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Research paper

Clinical characteristics of patients with newly developed acute cholecystitis after admission to the intensive care unit

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ABSTRACT

Introduction: Critical care patients have many risk factors for acute cholecystitis (AC). However, less data are available regarding newly developed AC in critically ill patients.
Objectives: To investigate the clinical features of AC occurring in critically ill patients after admission to an intensive care unit (ICU).
Methods: We performed a retrospective cohort study from January 2006 to August 2016 at a tertiary care university hospital. We included patients diagnosed with AC with or without gallstones after ICU admission. All cases of AC were confirmed by gastroenterologists or general surgeons. We excluded patients with AC diagnosed before or at the time of ICU admission.
Results: A total of 38 patients were diagnosed with AC after ICU admission between January 2006 and August 2016. Seventeen (44.7%) had acute acalculous cholecystitis, while 21 (55.3%) had acute calculous cholecystitis. The median age was 73 years (interquartile range = 63–81 years), and 22 (57.9%) patients were male. The most common reason for ICU admission was pneumonia or sepsis. The median interval from ICU admission to diagnosis of AC was 11 days (interquartile range = 4.8–22.8 days). Before AC diagnosis, almost 90% of patients used total parenteral nutrition, 68% used opioids, 76% were mechanically ventilated, and 42% received vasoactive drugs. More than half of patients underwent cholecystectomy, and all surgically resected gallbladders had pathology results for cholecystitis. Gangrenous cholecystitis was observed in five patients with acute calculous cholecystitis. The overall mortality was 42.1%, and 1/3 of these deaths were directly associated with AC. The average length of stay in the ICU and hospital was 26.5 and 44.5 days, respectively.
Conclusion: The development of AC in the ICU should be carefully monitored, especially in patients who have been infected and admitted to the ICU for more than 10 days. Proper diagnosis and treatment at a critical time could be lifesaving.

1. Introduction

Acute cholecystitis (AC) consists of acute inflammation that may or may not be associated with gallstones. Acute acalculous cholecystitis (AAC) is usually recognised as a complication of serious medical and surgical illness with high mortality.[1,2] Gallbladder ischaemia, which leads to hypoperfusion and bile stasis, is central to the pathogenesis of AAC. Hypoperfusion could be aggravated by

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hypotension, dehydration, or the administration of vasoactive drugs. Bile stasis is induced by opioid use, fasting with total parenteral nutrition (TPN), and mechanical ventilation with positive end-expiratory pressure. Diabetes mellitus, congestive heart failure, shock of any kind, and sepsis also have been associated with AAC.[2,3] These factors are frequently encountered in the intensive care unit (ICU). Therefore, critical illness requiring ICU care is a risk factor for AAC.[3]

Although not common, AC is known to occur in critically ill patients. Rady et al.[4] reported that 3% of patients admitted to the cardiothoracic ICU after cardiovascular surgery develop AC. Theodorou et al.[5] reported that AAC developed in 1.2% of patients admitted to the burn ICU of a university hospital and that AAC might reflect the severity of the patient's general condition. In trauma patients requiring intensive care for more than 4 days, AAC developed in 10.6% of patients.[6] Furthermore, critically ill patients who develop AC may also develop more serious complications. The incidence of gallbladder gangrene in ICU patients with AAC is greater than 50%, and the incidence of perforation is greater than 10%.[7] AAC has a high mortality ranging from 10 to 90% with early or late diagnosis, respectively.[3] Additionally, Papadakis et al.[8] reported that critically ill patients with American Society of Anesthesiologists physical status classification 3 and 4 had increased risk for extensive gallbladder inflammation when AC developed, which leads to increased risk of morbidity and mortality.

Therefore, clinical suspicion is important, and prompt diagnosis and active treatment can be lifesaving in patients with AC in ICU. However, diagnosis of AC is not easy because symptoms and laboratory findings are unspecific, and clinical characteristics of AC in the ICU have not been well established. Previous studies about critically ill patients have been limited to selected patients with burns,[5] trauma,[6] or cardiovascular surgery,[4] which are known risk factors of AAC.[9] Additionally, it was unclear whether AC developed before or after ICU admission, and AAC was confirmed with the operative specimen.[10,11] However, because of the poor general condition in a number of patients, surgery is not always an option in the ICU; in these cases, percutaneous gallbladder drainage (PTGBD) is frequently used as a safe alternative.[12–14] In critically ill patients, PTGBD should remain in place until the patient is deemed medically eligible for cholecystectomy.[15] Therefore, previous study does not reflect the real characteristics of AC in the ICU.

Little has been reported about newly developed AC with or without gallstones in patients admitted to the ICU without intra-abdominal problems. The objective of this study was to evaluate the clinical characteristics of AC developing after admission to the ICU.

2. Materials and methods

We performed a retrospective cohort study from January 2006 to August 2016 at a tertiary care university hospital, which is a referral hospital with a 759-bed capacity containing 55 ICU beds (cardiovascular ICU, 7 beds; medical ICU, 15 beds; neuro ICU, 18 beds; and surgical ICU, 15 beds).

Patients who were admitted to the cardiovascular, medical, and neuro ICUs were screened, and we included all patients who were diagnosed with AC after ICU admission. During the entire study period, our hospital operated an electronic medical record system. We identified cases using diagnostic codes of cholecystitis and a code indicating that the patient was admitted to the ICU. Patients diagnosed with AC before or at the time of ICU admission were excluded. Patients who were admitted for abdominal surgery or had abdominal problems before ICU admission were also excluded.

AC was diagnosed using abdominal sonography or computed tomography. Abdominal sonography was performed by board-certified radiologists. All cases were confirmed by board-certified gastroenterologists or general surgeons based on clinical features and imaging. AAC was defined as AC in the absence of gallstones on abdominal imaging studies. The date of diagnosis of AC was defined as the day of abdominal imaging.

Demographic and clinical data were collected based on medical records. Variables such as age, sex, body mass index, comorbidities including diabetes mellitus and congestive heart failure,[2,3] Charlson comorbidity index (CCI), cause of admission, interval from admission to diagnosis of AC, treatment of AC, lengths of hospital stay and ICU stay, and mortality were collected. Additionally, previous antibiotic usage including ceftriaxone, which is reported to induce biliary sludge in 25–45% of patients,[16] red blood cell transfusion history, prior vasoactive drug, opioid use, total parenteral nutrition, and mechanical ventilation, which are known risk factors of AAC, were also collected.[2,3]

The study protocol was approved by the Institutional Review Board of Ewha Woman's University Mokdong Hospital (IRB number: 2017-05-067) and was conducted in accordance with the amended Declaration of Helsinki.

2.1. Statistical analysis

Clinical characteristics were summarised using descriptive statistics, such as proportion, median, and interquartile range (IQR). AAC was compared with acute calculous cholecystitis (ACC). Continuous variables were compared using the Mann–Whitney test, and categorical variables were compared using the Chi-square test. A $P < 0.05$ was deemed to indicate statistical significance. All statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics of the patients with acute cholecystitis

During the study period between 2006 and 2016, the average number of total patients admitted to the ICU including cardiovascular, medical ICU, and neuro ICU was 1928/year. ICU mortality was 14.3%, and average length of ICU stay was 7.72 days.

A total of 38 patients were diagnosed with AC after ICU admission during the study period. There were 17 patients with AAC (44.7%) and 21 with ACC (55.3%) (Table 1). The median age was 73 years, and 59% were male. Although the differences did not reach statistical significance, patients with AAC were older (73.4 vs. 69.0 years, $P = 0.977$) and had a lower body mass index (22.2 vs. 24.2 kg/m^2, $P = 0.560$). Almost half the patients had diabetes mellitus (n = 18, 47.4%). CCI was not different between the two groups. The most common cause of ICU admission was pneumonia (n = 18, 47.4%) (Table 2). Four patients (10.5%) were admitted to the ICU due to sepsis without pneumonia.

3.2. Clinical factors associated with acute cholecystitis

The median interval from ICU admission to diagnosis of AC was 11.0 days (IQR = 4.8–22.8 days) (Table 3). AAC was diagnosed 14 days (IQR = 3.5–21.5 days) after ICU admission, while ACC was diagnosed 10 days (IQR = 6.0–29.0 days) after ICU admission. One-third of the patients were diagnosed with AC by abdominal ultrasonography.

Seventy-six percent of patients were mechanically ventilated before the AC diagnosis. The median fasting period before the diagnosis of AC was 5.5 days (IQR = 2.0–11.3 days). TPN was used in 89.5% of patients. Proportion of patients with serum albumin <3.5 mg/dL, which is an indicator of poor nutrition, was 86.8%.

Table 1
Baseline characteristics.

Variables	Total (n = 38)	Acalculous (n = 17)	Calculous (n = 21)	*P*-value
Age, years	73.3 [63.0–81.0]	73.4 [58.2–79.5]	69.0 [62.6–81.0]	0.977
Sex, male	22 (57.9)	10 (58.8)	12 (57.1)	1.000
Height, cm	161.5 [155.0–167.3]	160.0 [154.0–169.0]	163.0 [155.0–166.0]	0.617
Weight, kg	60.0 [53.5–68.5]	61.5 [50.5–66.8]	60.0 [58.0–70.0]	0.690
BMI, kg/m^2	23.0 [21.0–26.7]	22.2 [20.8–27.0]	24.2 [21.6–26.7]	0.560
CCI	4.0 [2.8–5.0]	4.0 [2.0–5.5]	4.0 [3.0–5.0]	0.743
Hypertension	25 (65.8)	13 (76.5)	12 (57.1)	0.212
Diabetes mellitus	18 (47.4)	7 (41.2)	11 (52.4)	0.492
Chronic kidney disease	2 (5.3)	1 (5.9)	1 (4.8)	1.000
Haemodialysis	1 (2.6)	1 (5.9)	0 (0)	0.447
Coronary artery disease	9 (23.7)	6 (35.3)	3 (14.3)	0.249
Heart failure	3 (7.9)	1 (5.9)	2 (9.5)	1.000
Atrial fibrillation	2 (5.3)	0 (0)	2 (9.5)	0.492
Cerebrovascular disease	5 (13.2)	2 (11.8)	3 (14.3)	1.000
Chronic obstructive airway disease	3 (7.9)	0 (0)	3 (14.3)	0.238
Cause of hospitalisation				0.384
Pneumonia	11 (28.9)	5 (29.4)	6 (28.6)	
Stroke	10 (26.3)	5 (29.4)	5 (23.8)	
Haemorrhagic	9 (23.7)	5 (29.4)	4 (19.0)	
Ischaemic	1 (2.6)	0 (0)	1 (4.8)	
Infection other than pneumonia	6 (15.6)	2 (11.8)	4 (19.0)	
Cardiovascular disease	4 (10.5)	2 (11.8)	2 (9.5)	
Fracture	2 (5.3)	2 (11.8)	0 (0)	
Acute kidney failure	1 (2.6)	0 (0)	1 (4.8)	
Acute myeloid leukaemia	1 (2.6)	1 (5.9)	0 (0)	
Chronic respiratory failure	1 (2.6)	0 (0)	1 (4.8)	
HHS	1 (2.6)	0 (0)	1 (4.8)	
Seizure	1 (2.6)	0 (0)	1 (4.8)	

BMI = body mass index; CCI = Charlson's comorbidity index; COPD = chronic obstructive pulmonary disease; HHS = hyperglycaemic hyperosmolar state.
Data are presented as n (%) or median [interquartile range].

Table 2
Cause of ICU admission.

Causes	Total (n = 38)	Acalculous (n = 17)	Calculous (n = 21)
Pneumonia	18 (47.4)	7 (41.2)	11 (52.4)
Stroke	11 (28.9)	6 (35.3)	5 (23.8)
Haemorrhagic	10 (26.3)	6 (35.3)	4 (19.0)
Ischaemic	1 (2.6)	0 (0)	1 (4.8)
Sepsis[a]	4 (10.5)	2 (11.8)	2 (9.5)
ARDS	2 (5.3)	1 (5.9)	1 (4.8)
HHS	1 (2.6)	0 (0)	1 (4.8)
Ischaemic heart disease	1 (2.6)	1 (5.9)	0 (0)
Seizure	1 (2.6)	0 (0)	1 (4.8)

ICU = intensive care unit; ARDS = acute respiratory distress syndrome; HHS = hyperglycaemic hyperosmolar state.
Data are presented as n (%) or median [interquartile range].
[a] Due to any cause except pneumonia.

Proportion of patients using opioid was 68.4%. Proportion of patients using morphine was higher in patients with ACC than in those with AAC, although the difference was not statistically significant (29.4% vs. 4.8%, $P = 0.071$). Vasoactive drugs were administrated in 42.1% of patients before diagnosis of AC. Almost two-thirds of patients required red blood cell transfusions before diagnosis of AC.

3.3. Treatment modality and outcomes

Thirteen patients (34.2%) underwent cholecystectomy, and seven (18.4%) were treated with PTGBD followed by cholecystectomy (Table 4). All surgically resected gallbladders had pathology results for cholecystitis (Table 5). Gangrenous cholecystitis was observed in five patients with ACC, and suppurative cholecystitis was observed in one patient with ACC. Another 13 patients (34.2%) underwent PTGBD only. Five (13.2%) patients underwent neither cholecystectomy nor PTGBD due to poor overall condition.

The mortality rate for patients diagnosed with AC was 42.1% (16 patients), and 1/3 (five patients) of these deaths were directly associated with uncontrolled sepsis due to AC. Of the 16 patients with AC who died, two (12.5%) underwent cholecystectomy and two (12.5%) received PTGBD followed by cholecystectomy; ten patients (62.5%) who died received only PTGBD, and two (12.5%) were treated with antibiotics alone. The average lengths of ICU stay and hospital stay were 26.5 (IQR = 1.45–48.5 days) and 44.5 days (IQR = 29.0–90.0 days), respectively. There were no significant differences between AAC and ACC.

4. Discussion

We evaluated newly developed AC in the ICU and demonstrated that AC developed approximately 10 days after ICU admission in critically ill patients. Most of the patients had pneumonia or other infection. Prolonged fasting and TPN, prior opioid or prior vasoactive drugs, and mechanical ventilation were frequently observed in

Table 3
Clinical factors associated with acute cholecystitis.

Variables	Total (n = 38)	Acalculous (n = 17)	Calculous (n = 21)	*P*-value
Radiological methods for diagnosis				0.796
Abdominal sonography	12 (31.6)	5 (29.4)	7 (33.3)	
Computed tomography	26 (68.4)	12 (70.6)	14 (66.7)	
Interval from hospitalisation to diagnosis	16.5 [6.0–26.3]	14.0 [5.0–22.5]	17 [9.5–37.5]	0.370
Interval from ICU admission to diagnosis	11.0 [4.8–22.8]	14.0 [3.5–21.5]	10.0 [6.0–29.0]	0.691
Mechanical ventilation[a]	29 (76.3)	13 (76.5)	16 (76.2)	1.000
Fasting duration, days[a]	5.5 [2.0–11.3]	5.0 [2.5–13.5]	6.0 [2.0–11.0]	0.941
TPN[a]	34 (89.5)	14 (82.4)	20 (95.2)	0.307
TPN, used days	6.0 [2.0–13.75]	4.0 [2.0–11.5]	7.0 [2.5–16.0]	0.393
Serum albumin <3.5 mg/dL	33 (86.8)	14 (82.4)	19 (90.5)	0.640
Opioids[a]	26 (68.4)	13 (76.5)	13 (61.9)	0.337
Days used	2.5 [0–8.0]	3.0 [1.0–17.0]	2.0 [0–7.0]	0.262
IV tramadol	17 (44.7)	8 (47.1)	9 (42.9)	0.796
IV morphine	6 (15.8)	5 (29.4)	1 (4.8)	0.071
Transdermal fentanyl	7 (18.4)	4 (23.5)	3 (14.3)	0.678
IV fentanyl	1 (2.6)	1 (5.9)	0 (0)	0.447
IV pethidine	2 (5.3)	2 (11.8)	0 (0)	0.193
IV remifentanil	5 (13.2)	1 (5.9)	4 (19.4)	0.355
Vasoactive drugs[a,b]	16 (42.1)	7 (41.2)	9 (42.9)	0.917
RBC transfusion[a]	25 (62.8)	12 (70.6)	13 (61.9)	0.575
Amount of RBC, pint	0 [0–3.5]	0 [0–4.5]	0 [0–3.5]	0.629
Antibiotics[a]				
Ceftriaxone	18 (47.4)	9 (52.9)	9 (42.9)	0.536
Piperacillin/tazobactam	21 (55.3)	11 (64.7)	10 (47.6)	0.292
Other beta-lactam	6 (15.8)	3 (17.6)	3 (14.3)	1.000
Carbapenem	13 (34.2)	5 (29.4)	8 (38.1)	0.575
Quinolone	14 (36.8)	6 (35.3)	8 (38.1)	0.859
Aminoglycoside	2 (5.3)	2 (11.8)	0 (0)	0.106
Vancomycin	10 (26.3)	7 (42.1)	3 (14.3)	0.078
Teicoplanin	11 (28.9)	5 (29.4)	6 (28.6)	1.000
Clindamycin	7 (18.4)	5 (29.4)	2 (9.5)	0.207
Metronidazole	3 (7.9)	1 (5.9)	2 (9.5)	1.000
Tigecycline	3 (7.9)	2 (11.8)	1 (4.8)	0.577
Colistin	6 (15.8)	4 (23.5)	2 (9.5)	0.378

AC = acute cholecystitis; ICU = intensive critical care unit; IV = intravenous; MV = mechanical ventilation; RBC = red blood cell; TPN = total parenteral nutrition.
Data are presented as n (%) or median [interquartile range].
[a] Before diagnosis of acute cholecystitis.
[b] Norepinephrine, dopamine, or vasopressin.

Table 4
Outcomes.

Outcomes	Total (n = 38)	Acalculous (n = 17)	Calculous (n = 21)	*P*-value
Treatment				0.584
Cholecystectomy	13 (34.2)	4 (23.5)	9 (42.9)	
PTGBD	13 (34.2)	6 (35.3)	7 (33.3)	
PTGBD followed by cholecystectomy	7 (18.4)	4 (23.5)	3 (14.3)	
Antibiotics only	5 (13.2)	3 (17.6)	2 (9.5)	
Mortality	16 (42.1)	7 (41.2)	9 (42.9)	1.000
Directly associated with AC	5 (31.3)	1 (14.3)	4 (44.4)	0.308
Indirectly associated with AC	11 (68.8)	6 (85.7)	5 (55.6)	
Length of ICU stay, days	26.5 [14.5–48.5]	27.0 [14.0–47.5]	26.0 [16.0–51.0]	0.816
Length of hospital stay, days	44.5 [29.0–90.0]	50.0 [28.0–84.5]	41.0 [30.0–90.0]	0.906

AC = acute cholecystitis; PTGBD = percutaneous gallbladder drainage; ICU = intensive care unit.
Data are presented as n (%) or median [interquartile range].

Table 5
Pathological findings of patients who underwent cholecystectomy.

Pathological findings	Total (n = 20)	Acalculous (n = 8)	Calculous (n = 12)	*P*-value
Acute cholecystitis	13 (65.0)	7 (87.5)	6 (50.0)	0.088
Gangrenous cholecystitis	5 (25.0)	0 (0)	5 (41.7)	
Suppurative cholecystitis	1 (5.0)	0 (0)	1 (8.3)	
Xanthogranulomatous cholecystitis	1 (5.0)	1 (12.5)	0 (0)	

patients who developed AC in the ICU. Additionally, half of AC patients had gallstones, and the clinical features of ACC in the ICU were similar to those of AAC.

A few studies have reported the clinical characteristics of AC in the ICU in selected patient groups, such as those with cardiovascular surgery, trauma, or burns.[4–6] Laurila et al.[10,11] reported operatively confirmed AAC was associated with severe illness, infection, long ICU stay, and multiple organ failure. Infection was the most common admission diagnosis in patients with operatively confirmed AAC.[10] In our study, pneumonia and sepsis accounted for more than half of ICU admissions. Gallbladder ischaemia can be secondary to shock from hypovolaemia or sepsis.[17] Additionally, sepsis and infection are most frequently linked to cholestasis, particularly in the ICU.[18,19] The pathophysiology of cholestasis in sepsis and severe bacterial infections is cytokine-mediated cholestasis resulting from reaction to bacterial endotoxins.[18] Pneumonia is one of the systemic causes of cholestasis.[19] In patients with pneumonia, liver biopsies showed patchy necrosis and dilated biliary canaliculi with bilirubinostasis.[19] The response to systemic inflammation and subsequent release of inflammatory mediators also induced an inflammatory process in the gallbladder.[20] Therefore, cholestasis, gallbladder ischaemia, and systemic inflammation caused by pneumonia or sepsis could affect the development of AC in ICU patients.

Interestingly, the median CCI of our patients was four, and in-hospital mortality rate of patients with this value is known to be 5.7-16.4%.[21] However, the mortality rate for our patients was 42.1%. These results suggest that AC leads to increased mortality in critically ill patients. Additionally, the interval from ICU admission to diagnosis of AC was 11 days in our study. Considering the average length of ICU stay was 7.72 days in our hospital during the study period, length of ICU stay of patients who developed AC was longer than that of other patients. This might reflect the severity of patients who develop AC in the ICU. Long ICU stay might be a result of development of AC, as well as a risk factor for AC. AC was associated with prolonged intensive care.[10] Laurila et al.[10] reported that the mean length of stay in the ICU before cholecystectomy was 8 days in patients with operatively confirmed AAC in the ICU.[10] In patients who underwent cardiovascular surgery, AC was diagnosed a median of 26 days after cardiovascular surgery (interquartile range, 11–41 days).[4] In trauma patients, the first ultrasonographic diagnosis of AAC was made after 13.2 days.[6] Patients with prolonged ICU stay could have greater risk of AC, such as TPN, opioids, vasoactive drugs, or mechanical ventilation. Therefore, if the patient has an infection and has been in the intensive care unit for more than one week, careful observation is needed to monitor for new development of AC.

In general, newly developed AC in critically ill patients was thought to be AAC. Most previous studies in critically ill patients assessed only for AAC. However, gallstones are common, with a prevalence of 10–15% in white adults[22]; intermediate prevalence rates occur in Asian populations and black Americans (13.9% of women; 5.3% of men).[23] Therefore, ACC could develop in critically ill patients. Rezende-Neto et al.[7] reported that approximately 50% of all cases of AC in postoperative patients in the ICU are acalculous. We found that more than half of patients who were diagnosed with AC after ICU admission had gallstones, which was compatible with a previous report.

A previous study reported that AAC is largely a manifestation of systemic critical illness, whereas ACC is a local disease of the gallbladder.[24] Gu et al.[25] reported that incidence of gangrenous cholecystitis was higher in AAC compared to ACC. On the other hand, gangrenous cholecystitis occurred in ACC patients in our study. The extent of gallbladder inflammation seems to depend on the duration of symptoms. In ICU patients, early diagnosis is difficult for both AAC and ACC due to their non-specific presentation. Additionally, ACC might share a pathogenesis with AAC. Gallstone might not be the only triggering factor of ACC in ICU patients. Gallbladder ischaemia and bile stasis could also affect development of ACC. Therefore, similar clinical features and outcomes were observed between AAC and ACC. Interestingly, the interval from ICU admission to diagnosis was shorter in patients with ACC than in those with AAC. Gallstones might be an aggravating factor for the development of AC in critically ill patients.

Ultrasound, a non-invasive and safe method, can be useful in the early diagnosis of AC. It has high sensitivity and specificity of more than 90%[26] and is readily usable in the ICU. One-third of our patients were diagnosed with AC via abdominal ultrasonography. Use of ultrasound in the ICU has increased, as this is useful for diagnosis of infections including AC in the ICU and affects treatment plans.[27] Lichtenstein et al.[28] suggested that routine ultrasound examination at the bedside can alter therapeutic plans in up to one-quarter of patients admitted to the ICU. A previous small prospective study demonstrated that routine and regular sonographic examination of the gallbladder in ICU patients facilitated the diagnosis of AC and guided prompt surgical treatment in 3 of 53 patients.[29] Additionally, ultrasound examination revealed a high prevalence of unsuspected clinical abnormalities, with the highest number of new ultrasound abnormalities detected in patients with septic shock.[30] However, there might be concern about the sensitivity and specificity of ultrasound because both depend on the operator. Clinical information should be combined with sonographic findings. Hwang et al.[31] reported that a higher rate of accurate diagnosis can be achieved using a triad of positive Murphy sign, elevated neutrophil count, and an ultrasound image showing cholelithiasis or cholecystitis. Therefore, in ICU, routine ultrasound might be more valuable in patients with risk factors of AC such as prolonged fasting, TPN, opioid use, or vasoactive drugs. It might also be more helpful to find and monitor patients with gallstone on baseline ultrasound in selected patients of ICU who had risk factors of AC. However, although sonographic examination of the gallbladder might contribute to early diagnosis of AC, the evidence is still lacking for routine sonographic evaluation of the gallbladder in critically ill patients. Further studies will be needed.

There are several limitations to our study. This study was a retrospective study in a single centre, so it could not reflect all critically ill patients in various hospital settings. Second, there might be concern regarding misdiagnosis of AC. Because some patients in our study did not have an operation or PTGBD and instead were treated with antibiotics, it is possible that the focus of infection was incorrect. However, all cases of AC in our study were confirmed based on compatible findings of imaging studies and the opinion of board-certified gastroenterologists or general surgeons. Third, diagnosis of AC could have been missed. Clinical suspicion is important to diagnose AC in the ICU. If the doctor did not suspect AC, the diagnosis might have been missed. Therefore, prevalence of AC could be underestimated in our study. Last, because only a small number of patients were included in our study, the statistical power was low.

5. Conclusion

AC was associated with high mortality and morbidity in critically ill patients. The development of AC in the ICU should be carefully monitored, especially in patients who have been infected and admitted to the ICU for more than 10 days. If prolonged fasting and TPN, opioid use, vasoactive drug use, or mechanical ventilation are observed in such patients, a high degree of suspicion is needed for timely diagnosis of AC when any abdominal pain, unexplained fever, or haemodynamic instability is observed. Regular ultrasound

at bedside might be helpful in some selected patients. Further studies to identify the characteristics and risk factors of AC in critically ill patients are needed.

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Authors' contributions

YJR contributed to the study conception and design, provided oversight of the studies and analysis of the data, and was responsible for the drafting, review, and final approval of the manuscript. SJK contributed to the study conception and design; the acquisition, analysis and interpretation of data from patients; and drafting, review, and approval of the manuscript. SJL, SHL, JHL, and JHC contributed to the study design, acquisition and analysis of data, revising contents, and approval of the manuscript. All authors read and approved the final manuscript.

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