



Acute Kidney Injury Associated with Severe Leptospirosis: Fatal Re-Emerging Disease in Latin America

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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 has become 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, the 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



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Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). organ dysfunction accompanied by jaundice, hemorrhage, meningitis, and acute kidney injury (AKI) requiring intensive care assistance [1,6]. In addition, there may be pulmonary involvement, and this is described as severe pulmonary hemorrhage syndrome, which 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 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, the early diagnosis of leptospirosis is essential to attenuate disease progression and obtain better outcomes [9]. In clinical practice, the use of IgM through ELISA, the microscopic agglutination test, and the polymerase chain reaction (PCR) are useful diagnostic tools for screening the disease [10]. Furthermore, detection via the direct growth of *Leptospira* spp. in culture samples is useful as a diagnostic tool [6]; however, it is seldom used in clinical practice due to the difficulty in achieving standardization.

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, demonstrates hematogenous spread, 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 a 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, there may be a drop in glomerular filtration rate, severe electrolyte imbalance [15], and the need for renal replacement therapy (RRT) in up to 31.6% of cases [16,17]. The recovery of kidney function may take several months; however, AKI exposure from severe leptospirosis can lead to long-term end-stage chronic kidney disease (CKD) [18–20].

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 words leptos (thin) and spira (coiled), referring to the shape of the microorganism [21]. *Leptospira* spp. is an aerobic bacterium, spirochete of the genus *Leptospira* [13], measuring approximately 0.15–0.3 μ m in diameter and 6–20 μ m in length [22]. Its growth is slow, and, in its incubation phase, it may take up to 90 days [23] with an ideal temperature that ranges between 27 and 30 degrees Celsius. The axial filaments or endoflagella of the bacteria are what facilitate its mobility [22].

Leptospira species have a lipopolysaccharide layer in their structure and are classified into three groups: pathogenic, intermediate (without demonstrated virulence), and non-pathogenic [24]. 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, five intermediate strains, and six non-pathogenic or saprophytic strains with more than 60 serovariants [25].

3. Pathophysiology of Leptospirosis and Acute Kidney Injury

The most common complication of leptospirosis is AKI [26]. *Leptospira* spp. colonization of the kidney can cause tubulointerstitial nephritis followed by fibrosis, and, if not treated in time, it culminates in CKD [19,20,27]. 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 urinary pH [10]. The pathophysiology spectrum is summarized in Figure 1.

Figure 1. Model of the biological effects on the proximal tubule caused by Leptospira spp. The persistence of this microorganism in the kidney tissue causes interstitial inflammation, accumulation of extracellular matrix, and damage to tubular epithelial cells. Abbreviations: LPS: lipopolysaccharides; PG: peptidoglycan; GLP: Glycolipoprotein; OM: outer membrane proteins; IM: inner membrane proteins; AQP-1: aquaporin 1 channel; H₂O: water; HPO₄: phosphoric acid; NHE₃: sodium–hydrogen exchanger; STAT3: Signal transducer and activator of transcription 3; TGF β 1: Transforming growth factor beta 1; NF-KB: Nuclear Factor-kappa B; IL-6: interleukin 6; IL-8: interleukin 8; TNF- α : tumor necrosis factor- α ; 3HCO₃: carbonic acid. Created with BioRender.com.

The epithelial cells of the renal tubules are the structures most affected by *Leptospira* spp. [28]. This microorganism, in its outer membrane, has proteins such as OmpL1, lipoprotein LipL41, LipL32, and lipopolysaccharides that can adhere and infiltrate mononuclear tubular epithelial cells, activating complement and causing direct injury [29–31]. On the other hand, during the acute phase of the disease, the existing cytokine storm amplifies the pro-inflammatory state, the migration of macrophages, and it favors kidney tissue injury (Figure 1) [1,32,33].

One of the preferred sites of the *Leptospire* spp. is the proximal tubule [30] due to its affinity for the Na/K-ATPase pumps, which alters their functioning by inhibiting their activity, also reducing the sodium/hydrogen ion exchanger and aquaporin 1 (AQP-1) in the apical and basolateral membrane (Figure 1) [34]. 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 [35].

The ascending branch of the loop of Henle is also affected by this microorganism [36]. When tubular cells are injured, they release nitric oxide, which facilitates a decrease in systemic vascular resistance, thus reducing renal blood flow and the glomerular filtration rate [37]. It can also reduce the expression of the Na/K/2Cl- cotransporter (NKCC2), which explains the loss of sodium and potassium in the urine [38]. 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 [36]. The dysregulation of ion pumps explains the hyponatremia, hypokalemia, hypomagnesemia, and non-oliguric AKI characteristic of leptospiral nephropathy.

Glycolipoprotein (GLP) is an endotoxin with the capacity to store fatty acids that contribute to the pathogenic action of *Leptospira* spp. [39,40]. Its main characteristic is its specificity for the Na/K-ATPase pump [41] on the cytosolic surface of cell membranes through the action of its lipid component on the cell membrane (oleic acid), and the poor adsorption of the albumin toward these fatty acids [42–44]. Synergistic inhibition reduces the co-transport activity of the Na/K-ATPase pump, increasing affinity for sodium and potassium loss [45,46]. GLP also induces a systemic inflammatory response with an increase in the production of IL-6, IL-8, and TNF- α from the expression of peripheral blood mononuclear cells with the expression of CD69, HLA-DR, leukotriene B4, prostaglandin E2, and nitric oxide; these contribute to cellular activation and cause a greater degree of tissue damage (Figure 1) [47,48].

Other factors that facilitate AKI are myoglobinuria induced by rhabdomyolysis, causing direct toxicity to the kidney, obstruction of the renal tubules, and renal vasoconstriction [6,49]. The persistence of this microorganism in the kidney tissue causes interstitial inflammation, the accumulation of extracellular matrix, and damage to tubular epithelial cells [18]. In addition, it has been reported that damage to these cells stimulates the mediator of tubulointerstitial fibrosis (STAT3 transcription factor) that favors the secretion of transforming growth factor beta (TGF β 1) and the production of type II and IV collagen that has been implicated in the progression of kidney disease [1,50,51].

After the initial injury, the residual and functional nephrons enter into a maladaptive compensation process to replace the work of the injured glomeruli and tubules [52]. If chronicity persists in the degree of inflammation, it can favor the invasion of immune cells, the abnormal migration of fibroblasts, and can lead to fibrosis [52,53]. In patients with existing chronic kidney disease, the repair and compensation processes are more limited and the risk of progression to terminal disease increases [54,55].

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 and 45% of patients with AKI are non-oliguric and have hypokalemia, which determines the characteristic presentation of leptospirosis [1]. Acute tubular nephritis and acute interstitial nephritis are the main pathological findings [6]. This is accompanied by skin rash, fever, emesis, frequency, and nocturia [56].

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 [57]. 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 [58].

5. Diagnosis

The early and accurate diagnosis of leptospirosis is essential to mitigate disease progression [9]. The use of IgM through ELISA and the microscopic agglutination test are useful diagnostic tools for screening the disease in Latin America [10]. In addition, there are rapid tests valid for the detection of *Leptospira* spp. antibodies through a portable reagent strip that provide immediate screening during the acute phase [59,60]. PCR tests continue to be important in diagnosis, but poor availability and a high cost make them difficult to apply in clinical practice in Latin America [10].

The early identification of AKI caused by severe leptospirosis is important to reduce associated morbidity and mortality [61]. The use of serum markers such as creatinine continues to be important in first care settings [62]. This marker of late kidney damage is correlated with a drop in the glomerular filtration rate by up to 50% and if it rises to 1.5 times its baseline value, it increases the risk of imminent kidney failure [63]. The RIFLE and AKIN stages are used to stratify the severity of patients with leptospirosis [64]. These systems, through the measurement of creatinine, can achieve greater sensitivity (84%) and specificity (48%) to determine severe AKI secondary to leptospirosis [65].

In recent decades, studies on the use of renal biomarkers to identify premature kidney damage due to leptospirosis have increased enormously [26]. The action of *Leptospira* spp. in the kidney involves the increased expression of proinflammatory molecules such as neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemotactic protein 1 (MCP-1) [66], kidney injury molecule 1 (KIM-1), and N-acetyl-D-glucosaminidase (NAG) [67]. Although these biomarkers are not specific for AKI and leptospirosis, their measurement has been important in the early detection of AKI to reduce associated 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 [68]. This biomarker is characterized by appearing 12–24 h after the onset of the injury [67], relating to the severity of the infection [69]. In a study in Sri Lanka, KIM-1 was detected on the third day of fever after admission and was at its highest concentration on the ninth day [63]. 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 [70]. Therefore, the measurement of this biomarker may be useful in diagnosing AKI in severe leptospirosis [67].

5.2. Monocyte Chemoattractant Protein 1 (MCP-1)

This is expressed when AKI occurs secondary to ischemia [63]. In a study at the Seattle hospital, they used kidney samples with kidney injury in rats and showed an increase in MCP-1 4 h after the onset of failure [71]. Nisansala et al. [26], in a cross-sectional study, verified the direct relationship between the increase in MCP-1 values in the presence of AKI and 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 h, initiating kidney damage. Srisawat et al. [72] 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 started 12 h after damage [67]. Two retrospective studies were conducted in Thailand in 2016 and 2020, where urinary NAG was related to leptospirosis-associated AKI [26].

6. Management Strategies

Antibiotic therapy is currently the cornerstone of managing severe leptospirosis [58]. Options include the use of intravenous penicillin [6], ceftriaxone [64], or doxycycline [73]

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 [64,74,75]. In a cohort published in Colombia, it was found that non-administration of antibiotics was associated with severe disease and admission to intensive care [76]. In the 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 [77]. Guaranteeing 2–2.5 L per 24 h for a urinary output greater than 0.5 mL/kg/h reduces the risk of AKI [78]. After starting water therapy and the poor diuresis response, a diuretic stimulus should be started, taking into account the high risk of requiring RRT [77].

If arterial hypotension is evident despite the administration of adequate fluid therapy, the use of vasoactive agents should be resorted to [58]. This is because the hemodynamic changes associated with severe leptospirosis are similar to a state of septic shock, finding a high cardiac index and low systemic vascular resistance (hemodynamic behavior of septic shock) [79]. 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 [80].

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 fundamental role in management [81,82]. Platelet transfusion should be considered if there is bleeding and a platelet count <50,000/uL [83].

In the advanced stages of the infection, where sepsis and septic shock reveal organ dysfunction [84], mechanisms mediated by immune complexes generate systemic tissue damage, and antibiotic therapy produces an excessive release of endotoxins due to bacterial death (Jarisch–Herxheimer reaction) [85]. The use of plasma exchange could be considered a reasonable option [86]. This rapidly eliminates circulatory endotoxins, catabolic products, and the inflammatory markers generated, reducing the risk of associated complications such as acute tubular necrosis and AKI [86,87]. In addition, it favors clinical recovery and a significant reduction in mortality in critically ill patients [87,88]. 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, the basic aspects that make up the dialysis emergency must be considered [77]. The latter, in patients with severe infection, is more frequently observed as severe metabolic acidosis, water overload refractory to diuretics, and anuric renal failure [89]. The indication of RRT should not be delayed, deferred, or underdosed if necessary since its early use generates a reduction in mortality [77,89]. The continuous modality (continuous venovenous hemodialysis or continuous venovenous hemodiafiltration) has beneficial effects in improving survival [16]. However, if this therapy is not available, peritoneal dialysis has also been associated with excellent results [90,91]. Because paradoxical hypokalemia is often present in patients with this type of AKI, kaliuretic diuretics and RRT methods mentioned in the text should be used with caution.

In those patients with respiratory compromise who develop acute respiratory failure, support for this condition will begin with oxygen therapy, devices such as a high-flow nasal cannula, and non-invasive mechanical ventilation (CPAP/BPAP). In the case of reaching the condition of severe ARDS, ventilatory support may be required and should be administered early [77], and, in this case, invasive mechanical ventilation should follow the current recommendations for protective ventilation for the management of ARDS [92–98]. In patients with severe ARDS, in conditions of refractory hypoxemia and multiple organ dysfunction, successful cases have been described with the use of extracorporeal membrane oxygenation therapy [99–101]; 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 [102]. According to PAHO estimates, leptospirosis reaches an estimated 10,702 cases annually [2]. Despite this, until now, AKI secondary to leptospirosis was 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"). Articles were limited to English and Spanish. Articles that presented bibliographic products with an unavailable abstract and duplicate article were excluded. Table 1 summarizes the selected articles that met the search criteria.

7.1. Overall Findings

Of the 18 published articles, 5 were published before 2010 (27.8%) [16,62,103–105], 11 between 2011 and 2020 (61.1%) [17,28,64,65,102,106–111], and 2 studies were published after 2021 [11,76]. In total, 72.2% (N = 13/18) of the articles included information from Brazil, 16.7% (N = 3/18) from Colombia, and 16.7% from Central America (N = 2/18) (see Table 1). In 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, with 90% (N = 9/10) of articles being from 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) [64,65,104,106,108,111] was found, and for Colombia it was found to be 29.3% (N = 122/416) [76,102,107]. However, only one article published by Herrmann-Storck et al. [105] described AKI corresponding to the Central American region, finding a prevalence of 41.5% (N = 54/130). These findings are summarized in Figure 2.



Acute kidney injury associated with severe leptospirosis in Latin-America

Figure 2. Epidemiology of acute kidney injury in patients with severe leptospirosis in Latin America. Created with BioRender.com.

Author	Type Study	AKI (%)	Hydroelectrolyte Imbalance (Na or K)	Oliguria ¹ (%)	Dialysis (%)	Global Mortality (%)	Country
Daher et al., 1999 [62]	Retrospective Cohort	-	No	n = 103/110 (93.6)	n = 89/110 (81)	n = 24/110 (22)	Brazil
Andrade et al., 2007 [16]	Retrospective Cohort	-	No	-	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 [103]	Retrospective Cohort	-	Yes	n = 64/196 (32.7)	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 [104]	Retrospective Cohort	n = 175/201 (87)	Yes	n = 64/201 (31.8)	n = 103/201 (51.2)	n = 31/201 (15.4)	Brazil
Herrmann-Storck et al., 2010 [105]	Retrospective Cohort	n = 54/130 (41.5)	No	n = 34/128 (26.6)	n = 10/110 (9.09)	n = 6/110 (5.45)	Guadalupe
Damasco et al., 2011 February [106]	Retrospective	n = 13/27 (48.1)	-	-	n = 3/27 (11.1)	n = 3/27 (11.1)	Brazil
Echeverri et al., 2011 June [107]	Case series	n = 2/14 (14.3)	-	-	n = 1/14 (7.1)	n = 2/14 (14.3)	Colombia
Silva Júnior et al., 2011 [65]	Retrospective Cohort	RIFLE: n = 237/287 (82) AKIN: n = 242/287 (84)	Yes	n = 55/287 (19)	n = 105/287 (36.6)	Total: n = 37/287 (13) Dialysis n = 21/37 (56.7)	Brazil
Reis et al., 2013 Septmeber [28]	Cases and controls	-	-	n = 65/172 (37.8)	n = 37/172 (21.5)	n = 25/172 (14.5)	Brazil
Daher et al., 2014 February [108]	Retrospective Cohort	n = 301/374 (80.5)	-	n = 79/374 (21.2)	n = 124/374 (33.2)	n = 47/374 (12.5)	Brazil
Daher et al., 2016 February [64]	Cross-sectional	n = 162/206 (78.6)	Yes	n = 42/206 (20.4)	n = 80/206 (38.8)	n = 26/206 (12.7)	Brazil
Sharp et al., 2016 February [109]	Cases and controls	-	-	-	n = 11/173 (6.36)	n = 21/173 (12.1)	Puerto rico
Cleto S et al., 2016 Ago [110]	Prospective	-	-	-	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

Table 1. Acute kidney	injury in patients	with severe leptospirosis in	Latin America.
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Table	1.	Cont.

Author	Type Study	AKI (%)	Hydroelectrolyte Imbalance (Na or K)	Oliguria ¹ (%)	Dialysis (%)	Global Mortality (%)	Country
Echeverri-Toro et al., 2017 [102]	Cross-sectional	n = 60/201 (29.9)	-	-	n = 14/119 (11.8)	n = 6/119 (5)	Colombia
Daher et al., 2017 [17]	Retrospective Cohort	-	Yes	n = 130/507 (25.6)	n = 193/507 (38.1)	n = 72/507 (14.2)	Brazil
Daher et al., 2019 [111]	Retrospective Cohort	n = 60/507 (76.1)	-	n = 127/207 (25)	n = 193/507 (39.2)	n = 75/507 (14.8)	Brazil
Meneses et al., 2022 [11]	Prospective	-	-	n = 4/27 (14.8)	n = 12/27 (44)	n = 2/27 (7.4)	Brazil
Parra et al., 2023 [76]	Retrospective Cohort	n = 60/201 (29.9)	-	n = 40/201 (19.9)	n = 37/201 (18.4)	n = 17/201 (8.5)	Colombia

¹ Urinary volume < 400 mL/day after 24 h of appropriate hydration. *Abbreviations*: AKI: acute kidney injury; K: potassium; Na: sodium; DAdD: delayed, alternate-day dialysis; PaDD: prompt and daily dialysis; SLED: sustained low-efficiency dialysis; SLEDf: sustained low-efficiency dialysis via hemodiafiltration.

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 [16,17,28,62,64,65,76,102-111]. Brazil was the country with the greatest scientific evidence, finding a prevalence of 40% (N = 1114/2785) [11,16,17,28,62,64,65,103,104,106,108,110,111], followed by Colombia with 15.6% (N = 52/334) [76,102,107].

Early implementation of effective RRT is key to slowing the progression of AKI into more severe forms and is associated with decreased mortality [17,110]. However, when evaluating the type of dialysis to use, i.e., 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 reduced the levels of pro-inflammatory cytokines faster, which may prevent disease progression [110].

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, 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) [11,16,17,28,62,64,65,103,104,106,108,110,111], Colombia 7.5% (N = 25/334) [76,102,107], and 14.8% (N = 27/183) in Puerto Rico and Guadeloupe [105,109]. However, in one cohort, there was a decreasing trend in mortality found 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 [64]. In a retrospective cohort, patients in AKIN 3 AND RIFLE "Failure" stages were associated with higher mortality [65]. However, in a cohort study published in Brazil, it was found that early intervention and the early initiation of dialysis in these groups reduced mortality in critically ill patients [16]. On the other hand, four articles were found where 13.5% (N = 44/327) of the patients in need of RRT died [16,65,102,110]. 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 three patients requiring RRT, two died (unpublished data).

8. Conclusions

AKI 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 AKI to disproportionately affect all age ranges, exacerbated by the similarity in clinical manifestations to other zoonoses, the absence of diagnostic tests, and the delay in the onset of antibiotic therapy. In this region, there is a discrepancy between the data, which underestimates the real burden of AKI 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 AKI to reduce the risk of end-stage CKD and death. **Author Contributions:** Conceptualization, E.O.-R. and D.R.-B.; writing—original draft preparation, E.O.-R., D.R.-B., J.P.-P., V.S.-D. and E.S.-O.; project administration, E.O.-R.; writing—review and editing, E.O.-R., D.R.-B., J.P.-P., C.R.-M., A.P.-B., M.A.-R. and A.B.-M. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors have read and agreed to the published version of the manuscript.

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