly, the proximal renal tubules [12,13]. By infiltrating the renal tubular cells, it leads to direct nephrotoxic action and triggers an immune response that results in tubulointerstitial nephritis, acute tubular necrosis, and risk of renal fibrosis [6].

Renal manifestations are variable and range from mild changes in urinary sediment to changes in tubular function, such as low urinary protein excretion to irreversible damage [14]. In severe cases, these precede the abrupt drop in the glomerular filtration rate, associated with a severe hydro electrolyte imbalance [15]; Therefore, renal replacement therapy (RRT) is likely to be required in up to 31.6% [16,17]. Recovery of kidney function may take several months, however, AKI exposure from severe leptospirosis can lead to long-term end-stage kidney disease [18].

Despite leptospirosis being a public health priority, estimates of AKI, identification, and the need for RRT are unknown. Therefore, the objective of this review is to describe the scientific, clinical, and therapeutic evidence of AKI attributed to *Leptospira spp.* and its relevance in patients with severe leptospirosis in Latin America.

2. Etiology

The word *Leptospira* comes from the Greek, leptos (thin) and spira (coiled), referring to the shape of the microorganism [19]. *Leptospira spp.* is an aerobic bacterium, spirochete of the genus *Leptospira* [13], measuring approximately 0.15-0.3 micrometers in diameter and 6-20 micrometers in length [20]. Its growth is slow and in its incubation phase, it may take up to 90 days [21] with an ideal temperature that ranges between 27 to 30 degrees Celsius. The axial filaments or endoflagella of the bacteria are what facilitate its mobility [20].

Leptospira species have a lipopolysaccharide layer in their structure and are classified into 3 groups: pathogenic, intermediate (without demonstrated virulence), and non-pathogenic [22]. To date, 13 pathogenic strains have been identified, the main one being *Leptospira interrogans*. It is estimated that this species has more than 260 serovariants, 5 intermediate strains, and 6 non-pathogenic or saprophytic strains with more than 60 serovariants [23].

3. Pathophysiology of leptospirosis and acute kidney injury

The most common complication of leptospirosis is AKI [24]. *Leptospira spp.* colonization of the kidney can cause tubulointerstitial nephritis followed by fibrosis, and if not treated in time it culminates in chronic kidney disease [25]. Once *Leptospira spp.* enters the body, it can cause direct nephrotoxicity, altering the sodium/phosphate cotransporter in the proximal tubule, which favors the generation of ammonia and an increase in pH [10]. This generates an ideal alkaline microenvironment for bacterial replication and to last longer in the kidney tissue [26].

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The epithelial cells of the renal tubules are the structures most affected by *Leptospira spp.* [27]. This microorganism, in its outer membrane, has proteins such as OmpL1, lipoprotein LipL41, and lipopolysaccharides that can adhere and infiltrate mononuclear tubular epithelial cells, activating complement and causing direct injury [28–30]. Once the attack occurs, interleukin 34 (IL-34) is released, a cytokine that drives greater destruction of tubular cells, and migration of macrophages and fibroblasts to kidney tissue [31].

One of the preferred sites of the *Leptospire spp.* is the proximal tubule [29], due to its affinity for the Na+/K+ATPase pumps, which alters their functioning by inhibiting their expression, also reducing the sodium/hydrogen ion exchanger and aquaporin 1 (AQP-1) in the apical and basolateral membrane [27]. As a consequence, it favors the loss of urinary sodium and potassium, while in the luminal part, there is an accumulation of free water, thus causing polyuria and secondary to this hypovolemia and hypotension [32].

The ascending branch of the loop of Henle is also affected by this microorganism [33]. When tubular cells are injured, they release nitric oxide, which facilitates the decrease in systemic vascular resistance, thus reducing renal blood flow and the glomerular filtration rate [34]. It can also reduce the expression of the Na+/K+/2Cl- cotransporter (NKCC2), which explains the loss of sodium and potassium in the urine [35]. When control of this ion channel is lost, the losses of positive electrical charges in the luminal space increase, leading to a decrease in the reabsorption of calcium and magnesium [33]. Dysregulation of ion pumps explains the hyponatremia, hypokalemia, hypomagnesemia, and non-oliguric AKI characteristic of leptospiral nephropathy.

Other factors that facilitate AKI are hyperbilirubinemia or myoglobinuria induced by rhabdomyolysis, release of free radicals, and increased blood viscosity obstructing the renal tubules [36]. The persistence of this microorganism in the kidney tissue causes interstitial inflammation, accumulation of extracellular matrix, and damage to tubular epithelial cells [37]. In particular, this stimulates the mediator of tubulointerstitial fibrosis (STAT3 transcription factor), which increases the secretion of transforming growth factor beta 1 (TGF-β1) and the production of type II and IV collagen that contribute to the progression of kidney disease. [38,39].

After this, the residual and functional nephrons enter into a maladaptive compensation process to replace the work of the glomeruli and tubules injured by this microorganism [40]. Damaged tubular cells enter a phase of structural and functional repair. If the degree of inflammation is chronic and severe, it can favor the invasion of immune cells, abnormal migration of fibroblasts, and lead to fibrosis [40,41]. In patients with existing chronic kidney disease, the repair and compensation process are more limited, and the risk of progression to terminal disease increases [42,43].

4. Clinical manifestations

The main manifestations of severe leptospirosis in AKI are oliguria, anuria, and renal failure with the possibility of RRT [6]. Between 41-45% of patients with AKI are non-oliguric and have hypokalemia that determines the characteristic presentation of leptospirosis [1]. Acute interstitial nephritis is the main pathological change in patients with leptospirosis even in the absence of AKI [6]. This is accompanied by skin rash, fever, emesis, frequency, and nocturia [44].

Laboratory findings are usually varied, finding hematological and urinary alterations. Among the findings of the urinalysis are pyuria, hematuria, bile pigments, granular casts, and mild proteinuria [6]. Hypokalemia and magnesiuria continue to be the most important findings, which can be found in 40%-87% and 75% of cases respectively [45]. Hyponatremia is also notable in leptospirosis (frequency), however, together with hypokalemia it is characteristic of the disease [10]. In atypical situations, the presence of Fanconi syndrome characterized by the excretion of phosphate, uric acid, bicarbonaturia, glucosuria, and defects in sodium reabsorption has been described [46].

5. Diagnosis

Early identification of AKI caused by severe leptospirosis is important to reduce associated morbidity and mortality [47]. The use of serum markers such as creatinine continues to be important in first care settings [48]. This marker of late kidney damage is correlated with a drop in the

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glomerular filtration rate by up to 50% and if it rises 1.5 times its baseline value, it increases the risk of imminent kidney failure [49]. RIFLE and AKIN stages are good markers to stratify the severity of patients with leptospirosis [50]. These systems, through the measurement of creatinine, can achieve greater sensitivity (84%) and specificity (48%) to determine severe AKI secondary to leptospirosis [51].

In recent decades, studies on the use of renal biomarkers to identify premature kidney damage due to leptospirosis have expanded enormously [24]. The action of *Leptospire spp.* in the kidney involves increased expression of proinflammatory molecules such as neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemotactic protein 1 (MCP-1) [52], kidney injury molecule 1 (KIM-1), and N-acetyl-D-glucosaminidase (NAG) [53]. Its measurement has been important in the early detection of AKI and allowing the appropriate approach with the aim of reducing complications in patients with leptospirosis [11].

5.1. Cellular immunoglobulin mucin domain 1 (KIM-1)

KIM-1 is a type I transmembrane glycoprotein that is expressed in the apical membrane of proximal renal tubule cells [54]. This biomarker is characterized by appearing 12-24 hours after the onset of the injury [53], relating to the severity of the infection [55]. In a study in Sri Lanka, KIM-1 was detected on the third day of fever after admission and the highest concentration on the ninth day [49]. Furthermore, it has the particularity of not being present in healthy individuals; it only increases once damage to the epithelial cells of the proximal tubule begins [56]. Therefore, the measurement of this biomarker may be useful in diagnosing AKI in severe leptospirosis [53].

5.2. Monocyte chemoattractant protein 1 (MCP-1)

This is expressed when AKI occurs secondary to ischemia [49]. In a study at the Seattle hospital, they used kidney samples with kidney injury in rats and showed an increase in MCP-1 4 hours after the onset of failure [57]. Nisansala et al.[24] in a cross-sectional study verified the direct relationship between the increase in MCP-1 values in the presence of AKI with leptospirosis. However, the sensitivity was lower compared to other renal biomarkers such as KIM-1.

5.3. Neutrophil gelatinase-associated lipocalin (NGAL)

This biomarker reaches a concentration of 20 ng/mL in plasma or urine and rises after 2-4 hours, initiating kidney damage. Srisawat et al.[58] determined that urinary NGAL was associated with AKI with a sensitivity of 86.1% and a specificity of 85.1% in patients with leptospirosis.

5.4. Urinary N-acetyl-B-D-glucosaminidase (NAG)

An increase in values starting 12 hours after damage [53]. Two retrospective studies were conducted in Thailand in 2016 and 2020, where urinary NAG was related to leptospirosis-associated AKI [24].

6. Management strategies

Antibiotic therapy is currently the cornerstone of managing severe leptospirosis [46]. Options include the use of intravenous penicillin[6], ceftriaxone[50], or doxycycline[59] for seven days. On the other hand, it has been shown that the use of ceftriaxone significantly reduces hospital stay, admission to intensive care, and the risk of AKI and RRT [50,60,61]. In a cohort published in Colombia, it was found that non-administration of antibiotics was associated with severe disease and admission to intensive care [62]. In case of neuroinfection due to leptospirosis, the antibiotic of choice is benzylpenicillin for 2 to 3 weeks [15].

Regarding fluid therapy, it should be guided by hemodynamic variables to reduce the risk of perpetuating pulmonary, renal, and hemodynamic complications [63]. Guaranteeing 2-2.5 liters per 24 hours for a urinary output greater than 0.5 mL/kg/hour reduces the risk of AKI [64]. After starting

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water therapy and the poor diuresis response, a diuretic stimulus should be started, taking into account the high risk of requiring RRT [63].

If arterial hypotension is evident despite having administered adequate fluid therapy, the use of vasoactive agents should be resorted to [46]. This is because the hemodynamic changes associated with severe leptospirosis are similar to a state of septic shock, finding behavior with high cardiac index and low systemic vascular resistance (hemodynamic behavior of septic shock) [65]. Therefore, due to the little scientific evidence regarding therapy at this point, it is advisable to follow the recommendations issued by the Surviving Sepsis Campaign for the use of vasoactive agents [66].

From 50 to 93% of patients with leptospirosis present thrombocytopenia, and although the mechanism of platelet consumption is not clear, it has been correlated with sepsis, AKI, and the severity of the infection, for which platelet transfusions can play a role. a fundamental role when they are involved in management [67,68]. Platelet transfusion should be considered if there is bleeding and a platelet count <50,000/uL [69].

In advanced stages of the infection, where sepsis and septic shock reveal organ dysfunction [70], mechanisms mediated by immune complexes generate systemic tissue damage and antibiotic therapy produces excessive release of endotoxins due to bacterial death (Jarisch reaction). Herxheimer) [71]. The use of plasma exchange could be considered a reasonable option [72]. This rapidly eliminates circulatory endotoxins, catabolic products, and inflammatory markers generated, reducing the risk of associated complications such as acute tubular necrosis and AKI [72,73]. Furthermore, it contributes to the clinical recovery of critically ill patients and the significant reduction in mortality in cases of severe complicated leptospirosis and associated multiple organ failure [73,74]. Regarding techniques such as hemoabsorption, no literature was found.

When addressing the possibility of starting RRT in the context of severe leptospirosis, in addition to AKI, those basic aspects that make up the dialysis emergency must be considered [63]. The latter, in patients with severe infection, is more frequently severe metabolic acidosis, water overload refractory to diuretics, and anuric renal failure [75]. The indication of RRT should not be delayed, deferred, or underdosed if necessary since its early use generates a reduction in mortality [63,75]. The continuous modality (continuous veno-venous hemodialysis or continuous venovenous hemodiafiltration) has had beneficial effects by improving survival [16]. However, if this therapy is not available, peritoneal dialysis has been associated with excellent results [76,77].

In those patients with respiratory compromise who develop acute respiratory failure, support for this condition will begin with oxygen therapy, devices such as high-flow nasal cannula and non-invasive mechanical ventilation (CPAP/BPAP). In case of reaching the condition of severe ARDS, ventilatory support may be required and should be administered early [63], and in this case, invasive mechanical ventilation should follow the current recommendations for protective ventilation for the management of ARDS [78–84]. In patients with severe ARDS in conditions of refractory hypoxemia, successful cases have been described with the use of extracorporeal membrane oxygenation therapy [85–87] in patients with severe leptospirosis and multiple organ dysfunction. However, there is no strong scientific evidence or guidelines for its use in these patients.

7. Overview of acute kidney injury secondary to severe leptospirosis in Latin-America

Leptospirosis is a disease of poor environments and high impact in Latin America [5]. This zoonosis is 100 times more common than in other parts of the world [88]. According to PAHO estimates, leptospirosis reaches an estimated 10 702 cases annually [2]. Despite this, until now AKI secondary to leptospirosis is poorly reported on the continent, making it difficult to determine the current incidence and burden of the disease.

Next, we describe through a literature mapping the studies on AKI associated with severe leptospirosis in Latin America. We include original articles and case series published in journals indexed in PubMed, Clinical Key, ScienceDirect, and Scielo with the terms Mesh (“Weil Disease” AND “Acute Kidney Injury” AND Latin America”) and (“Leptospirosis” AND “Acute Kidney Injury” AND “Latin America”). Limited articles in English and Spanish. Articles that presented

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bibliographic products with an unavailable abstract and duplicate article were excluded. Table 1 summarizes the selected articles that met the search criteria.

Table 1. Acute kidney injury in patients with severe leptospirosis in Latin-American.

Author	Type Study	Clinical and renal manifestations (%)	Dialysis (%)	Global mortality (%)	Country
Daher *et al.*, 1999 (48)	Retrospective Cohort	• The observed prevalence of oliguria [1] was n=103/110 (93.6) • There was no hydro electrolytic alteration (K, Na) • Oliguria presence was a risk factor in patients with leptospirosis (OR: 8.98, 95% CI: 1.81 - 44.6; p=0.006)	Total: n=89/110 (81)	Total: n=24/110 (22)	Brazil
Andrade *et al.*, 2007 (16)	Retrospective Cohort	On admission: • There was no hydroelectrolytic alteration (K, Na, Cl) • pH levels averaged between 7.26 - 7.28 Blood HCO_3 levels 17 - 18 (mEq/L)	Total: n=33/33 (100) DAdD: n=15/33 (45.5) PaDD: n=18/33 (54.5)	Total: n=13/33 (39.4) DAdD: n=10/15 (66.7) PaDD: n=3/18 (16.7)	Brazil
Daher *et al.*, 2009 (89)	Retrospective Cohort	• The observed prevalence of oliguria [1] was n=64/196 (32.7) • The mortality was significantly higher in oliguric than nonoliguric patients (27 vs. 8%; p<0.001) • Oliguric [1] patients had hiponatremia (<135 mEq/L) but not hypokalemia on admission	Total: n=103/196 (52) Oliguric [1]: n=43/103 (41.7) Nonoliguric: n=60/103 (58.3)	Total: n=27/196 (14) Oliguric [1]: n=17/64 (27) Nonoliguric: n=10/132 (8)	Brazil
Daher *et al.*, 2010 (90)	Retrospective Cohort	• The prevalence of acute kidney injury was n=175/201 (87) • The observed prevalence of oliguria [1] was n=64/201 (31.8) • The n=123/201 (63.7) had serum potassium lower than 3.5mEq/L	Total: n=103/201 (51.2)	Total: n=31/201 (15.4)	Brazil
Herrmann-Storck *et al.*, 2010 (91)	Retrospective Cohort	• The prevalence of acute kidney injury was n=54/130 (41.5) • The observed prevalence of oliguria [1] was n=34/128 (26.6) • There was no hydroelectrolytic alteration (K, Cl)	Total: n=10/110 (9.09)	Total: n=6/110 (5.45)	Guadalupe
Damasco *et al.*, 2011 Feb (92)	Retrospective	• The prevalence of acute kidney injury was n=13/27 (48.1) • The thirty-day survival rate in the AL group was higher than	Total: n=3/27 (11.1)	Total: n=3/27 (11.1)	Brazil

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Author	Type Study	Clinical and renal manifestations (%)	Dialysis (%)	Global mortality (%)	Country
		that of the without AL group (OR: 11.1, 95% CI: 1.12 - 110.9; p=0.04).			
Echeverri *et al.*, 2011 Jun (93)	Case series	• The prevalence of acute kidney injury was n=2/14 (14.3) • The n=8/14 (51.6) of patients present alterations in urinalysis	Total: n=1/14 (7.1)	Total: n=2/14 (14.3)	Colombia
Silva Júnior *et al.*, 2011 (51)	Retrospective Cohort	• The prevalence of acute kidney injury was n=237/287 (82) according to the RIFLE criteria and n=242/287 (84) according to the AKIN • The observed prevalence of oliguria[1] was n= 55/287 (19) • In more severe stages of AKI there was hiponatremia (<135 mEq/L)	Total: n=105/287 (36.6)	Total: n=37/287 (13) Dialysis n=21/37 (56.7)	Brazil
Reis *et al.*, 2013 Sep (27)	Cases and controls	• The observed prevalence of oliguria [1] was n=65/172 (37.8) • The levels of IL-10 and TNF-α were significantly higher in fatal cases compared to severe non-fatal cases (32.0 vs. 4.8, P=0.0019)	Total: n=37/172 (21.5) Total non-fatal: n=25/124 (20) Total fatal cases: n=12/25 (48)	Total: n=25/172 (14.5)	Brazil
Daher *et al.*, 2014 Feb (94)	Retrospective Cohort	• The prevalence of acute kidney injury was n=301/374 (80.5) • The observed prevalence of oliguria [1] was n=79/374 (21.2) • Thrombocytopenia was not associated with RRT or death (p>0.05)	Total: n=124/374 (33.2)	Total: n=47/374 (12.5)	Brazil
Daher *et al.*, 2016 Feb (50)	Cross-sectional	• The prevalence of acute kidney injury was n=162/206 (78.6) • The observed prevalence of oliguria [1] was n=42/206 (20.4) • On admission the Na levels averaged between 130 – 133 mEq/L	Total: n=80/206 (38.8)	Total: n=26/206 (12.7)	Brazil

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Author	Type Study	Clinical and renal manifestations (%)	Dialysis (%)	Global mortality (%)	Country
		• Potassium levels in the admission were without alteration (3.5 – 4 mEq/L)			
Sharp *et al.*, 2016 Feb (95)	Case-controls	The values of HCO_3, Cr and BUN were significantly higher in fatal leptospirosis (p <0.006).	Total: n=11/173 (6.36) Total fatal cases: n=7/21 (33.3) Total non-fatal: n=4/52 (7.7)	Total: n=21/173 (12.1)	Puerto rico
Cleto S *et al.*, 2016 Ago (96)	Prospective	• Dialysis mode has no apparent effect on mortality • Inflammatory interleukin levels decreased faster in the SLEDf group than in the SLED group	Total: n=39/138 (28.3) SLED: n=19/39 (48.7) SLEDf: n=20/39 (51.3)	Total: n=6/138 (4.3) SLED: n=3/19 (15.8) SLEDf n=3/20 (15)	Brazil
Echeverri-Toro *et al.*, 2017 (88)	Cross-sectional	• The prevalence of renal failure was n=60/201 (29.9) • Proteinuria was found in n=58/119 (48.7) and hematuria in n=51/119 (42.9)	Total: n= 14/119 (11.8)	Total: n=6/119 (5) Dialysis n=4//119 (3.4)	Colombia
Daher *et al.*, 2017 (17)	Retrospective Cohort	• The observed prevalence of oligo/anuria [1] n=130/507 (25.6) • The frequency of edema was n=57/507 (11.2) • pH levels averaged between 7.36 - 7.37 The Na levels averaged between 132.3 – 133.2	Total: n=193/507 (38.1)	Total: n=72/507 (14.2)	Brazil
Daher *et al.*, 2019 (97)	Retrospective Cohort	• The prevalence of renal failure was n=60/507 (76.1) • The observed prevalence of oliguria [1] was n=127/207 (25) • There was no hydro electrolyte alteration in any group evaluated (K, Na)	Total: n=193/507 (39.2) ≥60 years: n=35/64 (54.7) <60 years: n=164/443 (37)	Total: n=75/507 (14.8) ≥60 years: n=21/64 (32.8) <60 years: n=54/443 (12.2)	Brazil
Meneses *et al.*, 2022 (11)	Prospective	• Oligoanuria was found in n=4/27 (14.8) and hematuria in n=3/27 (11.1)	Total: n=12/27 (44)	Total: n=2/27 (7.4)	Brazil

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Author	Type Study	Clinical and renal manifestations (%)	Dialysis (%)	Global mortality (%)	Country
Parra *et al.*, 2023 (62)	Retrospective Cohort	• The patients who required haemodialysis presented significant higher levels of syndecan-1, angiopoietin-2, and FGF-23 ($p < 0.05$) • The prevalence of renal failure was n=60/201 (29.9) • Oliguria [1] was found in n=40/201 (19.9), dysuria n=44/201 (21.9), and proteinuria n=38/201 (18.9)	Total: n=37/201 (18.4)	Total: n=17/201 (8.5)	Colombia

[1] Urinary volume <400 ml/day after 24h of appropriate hydration. Abbreviations: K: Potassium; Na: Sodium; Cl: Chlorine; HCO3: Bicarbonate; DAdD: delayed, alternate-day dialysis; PaDD: prompt and daily dialysis; AL: atypical lymphocytosis; Cr: Creatinine; BUN: Blood Urea Nitrogen; SLED: sustained low-efficiency dialysis; SLEDf: sustained low-efficiency dialysis via hemodiafiltration.

7.1. Overall Findings

Of the 18 published articles, 5 were published before 2010 (27.8%) [16,48,89–91], eleven between 2011 and 2020 (61.1%) [17,27,50,51,88,92–97], and two studies were published after 2021 (11.1%) [11,62]. 72.2% (N = 13/18) of the articles included information from Brazil, 16.7% (N = 3/18) from Colombia, and two from Central America (16.7%). See **Table 1**. With the extracted articles, the epidemiology, need for RRT, and mortality in the region were described.

7.2. Epidemiology of acute kidney injury

Of the 18 articles found, 10 publications described the prevalence of AKI secondary to severe leptospirosis, obtaining 90% (N=9/10) of the articles in South America. When studying the frequency of the selected articles, 52.3% (N=1124/2148) presented AKI due to severe leptospirosis. When the manuscripts were reviewed by region in Brazil, a prevalence of 59.2% (N=948/1602) [50,51,90,92,94,97] and Colombia was found to be 29.3% (N=122/416) [62,88,93]. However, only one article published by Herrmann-Storck et al.[91] describes AKI, corresponding to the Central American region, finding a prevalence of 41.5% (N=54/130).

7.3. Renal Replacement Therapy

Of the articles reviewed, the need for RRT was 34.9% (N=1187/3402) in patients with severe leptospirosis in Latin America [16,17,27,48,50,51,62,88–97]. Brazil was the country with the greatest scientific evidence, finding a prevalence of 40% (N=1114/2785) [11,16,17,27,48,50,51,89,90,92,94,96,97], followed by Colombia with 15.6% (N=52/334) [62,88,93].

Early implementation of effective RRT is key to slowing the progression of AKI into more severe forms and is associated with decreased mortality [17,96]. However, when evaluating the type of dialysis to use sustained low-efficiency dialysis (SLED) vs. sustained low-efficiency dialysis via hemodiafiltration (SLEDf) no significant differences were found to reduce mortality; but the use of SLEDf impact on reducing the levels of pro-inflammatory cytokines faster which may prevent disease progression [96].

Currently, the search for biomarkers to predict the need for RRT in patients with severe leptospirosis has been of interest in the region. Meneses et al.[11] in a prospective study carried out in Brazil reported that patients with RRT presented significantly higher levels of Syndecan-1,

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angiopoietin-2, and FGF-23 compared to those without RRT. However, scientific progress is awaited to obtain more information on the use of these biomarkers in patients with severe leptospirosis.

7.4. Mortality

In our review, we found an overall mortality of 12.9% (N=440/3402) in patients with severe leptospirosis in Latin America. In Brazil, the prevalence was 13.9% (N=388/2785) [11,16,17,27,48,50,51,89,90,92,94,96,97], Colombia 7.5% (N= 25/334) [62,88,93] and 14.8% (N=27/183) corresponds to Puerto Rico and Guadeloupe [91.95]. However, in a cohort, it was found that there is a decreasing trend in mortality in recent years (decreasing from 22% to 14%, and to 11.6% in the last decade), which reflects the early diagnosis of complications. and the provision of appropriate treatment [17].

Advanced stages of the AKIN and RIFLE classification systems have been associated with an elevated risk of mortality [50]. In a retrospective cohort, patients in AKIN 3 AND RIFLE "Failure" stages were associated with higher mortality [51]. However, in a cohort published in Brazil, it was found that early intervention and early initiation of dialysis in these groups reduced mortality in critically ill patients [16]. On the other hand, 4 articles were found where 13.5% (N=44/327) of the patients in need of RRT died [16,51,88,96]. From our experience in a care center on the northern coast of Colombia (Barranquilla) during 2023, in patients with advanced stages according to AKIN, the use of antibiotic therapy, fluid therapy, and diuretics reduced the need for RRT and mortality. However, in 3 patients requiring RRT, 66.6% (n=2/3) died (unpublished data).

5. Conclusions

Acute kidney injury associated with leptospirosis is a serious complication that increases the need for admission to intensive care, and the likelihood of renal replacement therapy. In Latin America, high exposure to risk factors for leptospirosis has caused acute kidney injury to disproportionately affect all age ranges, exacerbated by the similarity of clinical manifestations with other zoonoses, the absence of diagnostic tests and the delay in onset. of antibiotic therapy. In the region, there is a discrepancy between the data, which underestimates the real burden of acute kidney injury associated with leptospirosis, making it a public health problem, particularly in countries with weaker health systems. Therefore, it is necessary to improve surveillance and notification systems and establish protocols for the management of acute kidney injury with the aim of reducing the risk of end-stage chronic kidney disease and death.

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