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REVIEW ARTICLE

Acute acalculous cholecystitis as a rare gastroenterological association of COVID-19: a case series and systematic review

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ABSTRACT

Background and Aim: Acute acalculous cholecystitis (AAC) is an acute inflammatory disease of the gallbladder in the absence of cholecystolithiasis. It is a serious clinicopathologic entity, with a high mortality rate of 30–50%. A number of etiologies have been identified that can potentially trigger AAC. However, clinical evidence on its occurrence following COVID-19 remains scarce. We aim to evaluate the association between COVID-19 and AAC.

Methods: We report our clinical experience based on 3 patients who were diagnosed with AAC secondary to COVID-19. A systematic review of the MEDLINE, Google Scholar, Scopus, and Embase databases was conducted for English-only studies. The latest search date was December 20, 2022. Specific search terms were used regarding AAC and COVID-19, with all associated permutations. Articles that fulfilled the inclusion criteria were screened, and 23 studies were selected for a quantitative analysis.

Results: A total of 31 case reports (level of clinical evidence: IV) of AAC related to COVID-19 were included. The mean age of patients was 64.7 ± 14.8 years, with a male-to-female ratio of 2.1:1. Major clinical presentations included fever 18 (58.0%), abdominal pain 16 (51.6%), and cough 6 (19.3%). Hypertension 17 (54.8%), diabetes mellitus 5 (16.1%), and cardiac disease 5 (16.1%) were among the common comorbid conditions. COVID-19 pneumonia was encountered before, after, or concurrently with AAC in 17 (54.8%), 10 (32.2%), and 4 (12.9%) patients, respectively. Coagulopathy was noted in 9 (29.0%) patients. Imaging studies for AAC included computed tomography scan and ultrasonography in 21 (67.7%) and 8 (25.8%) cases, respectively. Based on the Tokyo Guidelines 2018 criteria for severity, 22 (70.9%) had grade II and 9 (29.0%) patients had grade I cholecystitis. Treatment included surgical intervention in 17 (54.8%), conservative management alone in 8 (25.8%), and percutaneous transhepatic gallbladder drainage in 6 (19.3%) patients. Clinical recovery was achieved in 29 (93.5%) patients. Gallbladder perforation was encountered as a sequela in 4 (12.9%) patients. The mortality rate in patients with AAC following COVID-19 was 6.5%.

Conclusions: We report AAC as an uncommon but important gastroenterological complication following COVID-19. Clinicians should remain vigilant for COVID-19 as a possible trigger of AAC. Early diagnosis and appropriate treatment can potentially save patients from morbidity and mortality.

Relevance for Patients: AAC can occur in association with COVID-19. If left undiagnosed, it may adversely impact the clinical course and outcomes of patients. Therefore, it should be considered among the differential diagnoses of the right upper abdominal pain in these patients. Gangrenous cholecystitis can often be encountered in this setting, necessitating an aggressive treatment approach. Our results point out the clinical importance of raising awareness about this biliary complication of COVID-19, which will aid in early diagnosis and appropriate clinical management.

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1. Introduction

Acute acalculous cholecystitis (AAC) was first reported by Dr. Duncan in 1844 [1]. It is characterized by an acute inflammatory disease of the gallbladder in the absence of cholecystolithiasis and cystic duct obstruction [2]. It is a relatively uncommon entity, accounting for approximately 2–15% of all cases of acute cholecystitis [2]. However, it is a serious illness with an estimated mortality rate ranging from 30% to 50% [2,3]. AAC is often encountered in trauma centers in patients undergoing post-operative recovery and among critically ill individuals admitted to intensive care units [2-4]. It continues to remain an elusive diagnosis due to its predominant occurrence in the aforementioned settings and the limited available clinical evidence [5]. While a number of serious complications of AAC have been described, gangrenous cholecystitis remains the most common problem [5]. It has been reported in 2–30% of patients who are diagnosed with acute cholecystitis [6]. The gangrene often affects the fundus part of the gallbladder, which may lead to perforation [7]. As AAC is a life-threatening disease, heightened clinical vigilance is imperative for the early diagnosis. Therefore, knowledge of the newer clinical associations of AAC can play a critical role in its early detection.

The world has been devastated by the coronavirus disease-19 (COVID-19) pandemic. It was caused by the rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the World Health Organization data as of December 23, 2022, over 651 million confirmed cases have been reported, with more than 6.6 million deaths worldwide [8]. The etiopathogenesis of COVID-19 implicates the viral entry into the host cells by binding of the SARS-CoV-2 spike protein to the angiotensin-converting enzyme-2 (ACE-2) receptors located on the cell surface [9]. In addition to other body locations, these receptors are abundantly expressed on the alveolar cells of the lungs and the epithelial cells of the gastrointestinal tract [9]. Consequently, it can result in a variety of gastrointestinal manifestations [10]. In a prospective, controlled multinational GI-COVID-19 study, Marasco *et al.* revealed that gastrointestinal symptoms were encountered more often in hospitalized patients with COVID-19 (59.7%; 343/575 patients) compared to the control group (43.2%; 128/296 patients) ($P < 0.001$) [11]. In a meta-analysis of 25,252 cohorts regarding gastroenterology manifestations and COVID-19 outcomes, major gastrointestinal manifestations included anorexia (19.9%), dysgeusia or ageusia (15.4%), diarrhea (13.2%), nausea (10.3%), and hematemesis (9.1%) [12]. Atypical gastrointestinal involvement in certain medical conditions often poses a diagnostic and therapeutic challenge [13,14]. Therefore, community awareness about the atypical gastroenterological associations of COVID-19 may also have paramount clinical importance. While COVID-19 has previously been reported as a possible infectious etiology of AAC, no organized data is available on this association. We, hereby, delineate our clinical experience on 3 patients with AAC and COVID-19. Furthermore, we present the findings of a comprehensive systematic review on this topic. This article serves the purpose of raising awareness for this important biliary complication of COVID-19 that can aid clinicians and gastroenterologists in the early diagnosis and treatment.

2. Case Series

2.1. Case 1

A 35-year-old male presented to our medical center with the right upper quadrant abdominal pain and non-biliary vomiting. His medical and surgical histories were unremarkable. He denied smoking, alcohol consumption, and illicit drug use. On admission, he was hemodynamically stable, with an oxygen saturation of 99% on room air. Clinical examination revealed a positive Murphy's sign. Laboratory evaluation was significant for an elevated white blood cell count and a high serum level of C-reactive protein. Abdominal ultrasound revealed significant thickening of the gallbladder wall and a normal common bile duct, with no cholelithiasis or sludge formation. A nuclear medicine hepatobiliary iminodiacetic acid (HIDA) scan showed hepatic uptake and excretion of radiotracer into intra- and extra-hepatic biliary channels and the bowel, but no radiotracer uptake was evident in the gallbladder. These radiological findings were consistent with AAC. According to the Tokyo Guidelines 2018 criteria for severity, it was grade I cholecystitis [15].

Six hours after admission, the patient started to experience a new-onset cough, fever, and mild dyspnea. Given the suspicion of COVID-19, he underwent a chest computed tomography (CT). It showed bilateral patchy peripheral ground-glass opacities in the lungs, indicating COVID-19. He then underwent coronavirus testing using quantitative reverse transcription polymerase chain reaction (qRT-PCR) through nasopharyngeal swab, which turned out to be positive. Close family members and coworkers were informed about the COVID-19 diagnosis. They were advised on appropriate measures to limit the spread of the disease. Based on the findings of the diagnostic workup and the exclusion of probable causes of AAC, cholecystitis was likely triggered by COVID-19. The negative blood and urine cultures and negative workup results for viral etiologies such as cytomegalovirus further supported our diagnosis. The patient was treated with dexamethasone, vitamin supplements, fluid resuscitation, antipyretics, pain medications, and bowel rest. His oxygen saturation was regularly monitored. It did not show a significant decline. On day 7 of admission, his abdominal pain, vomiting, and fever showed marked improvement. He did not require surgical intervention for AAC. He was discharged home in a stable condition after a 9-day hospital stay. At the follow-up visit after 2 months, the patient showed complete clinical recovery.

2.2. Case 2

A 41-year-old female presented to the emergency department with the right upper quadrant pain for 4 days. The pain was severe in intensity, dull in nature, and aggravated with meals, mobility, and deep breathing. It started gradually but worsened over the next 3 days. It was associated with several episodes of nausea and vomiting. She denied other complaints such as chest pain, extremity edema, hemoptysis, or jaundice. She was previously

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healthy, with no prior medical conditions. She had no history of alcoholism, smoking, or illicit drug use. Her vital signs included: blood pressure of 135/83 mmHg, body temperature of 99.7°F, heart rate of 79 beats/min, respiratory rate of 17 breaths/min, and an oxygen saturation of 94% on room air. Physical examination revealed severe tenderness in the right upper quadrant with normal bowel sounds. Murphy's sign was positive. Abdominal ultrasonography was remarkable for a thickened gallbladder wall with pericholecystic fluid collection and no evidence of gallstones (Figure 1). The HIDA scan revealed homogeneous hepatic radiotracer uptake along with excretion into the biliary channels and bowel without gallbladder visualization. These findings were consistent with AAC. According to the Tokyo Guidelines 2018, it was grade I cholecystitis [15].

She also experienced symptoms of low-grade fever, a dry cough, and mild shortness of breath within 24 h of hospital admission. The coronavirus testing using qRT-PCR turned out to be positive. A CT scan of the chest confirmed viral pneumonia (Figures 2 and 3). The blood and urine cultures were negative for any growth. The results of diagnostic testing for all infectious causes, including cytomegalovirus, were negative. She was then transferred to the COVID-19 department. Contact tracing and education were conducted as per local recommendations. The patient was advised on prone positioning. Supplemental oxygen administration was started, and saturation was maintained at >94%. Regular monitoring of saturation was performed, but it did not decline to <90%. She was given 3 L of normal saline daily under cautious monitoring for pulmonary edema. Moreover, dexamethasone 6 mg once daily, remedesvir 200 mg on day 1 and 100 mg subsequently till day 5, intravenous paracetamol 1 g every 8 h, and prophylactic subcutaneous enoxaparin 40 mg once daily were administered. A surgical team was consulted for the management of AAC. An empiric antibiotic treatment was added on their recommendation. After 3 days of admission, the patient showed significant improvement with a diminution of her symptoms. She was started on oral fluids, which were subsequently advanced to semisolid and solid diets. She tolerated the solid diet well, with no recurrence of gastrointestinal symptoms. Her fever and shortness of breath were resolved. She was educated about her disease as a rare complication of COVID-19. She was then discharged from the hospital in stable condition. The patient did not report a recurrence of her symptoms at the outpatient follow-up visits.

2.3. Case 3

A previously healthy 24-year-old male presented to our medical center with the right upper abdominal pain and a low-grade fever for 2 days. The pain was moderate in intensity, dull in nature, and radiated to the right shoulder. The patient occasionally consumed alcohol, but his last intake was 1 week before his current presentation. He was a non-smoker and never used illicit drugs. He had no history of pre-existing gastrointestinal or cardiopulmonary disorders. Family history was negative for gallbladder disease and cancer. His vital signs were as follows: 100.1°F body temperature,

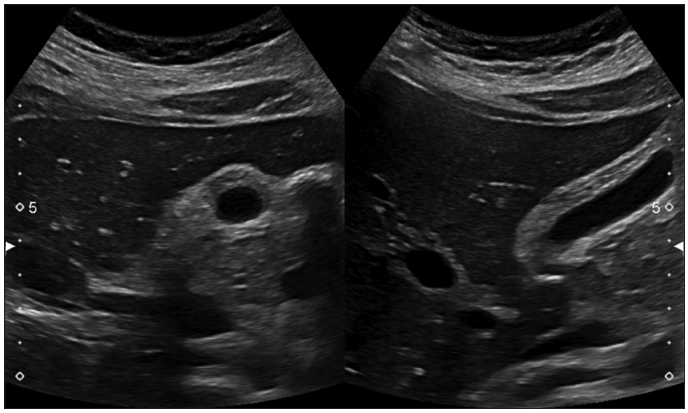

Figure 1. Abdominal ultrasound. Transverse and longitudinal sections using a curvilinear transducer demonstrate significant and diffuse echogenic gallbladder wall thickness along with edematous changes. No shadowing of gall bladder calculus or echogenic sludge was noted.

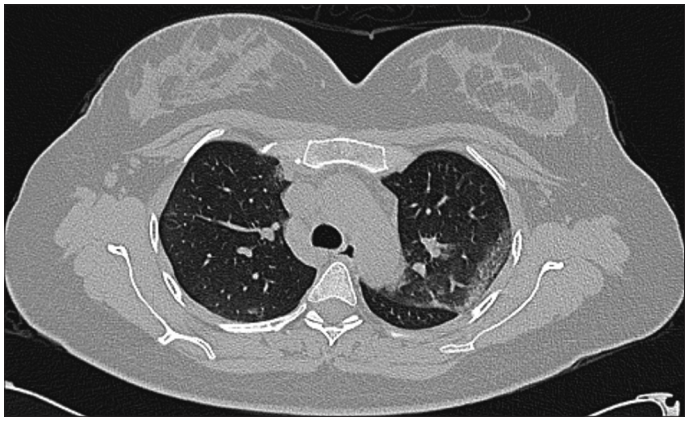

Figure 2. Chest computed tomography. An axial section through the upper lung (lung window) shows left upper lobe peripheral ground glass opacifications along with subtle intralobular septal lines.

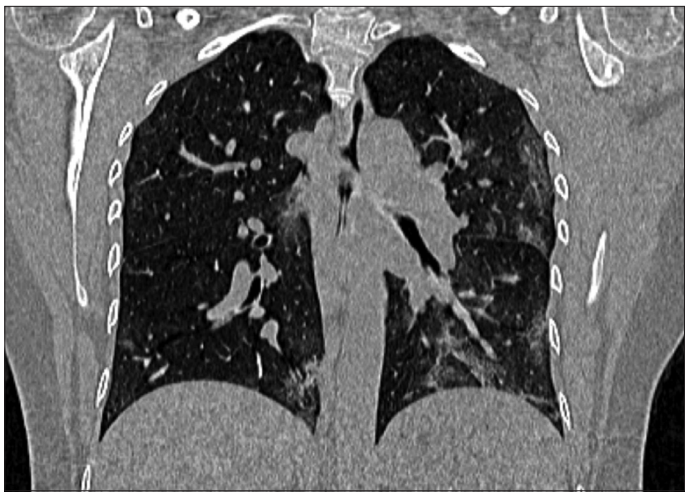

Figure 3. Chest computed tomography. A coronal section through the lung (lung window) shows bilateral multifocal peripheral and subpleural ground glass opacifications, which are more pronounced on the left side.

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108/74 mmHg blood pressure, 102 beats/min heart rate, and 16 breaths/min respiratory rate. Physical examination revealed mild-to-moderate tenderness in the right upper quadrant of the abdomen. His Murphy's sign was positive. Laboratory evaluation was remarkable for elevated levels of white cell count and C-reactive protein. Abdominal ultrasonography revealed a marked thickening of the wall of the gallbladder and pericholecystic fluid collection, with no evidence of stones or sludge in the gallbladder fossa **(**Figure 4**)**. The HIDA scan demonstrated hepatic uptake, and radiotracer was seen in biliary channels and bowel loops, but there was no visualization of the gallbladder. On the basis of these findings, the diagnosis of AAC was confirmed. The severity grading was performed using the Tokyo Guidelines 2018, and it was considered grade I cholecystitis [15].

Due to suspicion of COVID-19, the patient underwent a CT scan of the chest. It revealed bilateral patchy peripheral and subpleural ground-glass opacities in the lungs **(**Figure 5**)**. His coronavirus testing with qRT-PCR on a specimen obtained through nasopharyngeal swab came back positive. Family members were immediately informed of the possible exposure. The blood and urine cultures and standard testing for infectious causes, including cytomegalovirus, were negative. After ruling out other possible causes of AAC, COVID-19 was identified as a plausible etiology. The patient was administered 3 L of normal saline daily, intravenous paracetamol 1 g every 8 h, oral fexofenadine 120 mg/day, and prophylactic subcutaneous enoxaparin 40 mg once daily. In addition to the standard treatment of COVID-19 and resuscitation for AAC, the general surgery team recommended the initiation of intravenous meropenem 500 mg twice daily and azithromycin 500 mg daily. His clinical condition was closely monitored for possible deterioration. On day 7 of admission, his symptoms were significantly improved, and his biochemical profile became normal. Subsequently, he was discharged from the hospital with telephonic follow-up instructions. He did not report a recurrence of the symptoms at the 1-week follow-up. To date, the patient has continued to do well without the need for surgery.

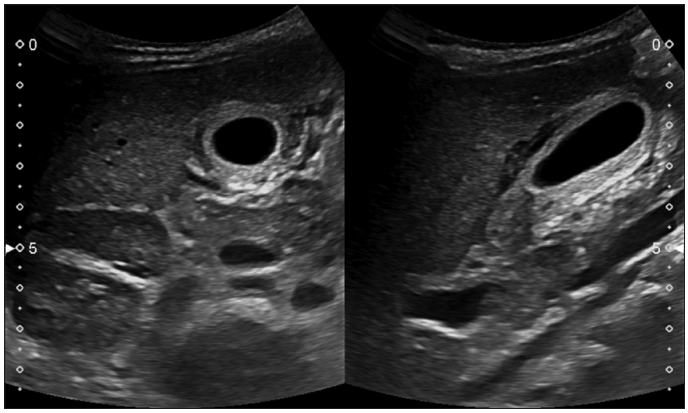

Figure 4. Ultrasound abdomen. Transverse and longitudinal sections using a curvilinear transducer reveal significant echogenic gallbladder wall thickness, especially in the body and fundus regions, along with hypoechoic pericholecystic edematous changes near the neck and proximal gallbladder body. No shadowing of gall bladder calculus or echogenic sludge was noted.

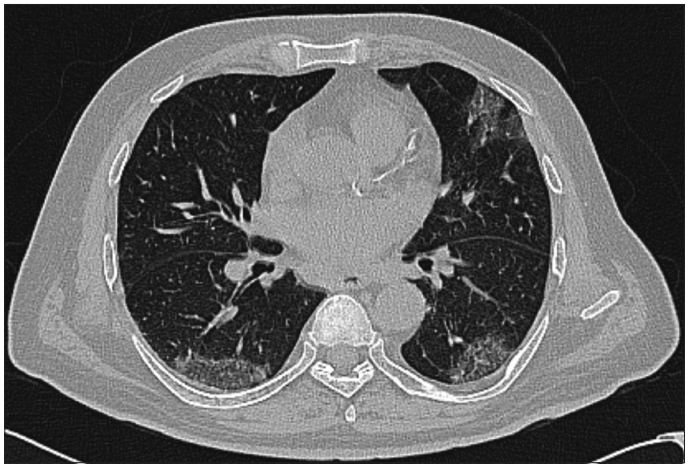

Figure 5. Chest computed tomography. An axial section through the lung (lung window) shows bilateral patchy peripheral and subpleural ground-glass opacifications along with subtle intralobular septal lines.

3. Methods

A systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. We queried multiple research databases, including MEDLINE (PubMed and Ovid), Google Scholar, Scopus, and Embase. The time filter was applied between inception and December 20, 2022. The language restriction was applied to English-only studies. A comprehensive search strategy was devised using specific terminologies. The search terms, including "AAC," "cholecystitis," "gallbladder," and "biliary," were combined using the Boolean operators "AND" and "OR" with the keywords "COVID-19," "SARS-CoV-2," "coronavirus," "extrapulmonary," and "complications," with all associated permutations. Only articles that involved adult human patients were considered for inclusion. AAC was characterized by 1) clinical features, laboratory studies, and imaging findings that fulfilled the Tokyo Guidelines 2018 diagnostic criteria for acute cholecystitis and 2) no cholelithiasis [15]. Exclusion criteria consisted of patients below 18 years of age, having a history or evidence of gallstone disease, the presence of concurrent pathologies responsible for AAC, or the absence of COVID-19.

Two authors screened search results for potentially relevant articles. They conducted an independent review of titles and abstracts collected by initial internet hits from databases. The initial review of databases yielded a total of 423 hits (PubMed and Ovid 187, Google Scholar 162, Scopus 54, and Embase 20). In addition, abstracts from major gastroenterology conferences, including the American College of Gastroenterology, Digestive Disease Week, and United European Gastroenterology Week were also screened. Subsequently, 2 authors conducted an independent screening of reference lists for all retrieved studies. For eligibility, full-text versions of the articles were accessed and meticulously reviewed by 2 of the authors. The eligibility disputes were resolved

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based on the mutual consensus of all the authors. Final inclusion into our comparative analysis was made based on the approval of the senior authors. A total of 23 articles fulfilled the inclusion criteria for AAC in the setting of COVID-19. The PRISMA flow diagram illustrates our systematic literature review and search methodology for data synthesis and extraction of results (Figure 6). Two authors independently verified the data after it was extracted into standardized Microsoft Excel sheets. The data points regarding patient demographic characteristics, clinical presentations, comorbidities, diagnostic imaging, coagulopathy, cholecystitis severity grading, treatment, and clinical outcomes were collected and outlined.

4. Results

A total of 31 case reports (level of clinical evidence: IV) of AAC in association with COVID-19 were included, dating from 2020 to 2022 [17-39]. The mean age of patients was 64.7 ± 14.8 years (range, 40 to 87 years). Interestingly, 25 (80.6%) patients were over 50 years of age. A clear male predominance was noted, with a male-to-female ratio of 2.1:1. Common clinical presentations included

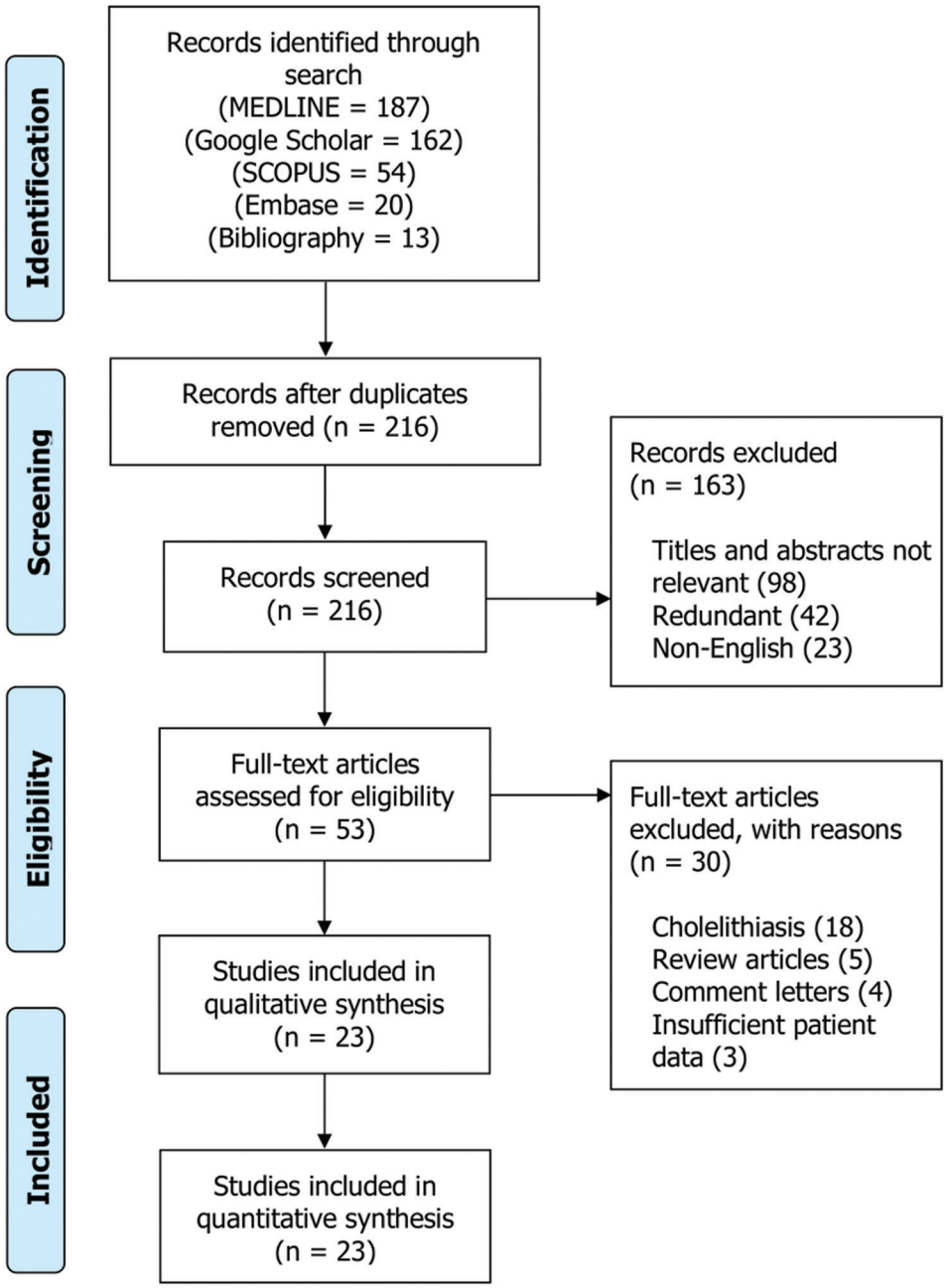

Figure 6. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the search methodology for data synthesis regarding acute acalculous cholecystitis secondary to COVID-19.

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Table 1. Clinical characteristics of patients diagnosed with acute acalculous cholecystitis secondary to COVID-19

Authors, year	Country	Age/ Gender	Clinical presentation	Comorbidity	Diagnostic abdominal imaging	Preceded by pneumonia	Coagulopathy	Grade	Basis for grade	Treatment intervention	Outcome, hospital stay
Alhassan *et al.*, 2020 [17]	Qatar	40/F	Fever, body aches, nausea, RH pain	Previously healthy	Ultrasound	Yes	Yes	I	Mild cholecystitis	Conservative	Recovered
Asti *et al.*, 2020 [18]	Italy	86/F	Acute abdomen	Not reported	CT	Yes	No	II	Gangrenous cholecystitis	Lap chole	Recovered
Asti *et al.*, 2020 [18]	Italy	72/F	Acute abdomen	Not reported	CT	Yes	No	II	Gangrenous cholecystitis	Lap chole	Recovered
Asti *et al.*, 2020 [18]	Italy	40/M	Acute abdomen	Not reported	CT	Yes	No	II	Gangrenous cholecystitis, fundal microperforation	Lap chole	Recovered
Balaphas *et al.*, 2020 [19]	Switzerland	84/F	UTI, fever	Not reported	CT	No	No	I	Mild cholecystitis	Lap chole	Died, multiorgan failure
Balaphas *et al.*, 2020 [19]	Switzerland	83/M	Fever	ESRD (dialysis), DM2, HTN, AS	Ultrasound	No	No	II	WBC >18000	Conservative	Recovered
Bruni *et al.*, 2020 [20]	Italy	59/M	Progressive respiratory symptoms, fever, sore throat	Overweight	Histological diagnosis	Yes	Not reported	II	WBC >18000, gangrenous Gallbladder perforation	Laparotomy	Recovered, 44 days
Cirillo *et al.*, 2020 [21]	Italy	79/M	Fever, cough, chest pain	Diabetes, HTN	CT	Yes	Yes	II	Perforation	Lap chole	Recovered
Hassani *et al.*, 2020 [22]	Iran	65/M	Abdominal pain, intermittent shaking chills	HTN, IHD sp CABG	EUS	No	No	I	Mild cholecystitis	Conservative	Recovered, 5 days
Lovece *et al.*, 2020 [23]	Italy	42/M	Acute dyspnea, fever	Overweight	CT	Synchronous/ coincident	No	I	Mild cholecystitis, fundal microperforation	Lap chole	Recovered, 5 days
Kabir *et al.*, 2020 [24]	Singapore	Middle-aged/M	Fever, productive cough	Previously healthy	CT	Yes	No	II	Gangrenous cholecystitis	Open chole	Recovered
Mattone *et al.*, 2020 [25]	Italy	66/M	Fever, cough, dyspnea	Ex-smoker	CT	Yes	No	II	Gangrenous cholecystitis	PTGBD, lap chole	Recovered, 58 days
Palmieri *et al.*, 2020 [26]	Colombia	67/M	Abdominal pain, nausea, malaise, myalgia, adynamia, fever	Not reported	CT	Synchronous	No	II	Thickened, friable, infiltrated walls, with necrotic areas	Open chole	Recovered, 6 days
Singh *et al.*, 2020 [27]	USA	66/M	Fever, cough, shortness of breath	ICM on HeartMate II, HTN, atrial flutter, ischemic stroke	Not reported	Synchronous	Yes	I	Mild cholecystitis	PTGBD	Recovered from AAC; overall clinical improvement

(Contd...)

Table 1. *(Continued)*

Authors, year	Country	Age/ Gender	Clinical presentation	Comorbidity	Diagnostic abdominal imaging	Preceded by pneumonia	Coagulopathy	Grade	Basis for grade	Treatment intervention	Outcome, hospital stay
Ying *et al*., 2020 [28]	China	68/F	Fever, chest stuffiness, diarrhea	Previously healthy	CT	Yes	No	II	Duration of complaints	PTGBD	Recovered, 25 days
Wahid *et al*., 2020 [29]	USA	60/F	Acute hypoxic respiratory failure	HTN, DM2, hypothyroidism	CT	Yes	No	II	WBC >18000	PTGBD	Recovered
Wahid *et al*., 2020 [29]	USA	68/M	Acute hypoxic respiratory failure	HTN, HLD, asthma, OSA	CT	Yes	No	II	WBC >18000	PTGBD	Recovered
Abaleka *et al*., 2021 [30]	USA	76/F	RUQ pain	AF, CHF on pacemaker, HTN, asthma	Ultrasound	Synchronous/ coincident	Yes	II	Pericholecystic abscess	Conservative	Recovered
Alam *et al*., 2021 [31]	Lebanon	84/F	Generalized abdominal pain, vomiting, diarrhea	Not reported	CT	No	Yes	II	Gangrenous cholecystitis	Conservative	Died, cardiopulmonary arrest
Riveria-Alfonso *et al*., 2021 [32]	Spain	51/M	RUQ pain, general discomfort, fever	Previously healthy	Abdominal CT	No	Yes	II	WBC >18000, left PVT, altered hepatic perfusion	Elective lap chole after 6 weeks	Recovered
Futagami *et al*., 2021 [33]	Japan	42/M	Fever, cough	Maintenance hemodialysis for renal failure	CT	Yes	Yes	II	WBC >18000	PTGBD, conservative treatment	Recovered, 30 days
Liapis *et al*., 2022 [34]	Greece	53/M	Epigastric pain, fever	Obesity	Ultrasound	Yes	Yes	II	Gangrenous cholecystitis	Lap chole	Recovered
Berdugo Hurtado *et al*., 2021 [35]	Canada	87/F	Fever, upper-abdominal pain	Not reported	Ultrasound	No	No	I	Mild acute cholecystitis	Conservative	Recovered, 8 days
Berdugo Hurtado *et al*., 2021 [35]	Canada	62/M	Fever, nausea, RUQ pain	Not reported	Ultrasound	No	No	I	Mild acute cholecystitis	Conservative	Recovered, 12 days
Puig *et al*., 2021 [36]	Spain	65/M	Fever, cough, dyspnea	HTN, allergy to aspirin and NSAIDs, ex-smoker	CT	Yes	Yes	I	Uncomplicated cholecystitis	PTGBD	Clinical improvement
Hajebi *et al*., 2022 [37]	Iran	86/F	Generalized abdominal pain, vomiting, loss of appetite, weight loss	HTN, appendectomy 20 years ago	CT	No	No	II	Gangrenous cholecystitis.	Open chole	Recovered
Hajebi *et al*., 2022 [37]	Iran	82/M	RUQ pain, vomiting	Previously healthy	Abdominal CT	No	No	II	Gangrenous and hemorrhagic cholecystitis	Open chole	Recovered
D'Introno *et al*., 2022 [38]	Italy	50/M	Generalized abdominal pain, low fever, nausea and vomiting	HTN, DM2	CT abdomen	No	No	II	Gangrenous gallbladder	Lap chole	Recovered

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Table 1. *(Continued)*

Authors, year	Country	Age/ Gender	Clinical presentation	Comorbidity	Diagnostic abdominal imaging	Preceded by pneumonia	Coagulopathy	Grade	Basis for grade	Treatment intervention	Outcome, hospital stay
Franch-Llasat *et al.*, 2022 [39]	Spain	73/M	ARDS	Not reported	Ultrasound	Yes	No	II	Gangrenous cholecystitis	Conservative	Recovered
Franch-Llasat *et al.*, 2022 [39]	Spain	42/M	ARDS	Not reported	CT abdomen	Yes	No	II	Gangrenous cholecystitis	Lap chole	Recovered
Franch-Llasat *et al.*, 2022 [39]	Spain	67/M	ARDS	Not reported	Ultrasound	Yes	No	I	Edematous gallbladder	Lap chole	Emergency reoperation for hemorrhagic shock secondary to cystic artery bleed then recovered

RH: Right hypochondrium; CT: Computed tomography; lap chole: Laparoscopic cholecystectomy; UTI: Urinary tract infection; ESRD: End-stage renal disease; DM: Diabetes mellitus, HTN: Hypertension; AS: Aortic stenosis; WBC: White blood cells; IHD: Ischemic heart disease; CABG: Coronary artery bypass graft; EUS: Endoscopic ultrasound; PTGBD: Percutaneous transhepatic gallbladder drainage; ICM: Ischemic cardiomyopathy; AAC: Acute acalculous cholecystitis; HLD: Hyperlipidemia; OSA: Obstructive sleep apnea; AF: Atrial fibrillation; CHF: Congestive heart failure; RUQ: Right upper quadrant; PVT: Portal vein thrombosis; NSAIDs: Non-steroidal anti-inflammatory drugs; ARDS: Acute respiratory distress syndrome.

fever 18 (58.0%), abdominal pain 16 (51.6%), cough 6 (19.3%), acute respiratory distress 5 (16.1%), nausea 4 (12.9%), and vomiting 4 (12.9%). Comorbid conditions were documented in 20 (64.5%) patients. Hypertension 17 (54.8%), diabetes mellitus 5 (16.1%), cardiac disease 5 (16.1%), end-stage renal disease 3 (9.6%), and smoking 3 (9.6%) were among the most commonly reported comorbidities. Notably, 8 (25.8%) patients had no underlying medical conditions at the time of admission. In our analysis of initial presentations, 17 (54.8%) patients had COVID-19 pneumonia before developing AAC, 10 (32.2%) presented as AAC before showing pulmonary symptoms of COVID-19, and 4 (12.9%) patients had concurrent presentations of pulmonary and biliary symptoms. A CT scan of the abdomen was the most frequently used abdominal imaging modality in 21 (67.7%), followed by ultrasonography in 8 (25.8%) patients. Endoscopic ultrasound was also used in 1 (3.2%) patient for AAC detection [22]. Based on the Tokyo Guidelines 2018 criteria for severity, grade II cholecystitis was identified in 22 (70.9%), whereas 9 (31.0%) patients had grade I disease [15]. In addition, it is important to note that 13 (41.9%) patients had gangrenous cholecystitis. At the time of AAC diagnosis, 9 (29.0%) patients had clinical, laboratory, or imaging evidence of coagulopathy.

Surgical intervention was performed in 17 (54.8%) patients as a primary therapeutic modality. Laparoscopic cholecystectomy was performed in 12 (38.7%), whereas open cholecystectomy was performed in 5 (16.1%) patients. Conservative treatment alone was employed in 8 (25.8%) patients. The procedure of percutaneous transhepatic gallbladder drainage was undertaken in 6 (19.3%) patients. Clinical outcomes were favorable in most cases, with 29 (93.5%) patients achieving clinical recovery from AAC. However, gallbladder perforation was encountered as a sequel in 4 (12.9%) patients, which was predominantly located in the fundus part. The mortality rate was 6.5% for COVID-19-associated AAC. The patients died following clinical deterioration due to multiorgan failure and cardiopulmonary arrest. A marked variation was noted regarding the length of hospitalizations, ranging from 5 to 58 days (Table 1).

5. Discussion

To the best of our knowledge, the present study represents the first case series and systematic review highlighting the occurrence of AAC in patients with COVID-19. This inconspicuous clinicopathologic entity often shows rapid progression. Therefore, a higher degree of clinical vigilance is needed to save patients from morbidity and mortality.

The precise pathophysiology of AAC in COVID-19 remains to be determined. Both direct and indirect mechanisms of injury have been studied in relation to coronaviruses. Direct injury is caused by the virus entering the target cells through ACE-2 receptors [9]. These receptors are present in various body organs, including the lungs, liver, gallbladder, biliary ducts, and vascular endothelium [9]. Therefore, the gallbladder can be a potential target organ for this family of viruses. The positive qRT-PCR testing of the bile after emergency cholecystectomy in 2 of these reported cases confirmed the presence of SARS-CoV-2 in the gallbladder [27,28]. Indirect injury, on the other hand, can result

from overshooting of immune responses, circulatory dysfunction in the form of microvascular thrombi and microvascular ischemia, and hypoxia [40,41]. It is suggested that the acute cytokine release syndrome caused by COVID-19 can be the pathogenic basis for AAC, presumably by increasing vascular permeability and causing a sustained increase in inflammatory cytokines such as interleukin 6 (IL-6), IL-8, and tumor necrosis factor (TNF)-alpha [42]. Alhassan *et al.* proposed systemic inflammation caused by a possible antibody complex-mediated reaction as the causal association between COVID-19-related cytokine release syndromes and AAC, especially in non-critically ill patients [17].

AAC frequently poses a diagnostic challenge due to a number of confounding factors. It is partially attributable to the lack of a specific set of clinical symptoms, clinical examination findings, and laboratory results [2,43]. Moreover, most patients are admitted to the ICU and often cannot express their symptoms while under sedation or in an unconscious state [2,43]. In our review of AAC in COVID-19 patients, non-specific clinical symptomatology (fever, nausea, and abdominal pain) and laboratory values (leukocytosis and elevated liver enzymes) were often observed. However, a high index of clinical suspicion and consistent imaging findings played a key role in detecting AAC. In our case series, the onset of COVID-19 symptoms was 6 and 24 h after hospital admission for AAC in Cases 1 and 2, respectively. In Case 3, the patient was concurrently diagnosed with both conditions. This pattern and duration of symptoms further support our notion that the AAC in these patients was a clinical presentation of an underlying COVID-19. Our subsequent inquiry also confirmed that all 3 patients had a positive history of family contact with COVID-19. These observations exclude the possibility of the COVID-19 infection being contracted during the same hospitalization. Furthermore, all patients in our case series had negative blood and urine cultures for any growth, making COVID-19 a plausible trigger for AAC.

To establish diagnosis, the Tokyo Guidelines 2018 diagnostic criteria recommend the use of abdominal ultrasonography, CT scan, and HIDA scan [15]. In our review, abdominal ultrasonography often helped with the diagnosis. It showed a markedly thickened, edematous gallbladder wall, and evidence of pericholecystic fluid but no stones in the gallbladder fossa. Similarly, a CT scan of the abdomen not only helped in the diagnosis of AAC but also ruled out probable abdominal pathologies. In this context, most of the diagnoses were confirmed after an abdominal CT scan. Notably, HIDA scan played a crucial role in diagnostic confirmation in our 3 patients. Our analysis of the temporal relationship between these 2 entities showed that a number of cases had pre-existing symptoms of COVID-19 pneumonia before the presentation of the AAC. However, patients may also present with AAC as the first presentation of COVID-19. In our case series, 2 of the 3 patients presented with ACC-related symptoms. Therefore, clinicians and gastroenterologists should be aware of this rare but important association. It is pertinent to suspect AAC in patients presenting with non-specific gastrointestinal or overlapping symptoms and signs, especially in outpatient departments. It warrants a gallbladder evaluation using appropriate imaging studies in the setting of COVID-19.

In terms of management, surgical societies across the globe have maintained laparoscopic cholecystectomy as the gold standard of treatment for acute cholecystitis during the COVID-19 pandemic [44]. However, some reports from China indicate poor surgical outcomes in asymptomatic COVID-19 patients [45]. It is imperative to start conservative treatment with proper antibiotics early in the course of the disease. As in our case series, there have been case reports of patients with AAC who were treated conservatively with antibiotics and had a good response. It highlights the importance of timely management for stable patients. It can prevent complications and unnecessary surgical intervention. However, complicated cases with gangrene, ischemia, or perforation require early, aggressive intervention. According to the Tokyo Guidelines 2018, percutaneous transhepatic cholecystostomy can also be a lifesaving alternative in critically ill or surgically high-risk patients after the failure of conservative therapy with antibiotics [46]. In our review, surgical intervention constituted the major therapeutic modality, including laparoscopic or open cholecystectomy. Conservative treatment alone and the procedure of percutaneous transhepatic gallbladder drainage were instituted in patients who either did not require or were unfit for surgery. Therefore, conservative treatment alone was mainly employed for grade I disease, while other interventions were used for grade II AAC. It is pertinent to note that standard diagnostic and therapeutic guidelines do not exist for this group of patients. Hence, clinicians can often face therapeutic conundrums while dealing with such clinical scenarios.

In our review, clinical outcomes were favorable in most patients. Early and appropriate therapeutic interventions commonly facilitated clinical recovery. While AAC frequently developed in critically ill patients with multiple comorbidities, COVID-19 severity did not predict clinical outcomes. Notably, there was a difference in the management of patients based on the symptom duration of AAC. In patients where AAC was diagnosed early, conservative management often helped to achieve complete recovery. However, in late-diagnosed patients, the disease had already progressed to gangrene of the gallbladder, requiring surgical intervention. The patients with grade II disease were also susceptible to developing gallbladder perforations. Furthermore, patients with AAC had longer hospital stays, particularly those with grade II disease who were treated with cholecystectomy. Therefore, it is important to note symptoms and signs suggestive of early post-cholecystectomy syndrome [47]. In patients who develop nonspecific post-operative gastrointestinal complaints, it merits proper investigation and etiology establishment [47].

6. Conclusions

This case series and systematic review illustrate that AAC is a rare but clinically significant gastroenterological association of COVID-19. AAC can also be the only presentation of COVID-19 with no associated pulmonary symptoms. Therefore, a high index of clinical suspicion is imperative for the early diagnosis, especially in patients presenting to outpatient departments. Prompt imaging evaluation followed by the exclusion of alternative causes of AAC can aid in the diagnosis. There are no clear guidelines for

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management, which can potentially cause problems in clinical practice. Grade I cholecystitis following COVID-19 may respond to conservative treatment alone. However, gangrenous cholecystitis can often be encountered due to delayed diagnosis, necessitating aggressive therapeutic intervention with laparoscopic or open cholecystectomy. Clinical outcomes can be favorable, but early detection can save patients from complications such as gallbladder gangrene or perforation. The increased awareness of this association and further investigation of the pathogenesis of AAC in COVID-19 patients can help improve clinical management.

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Conflicts of Interest

The authors disclose no conflicts of interest.

Consent for Publication

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