BMJ Open Gastroenterology

Incidence of acute pancreatitis among patients with leptospirosis requiring extracorporeal membrane oxygenation (ECMO): a descriptive study

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To cite: Madrigal TPR, Panlilio MTT, Burog AILD, *et al*. Incidence of acute pancreatitis among patients with leptospirosis requiring extracorporeal membrane oxygenation (ECMO): a descriptive study. *BMJ Open Gastro* 2023;**10**:e001094. doi:10.1136/bmjgast-2022-001094

Received 12 December 2022
Accepted 5 March 2023

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ABSTRACT

Background Acute pancreatitis (AP) is an infrequently reported manifestation of leptospirosis. It is more commonly seen in patients with acute respiratory distress syndrome. Despite novel modalities such as extracorporeal membrane oxygenation (ECMO), the mortality rate remains high and whether this is associated with the lung injury caused by the inflammation in AP remains unclear.

Objectives and methods A descriptive study was conducted at a tertiary hospital in the Philippines. Primary outcome was defined as the presence or absence of AP. Secondary outcomes were defined as 28-day mortality rate, length of hospital stay, ECMO days, renal replacement therapy (RRT) days, days on mechanical ventilation, presence of local complications of AP and development of nosocomial infections.

Results A total of 27 patients were included in the study, and 88.89% (n=24) were men. The mean age for all patients was 33.59±10.22 years. Out of the 27 patients, 19 (70.37%) were diagnosed with AP. Among these 19 patients, one (5.26%) had necrotising pancreatitis and two (10.52%) developed local complications of pancreatitis. Six patients (31.58%) died among those who developed AP, while one (12.50%) died among those who did not. The duration of hospital stay, ECMO, RRT, mechanical ventilation and development of nosocomial infections was also higher in the group who presented with AP.

Conclusion AP is an under-reported complication of leptospirosis. Our study demonstrated a higher mortality and morbidity in patients with leptospirosis who developed AP.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Acute pancreatitis (AP) in the setting of leptospirosis is infrequently reported. As a national referral centre for renal diseases, we have observed several cases of AP in patients with severe leptospirosis.

WHAT THIS STUDY ADDS

⇒ AP could be an unrecognised contributing factor to worse clinical outcomes in patients with severe leptospirosis. We have observed a higher mortality and morbidity among those who developed AP.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Early detection and management of AP could improve clinical outcomes in severe leptospirosis. Routine diagnostic testing for AP levels could be considered especially in patients presenting with other organ failures.

INTRODUCTION

Leptospirosis is a globally important zoonotic disease caused by spirochetes of the genus *Leptospira*. The incidence of the disease remains underestimated, although it is estimated at 1–10 per 100 000 population in tropical countries. South East Asia and Oceania have the highest incidence in the Asia Pacific Region. Outbreaks of the disease occur following severe floods, especially during the rainy season in both rural and urban areas.[1] The Philippines ranked 26th worldwide with a 4.8 annual incidence per million population of leptospirosis.[2] The disease remains a public health concern in the country with 3011 cases with a 10.4% mortality rate recorded in 2019.[3]

Leptospirosis may be acquired either by direct or indirect contact with the urine of an infected animal. Abrasions or cuts in the skin are the usual port of entry of the spirochetes. Transmission through the exposure of the conjunctiva, mucous membranes and sexual intercourse have also been reported.[4] Clinical manifestations typically appear after an incubation period of 1–2 weeks. The disease may manifest with mild symptoms such as fever, myalgia and anorexia to a fulminant course manifesting as multi-organ failure. In a retrospective study in India, multi-organ failure developed in 77% of leptospirosis cases admitted in the intensive care unit.[5] Leptospirosis mainly affects the liver, kidneys and lungs, although other organs such as

the pancreas, heart and brain may also be affected. The case fatality rate ranges from 32.4% to 46.5% in patients who present with pulmonary haemorrhage, liver failure or renal failure.[6] Novel treatment modalities are being applied and include therapeutic plasma exchange, intravenous immunoglobulin and extracorporeal membrane oxygenation (ECMO).[6 7] ECMO has become a promising modality in cases complicated by pulmonary haemorrhage and acute respiratory distress syndrome (ARDS).[7] In another retrospective study, four out of five of patients with leptospirosis placed on ECMO survived. However, despite these novel therapeutic measures, the mortality rate of severe leptospirosis remains high.[8]

Acute pancreatitis (AP) is reported to be an infrequent manifestation of leptospirosis, although it is more commonly seen in patients with leptospirosis who develop ARDS.[9] ARDS is a known complication of AP per se and is associated with a mortality rate as high as 37%.[10] It is still unclear whether the systemic inflammation in AP further adds to the lung injury caused by leptospirosis, thereby increasing the mortality rate in patients with leptospirosis; thus, the authors of this study investigated the incidence and impact of AP in this subset of patients.

OBJECTIVES

General objective

To determine the incidence of AP among patients with leptospirosis treated with ECMO.

Specific objectives

1. To compare the demographic profile, clinical characteristics and baseline laboratory findings on admission among patients with leptospirosis who developed AP versus those who did not.
2. To compare the treatment outcomes of patients with leptospirosis who developed AP versus those who did not.

METHODOLOGY

Study design and population

A descriptive study was conducted, which included all patients aged 19 years and above admitted for leptospirosis who were placed on ECMO from January 2018 to December 2020. Patients with incomplete data and pre-existing pancreatic disease were excluded.

Materials and methods

Patients admitted for leptospirosis and placed on ECMO were identified from the Medical Records Section. Inpatient charts were reviewed. Demographic profile, and clinical characteristics on admission, such as the presence of systemic inflammatory response syndrome (SIRS), need for vasopressor support, presence of gallstones, serum triglyceride levels and history of heavy alcohol use, were collected. Laboratory results on admission were also obtained: complete blood count, international normalised ratio of prothrombin time (INR), serum creatinine, blood urea nitrogen, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), lipase, calcium and albumin.

Definition of terms

1. Leptospirosis: diagnosis requires an acute febrile illness of at least 2 days in an individual either residing in a flooded area or has high-risk exposure, and presenting with at least two of the following symptoms: myalgia, calf tenderness, conjunctival suffusion, chills, abdominal pain, headache, jaundice or oliguria.[11]
2. AP: diagnosis requires two of the following three features: (i) abdominal pain (acute onset of a persistent, severe, epigastric pain often radiating to the back); (ii) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal and (iii) characteristic radiological imaging findings.[12]
3. ECMO: temporary form of life support providing a prolonged biventricular circulatory and pulmonary support for patients with pulmonary and cardiac failure unresponsive to standard therapy.[13]
4. ARDS: defined according to the Berlin definition; severity based on degree of hypoxaemia: mild (200 mm Hg<PaO2/FIO2≤300 mm Hg), moderate (100 mm Hg<PaO2/FIO2≤200 mm Hg) and severe (PaO2/FIO2≤100 mm Hg). Patient category was assigned according to the most severe P/F ratio obtained via arterial blood gas analysis.[13]
5. Heavy alcohol use: defined using the Alcohol Use Disorders Identification Test (AUDIT-C) questionnaire; a score of 4 or more, or 3 or more is considered positive in men and women, respectively.[14]
6. Bedside Index for Severity in Acute Pancreatitis (BISAP) score: a 5-point scoring system used in identifying patients at high risk for mortality or severe disease early during the course of AP; variables include: blood urea nitrogen >25 mg/dL, impaired mental status, SIRS, age >60 years and presence of pleural effusion.[15]

Primary and secondary outcomes

The primary outcome was defined as the presence or absence of AP. Secondary outcomes were defined as 28-day mortality rate, length of hospital stay, days on ECMO, days on renal replacement therapy (RRT), days on mechanical ventilation, presence of local complications of AP and development of nosocomial infections.

Statistical methods

Descriptive statistics were used to summarise the clinical and demographic characteristics of the patients. Frequency and proportion were used for nominal variables, median and IQR for ordinal variables, and mean and SD for interval/ratio variables. The incidence of AP among patients with leptospirosis was determined as a measure of frequency and proportion. Missing variables

were neither replaced nor estimated. STATA V.16.0 was used for data analysis.

RESULTS

In total, 28 patients with leptospirosis were placed on ECMO at the National Kidney and Transplant Institute from January 2018 to December 2020. One was excluded due to a lack of serum lipase levels during his admission. A total of 27 patients were included in the study. Serological testing for leptospirosis was done via immunochromatographic assay. A positive IgM test was detected in 51.8% (n=14) of patients on admission. Patients with an initially negative antibody test were subjected to a repeat assay on the second week of illness.[11] Thirty-seven per cent (n=10) of patients subsequently tested positive for IgM on their second week of illness. One patient died before a second sample was taken. The remaining 7.4% (n=2) of patients who tested negative on repeat serological testing underwent microagglutination test, which eventually turned out positive. The demographic and clinical characteristics are shown in table 1. Out of the 27 patients, 88.89% were men. The mean age for all patients was 33.59±10.22 years. All patients resided in urban areas, and 44.44% were involved in construction and related trade works.

Table 1 Demographic and clinical characteristics

	All (n=27)	With acute pancreatitis (n=19)	No acute pancreatitis (n=8)
	Frequency (%); mean±SD; median (range)		
Demographics			
Age (years)	33.59±10.22	35.26±10.58	29.63±8.63
Sex			
Male	24 (88.89)	17 (89.47)	7 (87.5)
Occupation			
None	7 (25.93)	7 (36.84)	–
Construction and related trade workers	12 (44.44)	8 (42.11)	4 (50.00)
Student	3 (11.11)	1 (5.36)	2 (25.00)
Food preparation assistants	3 (11.11)	2 (10.53)	1 (5.26)
Cleaners and helpers	1 (3.70)	–	1 (5.26)
Driver and vehicle operators	1 (3.70)	1 (5.26)	–
Place of residence			
Urban	27 (100)	19 (70.37)	8 (29.63)
Clinical characteristics			
Subtype of acute pancreatitis			
Interstitial edematous pancreatitis	–	18 (94.7)	–
Necrotising pancreatitis	–	1 (5.26)	–
BISAP score			
0–2	–	12 (63.16)	–
3–5	–	7 (36.84)	–
SIRS score			
≥2	24 (88.89)	17 (89.47)	7 (87.50)
Need for vasopressor support			
None	5 (18.52)	5 (26.32)	–
Single	13 (48.15)	6 (31.58)	7 (87.5)
At least two	9 (33.33)	8 (42.11)	1 (12.5)
Presence of gallstones			
With gallstones	3 (11.11)	3 (15.79)	–
Without gallstones	24 (88.89)	16 (84.21)	8 (100)
Heavy alcohol use			
With history	4 (14.81)	3 (15.79)	1 (12.50)
Without history	23 (85.19)	16 (84.21)	7 (87.50)
Body mass index (kg/m^2)	21.34±3.44	22.09±3.62	19.54±2.23

BISAP, Bedside Index for Severity in Acute Pancreatitis; SIRS, systemic inflammatory response syndrome.

Table 2 Baseline laboratory findings on admission

	All (n=27)	With acute pancreatitis (n=19)	No acute pancreatitis (n=8)
	Frequency (%); mean±SD; median (range)		
White cell count (x10^9/L)	16.48±8.40	16.71±7.64	15.95±10.54
Haematocrit (%)	35.56±6.02	35.93±6.35	34.7±5.47
Platelet count (×10^9/L)	57 (36–122)	61 (40–122)	38 (26–135.5)
Serum creatinine (mg/dL)	7.97±2.61	8.26±2.74	7.26±2.29
Blood urea nitrogen (mg/dL)	91.56±33.14	96.16±35.92	80.63±23.86
INR of prothrombin time	1.16 (1.09–1.32)	1.16 (1.1–1.34)	1.13 (1.08–1.24)
Total bilirubin (mg/dL)	9.75±5.12	9.95±4.65	9.26±6.43
AST (units/L)	77 (50–164)	101 (50–206)	76 (60.5–130)
ALT (units/L)	43 (32–81)	43 (32–81)	41.5 (30.5–101)
LDH (units/L)	697 (342–3093)	967 (631–1433)	550 (331–4110)
Lipase (units/L)	389 (251–1015)	622 (295–1015)	163.5 (116–906)
Serum calcium (mg/dL)	7.12±0.80	6.95±0.86	7.53±0.47
Triglyceride* (mg/dL)	261.76±108.81	278.83±99.35	217.86±127.55
Pleural effusion	7 (25.93)	5 (26.32)	2 (25.00)

*N=25, serum triglyceride levels were not obtained on day 1 of admission.
ALT, alanine aminotransferase; AST, aminotransferase; INR, international normalised ratio; LDH, lactate dehydrogenase.

Seventy per cent of patients were diagnosed with AP, of which 5.26% had necrotising pancreatitis. Among patients who developed AP, 63.16% and 36.84% had a BISAP score of 0–2 and ≥3, respectively. SIRS was present in almost 90% of patients in both groups. Forty-two per cent of patients with AP needed at least two vasopressors on admission, compared with 12.5% in those without pancreatitis. Gallstones and heavy alcohol use were detected in 15.79% of patients who developed AP. None in the group who did not develop AP had gallstones on abdominal imaging, while only 12.5% had a history of heavy alcohol use. All patients had a normal body mass index (BMI) (21.34±3.44 kg/m^2).

Baseline laboratory findings on admission are shown in table 2. Mean white cell count, haematocrit, serum creatinine, blood urea nitrogen, total bilirubin, AST, ALT and LDH were higher in those with AP. In contrast, mean serum calcium was lower in this subset of patients. Platelet count, INR and LDH values were expressed as median and range due to the non-normal distribution of data.

Serum lipase level is routinely requested as part of baseline work-up for patients with leptospirosis in our institution. Patients with AP had a median serum lipase value of 622 (295–1015) units/L. Pleural effusion was present in 26.32% and 25% of patients in the group with AP and without AP, respectively. Mean serum triglyceride levels (278.83±99.35 mg/dL) were also higher in the group with AP, although values were not obtained on day 1 of admission.

The treatment outcomes in both groups are shown in table 3. Among patients with AP, 10.52% developed local complications of AP (walled-off necrosis and acute peripancreatic fluid collection). The 28-day mortality rate was higher in the group with AP (31.58%) than in the no AP group (12.50%). Fifty per cent (n=3) of patients who died in the group with AP had a BISAP score of 0-2, while the remaining 50% of patients had a BISAP score of 3-5. The length of hospital stay, days on ECMO, days on RRT, days on mechanical ventilation and incidence of nosocomial infections were also higher in the group who presented with AP (table 3).

DISCUSSION

AP in the setting of leptospirosis is infrequently reported, and its mechanism is poorly understood. Activation of Toll-like 2 receptors, dysregulation in immunomodulation, small vessel vasculitis and ischaemia are some of the proposed mechanisms of pancreatic involvement in leptospirosis.[16 17] A two-centre observational study by Goswami *et al* reported a 5% incidence of AP among patients with leptospirosis.[18] In contrast, Herath *et al* reported a higher incidence at 66.67% in their case series.[19] In most cases reported, AP was seen in patients with severe leptospirosis requiring dialysis, ventilatory support or vasopressor support.[20–24] Our data showed a higher incidence of AP at 70.37%. This higher incidence may be attributable to the underlying severity of leptospirosis in our population.

AP is divided into two subtypes: interstitial edematous pancreatitis and necrotising pancreatitis, with the former comprising approximately 90%–95% of cases. Our data showed a 5.26% incidence of necrotising pancreatitis, consistent with the reported incidence of 5%–10%.[25] Both subtypes may present with pancreatic and peripancreatic fluid collections in up to 25% of cases. These local complications pose life-threatening complications such as peripancreatic abscess, biliary compression, gastric

Table 3 Treatment outcomes

Treatment outcomes	With acute pancreatitis (n=19)	No acute pancreatitis (n=8)
	Frequency (%); mean±SD; median (range)	
28-day mortality	6 (31.58)	1 (12.50)
Subtype of AP		
Interstitial edematous pancreatitis	5 (26.31)	–
Necrotising pancreatitis	1 (5.26)	–
BISAP score		
BISAP 0-2	3 (15.79)	–
BISAP 3-5	3 (15.79)	–
Length of hospital stay (days)	26 (19–35)	20.5 (19–22)
Length of days on ECMO	11 (7–16)	5 (5–8)
Length of days on RRT	8 (5–18)	5.5 (4–7.5)
Length of days on mechanical ventilation	14 (10–21)	8.5 (6–11)
Presence of local complications	2 (10.52)	
Acute peripancreatic fluid collection	1 (5.26)	–
Walled-off necrosis	1 (5.26)	–
Nosocomial infections		
Ventilator-associated pneumonia	18 (94.74)	5 (62.5)
Urinary tract Infection	6 (31.58)	2 (25)
Catheter-related bloodstream infection	10 (52.63)	–
Infected pressure ulcers	1 (5.26)	–

BISAP, Bedside Index for Severity in Acute Pancreatitis; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy.

outlet obstruction, peritonitis and haemoperitoneum.[26] In our study, two patients (10.52%) developed walled-off necrosis and acute peripancreatic fluid collection, one of which died due to massive haemoperitoneum secondary to necrotising pancreatitis.

Systemic complications such as multi-organ dysfunction or failure may develop in both leptospirosis and AP. In descending order, the most common organ involvement seen in patients with leptospirosis is renal, hepatic, coagulation and respiratory failure.[8] In contrast, respiratory failure followed by cardiovascular and renal failure are seen in patients with AP.[27] Factors associated with organ failure in AP include older age, obesity, hypertriglyceridaemia, the extent of local pancreatic injury, high BISAP score, persistent SIRS and elevation of C reactive protein and interleukin 6.[28] In our data, none of the patients were obese. However, we reported a higher mean BMI (22.09 vs 19.54 kg/m^2) in the group with AP. An observational study by Tariq *et al* concluded that a serum triglyceride level of ≥2.26 mmol/L (200 mg/dL) on admission in AP is an independent predictor for developing local and systemic complications as well as treatment outcomes.[29] Though our study reported a higher mean triglyceride level (278.83 vs 217.86 mg/dL) in the group with AP, most of these values were not obtained within 24 hours of admission. The majority of patients in both groups presented with SIRS (89.47% vs 87.5%), which may be attributable to both leptospirosis and AP.

Several scoring systems are available to predict mortality in patients with AP. These include Acute Physiology and Chronic Health Evaluation II score, Ranson criteria and BISAP score. BISAP score is a 5-point scoring system that can be accomplished bedside and has a median sensitivity of 71.4% and specificity of 87.6%.[15 30] A BISAP score of ≥3 is associated with a mortality rate of >15%. In comparison, those with scores of 0–2 are at a very low risk for mortality (<2%).[31] However, our data showed a 15.79% mortality in patients with a BISAP score of 0–2. Other factors, such as the underlying leptospirosis and the development of nosocomial infections, may have contributed to this higher mortality rate.

ARDS is a major complication of both leptospirosis and AP. ARDS per se is associated with a mortality rate of 35%–40%, although prognosis may also depend on the underlying cause of ARDS.[32] The mortality rate in ARDS associated with leptospirosis (23%) is lower than those reported with AP (44.5%–66.5%).[33–35] ECMO has been increasingly used in patients with ARDS with varying survival rates. In two retrospective studies, the survival rate with ECMO in leptospirosis-related ARDS ranges from 75% to 80%.[8 33] In contrast, the survival rate in ARDS secondary to AP is only 25%, even with the use of ECMO, although none of the patients had leptospirosis.[36] In our data, we reported a higher mortality rate in the group that developed AP (31.58%) versus those who did not (12.50%). Goswami *et al* also reported a

higher incidence of AP among patients with leptospirosis in the non-survivor group.[18] Duration of hospital stay, days on ECMO, RRT and mechanical ventilation were also longer in the group who developed AP in our study. Though more data are needed, AP appears to contribute to higher morbidity and mortality in patients with leptospirosis.

CONCLUSION AND RECOMMENDATION

AP is an under-reported complication of leptospirosis. Our study demonstrated a higher mortality and morbidity rates in patients with AP. This study presented several limitations, such as its descriptive study design, limited number of patients and inability to include mild to moderate severity of leptospirosis, thus no conclusion can be directly drawn from it and a larger cohort study is recommended to address these limitations. However, considering the low number of published cases, our findings are still important in the early detection and management of AP in patients with leptospirosis to limit mortality and morbidity in this subset of patients.

Acknowledgements This paper and the research behind it would not have been possible without the exceptional help of all my coauthors. Their knowledge and attention to detail have inspired me always to push myself forward and keep my work on track. I am also grateful to all the staff of the medical record section and the clinical trials and research unit (CTRU) of the National Kidney and Transplant Institute for extending their hands in assisting me from the initial submission of the protocol, data collection and until the submission of the final manuscript. The abstract of this manuscript was previously presented during the United European Gastroenterology (UEG) Week Virtual 2021 held last 3–5 October 2021.

Contributors TPM and MTP developed the main conceptual ideas and research outline. RD and JC reviewed and suggested improvements to the initial draft of the study. AILB worked out almost all of the technical aspect, and performed the statistical analysis. TPM took the lead in writing the manuscript. MTP, RD and JC contributed to the interpretation of the results. All authors provided critical feedback and helped improve the research and analysis. Similarly, all authors read and approved the final manuscript. TPM is the guarantor of the article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Research Ethics Committee of the National Kidney and Transplant Institute. REC Code: NKTI-REC-2021-16. Approval date: 07 March 2021. Strict confidentiality and anonymity were maintained by assigning a specific control number to each of the subjects. This was conducted in accordance with ICH-GCP Guidelines and Principles.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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