

## Predictors of Severity and Management of Severe Leptospirosis Patients in Intensive Care Unit

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### ABSTRACT

**Background:** Severe leptospirosis or Weil's syndrome occurs in 10% of leptospirosis cases, with a mortality rate of 5-40%. Misdiagnosis of leptospirosis often occurs due to nonspecific symptoms. Discussion of risk factors, causative agents, pathogenesis, clinical manifestations, diagnostic techniques, and predictors of disease severity are crucial for successful management.

**Cases:** We report 3 cases of leptospirosis with various clinical manifestations and management. In these 3 cases, older age was associated with severe leptospirosis and poor outcomes. The SPiRO score can identify patients with severe leptospirosis requiring intensive care. All three cases of leptospirosis were severe with complications in the kidneys, lungs, and hematological system requiring intensive care in the intensive care unit (ICU).

**Discussion:** Early and appropriate management can reduce patient mortality rates. ICU management of leptospirosis includes antibiotics, fluid balance, and support for affected organs. Patients with respiratory failure are given oxygenation using high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), or invasive mechanical ventilation with endotracheal intubation (ETT). Acute kidney failure in leptospirosis can be managed with hemodialysis as indicated or may improve with conservative therapy. Corticosteroids may be administered for thrombocytopenia associated with leptospirosis.

**Conclusion:** The three cases of leptospirosis were severe with complications in the kidneys, lungs, and hematological system requiring intensive care in the ICU. Early and appropriate management can reduce patient mortality rates. In these 3 cases, older age, mechanical ventilation, acute kidney failure, septic shock, thrombocytopenia, and elevated transaminase enzymes were associated with severe leptospirosis and poor outcomes.

**Keywords:** clinical manifestations; diagnosis; intensive care unit; management; severe leptospirosis

## INTRODUCTION

Leptospirosis is a major zoonotic disease transmitted by animals. Leptospirosis is caused by *Leptospira sp.* The term leptospirosis was first introduced by Noguchi based on its thin structure and spiral shape.<sup>1</sup> *Leptospira* has two genera which are *L. interrogans* which includes all pathogenic strains, and *L. biflexa*, which consists of all saprophytic strains. *L. interrogans* are responsible for causing leptospirosis.<sup>2</sup> *L. interrogans* and *L. biflexa* has over 200 and 60 serovar.<sup>3,4</sup> While various wild animals can act as reservoir hosts, the brown rat (*Rattus norvegicus*) is the primary source of human infection. Rats shedding large amounts of leptospire (10<sup>7</sup> organisms per ml) for months following their initial infection. *Leptospira* enters the body through skin cuts, abrasions, or mucous membranes of the eyes, nose, or throat, with symptoms appearing between 1 day to 4 weeks after exposure, and in survivors, the infection may persist for months.<sup>5</sup> Although any stratum of public status can be infected, individual with middle-low income is affected the most. Moreover, individuals living in unhygienic environments with inadequate sanitation are at risk of exposure to rats and leptospirosis.

One million leptospirosis cases are estimated to be reported and with a case fatality ratio of 6.85%, it is responsible for 58,900 deaths each year.<sup>7</sup> According to the Leptospirosis Burden Epidemiology Reference Group (LERG), risk factors for leptospirosis include increased rainfall, flooding, open sewers, high population density, animal contact, and poor hygiene. The transmission of leptospirosis is triggered by warm climates and humid conditions, leading to outbreaks that are common in tropical areas and occasionally occur during the summer or fall in temperate

regions.<sup>1</sup> The disease has a case fatality ratio of 26.89 out of 7,587 cases over a decade. It remains as one of the major global health problems. Lack of knowledge about leptospirosis exacerbates this issue. Efforts are being made to gather the most up-to-date information on leptospirosis, encompassing discussions on various aspects such as risk factors, causative agents, pathogenesis, clinical symptoms, and diagnostic methods.<sup>1</sup> Misdiagnosis of leptospirosis often occurs due to nonspecific symptoms documented in the literature. The disease can be fatal because severe leptospirosis or Weil's syndrome manifests as complex systemic complications, primarily kidney failure.<sup>1</sup>

Weil's syndrome or severe leptospirosis occurs in ten percent of patients and has 5-40% mortality rate. Common symptoms of this syndrome include the involvement of liver, kidney, and vascular. Symptoms typically appear 3 to 7 days after exposure and can include continuous jaundice, reduced urine production, anemia, skin rash, low blood pressure, shock, changes in consciousness, mucosal bleeding, and lung hemorrhage. Poor prognoses are associated with advanced age, kidney failure, pneumonia, and thrombocytopenia. Thrombocytopenia occurs without disseminated intravascular coagulation (DIC) and can follow the progressive kidney dysfunction.<sup>3</sup> The severity of leptospirosis is influenced by three factors: host vulnerability, epidemiological conditions, and pathogen virulence. Mortality rates increase with age, particularly in patients over 60. High levels of bacteremia are linked to worse clinical outcomes. Severe cases of leptospirosis involve cytokine storms, marked by elevated

levels of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- $\alpha$ ), and IL-10.<sup>6</sup>

This case series aims to understand the management of leptospirosis patients in intensive care units and the predictors that worsen the disease.

## CASES

### Case 1

Mr. J is a 53-year-old male with type 2 diabetes mellitus, worked as a farmer in rice fields without wearing footwear. Ten days before hospital admission, the chief complaint was fever, especially in the evening and at night, generalized body sores and pains, especially in the legs and hands. He visited a nurse and had paracetamol and amoxicillin. The fever decreased, however other complaints did not improve. Urination was reported to have decreased, occurring 3-4 times a day with a volume of approximately 200 cc each time. On the day of hospital admission, the patient visited the district hospital with persistent fever and weakness, however, nausea, vomiting, shortness of breath, and cough were denied. Decreased urination was remarked. At the district hospital, low blood pressure was reported, and fluid resuscitation and norepinephrine support were initiated. Treatment at the district hospital included 500 cc NaCl 0.9% infusion, 1 ampule of ranitidine injection, 1 ampule of citicoline injection, 1 ampule of mecobalamin injection, 1 ampule of ondansetron injection, and 1 gram of ceftriaxone injection. The patient was then referred to Dr. Sardjito Hospital for further management. Urine output over 6 hours was 400 cc (0.8 cc/kgBW/hour).

His initial vital signs were as follows: blood pressure (BP) of 97/47 mmHg with norepinephrine (NE) at 0.05

mcg/kg/minute, heart rate (HR) of 83 beats per minute (BPM), respiratory rate (RR) of 20 breaths per minute, temperature (T) of 36.6°C, and oxygen saturation (SpO<sub>2</sub>) of 98% using a nasal cannula at 3 liters per minute (LPM). The patient's nutritional status showed a body mass index (BMI) of 28.6 (weight 75 kg, height 162 cm). An abnormal initial physical examination finding was epigastric tenderness. The SEARO criteria for diagnosing leptospirosis, developed by the WHO's South-East Asia Regional Office (SEARO), were established during a meeting of experts at the 'Informal Expert Consultation on Surveillance, Diagnosis, and Risk Reduction of Leptospirosis' in Chennai, India, on September 18-19, 2009. These criteria are used to help identify suspected cases based on clinical symptoms and exposure history.<sup>8</sup> In this patient, persistent fever and/or headache with myalgia (+), weakness (+), conjunctival suffusion (-), and environmental history (+) were observed.

The patient was diagnosed with sepsis, leptospirosis complicated by acute kidney injury, hypokalemia, hypoalbuminemia, thrombocytopenia without bleeding signs, leukocytosis, and hyperglycemia stress with a differential diagnosis of type 2 diabetes mellitus. Abnormal initial diagnostic findings included positive anti-leptospira IgM, blood urea nitrogen (BUN) 110 mg/dL, creatinine 5.74 mg/dL, leukocytes 20,500, platelets 35,000, potassium 2.8 mmol/L, and albumin 2.6 mg/dL.

In the ward, the patient received ceftriaxone injection 1 gram/12 hours, methylprednisolone injection 20 mg/8 hours, proton pump inhibitor (PPI) injection 1A/24 hours, and furosemide injection 20 mg/12 hours. On the second


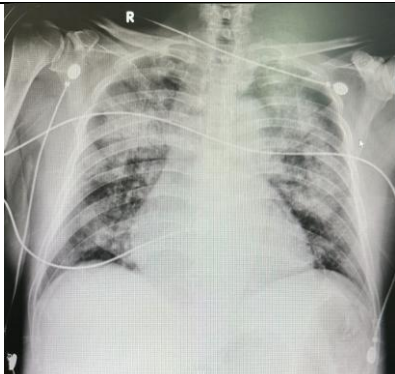
day, the patient developed respiratory distress, tachypnea, RR 37 breaths per minute, SpO<sub>2</sub> 94-95% with a non-rebreathing mask (NRM) at 15 LPM, BP 130/78 mmHg, HR 101 BPM with NE 0.05 mcg/kg/minute.

The patient was then transported to the intensive care unit (ICU) and remained hospitalized for 6 days. During treatment, the patient was conscious, and received respiratory support with NIV for 2 days, then weaned to NRM at 10 LPM, and continued therapy with ceftriaxone injection 1 gram/12 hours, levofloxacin injection 750 mg/24 hours (chest x-ray: bilateral pneumonia), methylprednisolone 31.25 mg/8 hours tapered off every 12 hours, furosemide injection, paracetamol injection, PPI

injection, and novorapid. The patient's acute kidney injury improved without hemodialysis, with BUN decreasing from 98 and creatinine from 3.39 on the first day in the ICU to BUN 105, creatinine 2.58, and BUN 82, creatinine 1.99 on the third day in the ICU. Chest x-ray on admission to the emergency room (ER) showed pulmonary edema and cardiomegaly with aortic elongation. Chest x-ray on the third day in the ICU showed bilateral pneumonia. (Table 1)

The patient was discharged after 14 days of hospitalization with levofloxacin therapy 500 mg every 24 hours (for 5 days), lansoprazole 1x30 mg, B complex 1x1 tab, furosemide 40 mg ½-0-0 tab, and methylprednisolone 8 mg (1-0-0).

**Table 1. Case 1 X-ray**

Day of care	Chest X-ray
ER Admission	
Day 3 ICU	

## Case 2

Mr. P, a 28-year-old male working as a scavenger, presented to the emergency room with a persistent fever for 3 days. He complained of having fever accompanied by nausea, weakness, headache, and 7 episodes of diarrhea over 2 days. He had previously visited a public health center and was diagnosed with thrombocytopenia before being referred to Universitas Gadjah Mada Academic Hospital. The last urination was 3 hours before arriving at the hospital. Currently (7 hours before hospital admission), the patient has not urinated at all.

In the emergency room, the vital signs were BP 79/55 mmHg, HR 83 BPM, RR 20 breaths per minute, T 36.6 °C, and SpO<sub>2</sub> 98%. An initial physical examination revealed epigastric tenderness. The initial diagnosis was suspected leptospirosis, acute kidney injury, and hyponatremia. Initial diagnostic tests showed urea 77.9 mg/dL, creatinine 2.5 mg/dL, sodium 126 mmol/L, and platelets 80,000.

In the ward, the patient received ceftriaxone 2 grams/24 hours, paracetamol 1 gram (as needed), and electrolyte correction with 3% NaCl at 20 cc/hour. On the second day of hospitalization, the patient experienced rapid breathing and low blood pressure, necessitating a transfer to the ICU. In the ICU, the patient remained conscious and was provided with respiratory support using a high-flow nasal cannula (HFNC)

as well as hemodynamic support with norepinephrine and dobutamine. The patient underwent hemodialysis once, had a central venous catheter inserted, received escalated antibiotic therapy with meropenem 1 gram/12 hours, N-acetylcysteine 200 mg/8 hours, furosemide injection, and salbutamol nebulization. After 7 days of treatment in the ICU, the patient improved and was transferred back to the ward.

During ICU treatment, abnormal diagnostic findings included positive leptospira IgM, procalcitonin 136.83, platelets increased from 82,000 to 123,000 without platelet transfusion, hyponatremia (126), increased urea 109.20, and creatinine 4.86. After hemodialysis, urea decreased to 72.2, creatinine 3.16, and improved to urea 70.5 and creatinine 2.25 on the 4th day in the ICU without further hemodialysis. The initial chest x-ray on the first day of admission in the emergency room showed normal lungs and heart, as well as thoracic scoliosis. On the 4th day in the ICU, there was pulmonary edema, and on the 7th day in the ICU, improvement was observed compared to previous x-rays. On the 10th day, the lungs and heart appeared normal. (Table 2)

The patient was discharged from the hospital after 13 days of treatment and received B complex tablets every 8 hours upon discharge.



**Case 3**

Mr. S, a 71-year-old male with an unknown occupation, was referred from a type D hospital with decreased consciousness, chronic kidney failure, and suspected leptospirosis. He presented with a fever that had been fluctuating for 5 days and did not improve with antipyretic medication. He also complained of increasing weakness. However, he denied cough, nausea, vomiting, and runny nose. He was noted to have jaundice and restlessness. His urine output was reportedly decreased by approximately 100 ml, while bowel movements were normal. He was hospitalized at the type D hospital for 3 days, receiving therapy including intravenous levofloxacin 500 mg/12 hours, intravenous ranitidine 1 ampule/12 hours, intravenous ondansetron as needed, intravenous paracetamol as needed, folic acid 1 tablet daily, and harnal 1 tablet daily. He was referred to Dr. Sardjito Hospital due to decreased consciousness for intensive management. Previous medical history included diabetes mellitus, hypertension, heart disease, kidney disease, stroke, and COVID were denied.

Upon initial examination in the emergency room, the vital signs were BP 77/54 mmHg, HR 120 beats per minute, RR 20 breaths per minute, T 36 °C, and SpO<sub>2</sub> 98% with a NRM at 15 litres per minute. Initial physical examination revealed icteric sclera and epigastric tenderness. The SEARO criteria for diagnosis leptospirosis in this patient included persistent fever and/or headache with myalgia (+), weakness (+), and environmental history (+).

Initial diagnostic tests upon referral showed positive anti-leptospira IgM, platelets 35,000, blood glucose 59 mg/dL, BUN 131 mg/dL, creatinine 7.73

mg/dL, albumin 2.43 mg/dL, SGOT 135, SGPT 72, total bilirubin 9.73, direct bilirubin 9.43, and indirect bilirubin 0.30. Arterial blood gas analysis (ABG) showed FiO<sub>2</sub> 0.80, pH 7.30, pCO<sub>2</sub> 23.8, PO<sub>2</sub> 86.8, HCO<sub>3</sub> 11.4, base excess (BE) -14.98, SO<sub>2</sub> 97.4, and AaDO<sub>2</sub> 448.5.

The patient was diagnosed with respiratory failure, uremic syndrome, severe leptospirosis, septic shock, acute kidney injury, hypoalbuminemia, thrombocytopenia, and jaundice.

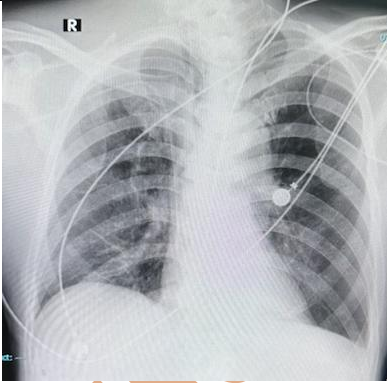

He was subsequently admitted to the ICU, intubated, and received mechanical ventilation, as well as hemodynamic support with norepinephrine. Treatment included intravenous ceftriaxone 1 gram/12 hours, intravenous methylprednisolone 20 mg/8 hours, intravenous omeprazole 40 mg/24 hours, albumin transfusion, urdalfalk 250 mg/8 hours, and hemodialysis twice. The patient also underwent central venous catheter placement and tunnelled hemodialysis catheter insertion. On the fourth day of ICU treatment, he underwent a second hemodialysis session, but experienced pulseless electrical activity (PEA). Hemodialysis was stopped. Cardiac pulmonary resuscitation (CPR) was performed and return of spontaneous of circulation (ROSC). Later at that night, the BP was undetectable, PEA was detected and another CPR was performed. Despite receiving resuscitation, the patient did not survive.

Abnormal diagnostic findings during ICU treatment included metabolic acidosis, thrombocytopenia (lowest 51,000), increased BUN (highest 167 mg/dL), increased creatinine (highest 7.01 mg/dL), increased total bilirubin (15.4 mg/dL), increased direct bilirubin (13.1 mg/dL), increased indirect

bilirubin (2.3 mg/dL), hyponatremia (sodium 125), and elevated procalcitonin (5.82). Chest x-ray on the first day of admission in the emergency room

showed pulmonary edema, and on the fourth day, it revealed right lung pneumonia. (Table 3)

**Table 3.** Case 3 X-ray

Day of care	Chest X-ray
Day 1 ICU	
Day 4 ICU	

**DISCUSSION**

**Epidemiology**

Approximately 73% of leptospirosis cases occur in tropical regions, especially in Southeast Asia, eastern Sub-Saharan Africa, the Caribbean, and Oceania. The disease primarily affects the agricultural population in impoverished rural and urban areas, often targeting young adult males. Those at high risk include farmers, individuals in contact with livestock, people exposed to rodents at work, and residents of areas with poor sanitation. Outbreaks frequently occur in unsanitary environments where rats are abundant and are often linked to flood disasters. Rats are the primary carriers responsible for transmitting leptospirosis to humans. This is due to their presence in human habitats and the high

concentration of organisms they excrete. Human transmission is most common through skin's and mucous membranes' lacerations that are exposed water contaminated by the urine of infected rats.<sup>7</sup> In Case 1, the patient had a history of working in rice fields without footwear, and in Case 2, the patient worked as a scavenger, while in Case 3, no data on the patient's occupation was available.

**Clinical manifestation**

Leptospirosis, a zoonotic infection affecting both humans and animals, is caused by *Leptospira* species from the spirochaete family. The incubation period ranges from 2 to 20 days, with 7 to 12 days being typical. The disease progresses through two stages. The first



stage, known as the bacteremic, septicemic, or leptospiraemic phase, involves active leptospiral infection. The initial stage is characterized by flu-like symptoms such as conjunctival suffusion, fever, severe headache, loss of appetite, muscle pain, chills, abdominal pain, cough, and sore throat, which last for more than 5-7 days. The second stage, known as the immunologic or immune phase, begins immediately after the bacteremic phase or 1-3 days following an asymptomatic period. During this phase, patients may experience a range of symptoms, including mild fever, headache, vomiting, and rash.<sup>3</sup>

After the leptospiraemic or septicemic phase, the immune phase ensues, characterized by the presence of IgM antibodies in the blood and the excretion of the organism in the urine. During this phase, the organism tends to accumulate in higher concentrations in the proximal renal tubules and other organs. Severe symptoms manifest in accordance to the level of organ involvement and organism virulence.<sup>3</sup>

Ten percent of patients with leptospirosis exhibit severe symptoms or Weil's syndrome, with a mortality rate of 5-40%. Symptoms of this syndrome result from involvement of the liver, kidneys, and blood vessels. Symptoms typically appear 3-7 days post-exposure and can include continuous jaundice, reduced urine output, anemia, skin rash, low blood pressure, shock, changes in consciousness, mucosal and skin hemorrhagic lesions, and lung hemorrhage. This syndrome was observed in Case 3, where the patient appeared jaundiced with decreased urine output, decreased consciousness, and shock. Severe vascular injury can occur, leading to pulmonary hemorrhage, renal

cortical ischemia, tubular epithelial necrosis, hepatic architecture destruction causing jaundice, and hepatocellular injury, with or without necrosis. In Case 3, the patient was an elderly (71 years old) and had complications of pneumonia, kidney failure, and thrombocytopenia that were associated with poor prognosis. This patient (Case 3) ended in death.<sup>3</sup>

The pathogenesis of severe leptospirosis is not well understood, but it is suspected to be caused by vasculitis. Like other bacterial infections, leptospira causes direct tissue damage and triggers immune-mediated mechanisms that lead to organ and tissue damage, disturbances in tissue microcirculation, and endothelial dysfunction. While jaundice is a notable symptom, death often results from complications such as acute kidney injury, myocardial involvement, or pulmonary hemorrhage. Lung complications, particularly severe pulmonary hemorrhage, and myocarditis are critical manifestations associated with high mortality rates.<sup>3</sup>

### Diagnosis

The diagnosis of leptospirosis relies primarily on clinical features suggestive of the disease, combined with a history of exposure to risk factors. Any patient with a history of exposure to risk factors and presenting with one or more of the following symptoms should be suspected: conjunctival suffusion, oliguria, headache, myalgia, jaundice, symptoms of meningeal irritation, hemorrhage, heart failure or arrhythmia, cough, dyspnea, skin rash, organ involvement, or dysfunction.<sup>3</sup>

Several diagnostic examinations are available for leptospirosis, but not all tests are available in resource-limited settings.

**Table 4. Organ involvement in leptospirosis<sup>3</sup>**

Organ involvement in leptospirosis
Kidney Involvement
<ul style="list-style-type: none"> <li>- Decrease urine output</li> <li>- Hematuria</li> <li>- Acute kidney failure (vary in degree)</li> </ul>
Liver Involvement
<ul style="list-style-type: none"> <li>- Hepatomegaly</li> <li>- Jaundice</li> <li>- Increased serum aspartate transaminase (AST) or alanine transaminase (ALT) levels to three times above normal.</li> <li>- Elevated bilirubin serum, alkaline phosphatase, or gamma-glutamyl transferase (GGT) levels.</li> <li>- Prolongation of prothrombin time.</li> </ul>
Pulmonary Involvement
<ul style="list-style-type: none"> <li>- Cough, shortness of breath, hemoptysis.</li> <li>- Hypoxia.</li> <li>- Respiratory rate &gt; 30 breaths/minute.</li> <li>- Rhonchi and wheezing upon auscultation.</li> <li>- Involvement of pulmonary parenchymal based on radiology finding (CT scan)</li> <li>- Acute Respiratory Distress Syndrome</li> </ul>
Heart Involvement
<ul style="list-style-type: none"> <li>- Chest pain, heart rate &gt;100 bpm, palpitation</li> <li>- Low blood pressure</li> <li>- ECG abnormalities such as arrhythmia, ST/T changes, conduction abnormalities.</li> <li>- Echocardiography abnormalities</li> </ul>
Hematology Involvement
<ul style="list-style-type: none"> <li>- Bleeding manifestation</li> <li>- Thrombocytopenia</li> <li>- Coagulation disorders</li> <li>- Disseminated intravascular coagulation (DIC)</li> </ul>
Neurology Involvement
<ul style="list-style-type: none"> <li>- Altered consciousness</li> <li>- Meningism</li> <li>- Focal neurological signs</li> </ul>

**Table 5. Diagnostic test for leptospirosis<sup>3</sup>**

Diagnostic tests for leptospirosis
Leptospira isolation
<ul style="list-style-type: none"> <li>• Blood culture, considered the gold standard for diagnosing leptospirosis, should be conducted during the first week of illness. It is used to identify serovars and determine antibiotic susceptibility.</li> <li>• Polymerase chain reaction (PCR) is highly sensitive and specific for early diagnosis (within the first week of acute illness). It is particularly useful for genomic classification.</li> <li>• Dark-field microscopy of body fluids has low sensitivity.</li> </ul>
Serological Method <sup>9</sup>
Antibodies are typically detected around days six to ten of leptospirosis and peak around three to four weeks.
<ul style="list-style-type: none"> <li>• Microscopic agglutination test</li> <li>• IgM enzyme-linked immunosorbent assay (ELISA), readily available. Sensitivity and specificity depend on regional seropositivity patterns.</li> </ul>

### Management in the ICU

Severe cases of leptospirosis necessitate intensive critical care management. Acute kidney injury resulting from low volume should be treated with intravenous saline fluid, given carefully to avoid fluid overload. Acute tubular necrosis (ATN), causing non-oliguric kidney failure, may necessitate renal replacement therapy (RRT). Recent research suggests that early dialysis in leptospirosis is advantageous and contributes to reduced mortality.<sup>10</sup>

Patients experiencing respiratory failure require mechanical ventilation. Fresh frozen plasma and packed red blood cell transfusion are needed to correct coagulation parameters in disseminated intravascular coagulation (DIC). There are differences between mild and severe leptospirosis of antibiotic treatment. For severe leptospirosis is using intravenous whereas mild is oral antibiotic. Recommended antibiotics for treating leptospirosis include benzylpenicillin given every 6 hours intravenously for 1.5 million units per dose, doxycycline given every 12 hours intravenously for 100 mg per dose, ceftriaxone intravenously every 24 hours given 1-2 grams per dose, or cefotaxime given every 6 hours intravenously for 1 gram each dose for 7 days. According to a study in Brazilian ICUs, early administration of ceftriaxone was found to prevent severe cases of leptospirosis.<sup>10</sup>

### Thrombocytopenia in leptospirosis

Thrombocytopenia is associated with a poor prognosis for leptospirosis. In Case 1, a patient with leptospirosis and severe thrombocytopenia (platelet count: 35,000) received methylprednisolone 31.25 mg/8 hours IV. In Case 2, a patient with moderate thrombocytopenia (82,000) did not receive corticosteroids. In Case 3, a patient with severe

thrombocytopenia was given methylprednisolone 20 mg/8 hours IV.

To date, there have been five studies on patients with severe leptospirosis treated with corticosteroids, most of which have focused on pulmonary hemorrhage and multiorgan failure.<sup>11</sup>

In a research reported by Alian S et al. (2014), regarding the effect of corticosteroids in improving thrombocytopenia in leptospirosis with moderate thrombocytopenia (platelet count <100,000) and severe thrombocytopenia (platelet count <50,000), found no significant differences in terms of fatality rate, the need of intratracheal tube, thrombocytopenia count, length of stay in the ICU, and involvement of the lungs, kidneys, and liver in the group receiving corticosteroids (prednisolone 1mg/kgBW/day, maximum one week) compared to the control group. On the other hand, treatment with glucocorticoids led to faster recovery of thrombocytopenia and shorter hospital stay.<sup>6</sup>

Prednisolone is the active form of prednisone. Prednisone is a prodrug or pharmacologically inactive drug that must be converted into its active form through a chemical reaction in the liver by the enzyme 11- $\beta$ -hydroxy steroid dehydrogenase. Therefore, prednisolone is more recommended for patients with liver dysfunction.<sup>12</sup>

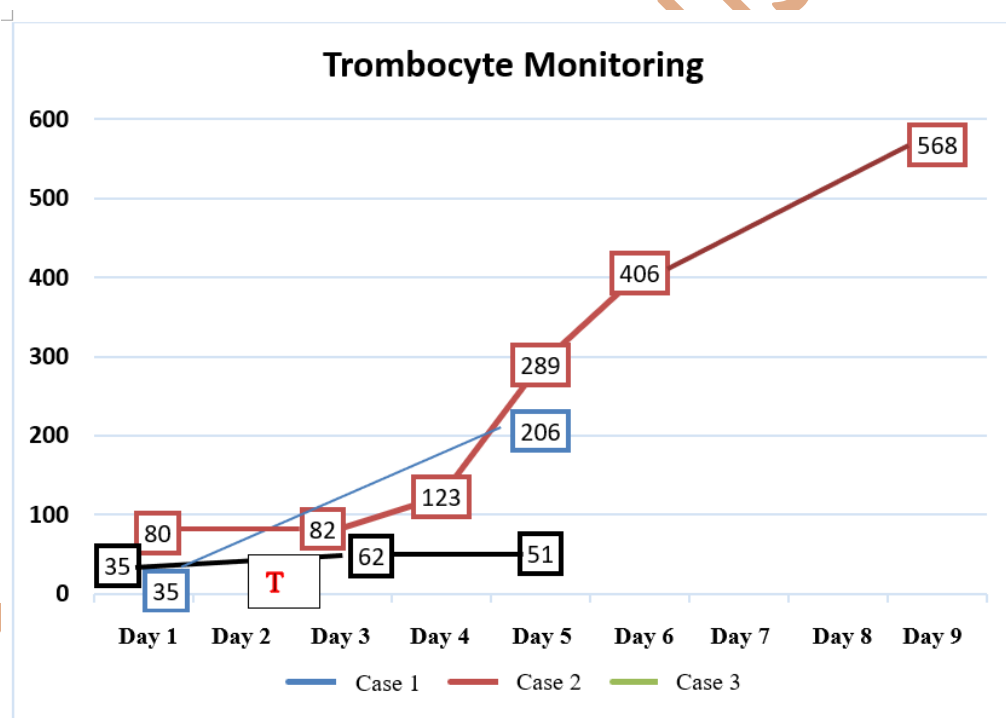
Metilprednisolon has an equivalent dose of 4 mg every 24 hours compared to Prednisolone 5 mg every 24 hours. Metilprednisolon has a higher anti-inflammatory potency, which is 5 compared to Prednisolone's potency of 4. The mineralocorticoid potency of methylprednisolone is smaller at 0.25

compared to prednisolone's 0.6. mineralocorticoids contribute to sodium retention, water retention, and increased blood pressure. It can be concluded that methylprednisolone is more effective in terms of anti-inflammatory action compared to prednisolone. Methylprednisolone is available in tablet and injectable forms.<sup>12</sup>

Methylprednisolone and dexamethasone are corticosteroids that exhibit anti-inflammatory effects, increase steroid hormones, and suppress an overactive immune system. Methylprednisolone belongs to the intermediate-acting group, while dexamethasone belongs to the

long-acting group. Methylprednisolone is used in acute cases, whereas dexamethasone is used in chronic cases. A dose of 4 mg of methylprednisolone is equivalent to 0.75 mg of dexamethasone. Methylprednisolone has fewer side effects compared to dexamethasone.<sup>12</sup>

Rodrigo *et al.*, mentions that corticosteroids increase the risk of nosocomial infections and states that administering methylprednisolone earlier (within 12 hours of diagnosis) may provide benefits in severe leptospirosis with pulmonary complications.<sup>13</sup>



Graphic 1. Comparison of platelet count in the three cases

**Table 6.** Corticosteroid systemic acting.<sup>12</sup>

	Drug Name	Glucocorticoid	Mineralocorticoid	Equivalent Dose
Short Acting	Hydrocortisone	1	1	20 mg
Medium Acting	Prednisolone	4	0.8	5 mg
	Methylprednisolone	5	0.5	4 mg
	Triamcinolone	5	0	4 mg
Long Acting	Dexametasone	25	0	0.75 mg
	Betametasone	25	0	0.75 mg

### Acute kidney injury

In patients with leptospirosis, 16-40% of acute kidney injury cases can result from prerenal or renal factors. Prerenal mechanisms include hypovolemia and hypotension due to fluid loss into the third space caused by vasculitis induced by leptospirosis. Tubular injury leads to acute tubulointerstitial nephritis either directly or through toxin-induced immune mechanisms. In all three cases, the patients experienced acute kidney injury.<sup>6</sup> In Case 1, renal function improved without the need for hemodialysis. In cases 2 and 3, hemodialysis was performed.

In a study conducted in the ICU by Andrade et al., significant reduction in mortality was observed in 33 patients with leptospirosis-associated kidney failure who received early dialysis and daily dialysis compared to those who received late onset dialysis (16.7% vs. 66.7%).<sup>10</sup>

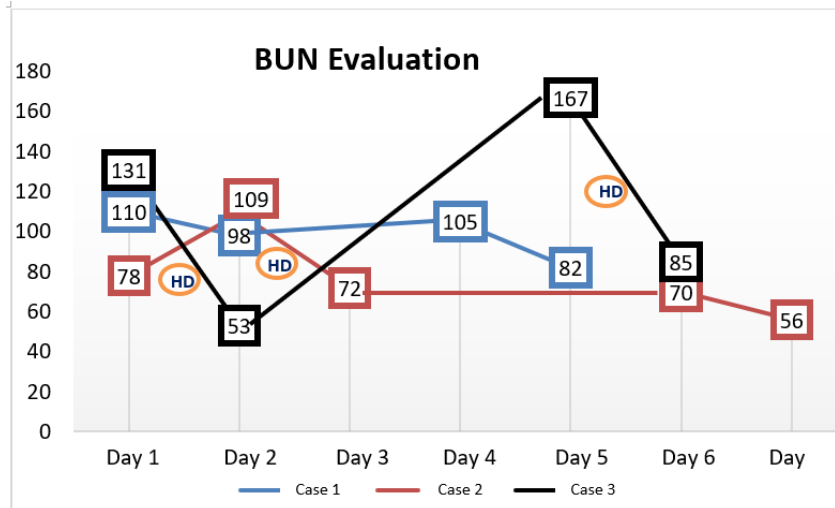
Acute kidney injury refers to a sudden reduction in glomerular filtration rate (GFR) that occurs over hours to days. Signs of acute kidney injury include

Generally, the goals of kidney replacement therapy in acute renal injury are as follows: maintaining fluid, electrolyte, and acid-base balance, preventing the harmful consequences of

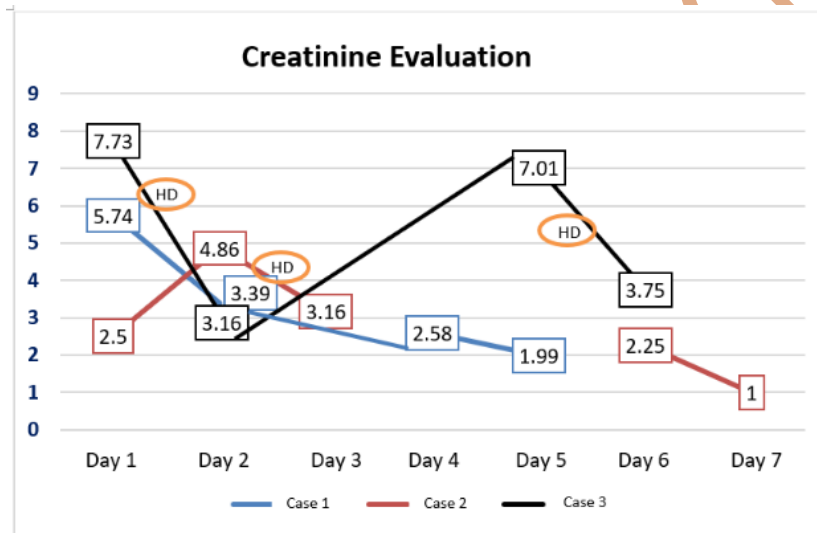
elevated blood urea nitrogen (BUN), serum creatinine levels, and reduced urine output. In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on acute kidney injury integrated two earlier criteria (RIFLE and AKIN).<sup>14</sup>

The decision to initiate renal replacement therapy is based on the most common clinical manifestations, namely volume overload and abnormalities in serum biochemistry (azotemia, hyperkalemia, severe metabolic acidosis). The overall approach should be tailored to the individual context. Indicators that may warrant initiation of renal replacement therapy include anuria (no urine production for up to 6 hours), severe oliguria (urine output < 200 ml for more than 12 hours), hyperkalemia (potassium concentration > 6.5 mmol/L), severe metabolic acidosis (pH < 7.2), volume overload (particularly pulmonary edema unresponsive to diuretics), severe azotemia, and the development of clinical complications related to uremia (e.g., uremic encephalopathy, pericarditis, neuropathy).<sup>14</sup>

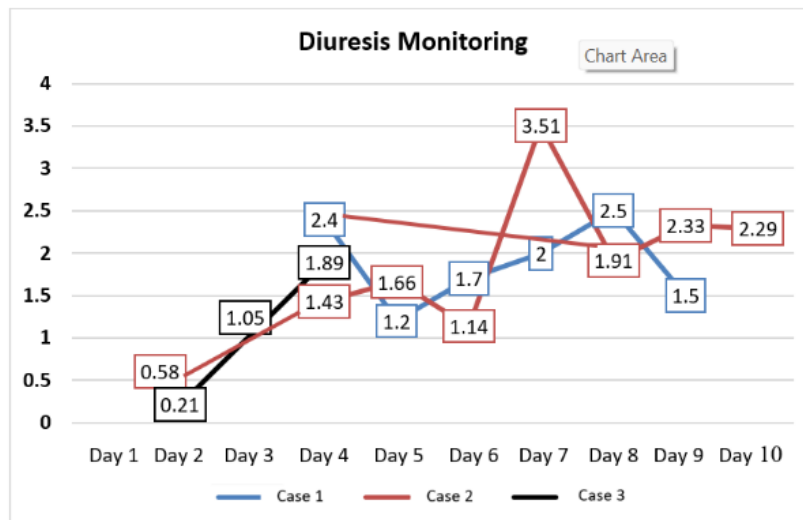
acute kidney injury, providing time for kidney recovery, and allowing for the administration of other therapies such as antibiotics and nutrition without additional complications.<sup>14</sup>



Graphic 2. Patients' BUN comparison in three cases



Graphic 3. Patients' creatinine comparison in three cases



Graphic 4. Patients' diuresis comparison in three cases

### Icteric leptospirosis

The liver manifestations are jaundice (72%), liver enlargement (67%), transaminitis (81%), and increased level of bilirubin (60%). In cases 1 and 2, no hepatic involvement was found<sup>6</sup>. However, in Case 3, the patient experienced jaundice with elevated bilirubin and transaminase enzymes.

Jaundice is a significant indicator of hepatic dysfunction. In the liver, leptospirosis disrupts the organization of hepatocytes and damages intercellular junctions, leading to a moderate increase in liver transaminases and direct bilirubin cholestasis, which results in jaundice.<sup>15</sup> Same as recent report by Miyhara et al., using a scanning electron microscope in a hamster model of experimental leptospirosis, suggests that jaundice in the disease is caused by the destruction of hepatocytic intercellular

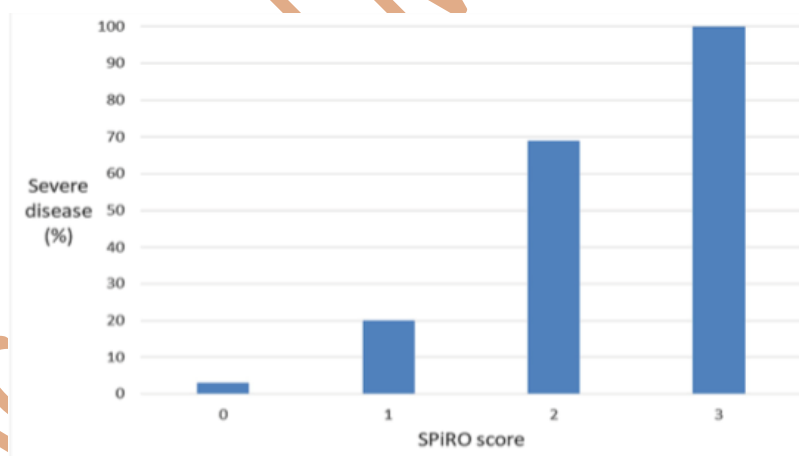
junctions due to the direct intercellular migration of leptospire.<sup>16</sup>

### Risk stratification

Smith et al. developed a 3-point score (SPiRO score) to predict severe leptospirosis, which includes:

Clinical Manifestation	Score
Systolic blood pressure < 100 mmHg	1
Respiratory auscultation abnormality	1
Oliguria	1

In adult patients with leptospirosis, the SPiRO score can identify patients with severe disease requiring ICU care. An SPiRO score of 0 helps identify patients at low risk. The risk of disease severity increases gradually according to the SPiRO score.<sup>17</sup>



**Graphic 5.** Predictive positive value on developing severe leptospirosis using SpiRO score<sup>17</sup>

A score of zero indicates a negative predictive value for disease severity of 97.2%. Scores above one point have a positive predictive value for disease severity of 77.1%, and a score of three has a positive predictive value of 100%.<sup>17</sup>

### Severe leptospirosis predictor

In a prospective multicenter observational study conducted by Philip N. et al. in Central Malaysia, clinical predictors associated with severe leptospirosis were identified. Independent factors for disease severity included mechanical ventilation, acute

renal injury, bacteremic shock, elevated creatinine (> 1.13 mg/dl), urea (> 7 mmol/L), alanine aminotransferase (> 50 IU), aspartate aminotransferase (> 50 IU), and low trombosit count (< 150 x 10<sup>9</sup>/L). The study concluded that lung, liver, and kidney involvement are prognostic indicators for severe leptospirosis, with acute renal injury, elevated alanine aminotransferase levels, and decreased platelet counts serving as independent predictors of severity.<sup>18</sup> Age is a significant predictor of leptospirosis mortality.<sup>19</sup> Identifying clinical predictors of disease severity is vital for reducing complications and mortality associated with leptospirosis.<sup>18</sup>

Early recognition of potentially fatal cases allows for timely intensive care interventions. There is evidence indicating that an exaggerated immune response, characterized by cytokine storms with elevated levels of interleukin-6 (IL-6), TNF alpha (TNF- $\alpha$ ), and IL-10, plays a significant role in the pathophysiology of severe leptospirosis. Hemodynamic changes, including increased intravascular permeability secondary to cytokine storms, may contribute to shock development in severe cases of the disease.<sup>20</sup> Severe leptospirosis can induced septic shock. This severe condition requires immediate medical attention and aggressive treatment to prevent mortality.<sup>21, 22</sup>

**Table 7.** Patients' profile

	Case 1	Case 2	Case 3
Gender	Male	Male	Male
Age	53 y.o	28 y.o	71 y.o
Risk Factor	Activity at rice fields without using shoes	Schavenger	Unknown
Comorbidity	DM	-	-
Organ involvement			
Kidney	+	+	+
Hemodialysis	-	+	+
Liver/ Hyperbilirubinemia	-	-	+
Pulmonary	+	+	+
Septic shock	+	+	+
Radiology	Oedema pulmo, pneumonia bilateral	Oedema pulmo	Oedema pulmo, pneumonia dextra
Respiratory support	NIV	HFNC	ETT
Thrombocytopenia	+	+	+
Cause of ICU admission	Dyspnea and shock	Dyspnea and shock	Critical Care
Corticosteroid	+	-	+
Length of stay	6 Days	7 Days	4 Days
Condition when leaving ICU	Alive	Alive	Death



## CONCLUSION

The three cases of leptospirosis were severe cases with complications affecting the kidneys, lungs, and hematologic system, that required intensive care unit (ICU) management. Prompt and appropriate management can reduce patient mortality rates. ICU management of leptospirosis involves antibiotics, fluid balance, and support for involved organs. For respiratory failure, patients are provided with oxygenation using a high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), and invasive mechanical ventilation with endotracheal intubation if necessary. Acute kidney injury in leptospirosis may require hemodialysis as indicated or may improve with conservative therapy. Corticosteroids may be administered for thrombocytopenia associated with leptospirosis. The SPIRO score can identify patients with severe leptospirosis requiring ICU care. In these three cases, older age, mechanical ventilation, acute kidney injury, septic shock, thrombocytopenia, and elevated transaminase enzymes were associated with severe leptospirosis and poor outcomes.

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