INVITED ARTICLE

Leptospirosis in Intensive Care Unit

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Abstract

Tropical infections constitute 20 – 30% of intensive care unit (ICU) admissions in developing countries. Leptospirosis is a spectrum with mild form presenting as an acute febrile illness with jaundice, complicating in few as acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and multi-organ dysfunction syndrome (MODS). The poor prognostic markers are hemorrhagic ARDS, acute renal failure, DIC, severe metabolic acidosis, older age, chronic alcohol abuse, high SOFA score, and septic shock. The confirmatory diagnosis relies on antibody testing, such as microscopic agglutination test (MAT) and IgM ELISA, while the reverse transcription-polymerase chain reaction test being reserved for clinically suspected antibody negative cases. The spectrum of multi-organ involvement necessitates a complete hematological, biochemical workup, including electrocardiogram (ECG), chest X-ray, and two-dimensional echocardiography. Specific antimicrobial therapy consists of the following—benzylpenicillin, ceftriaxone, cefotaxime, and doxycycline. The reported mortality ranges from 6% to as high as 44%. Various ICU scores like SPiRO, THAI LEPTO score, and Faine's criteria have been useful in risk stratification. Optimizing intensive care treatment with appropriate antibiotics, lung protection ventilation strategies, strict fluid management, and if need be timely initiation of renal replacement therapy (RRT) helps in reducing mortality.

Keywords: Critical care, Leptospirosis, SpiRO score, THAI LEPTO score, Topical infections.

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Introduction

Tropical infections constitute 20 – 30% of intensive care unit (ICU) admissions in Asia, Africa, and South America.[1] Leptospirosis has travelled a long way from its discovery in Andaman and Nicobar islands in 1929 to become one of the leading causes of critical care admissions in developing countries. Its global burden is estimated to be 8,73,000 cases annually with 48,600 deaths.[2] Leptospirosis, a zoonotic disease, is caused by spirochete *Leptospira interrogans*. . Contact of mucosa with the urine of infected rodents, wolves, cattle, and sheep leads to infection. Rodents are a major reservoir. It is endemic in India with peak coinciding with the late monsoon. Clinical presentation is biphasic. The first phase is the "anicteric phase," which lasts for 3 – 7 days in which the patient presents with fever, chills, headache, anorexia, diarrhea, abdominal pain, severe myalgia, and conjunctival suffusion or hemorrhage; of which 90% recover. In the remaining 10% of patients, the symptoms relapse within 1 – 3 days of initial improvement and progress to a more severe form of the disease called "Weils disease." It is characterized by deepening of jaundice, acute kidney injury (AKI) with renal failure, acute respiratory distress syndrome (ARDS) with pulmonary hemorrhages, disseminated intravascular coagulation (DIC), and multi-organ dysfunction syndrome (MODS). This is exemplified even way back in 2004 in a study from Sion Hospital conducted by Chawla et al., "*Epidemic of leptospirosis: an ICU experience*." Forty-six out of sixty confirmed leptospirosis patients had MODS, and 26 needed ventilatory support with mortality of 52%.[3] The biphasic phase is not clinically apparent now with most of the severe leptospirosis patients presenting with MODS within 3 – 5 days of fever onset.

Leptospirosis: Clinical Spectrum in Critical Care

MODS, ARDS with thrombocytopenia, and renal failure were the causes for mortality in a study conducted by Ittyachen in Kerala (n = 53) on severe cases of leptospirosis admitted to ICU.[4] All the patients who died in his study presented late in the course of illness. The clinical presentations of leptospirosis in intensive care are as follows.

Icteric Leptospirosis

Serum bilirubin levels of 25 – 30 mg/dL are observed. There is moderate transaminitis and minor elevation in alkaline phosphatase. In a study done by Deodhar et al. (n = 244), the hepatic manifestations observed were jaundice (72%), hepatomegaly (67%), transaminitis (81%), and raised bilirubin (60%).[5] Jaundice occurring in leptospirosis is not a consequence of hepatocellular necrosis, and liver dysfunction is reversible after treatment.

Acute Renal Failure

Acute kidney injury in leptospirosis could be prerenal or renal and is seen in 16 – 40% of cases. The prerenal mechanisms include hypovolemia and hypotension secondary to third space fluid losses caused by leptospirosis-induced vasculitis. Bleeding due to thrombocytopenia aggravates hypovolemia. Tubular injury causing acute tubulointerstitial nephritis can be direct or through toxin-induced immune mechanisms. Rhabdomyolysis secondary to severe myalgia of leptospirosis contributes to tubular injury. The AKI

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of leptospirosis is non-oliguric with reduced serum potassium levels. Decreased sodium absorption due to proximal tubule damage results in an increased sodium load in medullary collecting tubule (MCT) where it is exchanged for potassium, explaining hypokalemia. The non-oliguric nature of this renal failure may be due to resistance of MCT to vasopressin.

Acute Respiratory Distress Syndrome

Patients present with cough, dyspnea, mild-to-severe hemoptysis, or ARDS. Radiography may reveal diffuse intra-alveolar hemorrhage even without overt symptoms. In a study done by Smith et al. in ICUs in Australia, moderate to severe ARDS developed in 37/55 (67%), 32/55 (58%) had a pulmonary hemorrhage, and mechanical ventilation was required in 27/55 (49%) cases.[6] Dyspnea and chest infiltrates are poor prognostic indicators and mortality predictors in severe leptospirosis.

Disseminated Intravascular Coagulopathy and Thrombocytopenia

Thrombocytopenia is increasingly observed in leptospirosis-induced disseminated intravascular coagulopathy (DIC) in intensive care, a feature that was previously a hallmark of dengue, malaria, and rickettsia. Bleeding tendency is manifested as subconjunctival hemorrhages, dependent ankle petechiae, and ecchymosis around venipuncture sites. A sudden bout of hemoptysis in stable patients of leptospirosis is often a marker of fatality reflecting extensive alveolar hemorrhage with DIC being a secondary contributory factor. Occasionally, a massive upper gastrointestinal hemorrhage may occur as a preterminal event. Macrophage activation syndrome (MAS) has been reported as a cause of pancytopenia in leptospirosis.

Cardiac

Electrocardiographic changes of atrial fibrillation, atrioventricular conduction blocks, and nonspecific ventricular repolarization occur secondary to myocarditis and electrolyte abnormalities. In a study done by Simi et al in Kerala (n = 100), atrial fibrillation (12%) was the commonest electrocardiogram (ECG) abnormality.[7] It was followed by T wave inversion (10%), type 1 A-V block (8%), and sinus bradycardia (6%). Twenty percent had clinical evidence of myocarditis. Eighty-eight percentage of patients recovered, whereas 12% died. Of those with abnormal ECG, 7.5% (3/40) died. ECG abnormalities predicted the development of ARDS, dialysis requiring renal failure, MODS, and morbidity. However, reduced left ventricular ejection fraction on two-dimensional echocardiography was seen in only five patients in this study.

Neurological Manifestations

These are seen in 10 – 15% of patients. The differential diagnosis in a comatose patient with leptospirosis includes uremia and hepatic encephalopathy, meningoencephalitis, intracerebral hemorrhage due to bleeding diathesis, electrolyte abnormalities, and secondary bacterial meningitis; with aseptic meningitis being the commonest. The other rarer presentations include Guillain–Barré syndrome, myelopathy, and cerebellar dysfunction. Mathews et al. reported 31 cases of neurological manifestations of leptospirosis.[8] Twenty-five patients (81%) had altered sensorium, 11 (35.5%) had acute symptomatic seizures at the time of presentation, and only three patients had localizing deficits. Eight patients (26%) died. Coma at presentation and raised cerebrospinal fluid (CSF) protein were two poor prognostic indicators.

Pancreatitis

Pancreatitis is being increasingly recognized in tropical infections like leptospirosis, malaria, and dengue presenting to ICU. The mechanism is attributed to ischemic injury of the pancreas leading to "autodigestion" due to proteolytic enzyme activation. In leptospirosis, renal failure may contribute to elevated serum amylase levels. Hence, the elevation of serum lipase level is more specific for diagnosing pancreatitis. Necrotizing pancreatitis has been rarely detected at autopsy. In a case series of four cases of severe leptospirosis presenting with pancreatitis from Sri Lanka, published by Herath et al., all had serum amylase >900 # IU/L and low serum calcium.[9] Out of these, one patient succumbed.

Leptospirosis: Laboratory Investigations in Critical Care

Complete blood counts reveal leukocytosis secondary to sepsis, thrombocytopenia, and occasionally pancytopenia secondary to MAS. DIC may result in deranged prothrombin time, low fibrinogen, and high D-dimer levels. Increased levels of serum creatinine, blood urea, bilirubin, and transaminitis are found. Electrolyte abnormalities include hyponatremia, hypokalemia, and hypomagnesemia. Electrolyte abnormalities may result in ECG changes and arrythmias. Urinalysis may show proteinuria, granular casts, and occasionally microscopic hematuria suggestive of glomerulonephritis. Serum creatine kinase may be elevated due to rhabdomyolysis. In cases of aseptic meningitis, in a study by Mathews et al., 18 of 27 (67%) had normal computed tomography (CT) imaging, while 7 (26%) had diffuse cerebral oedema. CSF studies showed lymphocytic pleocytosis with elevated protein levels. *Leptospira* antibody was detected in 5 of 22 CSF samples.[8] Chest X-ray of leptospirosis with ARDS often mimic military mottling. The chest CT scan may reveal ground-glass opacities. In a study by Mona et al. (n = 275), 54 patients (19.65%) had signs of pulmonary hemorrhage (diffuse opacities) on chest radiograph.[10] Fifty of these expired (92%), thereby emphasizing the role of a simple chest X-ray as a mortality predictor in ICU settings. Diagnosis of leptospirosis is most frequently done by serology. Antibodies appear from day 5 to 7 of illness. The sensitivity and specificity of IgM ELISA is 89 and 94%, while that of microscopic agglutination test (MAT) test is 63 and 97%, respectively.[5] A single titer of >1:800 of MAT is a sufficient indicator of present or recent infection. During the bacteremia phase, the organism may be isolated from blood cultures and after the first week from urine. Molecular techniques, such as real-time reverse transcription-polymerase chain reaction, are useful for rapid, accurate diagnosis of acute leptospirosis and have advantage over serology of earlier positivity. Its high cost and need for a reference laboratory mandate reserving the test for patients who are persistently leptospirosis antibody negative but in whom leptospirosis is highly suspected.

Leptospirosis in ICU: Risk Stratification

Initially in 1982, World Health Organization guidelines advocated the use of Faine's criteria for the diagnosis and severity assessment of leptospirosis. Faine's criteria used nine clinical parameters(part A), three epidemiological factors (part B), and four bacteriological and lab findings (part C). It had a sensitivity

and specificity of 81.8 and 72.9%, respectively.[11] But it relied on MAT, which was difficult to be performed in third world countries. Ajjimarungsi et al., in "*Clinical characteristics, outcomes and predictors of patients with leptospirosis admitted to medical intensive care unit: a retrospective review,*" used the THAI LEPTO score for risk stratification of leptospirosis.[12] This score consists of seven parameters. A score of more than six indicates the need for ICU admission, mechanical ventilation, and inotrope or vasopressor support. Smith et al. in Australia devised a three-point score (the SPiRO score) using systolic blood pressure ≤100 mm Hg, respiratory auscultation abnormalities, and oliguria as clinical variables, with each component awarded a single point.[13] In this study, SPiRO score was calculated in 392 (98%) patients. The chances of severe disease were 3, 20, 69, and 100% for a score of 0, 1, 2, and 3, respectively. A SPiRO score <1 had a negative predictive value for a severe disease of 97%. It can be quickly calculated in emergency medical service (EMS) instead of the routinely used qSOFA score for triage of patients with leptospirosis in need of intensive care. SPiRO score was found to be superior to qSOFA in EMS settings.[13]

Leptospirosis: ICU Management

Severe illness due to leptospirosis needs intensive critical care management. AKI secondary to hypovolemia needs correction by intravenous saline fluids with potassium supplementation done carefully avoiding side effects of fluid overload. Acute tubular necrosis (ATN) causing non-oliguric renal failure may necessitate renal replacement therapy (RRT). Recent studies have shown that early initiation of dialysis in leptospirosis is beneficial and helps in mortality reduction. In an ICU study carried out by Andrade et al. in São Paulo, in 33 patients of leptospirosis with renal failure, a significant reduction in mortality was observed in the group undergoing early (on admission) and daily dialysis, as compared to the group receiving late-onset alternate day dialysis (16.7 vs 66.7%).[14] A study from Thailand comparing hemodialysis and hemofiltration with standard peritoneal dialysis showed lesser mortality, early recovery, and a faster reduction in the serum levels of bilirubin, urea, and creatinine with former.[15] Patients suspected to have ARDS or alveolar hemorrhage need mechanical ventilation and lung protection strategies. DIC needs correction of coagulation parameters with fresh frozen plasma and packed red cell transfusion.

The recommended antimicrobial agent is with benzylpenicillin (1.5 million units intravenously every 6 hours), doxycycline (100 mg IV twice daily), ceftriaxone (1–2 g IV once daily), or cefotaxime (1 g IV every 6 hours) given for a period of 7 days. Patients with leptospirosis with meningoencephalitis may need a higher dose of benzylpenicillin of 20 L IV at 6 hourly duration for 2 – 3 weeks. In a study done by Daher et al.[16] in Brazilian ICU, early use of ceftriaxone was found to prevent severe leptospirosis. Antibiotic susceptibility testing is not done routinely as resistance is rare. An inflammatory response to clearance of spirochetes called as Jarisch–Herxheimer reaction occurs post-treatment. It is characterized by fever, rigors, and hypotension. Alian et al. found corticosteroids beneficial in patients of moderate to severe thrombocytopenia due to leptospirosis.[17] They used prednisolone in a dose of 1 mg/kg for a period of 1 week. Trivedi et al. found beneficial effects of using IV high-dose pulse methyl prednisolone for 3 days followed by 1 mg/kg prednisolone for 7 days in patients with ARDS and myocarditis.[18] Out of 13 patients who developed pulmonary complications, eight had been treated with high-dose steroids. Six patients out of this group of eight survived, while only one patient survived in the group that was not treated with steroids. Similar beneficial effects were also observed by Shenoy et al.[19] However, this data on the use of corticosteroids in leptospirosis is case series based and anecdotal with randomized trials needed.

Difficult to Manage Patients

- The highest mortality in leptospirosis in critical care is seen in hemorrhagic ARDS. Prone ventilation has recently proved to be useful in COVID-19 ARDS.[20] Published data on the use of prone ventilation in hemorrhagic ARDS due to leptospirosis will go a long way in encouraging its use in ICUs in the developing world to bring down leptospirosis mortality.
  - The renal failure of leptospirosis is usually non-oliguric. Hemodialysis is beneficial in patients with uremia or fluid overload when indicated. Rarely septic ATN may cause prolonged oligo-anuric renal failure needing maintenance of hemodialysis till the kidney recovers. Such patients especially those on invasive ventilation are highly likely to develop secondary bacterial sepsis. Appropriately timed blood cultures, judicious use of higher antibiotics combined with excellent day to day nursing care will salvage such patients who otherwise have a poor outcome.
- Persistent hypotension despite optimal fluid resuscitation points to the presence of myocarditis and/or septic shock. In combination with a hemorrhagic ARDS and oligo-anuric renal failure, it confers the worst prognosis. Vasopressors (noradrenaline, dobutamine, and vasopressin) and fluids need careful titration especially in patients with high positive end-expiratory pressure requiring ARDS and/or for those on hemodialysis to avoid hypotension.
- In a patient with leptospirosis with persistent ongoing vasculitis, intravenous immunoglobulin has been suggested as the last option to tackle this immune-mediated phenomenon.[21]
- Leptospirosis in pregnancy: This is associated with higher fetal and maternal mortality. The differentials of a hepatorenal presentation in pregnancy include acute fatty liver of pregnancy, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), and viral hepatitis apart from classical infections like malaria and dengue. Diagnosis needs a high index of suspicion. The onset of labor in the setting of DIC and thrombocytopenia needs careful monitoring. Delivery, if vaginal is preferably conducted in the ICU itself.

Leptospirosis: Outcome in ICU

Published data are available from both developed and developing countries. In an encouraging study by Smith et al. to reduce mortality ($n = 55$), it was found that ICU support and corticosteroid therapy are associated with a reduction in case fatality rate All patients in this study were treated with antibiotic therapy initiated within the first 6 hours. Forty-eight patients had AKI; out of which 18 required RRT, while 34 patients needed vasopressor support. Twenty patients received corticosteroids. Two patients (4%) who succumbed were elderly with multiple comorbidities. Delmas et al. in a study of 134 patients found that severe leptospirosis has lower mortality with prompt resuscitation despite high initial SpiRO scores.[22] Costa et al. found that late presentation to health-care facilities in severe cases contributed to a high mortality rate of 5 to 15%.[23] In a

multicenter study conducted in 79 ICUs of France, mortality at 9% was associated with an elderly population, leukocytosis, invasive ventilation, need for dialysis, ethanol addiction, and hepatic encephalopathy.[24] Leptospirosis causing hepatorenal (n = 101, 63%), neurological (n = 8, 5%), and respiratory complications (n = 17, 11%) with pulmonary hemorrhage had highest mortality predictability. In Weeratunga et al.'s study done in Sri Lanka (n = 45), high mortality of 44.4% was associated with low pH very high CRP levels, hyperkalemia, metabolic acidosis, and multi-organ system failure.[25] Chronic alcohol abuse in Indian settings may be a hidden contributory factor toward mortality in leptospirosis.

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References

1. Karnad DR, Richards GA, Silva GS, Amin P. Tropical diseases in the ICU: a syndromic approach to diagnosis and treatment. J Crit Care 2018;46:119–126. DOI: 10.1016/j.jcrc.2018.03.025.
2. WHO|Leptospirosis Burden Epidemiology Reference Group (LERG). WHO 2013.
3. Chawla V, Trivedi TH, Yeolekar ME. Epidemic of leptospirosis : an ICU experience (multiple letters). J Assoc Physicians India 2004;52:1010–1011. PMID: 15847354
4. Ittyachen A, Krishnapillai T, Nair MC, Rajan AR. Retrospective study of severe cases of leptospirosis admitted in the intensive care unit. J Postgrad Med 2007;53(4):232. DOI: 10.4103/0022-3859.37510. Available from: http://www.jpgmonline.com/text.asp?2007/53/4/232/37510.
5. Deodhar D, John M. Leptospirosis: experience at a tertiary care hospital in northern India. Natl Med J India 2011;24(2):78–80. PMID: 21668048
6. Smith S, Liu YH, Carter A, Kennedy BJ, Dermedgoglou A, Poulgrain SS, et al. Severe leptospirosis in tropical Australia: Optimising intensive care unit management to reduce mortality. PLoS Negl Trop Dis 2019;13(12):e0007929. DOI: 10.1371/journal.pntd.0007929.
7. Simi S, Jacob C, John TM, George K, Jayaprakash R. 1745 cardiac abnormalities in leptospirosis and prognostic significance of electro-cardiographic manifestations – a cross-sectional study from South-India. Open Forum Infect Dis 2014;1(suppl_1):S469–S470. DOI: 10.1093/ofid/ofu052.1291. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5782093/.
8. Mathew T, Satishchandra P, Mahadevan A, Nagarathna S, Yasha TC, Chandramukhi A, et al. Neuroleptospirosis – revisited: experience from a tertiary care neurological centre from south India. Indian J Med Res 2006;124(2):155–162. Available from: https://pubmed.ncbi.nlm.nih.gov/17015929/. PMID: 17015929
9. Herath NJ, Kamburapola CJ, Agampodi SB. Severe leptospirosis and pancreatitis: a case series from a leptospirosis outbreak in Anuradhapura district, Sri Lanka. BMC Infect Dis 2016;16(1):644. DOI: 10.1186/s12879-016-2010-4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5100107/.
10. Shastri M, Diwanji N, Desai E, Chitara M, Bhatt A. Spectrum of radiological findings in leptospirosis on chest radiograph and ultrasonography-study during epidemics in south Gujarat region of India. Int J Anatomy 2017;6(4):2–7. DOI: 10.7860/IJARS/2017/26056:2306.
11. Sethi S, Sharma N, Kakkar N, Taneja J, Chatterjee SS, Banga SS, et al. Increasing trends of leptospirosis in Northern India: a clinico-epidemiological study. PLoS Negl Trop Dis 2010;4(1):e579. DOI: 10.1371/journal.pntd.0000579.
12. Ajjimarungsi A, Bhurayanontachai R, Chusri S. Clinical characteristics, outcomes and predictors of patients with leptospirosis admitted to medical intensive care unit: a retrospective review. medRxiv. DOI: 10.1101/2020.05.18.20105601.
13. Smith S, Kennedy BJ, Dermedgoglou A, Poulgrain SS, Paavola MP, Minto TL, et al. A simple score to predict severe leptospirosis. Caimano MJ, editor. PLoS Negl Trop Dis 2019;13(2):e0007205. DOI: 10.1371/journal.pntd.0007205.
14. Andrade L, Cleto S, Seguro AC. Door-to-dialysis time and daily hemodialysis in patients with leptospirosis: impact on mortality. Clin J Am Soc Nephrol 2007;2(4):739–744. DOI: 10.2215/CJN.00680207.
15. Wiwanitkit V. Peritoneal dialysis in leptospirosis-induced acute renal failure: an appraisal on Thai patients. Ren Fail 2006;28(2):201. DOI: 10.1080/08860220500531302. Available from: https://pubmed.ncbi.nlm.nih.gov/16538983/.
16. De Francesco Daher E, Soares DS, de Menezes Fernandes ATB, Girão MMV, Sidrim PR, Pereira EDB, et al. Risk factors for intensive care unit admission in patients with severe leptospirosis: a comparative study according to patients' severity. BMC Infect Dis 2016;16(1):40. DOI: 10.1186/s12879-016-1349-x.
17. Alian S, Asghari H, Najafi N, Davoudi A, Yazdani J. Corticosteroid in the treatment of moderate to severe thrombocytopenia due to leptospirosis. Iran Red Crescent Med J 2014;16(10):16030. DOI: 10.5812/ircmj.16030. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4329749/.
18. Trivedi SV, Chavda RK, Wadia PZ, Sheth V, Bhagade PN, Trivedi SP. The role of glucocorticoid pulse therapy in pulmonary involvement in leptospirosis. J Assoc Physicians India 2001;49:901–903. Available from: https://pubmed.ncbi.nlm.nih.gov/11837758/. PMID: 11837758
19. Shenoy V V., Nagar VS, Chowdhury AA, Bhalgat PS, Juvale NI. Pulmonary leptospirosis: an excellent response to bolus methylprednisolone. Postgrad Med J 2006;82(971):602–606. DOI: 10.1136/pgmj.2005.044255. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2585719/.
20. Mittermaier M, Pickerodt P, Kurth F, de Jarcy LB, Uhrig A, Garcia C, et al. Evaluation of PEEP and prone positioning in early COVID-19 ARDS. EClinicalMedicine 2020;28:100579. DOI: 10.1016/j.eclinm.2020.100579. Available from: http://creativecommons.org/licenses/by/4.0/.
21. Meaudre E, Asencio Y, Montcriol A, Martinaud C, Graffin B, Palmier B, et al. Immunomodulation in severe leptospirosis with multiple organ failure: plasma exchange, intravenous immunoglobulin or corticosteroids? Ann Fr Anesth Reanim 2008;27(2):172–176 [French]. DOI: 10.1016/j.annfar.2007.10.034. PMID: 18155391.
22. Delmas B, Jabot J, Chanareille P, Ferdynus C, Allyn J, Allou N, et al. Leptospirosis in ICU: a retrospective study of 134 consecutive admissions. Crit Care Med 2018;46(1):93–99. DOI: 10.1097/CCM.0000000000002825. Available from: https://pubmed.ncbi.nlm.nih.gov/29116996/.
23. Costa F, Hagan JE, Calcagno J, Kane M, Torgerson P, Martinez-Silveira MS, et al. Global morbidity and mortality of leptospirosis: a systematic review. PLoS Negl Trop Dis 2015;9(9):e0003898. DOI: 10.1371/journal.pntd.0003898. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4574773/.
24. Miailhe AF, Mercier E, Maamar A, Lacherade JC, Le Thuaut A, Gaultier A, et al. Severe leptospirosis in non-tropical areas: a nationwide, multicentre, retrospective study in French ICUs. Intensive Care Med 2019;45(12):1763–1773. DOI: 10.1007/s00134-019-05808-6. Available from: https://pubmed.ncbi.nlm.nih.gov/31654079/.
25. Weeratunga PN, Fernando S, Sriharan S, Gunawardena M, Wijenayake S. Determinants of mortality and impact of therapy in patients with leptospirosis admitted for intensive care in a Sri Lankan hospital – a three year retrospective study. Pathog Glob Health 2015;109(8):387–394. DOI: 10.1080/20477724.2015.1126032. Available from: https://pubmed.ncbi.nlm.nih.gov/26924349/.