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Clinical characteristics and outcomes of patients with leptospirosis complicated with acute pancreatitis: a systematic review

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Abstract

Objectives: Acute pancreatitis (AP) is a severe complication of leptospirosis. This review focuses on the current evidence of AP in patients with leptospirosis.

Methods: Data on clinical characteristics, biochemical parameters, diagnosis, complications, critical care, fluid management, operative management, and outcomes were analyzed. This study was registered in PROSPERO (CRD42022360802).

Results: We included 35 individual case reports and 4 case series involving 79 patients. Sex was reported for 48 (60.7%) patients; 38 (48.1%) were male and 10 (12.6%) were female. The patients' mean age was 45.13 (15–83 years). Acute kidney injury, thrombocytopenia, hypotension, and liver injury were the most common complications reported. Complete recovery was reported for 36 (45.5%) patients. Biochemical and radiological recovery was reported for 10 (12.6%) and 9 (11.3%) patients, respectively. Death was reported in 18 (22.7%) patients.

Conclusion: A high degree of clinical suspicion and different modalities of investigations are essential in the diagnosis of AP in leptospirosis. AP can be easily missed in leptospirosis because both conditions share similar clinical presentations and complications. Because of the high prevalence of acute kidney injury, judicious fluid management and close monitoring are mandatory.

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Introduction

Leptospirosis is a common zoonotic illness caused by *Leptospira icterohaemorrhagiae* and other subspecies.[1] It has a significant impact on health expenditures in developing countries.[2] Leptospirosis has a wide spectrum of presentations ranging from asymptomatic self-limiting illness to fatal multiorgan involvement.[3] The incubation period of leptospirosis is approximately 1 to 2 weeks.[4] The bacterium is present in water contaminated by excreta of chronically infected rodents, and it enters the human body through mucous membrane and skin aberrations.[5] People at risk include farmers and slum dwellers.[6] Complications are mainly caused by vasculitis involving medium and small vessels.[1] Widespread activation and damage of endothelial cells in these vessels occurs by either direct injury by the microorganism or immune-mediated destruction following cytokine storm.[7] Leptospirosis often occurs in tropical and subtropical countries because the climate favors the transmission.[7] Because most tropical regions contain developing countries, leptospirosis continues to have a negative impact on the healthcare systems in these countries with each outbreak that occurs.[4]

The mild form of leptospirosis has two distinctive phases: the septicemic and immune phases.[8] The acute septicemic phase lasts for 5 to 7 days and is followed by transient symptomatic improvement.[7] The disease then either progresses to the severe form or regresses to an asymptomatic illness.[7] The severity of leptospirosis is not predictable at symptom onset[7]; it is influenced by host-related factors and the pathogenicity of the microorganism.[7] Weil syndrome is a severe form leptospirosis manifesting as renal failure, hepatic dysfunction, pulmonary hemorrhage, and multiple hemorrhagic diathesis.[9–12]

The mortality rate is higher in patients with Weil syndrome, reaching 10% to 15%,[12] and exceeds 50% when severe pulmonary hemorrhagic syndrome occurs.[5,13] Acute pancreatitis (AP) is an uncommon but known complication of leptospirosis.[12] However, very few studies have focused on the incidence, pathogenesis, and risk factors of AP in leptospirosis. AP has a wide spectrum of presentations ranging from mild symptomatic illness to severe hemorrhagic pancreatitis causing peripancreatic necrotic collections (PPNC) and fatal multiorgan failure (MOF).[6]

Diagnosis of AP in patients with leptospirosis is important because both AP and leptospirosis can lead to MOF, and early diagnosis with prompt management may reduce the risk of mortality.[14] The diagnosis of AP is reached after correlating the biochemical and radiological findings with the clinical presentation (CP).[10] Serological testing of leptospirosis is also important to confirm the etiology of AP.[15] The modified Atlanta criteria are used to diagnose AP, and two of the following three criteria must be fulfilled[16]: clinical features including abdominal pain, nausea, and vomiting; biochemical features including a serum lipase or amylase concentration higher than three times the upper limit of

normal; and characteristic imaging findings on computed tomography (CT) or magnetic resonance imaging.[16]

The severity of AP is classified as mild, moderate, or severe based on local and systemic complications.[17] Various scoring systems are available to classify the severity of AP.[16] The revised Atlanta classification is one such system that is widely accepted for defining the severity of AP.[16] Persistent organ failure is the hallmark of severe AP and is associated with an increased mortality rate (20%) and admission to the intensive care unit (ICU).[18]

It should be noted that clinical manifestations are not reliable because both AP and leptospirosis have common symptoms and signs.[19] Early identification and treatment, including both operative and nonoperative measures, are important to minimize complications.[20] A synopsis of existing evidence on leptospirosis complicated by AP is needed. The primary objective of this review was to systematically examine the clinical characteristics, biochemistry, imaging, complications, management, and outcomes of AP in the setting of leptospirosis.

Methods

Search strategy

We systematically searched the electronic databases of PubMed, Scopus, EMBASE, Cochrane CENTRAL, and Latin American and Caribbean Health Sciences Literature (LILACS) from database inception to December 2021 with no language restriction. Key words related to AP and its complications as well as leptospirosis were searched in the title and abstract fields. The detailed search strategy is shown in the supplementary file. Additionally, the reference list of each eligible article was manually searched to identify more publications (Figure 1). This study was registered in PROSPERO (Number: CRD42022360802).

Eligibility criteria and screening of articles

All types of observational studies (e.g., cohort studies, case-control studies, descriptive cross-sectional studies, case reports, and series) were included in the review. Articles were screened using three key criteria:

1. The article must describe AP as a complication of leptospirosis.
2. The article must be based on primary data of actual patients.
3. The article must include an interim or full analysis and not be restricted to a description of a protocol.

In the first round, two investigators independently performed the initial screening based on the titles and abstracts. In the second round, the full texts of relevant records were assessed based on the eligibility criteria. In doubtful situations, a consensus was reached after discussion with a third investigator.

Data extraction

Two reviewers independently performed the data extraction using a predesigned template. All data pertaining to the CP, investigations, treatment, and outcomes were extracted, categorized, and tabulated. The extracted data were cross checked for any discrepancy by a third reviewer.

Data analysis

The risk-of-bias assessment of eligible studies was performed using the Downs and Black checklist, and the findings are shown in Table S1. A narrative synthesis was performed with the available data. A meta-analysis of the quantitative parameters (e.g., outcome) was not performed because of the heterogeneity in the reporting and the limited number of studies.

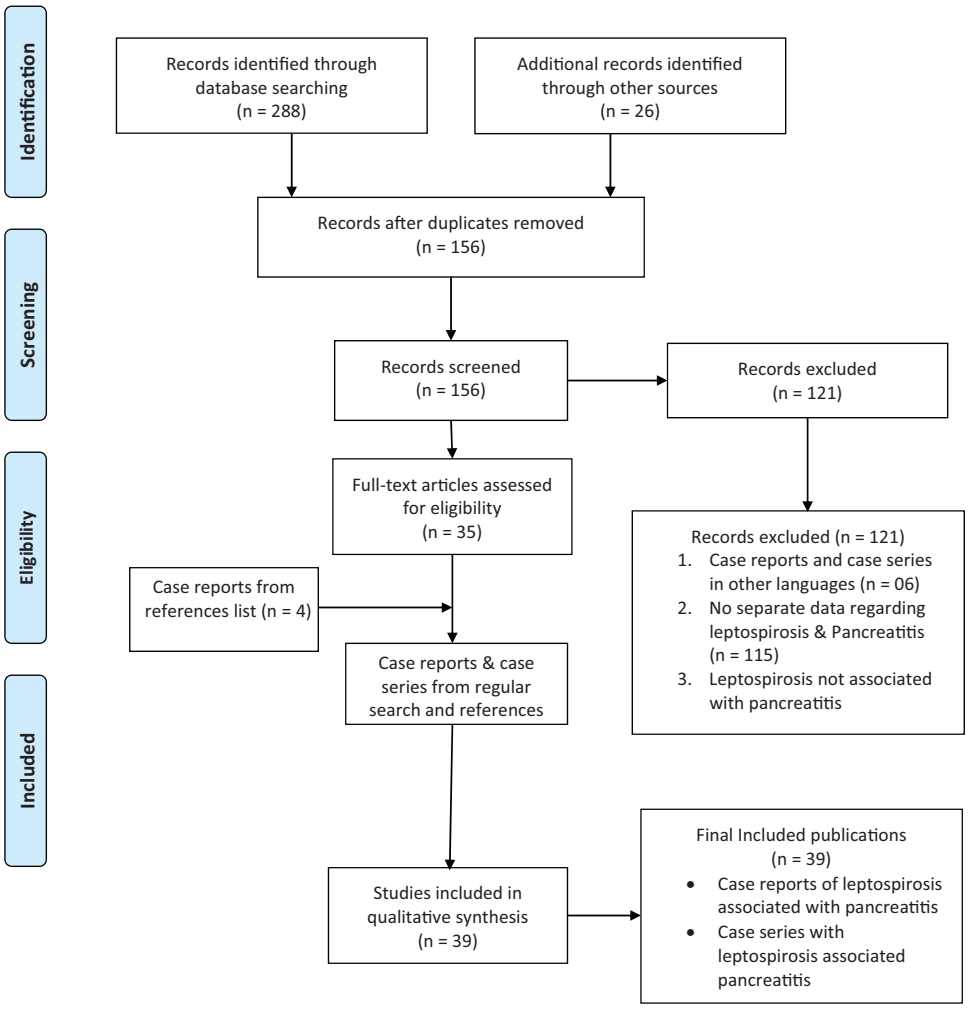

Figure 1. PRISMA flow chart.

Data analysis

Ethics approval and consent to participate are not applicable because of the nature of this study (systematic review with no patient involvement).

Results

Clinical characteristics

The screening process resulted in the inclusion of 35 individual case reports and 4 case series involving a total of 79 patients. Sex was reported for 48 (60.7%) patients and was not available for 31 (39.2%) patients. Of the 48 patients with available data on sex, 38 (48.1%) were male and 10 (12.6%) were female. The patients' mean age was 45.13 (range, 15–83) years.

Abdominal pain (n = 51, 64.5%), fever (n = 45, 56.9%), vomiting (n = 30, 37.9%), and oliguria (n = 11, 13.9%) were the most common symptoms. Other manifestations included bleeding (n = 12, 15.1%),

arthralgia (n = 8, 10.1%), lethargy (n = 8, 10.1%), diarrhea (n = 6, 7.5%), and chills and rigors (n = 5, 6.3%). Headache (n = 4, 5.0%), dyspnea (n = 3, 3.7%), occipital headache (n = 2, 2.5%), cough (n = 2, 2.5%), and back pain (n = 2, 2.5%) were also reported as common symptoms. Icterus (n = 34, 43.0%), tachycardia (n = 19, 24.0%), and hypotension (n = 17, 21.5%) were the most common examination findings described. Other clinical signs were abdominal tenderness (n = 15, 18.9%), conjunctival suffusion (n = 13, 16.4%), tachypnea (n = 10, 12.6%), and basal crepitation (n = 9, 11.3%) (Table 1).[3,6,8,11–15,17,19,21–47]

Biochemical and electrocardiographic findings

Among all 79 patients, hyperamylasemia (n = 56, 70.8%), leukocytosis (n = 38, 48.1%), and thrombocytopenia (n = 31, 39.2%) were the most common findings. Other common findings were hyperbilirubinemia (n = 20, 25.3%), altered liver enzymes (n = 23, 29.1%), hyperlipasemia (n = 20, 25.3%), and anemia (n = 10, 12.6%). Metabolic acidosis (n = 9, 11.3%), hypocalcemia (n = 9, 11.3%), microscopic hematuria (n = 6, 7.5%), an increased alkaline phosphatase concentration (n = 8, 10.1%), and proteinuria (n = 6, 7.5%) were the remaining findings. Electrocardiographic findings were available for seven (8.8%) patients. The most common electrocardiographic findings noted were atrial fibrillation (n = 3, 3.7%), bradycardia (n = 3, 3.7%), and atrioventricular block (n = 1, 1.2%) (Table 2).[3,6,8,11–15,17,19,21–47]

Radiological findings

At least one modality of imaging was reported for 48 (60.7%) patients. An abdominal ultrasound scan (USS), abdominal contrast-enhanced CT (CECT), chest X-ray (CXR), and abdominal X-ray (AXR) were used as imaging modalities. USS was performed in 41 (51.8%) patients. Abnormalities consistent with pancreatitis (n = 19, 24.0%) and ascites (n = 4, 5.0%) were the most common findings. CECT findings were reported for 21 (26.5%) patients.

The most common findings in CECT were a large bulky pancreas (n = 5, 6.3%), peripancreatic fat stranding (n = 5, 6.3%), an edematous pancreatitis (n = 5, 6.3%), hepatosplenomegaly (n = 4, 5.0%), and PPNC (n = 4, 5.0%). The remaining findings were ascites (n = 3, 3.7%), bilateral pleural effusion (n = 2, 2.5%), and isolated hepatomegaly (n = 1, 1.2%). CXR was performed examine the concomitant lung involvement in six (7.5%) patients, and diffuse pulmonary hemorrhage (n = 1, 1.2%) was the most common finding. AXR was performed in five (6.3%) patients, and the presence of dilated intestinal loops (n = 2, 2.5%) was the most common finding (Table 3).[3,6,8,11–15,17,19,21–47]

Diagnosis of AP and leptospirosis

The serum concentration of either amylase or lipase was reported for 43 (54.4%) patients. Only the enzyme concentrations and CP were reported for 18 (22.7%) patients. Amylase with CP (n = 3, 3.7%), lipase with CP (n = 4, 5.0%), and both amylase and lipase with CP (n = 9, 11.3%) were reported. Radiological findings were used in the diagnosis of AP in 27 (34.1%) patients. USS, amylase, and CP were reported for 15 (18.9%) patients. Only CECT with CP was reported for six (7.5%) patients. CECT findings, both amylase and lipase, and CP were reported for five (6.3%) patients. CECT findings, amylase, and CP were reported for three (3.7%) patients. CECT findings, lipase, and CP were reported for one (1.2%) patient.

At least one type of leptospirosis diagnostic workup was performed in 54 (68.1%) patients. Measurement of immunoglobulin

Table 1. General and clinical characteristics of patients with leptospirosis and acute pancreatitis.

SN	Authors (year)	Sex	Age (y)	Strain	Method of diagnosis	Clinical presentation	Physical examination findings
1	Maier et al.[21] (2019)	M	73	*Leptospira interrogans*	Lipase, CP	Sore throat, mucosal congestion, high-grade fever, jaundice, back pain, leg weakness	Jaundice, minor petechiae in lower legs, distended abdomen, right hypochondrial tenderness
2	Jain and Mohan[6] (2013)	M	45	NA	CT, amylase, lipase	Abdominal pain, progressive abdominal distention	Tachypnea, tachycardia, fever, frank signs of peritonitis in abdominal examination
3	Silva et al.[22] (2011)	M	48	NA	Lipase, amylase	Progressive weakness of limbs, severe leg pain, high-grade fever, occipital headache, diarrhea, weight loss	Ill-looking, dehydrated, PR of 108/min, BP of 140/80 mmHg, paraparesis, muscle tenderness, absent patella and ankle reflexes
4	Spichler et al.[20] 2007	M	18	NA	Lipase, amylase	Fever, myalgia, diffuse abdominal pain, progressive dyspnea	Ill-looking, BP of 100/60 mmHg, PR of 112/min, RR of 48/min, SpO_2 of 80%
5	Kaya et al.[24] (2005)	F	68	*Leptospira biflexa* serovar Patoc	Lipase, amylase	Abdominal pain, nausea, vomiting, jaundice	Ill-looking, dehydrated, icteric, PR of 120/min, tachypnea, abdominal tenderness, guarding and rebound tenderness
6	Kaya et al.[24] (2005)	M	62	*Leptospira icterohaemorrhagiae*	CT, amylase, lipase	Fever, jaundice, nausea, vomiting, malaise, dizziness	Icterus, conjunctival hyperemia
7	Prasanthie and De Silva[15] (2009)	M	28	*Leptospira icterohaemorrhagiae*	Lipase, amylase	Fever, myalgia, vomiting for 3 days	Icterus, conjunctival suffusion, diffuse abdominal tenderness
8	Afzal et al.[25] (2020)	M	61	NA	Lipase, CP	Nausea, vomiting, abdominal pain for 1 week	Icterus, conjunctival suffusion, hypertension, supple neck, heaving laterally displaced point of maximum impulse, regular heart rate and rhythm
9	Mazhar et al.[26] (2016)	M	23	*Leptospira interrogans*	Lipase, CP	Fever, chills, headache, neck stiffness, productive cough, nausea, diffuse myalgia, photophobia, non-bloody watery stools, non-bloody non-bilious vomiting,	Hypertension, tachycardia, tachypnea, SpO_2 of 94%, conjunctival injection, icterus, reduced bilateral air entry in lung examination, abdominal rigidity,

(continued)

Table 1. Continued.

SN	Authors (year)	Sex	Age (y)	Strain	Method of diagnosis	Clinical presentation	Physical examination findings
						bloodstained sputum, dark-colored urine for 2 days	tenderness, hyperactive bowel sounds, hip/knee/ankle tenderness
10	Ranawaka et al.[13] (2013)	M	15	*Leptospira interrogans*	CT, CP	High-grade intermittent fever with epigastric discomfort and backache without severe myalgia for 5 days	Hypotension, tachycardia, tachypnea, ill-looking
11	Yew et al.[27] (2015)	M	53	NA	Amylase, CP	Fever, headache, lethargy, myalgia, arthralgia, epigastric pain, nausea for 4 days	Normal examination
12	Gomes et al.[54] (2019)	M	48	NA	Lipase, amylase	Diffuse abdominal pain, vomiting, myalgia, calf pain, fever, conjunctival hyperemia, progressive jaundice, dark urine for 10 days	Diminished turgor, pallor, jaundice, enlarged abdomen with tenderness on superficial and deep palpation, BP of 100/60 mmHg, PR of 160/min, RR of 17/min, SpO_2 of 97%
13	Panagopoulis et al.[29] (2014)	M	32	*Leptospira interrogans*	Amylase	Fever, headache, confusion, rigor, for 1 week	Fever, headache, confusion, rigor, tachycardia
14	Popa et al.[30] (2013)	M	34	*Leptospira icterohaemorrhagiae*	CT, CP	Transferred from another hospital for further management of pancreatitis and sepsis, initial presentation not clearly mentioned	Abdominal distension, icterus, epigastric mass, painful induration in left iliac fossa and left flank, epigastric guarding, epigastric dullness
15	Lim et al.[31] (2014)	M	83	NA	CT, CP	Fever, abdominal pain, vomiting for 2 days	Ill-looking, normal BP, mild epigastric tenderness, bilateral basal crepitations in lung examination
16	Mondal et al.[32] (2014)	M	32	*Leptospira icterohaemorrhagiae*	CT, amylase, CP	Moderate-grade intermittent fever, mild cough, redness of eyes, pain in muscles (especially in calf region) for 10 days	Icterus, confusion, GCS score of 11/15, severe pallor, neck rigidity, positive Kernig sign, hepatomegaly, sluggish peristalsis

(continued)

Table 1. Continued.

SN	Authors (year)	Sex	Age (y)	Strain	Method of diagnosis	Clinical presentation	Physical examination findings
17	Desai and Hattangadi[14] (2008)	M	45	*Leptospira icterohaemorrhagiae*	CT, CP	Epigastric pain with back radiation, bilious vomiting, mild fever, steatorrhea, hematuria, reduced urinary output	Tachycardia, tachypnea, mild hypotension
18	Schattner et al.[19] (2020)	M	63	*Leptospira interrogans* serovar Bratislava	CT, amylase, lipase	Extreme lassitude and fatigue	Normal examination
19	Law et al.[33] (2014)	M	34	NA	CT, amylase, lipase	Fever, nonproductive cough, progressive breathlessness for 10 days	Fever, tachypnea, coarse crepitations in lung examination
20	Castillo et al.[34] (2006)	M	32	NA	Lipase, amylase	Fever, nonproductive cough, progressive breathlessness for 10 days	Jaundice
21	Taher et al.[35] (2005)	F	36	*Leptospira interrogans* serovar Bataviae	Lipase, amylase	Severe abdominal pain and generalized malaise for 1 week	Moderately ill, alert and oriented, pale icterus, BP of 120/80 mmHg, PR of 100/min, RR of 20/min, hepatosplenomegaly
22	Krati et al.[36] (2019)	M	18	NA	CT, CP	Fluctuating fever, icterus, epigastric pain, muscle pain, diarrhea, liquid yellowish stool	Fever, tachycardia, discrete hepatomegaly
23	Tanrıverdi[42] (2009)	F	67	NA	NA	Flulike presentation, headache, arthralgia, myalgia, functional impotence, occipital headache, diplopia, unusual neck pain, abdominal pain, fever, nausea, bilious vomiting	Ill-looking, PR of 110/min, BP of 145/85 mmHg, tachypnea
24	Baburaj et al.[37] (2008)	M	63	NA	Lipase, amylase	Nausea, vomiting, diarrhea, malaise, pain, and weakness for 2 days	Ill-looking, fever, jaundice, bilateral conjunctival congestion, pedal edema, tachycardia, abdominal distention, diffuse tenderness, guarding, hepatomegaly, reduced bowel sounds, free fluid in abdomen, left lung crepitation

(continued)

Table 1. Continued.

SN	Authors (year)	Sex	Age (y)	Strain	Method of diagnosis	Clinical presentation	Physical examination findings
25	Pribadi et al.[12] (2012)	M	42	NA	Lipase, amylase	Fever, diarrhea, body aches for 3 days	GCS of 13, icterus, ciliary injection, greenish fluid in nasogastric tube, generalized abdominal tenderness, bilateral calf tenderness
26	Khan et al.[38] (2015)	M	35	*Leptospira icterohaemorrhagiae*	CT, CP	Fever, reduced appetite, diffuse abdominal and calf pain for 1 week	Conscious, oriented, febrile, normal BP, PR of 100/min, low-volume regular pulse, RR of 18/min
27	Thungag et al.[3] (2008)	F	45	NA	Amylase, CP	High-grade fever with chills and rigors for 3 days	Normal examination
28	Bourquin et al.[8] (2011)	M	65	*Leptospira icterohaemorrhagiae*	NA	High-grade fever with chills and rigors, sweating, chest pain of pricking nature for 3 days	Fever, icterus
29	Sharma et al.[39] (2019)	M	60	NA	CT, amylase, lipase	Fever, epigastric pain, myalgia, jaundice for 1 week	Ill-looking, icterus, bilateral conjunctival congestion, pedal edema, tachycardia, BP of 90/60 mmHg, abdominal distension, diffuse tenderness, guarding, rigidity, reduced bowel sounds
30	Pal[11] (2019)	M	57	NA	CT, amylase, CP	Fever, body aches, and diarrhea for 3 days	Hypotension, tachycardia, scleral icterus, subconjunctival hemorrhage, rebound tenderness, guarding, sluggish peristaltic sounds
31	Casella and Scatena[43] (2000)	M	42	*Leptospira interrogans* serovar Pomona	Lipase, amylase	High-grade continuous fever, jaundice, myalgia, redness of right eye, cough, hemoptysis, reduced urine output, diffuse abdominal pain, nausea, vomiting, drowsiness	Poor general condition, severe dehydration and hypotension, hepatosplenomegaly
32	Maria-Rios et al.[40] (2020)	M	43	NA	CT, lipase, CP	Fever, diarrhea, sore throat, headache	Diffuse icterus, mild epigastric tenderness

(continued)

Table 1. Continued.

SN	Authors (year)	Sex	Age (y)	Strain	Method of diagnosis	Clinical presentation	Physical examination findings
33	Simon et al.[41] (2012)	M	37	*Leptospira interrogans*	Lipase, CP	Intermittent fever, myalgia, and general weakness	Generalized rash with desquamation and purpura
34	Monno and Mizushima[44] (1993)	M	66	*Leptospira interrogans* serovar Autumnalis	Amylase, lipase, CP	Fever, chills, myalgia, arthralgia, fatigue, headache, retro-orbital pain	Jaundice, conjunctival suffusion, erythema, right hypochondrial tenderness, calf tenderness, mild lymphadenopathy
35	Chong and Goh[45] (2007)	M	41	NA	Amylase, CT	Fever, myalgia, anorexia, and fatigue	Jaundice, lethargy, nonspecific abdominal tenderness
36	Herath et al.[46] (2016)	NA	43	NA	NA	Fever, myalgia, and arthralgia in all six patients; nausea, vomiting, and radiation to back in four patients	Hypotension and bilateral basal crepitation in lung examination in six patients; epigastric tenderness, guarding, conjunctival suffusion, and tachycardia in four patients; tachypnea, hepatomegaly, and icterus in three patients; pallor and bleeding in one patient
37	O'Brien et al.[47] (1999)	7M, 6F	MA 42	*Leptospira interrogans* serovar Bratislava in three patients, serovar Autumnalis in two patients	Lipase, amylase, CP	NA	NA
38	Kishor et al.[10] (2002)	NA	NA	NA	Amylase, abdominal USS	Fever, epigastric pain, and vomiting in 15 patients	NA
39	Daher et al.[17] (2003)	NA	16	NA	Histology (autopsy)	Fever in12 patients; vomiting, myalgia, and dyspnea in 11 patients; chills in 10 patients; abdominal pain and diarrhea in 8 patients; oliguria in 1 patient	Jaundice in 12 patients, tachycardia and dehydration in 8 patients, hypotension in 7 patients

SN, serial number; M, male; F, female; NA, not available; MA, mean age; CP, clinical presentation; BP, blood pressure; PR, pulse rate; RR, respiratory rate; CT, computed tomography; USS, ultrasound scan; GCS, Glasgow Coma Scale.

Table 2. Biochemical findings of patients with leptospirosis and acute pancreatitis

SN	Authors (year)	WBC (/μL)	Hb (g/dL)	PCV	Platelets (/μL)	Na (mol/L)	K (mmol/L)	Amylase (U/L)	Lipase (U/L)	CRP (mg/L)	AST (U/L)	ALT (U/L)	TBr (μmol/L)	SCr (mg/dL)	Ca (mmol/L)
1	Maier et al.[21] (2019)	13,200	14	42%	NA	NA	NA	69	2417	174	36	55	15	2.95	NA
2	Jain and Mohan[6] (2013)	4500	11	NA	NA	NA	NA	5300	1200	NA	22	85	1.9	Normal	NA
3	Silva et al.[22] (2011)	6770	12.8	NA	NA	NA	NA	478	898	NA	130	213	11.05	1.3	NA
4	Spichler et al.[20] (2007)	54,800	NA	NA	NA	NA	NA	2860	14,900	NA	223	158	3.4	5	NA
5	Kaya et al.[24] (2005)	9000	13	NA	NA	NA	NA	630	642	192	1900	2500	6.5	2.7	NA
6	Kaya et al.[24] (2005)	23,000	8.6	NA	NA	NA	NA	830	797	NA	85	70	48	NA	NA
7	Prasanthie and de Silva[15] (2008)	13,000		NA	NA	NA	NA	1834	198	NA	106	60	NA		NA
8	Afzal et al.[25] (2020)	10,100	13	39%	12,800	141	40	NA	NA	NA	0.3	4.9	NA	1.4	NA
9	Mazhar et al.[26] (2016)	18,000	42	NA	NA	132	3	NA	1750	NA	144	184	13	4.4	NA
10	Ranawaka et al.[13] (2013)	7000	13	NA	12,500	NA	NA	4200	NA	NA	96	141	NA	521	Low
11	Yew et al.[13] (2015)	NA	12.7	NA	32,000	NA	NA	2707	NA	NA	59	NA	NA	233	NA
12	Gomes et al.[54] (2019)	20,000	12.8	36.9%	32,000	142	4.5	664	4277	NA	96	81	18.48	2.73	NA
13	Panagopoulis et al.[29] (2014)	15,000	NA	NA	5000	NA	NA	1000	NA	NA	5 times	NA	NA	3	NA
14	Popa et al.[30] (2013)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
15	Lim et al.[31] (2014)	11,700	12.4	NA	169,000	NA	NA	820	NA	NA	49	66	0.91	1.57	8.6
16	Mondal et al.[32] (2014)	15,600	9.4	NA	Normal	NA	NA	750	3720	NA	168	71	11.7	4.1	NA
17	Desai and Hattangadi[14] (2008)	16,500	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.6	1.7	NA

(continued)

Table 2. Continued.

SN	Authors (year)	WBC (/μL)	Hb (g/dL)	PCV	Platelets (/μL)	Na (mol/L)	K (mmol/L)	Amylase (U/L)	Lipase (U/L)	CRP (mg/L)	AST (U/L)	ALT (U/L)	TBr (μmol/L)	SCr (mg/dL)	Ca (mmol/L)
18	Schattner et al.[19] (2020)	23,300	12.06	NA	201,000	NA	3.3	428	373	43.4	Normal	Normal	31.1	Normal	7
19	Law et al.[33] (2014)	Increased	Normal	NA	Normal	NA	NA	156	111	NA	Mildly elevated	Mildly elevated	NA	Normal	NA
20	Castillo et al.[34] (2006)	15,000	15	NA	316,000	139	3.3	1275	2800	NA	NA	NA	NA	0.9	9.5
21	Taher et al.[35] (2005)	12,600	8.4	NA	NA	127	3	327	445	NA	73	94	NA	7.4	NA
22	Krati et al.[36] (2019)	13,850	NA	NA	3900	3.8	NA	>550	NA	142.5	1044	1740	NA	13	NA
23	Tanriverdi[42] (2009)	3400	11.8	34.5%	79,000	122	3.1	32.4	NA	211.4	41.8	32.4	0.9	5.42	8.9
24	Tanriverdi[42] (2009)	12,500	NA	Normal	45,000	NA	NA	1176	412	NA	921	52	5.9	2	NA
25	Pribadi et al.[12] (2012)	13,000	12.3	33.5%	233,000	NA	6.4	224	314	NA	50	60	18.78	6.6	NA
26	Khan et al.[38] (2015)	14,600	10.8	NA	78,000	NA	140	4.6	NA	NA	46	50	1.9	1.4	8.2
27	Thungag et al.[3] (2008)	15,000	NA	NA	22,000	NA	NA	1429	60	NA	NA	NA	9.8	3.1	NA
28	Bourquin et al.[8] (2011)	NA	11.5	NA	22,000	NA	2.7	NA	NA	209	185	108	285	486	NA
29	Sharma et al.[39] (2019)	12,500	NA	NA	40,000	NA	NA	1106	412	NA	92	52	NA	2.4	NA
30	Pal[11] (2019)	15,900	11.8	NA	20,000	110	3.1	984	1012	NA	82	27	22	5.1	NA
31	Casella and Scatena[43] (2000)	11,800		NA	122	NA	NA	1116	802	NA	NA	NA	4.77	4.77	NA
32	Maria-Rios et al.[40] (2020)	NA	NA	NA	9000	NA	NA	NA	NA	NA	564	462	12	NA	NA
33	Simon et al.[41] (2012)	12,500	12.6	34.3%	42,000	NA	NA	NA	402	231	90	70	42.6	1.1	NA
34	Monno and Mizushima[44] (1993)	8800	13.9	40.4%		131	4.1	344	1400	5	243	106	6.5	NA	NA
35	Chong and Goh[45] (2007)	17,000	NA	NA	105,000	NA	NA	328	NA	NA	NA	NA	17.1	1.4	NA

(continued)

Table 2. Continued.

SN	Authors (year)	WBC (/μL)	Hb (g/dL)	PCV	Platelets (/μL)	Na (mol/L)	K (mmol/L)	Amylase (U/L)	Lipase (U/L)	CRP (mg/L)	AST (U/L)	ALT (U/L)	TBr (μmol/L)	SCr (mg/dL)	Ca (mmol/L)
36	Herath et al.[46] (2016)	Leukocytosis in 8 patients	NA	Thrombocytopenia in 6 patients	NA	NA	NA	Hyperamylasemia in 6 patients	NA	NA	NA	NA	Hyperbilirubinemia in 5 patients	Increased creatinine in 6 patients	Hypocalcemia in 4 patients
37	O'Brien et al.[47] (1999)	NA	NA	NA	NA	NA	NA	Hyperamylasemia in 8 patients	Hyperlipasemia in 8 patients	NA	NA	NA	NA	Increased creatinine in 10 patients	NA
38	Kishor et al.[10] (2002)	NA	NA	NA	NA	NA	NA	Hyperamylasemia in 15 patients	NA	NA	NA	NA	NA	NA	NA
39	Daher et al.[17] (2003)	Leukocytosis in 8 patients	NA	Thrombocytopenia in 10 patients	NA	NA	Hyperkalemia in 6 patients	Hyperamylasemia in 3 patients	Hyperlipasemia in 5 patients	NA	Elevated transaminases in 4 patients	Elevated transaminases in 4 patients	Hyperbilirubinemia in 9 patient	Increased creatinine in 12 patients	NA

SN, serial number; WBC, white blood cell count; PCV, packed cell volume; NA, not available; Hb, hemoglobin; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; TBr, total bilirubin; SCr, serum creatinine.

Table 3. Microbiological and radiological investigations of patients with leptospirosis and acute pancreatitis

SN	Authors (year)	Lepto IgM	DFM	Blood PCR	MAT	Urine PCR	Lepto IgG	CXR findings	AXR findings	USS findings	CECT findings
1	Maier et al.[21] (2019)	Present	Absent	NA	NA	NA	Present	Normal	NA	Prominent edematous pancreas	NA
2	Jain and Mohan[6] (2013)	Present	Absent	NA	NA	NA	NA	Normal	NA	Moderate ascites, pancreas not visualized	Bulky pancreas with areas of necrosis and peri-pancreatic fluid collections
3	Silva et al.[22] (2011)	Present	Absent	NA	NA	NA	NA	NA	NA	Free peritoneal fluid	Free fluid in the pelvis and bilateral pleural effusion
4	Spichler et al.[20] (2007)	Present	Absent	NA	NA	NA	Present	NA	NA	Mild hepatomegaly	Normal no pancreatic abnormalities

(continued)

Table 3. Continued.

SN	Authors (year)	Lepto IgM	DFM	Blood PCR	MAT	Urine PCR	Lepto IgG	CXR findings	AXR findings	USS findings	CECT findings
5	Kaya et al.[24] (2005)	NA	Absent	NA	Present	NA	NA	NA	NA	Acute calculous cholecystitis and abdominal fluid collection	NA
6	Kaya et al.[24] (2005)	NA	Present	NA	Present	NA	NA	NA	NA	NA	Bilateral pleural effusion, intra-abdominal minimal fluid collection/ peripancreatic tissue heterogeneity
7	Prasanthie and de Silva[15] (2008)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
8	Afzal et al.[25] (2020)	NA	NA	Positive	NA	NA	NA	NA	NA	Isolated hepatofugal flow in right portal vein suspicious for portal vein thrombosis; normal directional flow in left portal vein	Normal except for subtle sludge and gallstones in GB
9	Mazhar et al.[26] (2016)	Present	NA	NA	NA	NA	NA	Bilateral diffuse alveolar shadows suggesting diffuse pulmonary hemorrhage	NA	Hepatomegaly without ascites or biliary dilation	Presence of hepatosplenomegaly without biliary dilation and unremarkable pancreas
10	Ranawaka et al.[13] (2013)	Present	NA	NA	Present	NA	NA	NA	NA	NA	Prominent edematous pancreas suggesting pancreatitis; hepatomegaly also present
11	Yew et al.[27] (2015)	Present	NA	NA	NA	NA	NA	NA	NA	NA	NA
12	Gomes et al.[54] (2019)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
13	Panagopoulis et al.[29] (2014)	Present	NA	Positive	NA	NA	NA	NA	NA	NA	NA

(continued)

Table 3. Continued.

SN	Authors (year)	Lepto IgM	DFM	Blood PCR	MAT	Urine PCR	Lepto IgG	CXR findings	AXR findings	USS findings	CECT findings
14	Popa et al.[30] (2013)	NA	NA	NA	NA	NA	NA	NA	Air–fluid levels in small bowel in center of abdomen	Hepatic steatosis, peritoneal ascites in Morrison's pouch, homogeneous pancreas with cephalic diameter of 20 mm	Diffuse enlargement of the pancreas with necrosis associated with necrotic collections in the lesser sac, anterior and inferior to the pancreatic tail; necrotic retroperitoneal extensions, anterior to the left prerenal fascia and behind the descending colon
15	Lim et al.[31] (2014)	Present	NA	NA	Present	NA	NA	NA	NA	NA	Patchy area of non-enhancement at the pancreatic head region, representing an area of necrosis and streaky peripancreatic fat; ill-defined fluid collection present inferior, posterior, and anterior to the pancreatic head and neck; pericholecystic fluid with enhancement of GB wall
16	Mondal et al.[32] (2014)	Present	NA	NA	NA	NA	NA	NA	NA	NA	Bulky pancreas with mild peripancreatic fat stranding
17	Desai and Hattangadi[14] (2008)	Present	NA	NA	NA	NA	NA	NA	Ground glass appearance	Pancreatitis features	Free fluid in the abdomen, edematous pancreas, peripancreatic fat stranding

(continued)

Table 3. Continued.

SN	Authors (year)	Lepto IgM	DFM	Blood PCR	MAT	Urine PCR	Lepto IgG	CXR findings	AXR findings	USS findings	CECT findings
18	Schattner et al.[19] (2020)	NA	NA	Positive	NA	NA	NA	Normal	NA	NA	Non-enlarged and homogeneously enhancing liver and spleen, mild fat stranding in the lesser omentum, acute interstitial edematous pancreatitis without tissue necrosis
19	Law et al.[33] (2014)	Present	NA	NA	NA	NA	NA	NA	NA	NA	Bulky pancreas with peripancreatic fat stranding
20	Castillo et al.[34] (2006)	Present	NA	NA	NA	NA	NA	NA	NA	NA	NA
21	Taher et al.[35] (2005)	Present	NA	NA	Present	NA	NA	Normal	NA	Mild hepatomegaly of left lobe with chronic parenchymal liver disease and renal disease	Computed tomography not performed
22	Krati et al.[36] (2019)	Present	NA	NA	NA	NA	Present	NA	NA	Increased pancreatic volume without an identifiable obstruction	Homogeneous increase in pancreatic volume without identifiable lithiasis but with homogeneous hepatosplenomegaly
23	Tanriverdi[42] (2009)	Present	Present	NA	Present	NA	NA	NA	NA	Thickened GB with pericholecystic fluid collection	CECT normal
24	Baburaj et al.[37] (2008)	Present	NA	NA	NA	NA	NA	NA	Dilated intestinal loops	Mild hepatomegaly with consolidation of left lower lobe of lung and bilateral minimal pleural effusion	Bulky edematous pancreas with mild hepatosplenomegaly

(continued)

Table 3. Continued.

SN	Authors (year)	Lepto IgM	DFM	Blood PCR	MAT	Urine PCR	Lepto IgG	CXR findings	AXR findings	USS findings	CECT findings
25	Pribadi et al.[12] (2012)	Present	NA	NA	NA	NA	NA	NA	NA	CKD, CLCD, bile sludge, bilateral hydronephrosis	NA
26	Khan et al.[38] (2015)	Present	NA	NA	Present	NA	NA	Normal	Normal	Bulky pancreas	Peripancreatic necrosis with diffuse pancreatitis
27	Thungag et al.[3] (2008)	NA	NA	NA	NA	NA	NA	NA	NA	Normal	NA
28	Bourquin et al.[8] (2011)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
29	Sharma et al.[39] (2019)	Present	NA	NA	NA	NA	NA	NA	Dilated intestinal loops	Mild hepatomegaly with consolidation of left lower lobe of lung and bilateral minimal pleural effusion	Bulky edematous pancreas with mild hepatosplenomegaly
30	Pal[11] (2019)	Present	NA	NA	NA	NA	NA	NA	NA	NA	Evidence of AP
31	Casella and Scatena[43] (2000)	Present	NA	NA	NA	NA	NA	NA	NA	Splenomegaly	NA
32	Maria-Rios et al.[40] (2020)	NA	NA	Present	NA	Present	NA	Features of ARDS	NA	Normal	Peripancreatic fat stranding
33	Simon et al.[41] (2012)	Present	NA	NA	Present	Present	NA	NA	NA	NA	NA
34	Monno and Mizushima[44] (1993)	NA	NA	NA	Present	NA	NA	NA	NA	Enlarged tender GB with sludge	NA
35	Chong and Goh[45] (2007)	Present	NA	NA	NA	NA	NA	Normal	NA	Thickened GB with pericholecystic fluid collection	Mild AP
36	Herath et al.[46] (2016)	NA	NA	NA	Present in 6 patients	NA	NA	NA	NA	NA	NA
37	O'Brien et al.[47] (1999)	NA	NA	NA	NA	NA	NA	NA	NA	Present in 5 patient and normal	NA

(continued)

Table 3. Continued.

SN	Authors (year)	Lepto IgM	DFM	Blood PCR	MAT	Urine PCR	Lepto IgG	CXR findings	AXR findings	USS findings	CECT findings
										pancreas in all 5 patients	
38	Kishor et al.[10] (2002)	Present in 15 patients	NA	NA	NA	NA	NA	NA	NA	Pancreatitis in 15 patients	NA
39	Daher et al.[17] (2003)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Lepto IgM, *Leptospira* immunoglobulin M; Lepto IgG, *Leptospira* immunoglobulin G; SN, serial number; AP, acute pancreatitis; ARDS, acute respiratory distress syndrome; CKD, chronic kidney disease; CLCD, chronic liver cell disease; DFM, dark field microscopy; PCR, polymerase chain reaction; MAT, microscopic agglutination test; CXR, chest X-ray; AXR, abdominal X-ray; USS, ultrasound scan; GB, gallbladder; NA, not available; CECT, contrast-enhanced computed tomography.

M (IgM) (n = 39, 49.3%) and performance of a microscopic agglutination test (MAT) (n = 18, 22.7%) were the most common diagnostic modalities. Urine polymerase chain reaction (n = 5, 6.3%), blood polymerase chain reaction (n = 4, 5.0%), dark field microscopy (n = 2, 2.5%), and measurement of immunoglobulin G (n = 3, 3.7%) were the other reported modalities.

Various serovars of *Leptospira* species were mentioned. *Leptospira interrogans* Icterohaemorrhagiae (n = 7, 8.8%) and *L. interrogans* unspecified (n = 5, 6.3%) were the most common types mentioned. *Leptospira interrogans* Autumnalis and (n = 3, 3.7%) *L. interrogans* Bratislava (n = 3, 3.7%) were the other common strains reported.

Local and systemic complications

Hemorrhagic pancreatitis (n = 2, 2.5%) and necrotizing pancreatitis (n = 2, 2.5%) were the most common local complications noted. Others included extensive PPNC (n = 1, 1.2%), paralytic ileus (n = 1, 1.2%), and acalculous cholecystitis (n = 4, 5.0%). Acute kidney injury (AKI) (n = 55, 69.6%), thrombocytopenia (n = 32, 40.0%), hypotension (n = 19, 24.0%), liver injury (n = 13, 14.4%), acidosis (n = 10, 12.6%), cardiac involvement (n = 10, 12.6%), and sepsis (n = 8, 10.1%) were the most common complications reported. MOF (n = 6, 7.5%) and acute respiratory distress syndrome (n = 4, 5.0%) were other common complications. Atrial fibrillation (n = 4, 5.0%), bradycardia (n = 4, 5.0%), and meningitis (n = 2, 2.5%) were other notable complications (Table 4).[3,6,8,11–15,17,19,21–47]

Management and outcomes of AP in patients with leptospirosis

Admission to the ICU was needed for 17 (21.5%) patients. Noninvasive ventilation and intubation were performed in 4 (5.0%) and 11 (13.9%) patients, respectively. Ionotropic support was needed for four (5.0%) patients. Among patients with AKI, hemodialysis (HD) was needed for 20 (25.3%) patients. Urine output and central venous pressure were used for objective assessment of the fluid status in four (5.0%) and one (1.2%) patient, respectively. A judicious fluid regimen was used in six (7.5%) patients, and a liberal fluid regimen was used in one (1.2%) patient (Table 4).[3,6,8,11–15,17,19,21–47]

Among all 79 patients, intravenous (IV) penicillin G (n = 22, 27.8%), IV ceftriaxone (n = 18, 22.7%), and doxycycline (n = 9, 11.3%) were the most commonly used drugs. Other commonly used drugs were IV hydrocortisone (n = 8, 10.1%), IV meropenem (n = 3, 3.7%), IV imipenem (n = 3, 3.7%), and IV ampicillin sulbactam (n = 3, 3.7%).

Complete recovery was reported for 36 (45.5%) patients. Biochemical and radiological recovery was reported for 10 (12.6%) and 9 (11.3%) patients, respectively. Death was reported in 18 (22.7%) patients. Respiratory failure due to pulmonary hemorrhage (n = 6, 7.5%) and MOF (n = 4, 5.0%) were the most common causes of death. Septic shock (n = 3, 3.7%) and bleeding (n = 2, 2.5%) were the other causes. The cause was not established in two patients.

Operative management was mentioned in only three (3.7%) patients, all of whom underwent exploratory laparotomy. All three patients had features of acute abdomen due to necrotizing pancreatitis, and two patients also had ascites. Two patients underwent necrosectomy and drainage of PPNC. One patient also had acute cholecystitis for which cholecystectomy and bile duct exploration were performed. The histologic findings were compatible with acute cholecystitis. Two patients achieved

Table 4. Complications and management of patients with leptospirosis and acute pancreatitis.

SN	Authors (year)	Local complications	ICU admission	Duration of ICU stay	Duration of hospital stay	Intubation	Treatment	Fluid management (liberal/judicious)	Objective assessment of fluid status	Operative management	Exact type of operative management
1	Maier et al.[21] (2019)	None	Present	NA	18	Ventilation given	Meropenem, noradrenaline	NA	NA	Nonoperative management	Not applicable
2	Jain and Mohan[6] (2013)	Hemorrhagic pancreatitis, extensive peri-pancreatic fluid collection	Present	NA	Died after 3 days	NA	NA	NA	NA	Operative management	Emergency laparotomy, drain in lesser sac, peritoneal lavage, feeding jejunostomy
3	Silva et al.[22] (2011)	None	NA	NA	22	NA	Ceftriaxone, penicillin G	Liberal	NA	Nonoperative management	Not applicable
4	Spichler et al.[20] (2007)	Severe pancreatitis	Present	NA	Died after 17 days	NA	Ceftriaxone, ciprofloxacin	NA	NA	Nonoperative management	Not applicable
5	Kaya et al.[24] (2005)	Hemorrhagic pancreatitis	NA	NA	Died after 6 days	NA	Penicillin G (3 million units IV once daily)	NA	NA	Operative management	Exploratory laparotomy with cholecystectomy and common bile duct exploration
6	Kaya et al.[24] (2005)	None	NA	NA	19	NA	Ampicillin/sulbactam	NA	NA	Operative management	Endoscopic nasojejunal feeding tube insertion
7	Prasanthie and de Silva[15] (2009)	None	NA	NA	NA	NA	IV Penicillin, calcium gluconate, sodium bicarbonate, inotropes, platelet transfusion	NA	NA	Nonoperative management	Not applicable
8	Afzal et al.[25] (2020)	None	NA	NA	NA	NA	Doxycycline, anti-coagulation	NA	NA	Nonoperative management	Not applicable
9	Mazhar et al.[26] (2016)	None	Present	NA	7	Ventilation given	Doxycycline, ceftriaxone, metronidazole	NA	NA	Nonoperative management	Not applicable
10	Ranawaka et al.[13] (2013)	None	NA	NA	NA	NA	IV Meropenem (500 mg every 8 h) with penicillin (2 million units every 6 h) for 2 days	Judicious	CVP	Nonoperative management	Not applicable
11	Yew et al.[27] (2015)	None	Present	NA	NA	Ventilation given	Ceftriaxone (2 g/day)	NA	NA	Nonoperative management	Not applicable
12	Gomes et al.[54] (2019)	None	Present	NA	Died after 4 days	Intubated	Ampicillin/sulbactam	Judicious	UOP	Nonoperative management	Not applicable
13	Panagopoulis et al.[29] (2014)	None	Present	NA	NA	NA	Penicillin (1.5 million units every 6 h), meropenem, vancomycin	NA	NA	Nonoperative management	Not applicable
14	Popa et al.[30] (2013)	Acute necrotizing pancreatitis	NA	NA	NA	NA	Moxifloxacin (1 tablet/day), imipenem/cilastatin (3 g/day), teicoplanin (400 mg/day), rifampicin (600 mg/day)	NA	NA	Operative management	(1) Exploratory laparotomy, drainage of pancreatic head/body abscess, incision and evacuation

(continued)

Table 4. Continued.

SN	Authors (year)	Local complications	ICU admission	Duration of ICU stay	Duration of hospital stay	Intubation	Treatment	Fluid management (liberal/judicious)	Objective assessment of fluid status	Operative management	Exact type of operative management
											of retroperitoneal extensions, abdominal extensive lavage, and multiple drains (2) Exploratory laparotomy, mesh removal, re-evacuation and drainage of retroperitoneal extension, extensive lavage and drainage of abdominal cavity (3) Damage control laparotomy and drainage of left retroperitoneal extension, left colic parietal space, and right extremity of transverse mesocolon root
15	Lim et al.[31] (2014)	Necrotizing pancreatitis, acalculous cholecystitis	NA	NA	14	NA	IV Ceftriaxone (2 g once daily for 1 week), IV imipenem (500 mg three times daily for 1 week), IV pantoprazole (40 mg once daily)	NA	NA	Nonoperative management	Not applicable
16	Mondal et al.[32] (2014)	None	NA	NA	NA	NA	Ceftriaxone (1 g IV twice daily or daily)	NA	NA	Nonoperative management	Not applicable
17	Desai and Hattangadi[14] (2008)	Paralytic ileus	NA	NA	10	NA	Cefotaxime, amikacin, metronidazole, octreotide, pantoprazole amoxicillin	NA	UOP	Nonoperative management	Not applicable
18	Schattner et al.[19] (2020)	None	NA	NA	NA	NA	IV Ceftriaxone for 7 days	NA	NA	Nonoperative management	Not applicable
19	Law et al.[33] (2014)	None	NA	NA	7	Ventilation given	Ceftriaxone, azithromycin	NA	NA	Nonoperative management	Not applicable
20	Castillo et al.[34] (2006)	None	NA	NA	NA	NA	NA	NA	NA	Nonoperative management	Not applicable
21	Taher et al.[35] (2005)	None	Present	NA	12	NA	Procaine penicillin, cefoperazone, cefotaxime	NA	NA	Nonoperative management	Not applicable
22	Krati et al.[36] (2019)	None	NA	NA	NA	NA	NA	NA	NA	Nonoperative management	Not applicable
23	Tanriverdi[42] (2009)	None	NA	NA	NA	NA	Ampicillin/sulbactam (2 g daily)	NA	NA	Nonoperative management	Not applicable

(continued)

Table 4. Continued.

SNAuthors (year)	Local complications	ICU admission	Duration of ICU stay	Duration of hospital stay	Intubation	Treatment	Fluid management (liberal/judicious)	Objective assessment of fluid status	Operative management	Exact type of operative management
24 Baburaj et al.[37] (2008)	None	NA	NA	NA	NA	Penicillin C (2 million units every 6 h for 7 days), octreotide (50-mcg infusion every 8 h for 3 days)	Judicious	NA	Nonoperative management	Not applicable
25 Pribadi et al.[12] (2012)	None	NA	NA	19	NA	Ceftriaxone (2 g once daily)	NA	NA	Nonoperative management	Not applicable
26 Khan et al.[38] (2015)	None	NA	NA	15	NA	Ceftriaxone (1 g every 12 h)	Judicious	UOP	Nonoperative management	Not applicable
27 Thungag et al.[3] (2008)	None	NA	NA	15	NA	Penicillin B (1 million units), analgesics and sedatives on as-needed basis	NA	NA	Nonoperative management	Not applicable
28 Bourquin et al.[8] (2011)	None	Present	45 days	70	Intubated	NA	Judicious	UOP	Nonoperative management	Not applicable
29 Sharma et al.[39] (2019)	None	NA	NA	NA	NA	Penicillin C (2 million units every 6 h), octreotide (500 mcg every 8 h), pantoprazole (40 mg daily)	Judicious	NA	Nonoperative management	Not applicable
30 Pal[11] (2019)		NA	NA	NA	NA	NA	NA	NA	Nonoperative management	Not applicable
31 Casella and Scatena[43] (2000)	Acute cholecystitis, cholangitis	NA	NA	NA	NA	Dopamine, amoxicillin	NA	NA	Nonoperative management	Not applicable
32 Maria-Rios et al.[40] (2020)	NA	Present	NA	Discharged after 18 days	Intubated	Vancomycin, metronidazole, ceftriaxone, norepinephrine, vasopressin	NA	NA	Nonoperative management	Not applicable
33 Simon et al.[41] (2012)	NA	NA	NA	NA	NA	NA	NA	NA	Nonoperative management	Not applicable
34 Monno and Mizushima[44] (1993)	NA	NA	NA	NA	NA	Streptomycin, Clindamycin, Piperacillin.	NA	NA	Nonoperative management	Not applicable
35 Chong and Goh[45] (2007)	NA	NA	NA	Discharged after 40 days	Intubated	NA	NA	NA	Nonoperative management	Not applicable
36 Herath et al.[46] (2016)	NA	(6/6)	NA	NA	NA	IV Penicillin, IV Cefotaxime, Doxycycline & IV Hydrocortisone in 6 patients	NA	NA	NA	Not applicable
37 O'Brien et al.[47] (1999)	NA	NA			NA	NA	NA	NA	NA	Not applicable

(continued)

Table 4. Continued.

SN	Authors (year)	Local complications	ICU admission	Duration of ICU stay	Duration of hospital stay	Intubation	Treatment	Fluid management (liberal/judicious)	Objective assessment of fluid status	Operative management	Exact type of operative management
38	Kishor et al.[10] (2002)	NA	NA	NA	NA	NA	NA	NA	NA	NA	Not applicable
39	Daher et al.[17] (2003)	NA	AKI in 12 patients; hypoxia in 11 patients; respiratory failure and hypotension in 7 patients; ARDS in 6 patients; atrial fibrillation, bradycardia, and septic shock in 3 patients; hemorrhagic CVA, hypovolemic shock, splenic rupture, and AV block in 1 patient	NA	Not applicable	Intubation in 7 patients	IV Penicillin, metronidazole, IV furosemide, IV hydrocortisone, and ranitidine in 6 patients	NA	NA	NA	Not applicable

SN, serial number; NA, not applicable; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AV block, atrioventricular block; ICU, intensive care unit; IV, intravenous; CVA, cerebrovascular accident; CVP, central venous pressure; UOP, urine output.

complete recovery. The outcome of the remaining patient was not reported.

Histological findings were obtained through autopsy and were available in only 13 (17.4%) patients. Among these 13 patients, edema (n = 9, 11.3%) and inflammatory lymphocytic infiltration (n = 8, 10.1%) were the most commonly reported findings. Hemorrhage (n = 5, 6.3%), fat necrosis (n = 3, 3.7%), congestion (n = 3, 3.7%), and calcification (n = 1, 1.2%) were the other findings.

Discussion

This systematic review revealed the clinical characteristics and outcomes of AP associated with leptospirosis. In general, the most common symptoms in patients with leptospirosis included fever, myalgia, occipital headache, red eye, and jaundice.[7] Compared with the aforementioned symptoms, abdominal pain was reported less commonly (30%–40%).[7] In patients with AP, however, abdominal pain was a predominant symptom that was observed in 97% of patients, and it has diagnostic significance according to the modified Atlanta criteria.[16,48] Interestingly, abdominal pain in patients with concurrent AP and leptospirosis was not as common in the present review (64.5%). Thus, a high degree of clinical suspicion is required for a definitive diagnosis.

Leptospirosis occurs in two distinct phases: icteric and nonicteric.[49] Most patients with leptospiral infections are asymptomatic and have a nonicteric presentation.[50] Icterus was identified as one of the most common signs in the present review (43%). Frieden[51] reported that the incidence of icterus in patients with AP was 41.3% (n = 75) and that icterus originated from common bile duct enlargement secondary to the inflamed head of the pancreas as evidenced by autopsy. However, icterus is unlikely to be present solely due to pancreatitis in the absence of duct obstruction.[51]

Goswami et al.[52] reported that 61.4% of patients with leptospirosis had icterus. Another study showed that among patients with leptospirosis, those with icterus had a higher mortality rate (5%–10%) than those without icterus (1%).[53] In the present review of patients with AP secondary to leptospirosis, the mortality rate was higher among patients with icterus (n = 16, 89%) than among those without icterus (n = 2, 11%). The sensitivity and specificity of an elevated amylase concentration are high on the first day of the CP of AP but decrease thereafter.[54] Smith et al.[55] reported a 76.8% sensitivity and 92.6% specificity for amylase in patients with AP. In the present review, hyperamylasemia was seen in 70.8% of patients with AP secondary to leptospirosis. In previous studies, however, hyperamylasemia has been noted in association with nonpancreatic etiologies. Furthermore, Edwards[49] reported the presence of hyperamylasemia in 65% of patients diagnosed with leptospirosis in the absence of pancreatitis. Daher et al.[17] reported that the presence of AKI in patients with leptospirosis may increase the amylase concentration and make the diagnosis of AP difficult. Therefore, hyperamylasemia must be carefully interpreted to diagnose AP when AKI is present in patients with leptospirosis.[17] A combined assay of elevated lipase and amylase is superior in achieving a diagnosis of AP.[56] This combined assay can be used when hyperamylasemia cannot be interpreted in the context of AP associated with leptospirosis.[56]

In this review, IgM enzyme-linked immunosorbent assay (49.3%) and MAT (22.7%) were the most common methods of diagnosing leptospirosis. MAT is widely used in the diagnosis of leptospirosis because of its high sensitivity and remains the gold standard.[7] Furthermore, long-term persistence of IgM in the serum may

interfere with the identification of acute infection and give rise to false positives.[7]

In the present review, AKI (70%), hemodynamic instability (24%), and liver injury (14%) were the most common complications reported. The reported incidence of AKI in patients with leptospirosis ranges from 40% to 60%.[17] The presence of AKI increases the risk of mortality in patients with leptospirosis.[57] Daher et al.[17] reported a 22% mortality rate in patients with leptospirosis complicated by AKI. AKI also occurs in patients with severe AP.[58] Devani et al.[59] reported that the incidence of AKI in patients with AP was 7.9% (n = 3,466,493). The mortality rate is increased in patients with concurrent AKI and AP.[60] Thus, the presence of AKI carries a poor prognosis in patients with both leptospirosis and AP.[59] Furthermore, oliguria has been found to be an important prognostic factor in patients with leptospirosis.[7,61] Therefore, patients with AP and leptospirosis should be carefully monitored and managed for AKI, and care should be taken to avoid iatrogenic causes of AKI such as drugs and contrast-induced nephropathy. In our review, we found that most patients with AKI needed HD (n = 20, 25.3%). Previous studies have shown that HD can be delayed up to 72 hours following the identification of AKI in patients with leptospirosis.[61] Low-volume HD is preferred to prevent pulmonary hemorrhage in patients with concurrent leptospirosis and AKI.[5] In our review, the mortality rate among patients with AKI was considerably high (29%).

Thrombocytopenia is an important hematological marker in the diagnosis and prognostication of leptospirosis and has been identified in more than 50% of patients.[49,62] Furthermore, thrombocytopenia is a significant predictor of AKI in patients with leptospirosis and has been shown to correlate with mortality.[63,64] However, various platelet abnormalities may be noted in patients with severe AP, including thrombocytopenia, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation.[65–67] The recorded incidence of thrombocytopenia in patients with AP ranges from 36% to 43%.[66] Furthermore, the presence of thrombocytopenia has been shown to correlate with severe complications and ICU admission in patients with AP.[65] In the present review, thrombocytopenia was present in 50% of patients with concurrent AP and leptospirosis and could be attributable to the combined influence of both AP and leptospirosis. Furthermore, approximately 16% of patients with thrombocytopenia were admitted to the ICU. However, only one (3.2%) patient died among all patients with thrombocytopenia.

In our review, the most common radiological modalities used to diagnose pancreatitis were CECT (26.5%) and abdominal USS (21.0%). USS has a sensitivity of 62% to 90% in diagnosing pancreatitis in general, whereas CECT has an accuracy of 82% to 90% with 100% specificity.[68–70] Furthermore, less than 3% of PPNC is missed in CECT.[69] USS is the preferred initial imaging modality to exclude biliary stones, which are among the most common etiologies of AP.[68] Silverstein et al.[71] conducted a study on pancreatic imaging and concluded that pancreatic CECT was superior to abdominal USS because CECT had an increased diagnostic yield (38%). However, CECT has the disadvantage of contrast administration to patients with leptospirosis who have impaired renal function.[68] Magnetic resonance imaging can be a good alternative in such patients.[68] In patients with the severe form of leptospirosis (Weil disease), the mortality rate ranges from 10% to 15%.[23,72,73] Severe AP is associated with a mortality rate of 20%.[74,75] In our review, death was reported in 18 (31.03%) patients who had concurrent AP and leptospirosis.

Furthermore, respiratory failure due to pulmonary hemorrhage was the most common cause of death found in our review.

To overcome the challenges in diagnosing AP in patients with leptospirosis, we recommend a high degree of clinical suspicion combined with routine biochemical assays, including measurement of the serum amylase and lipase concentrations, and a basic USS. CECT should be reserved for select patients with diagnostic uncertainty and assessment of complications, and extreme caution is needed in the presence of AKI. Among patients who live in or have traveled to an area endemic for leptospirosis, those who have AP and jaundice without bile duct dilation should be promptly screened for leptospirosis. Although management includes antibiotics and supportive care, judicious fluid management is also required, preferably with monitoring of the central venous pressure or inferior vena cava filling and close examination for AKI. Surgical management should be the last option. Minimally invasive approaches are more advisable than exploratory laparotomy to avoid the morbidity induced by major surgery in physiologically compromised patients. A consensus statement or guidelines to manage severe pancreatitis in the context of leptospirosis should be developed by experts.

Limitations

This review had several limitations. Heterogeneity in the reporting of case reports and case series was noted, and a meta-analysis was therefore not feasible. Relatively few patients with concurrent AP and leptospirosis have been reported in the literature. Many data were missing and the reporting was incomplete, leading to inaccuracies in the data extraction and analysis. There were also considerable variations in the choice of investigations and management because of the lack of standard guidelines for management of AP in the setting of leptospirosis. Furthermore, the disease outcomes are likely to have been influenced by other complications of leptospirosis.

Conclusion

AP is uncommon but may give rise to severe complications in patients with leptospirosis. A high degree of clinical suspicion and different modalities of investigations are essential to achieve a correct diagnosis. AP can be easily missed in patients with leptospirosis because both conditions share similar CPs and complications. Judicious fluid management with monitoring for AKI is an essential component of supportive management. Mortality and morbidity are considerably higher when both AP and leptospirosis are present. A consensus statement or guidelines to manage severe pancreatitis in the context of leptospirosis is warranted.

Authors' contributions

UJ, JCC, and DS conceived and designed the study, acquired and analyzed the data, and drafted the article. UJ, JCC, and DS collected, analyzed, and interpreted the data and wrote the article. UJ, JCC, and DS contributed to the design and conception of the study, revised it critically for important intellectual content, and approved the final version to be published. All authors have read and approved the final version of the manuscript.

Availability of data and materials

The data used in the above analysis will be available on reasonable request from the corresponding author.

Declaration of competing interests

The authors declare that there is no conflict of interest.

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