Acute Cholecystitis Management During the COVID-19 Pandemic—A Systematic Review and Meta-analysis

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ABSTRACT:
Aim: The aim of this study is to evaluate the prevalence of acute cholecystitis (AC) and review its possible management options during the COVID-19 pandemic.

Methods: The present systematic review and meta-analysis was done in accordance with the PRISMA guideline. In August 2021, two independent reviewers reviewed a number of articles with the aim of finding studies on the management of acute cholecystitis during the COVID-19 pandemic. Articles were searched in the Cochrane, Embassies, and Medline libraries. Using the Stata statistical software 14, the estimated pooled rates were calculated. Funnel plot and I2 indices were applied for evaluating the heterogeneity between the studies.

Results: An overall of 8 studies consisting of 654 patients suspected for AC were included. The prevalence of COVID-19 among our included patients was 82% (95% CI: 79–84%, I2: 99.2%). Regarding the type of management, 35% (95% CI: 26–45%, I2: 46.9%) of patients underwent cholecystectomy, 47% (95% CI: 43–51%, I2: 54.4%) were managed by non-surgical methods, and 19% (95% CI: 14–23%, I2: 68.1%) of patients were treated by percutaneous cholecystostomy. The prevalence of grade 2 and 3 among our patients was 44 and 15%, respectively.

Conclusions: Considering the fact that due to the current pandemic, the number of patients referring with higher grades is assumed to be increased, early cholecystectomy remains the best management option for AC patients. However, LC seems not to be the most favorable option since it is associated with a relatively higher risk of contamination with COVID-19. PC can also be considered as a temporary and safe method in high-risk patients which might enable us to protect both patients and healthcare providers.

KEYWORDS: acute cholecystitis, cholecystectomy, COVID-19, laparoscopy, percutaneous cholecystostomy

ABBREVIATIONS
AC – acute cholecystitis
COVID-19 – coronavirus disease 2019
LC – laparoscopic cholecystectomy
PC – percutaneous cholecystostomy
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
WHO – World Health Organization

INTRODUCTION
COVID-19 is a respiratory infection caused by the a coronavirus and results in acute respiratory syndrome 2 (SARS-CoV-2) [1]. After the emergence of this virus in December 2019, it spread around the world and a pandemic was declared on March 11, 2020, according to the World Health Organization. The rapid spread of this pandemic, the ease of transmission from person to person, the high mortality rate, and the fear of disease transmission in the hospital led to a reduced rate of hospitalizations for non-COVID-19 patients [1]. In this situation, the treatment of patients with other acute conditions such as acute cholecystitis, for which the prevalence is not expected to change during the pandemic, will be delayed [3]. Acute cholecystitis (AC) is one of the most common causes of daily clinical surgery. Early cholecystectomy within 7 days of the onset of symptoms is the selected treatment for acute cholecystitis [4]. Delayed treatment during the SARS-CoV-2 pandemic indicates an increase in the severity of the disease and its complications [5]. Moreover, the rapid spread of COVID-19 resulted in a significant increase in the number of patients admitted to emergency departments and hospitals [1]. Due to potential pathologies that require surgery, during this pandemic, surgeons should evaluate available resources (hospital beds and empty ICUs), available operating rooms (since many of them have been allocated for hospitalization of critically ill patients), the number of patients in line, and possible contamination of patients and medical staff during the admission process. Early cholecystectomy is the gold standard for the treatment of acute cholecystitis, and laparoscopy, except for contraindicated cases, is suggested as the first-line management [6, 7]. This method leads to shorter hospital stays and fewer complications. Some European guidelines and publications recommend a non-surgical approach to acute non-severe cholecystitis [8, 9].

AIM
The aim of this study is to evaluate the prevalence of acute cholecystitis and review its possible management options during the COVID-19 pandemic.

METHODS
The present systematic review and meta-analysis were carried out in accordance with the Preferred Reporting Items for Systematic
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Number of Males and Females</th>
<th>Age Mean ± SD or Range</th>
<th>Duration</th>
<th>Study Design</th>
<th>Acute Cholecystitis (AC)</th>
<th>COVID-19</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caballero</td>
<td>Spain</td>
<td>2021</td>
<td>257</td>
<td>146/118</td>
<td>69 (32–80)</td>
<td>between 1st March and 30th May 2020</td>
<td>Multicenter-combined (retrospective–prospective)</td>
<td>42 patients (16.3%)</td>
<td>19/42</td>
<td>31.5% (47.9%) Non-Surgical</td>
</tr>
<tr>
<td>Murphy</td>
<td>Ireland</td>
<td>2021</td>
<td>80</td>
<td>N/A</td>
<td>N/A</td>
<td>24 March to 27 April 2020</td>
<td>Retrospective</td>
<td>18</td>
<td>8/8</td>
<td>N/A N/A</td>
</tr>
<tr>
<td>Çiyiltepe</td>
<td>Turkey</td>
<td>2021</td>
<td>72</td>
<td>32/40</td>
<td>57.3 years</td>
<td>March 11 and May 31, 2020</td>
<td>Retrospective</td>
<td>N/A</td>
<td>7</td>
<td>0 (36) 0</td>
</tr>
<tr>
<td>Somuncu</td>
<td>Turkey</td>
<td>2021</td>
<td>36</td>
<td>17/19</td>
<td>53 years (range 26–78 years)</td>
<td>March 10, 2020 and June 10, 2020</td>
<td>Retrospective</td>
<td>50</td>
<td>4/36</td>
<td>1/4 2/4 1/4</td>
</tr>
<tr>
<td>Çakır</td>
<td>Turkey</td>
<td>2021</td>
<td>18</td>
<td>14/4</td>
<td>73.4 years (range, 67–81)</td>
<td>March 2020 and June 2020</td>
<td>Retrospective</td>
<td>18</td>
<td>18</td>
<td>5 (27.7%) N/A N/A</td>
</tr>
<tr>
<td>Matías-García</td>
<td>Spain</td>
<td>2021</td>
<td>19</td>
<td>11/8</td>
<td>69 ± 16.1 years</td>
<td>11 March to 21 June 2020</td>
<td>Retrospective</td>
<td>19</td>
<td>19</td>
<td>52.6% (n = 10) 42.1% (n = 8) 5.3% (n = 1)</td>
</tr>
<tr>
<td>Baglaenko</td>
<td>Russia</td>
<td>2021</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td>Retrospective</td>
<td>16</td>
<td>16</td>
<td>9 (36.25%) 3 (18.75%) 4 (25%)</td>
</tr>
<tr>
<td>Valles</td>
<td>USA</td>
<td>2021</td>
<td>157</td>
<td>41/27</td>
<td>45.92 (15.15)</td>
<td>January 1, 2020-May 31, 2020</td>
<td>Retrospective</td>
<td>157</td>
<td>N/A</td>
<td>N/A N/A</td>
</tr>
</tbody>
</table>
Fig. 1. PRISMA flow chart describing the selection process.

Tab. II. Patients’ characteristics.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cholecystectomy was performed laparoscopically</th>
<th>Follow-up</th>
<th>COPD/other chronic lung diseases (%)</th>
<th>Obesity (%)</th>
<th>Arterial hypertension</th>
<th>DM</th>
<th>Heart disorder</th>
<th>Tokyo grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caballero 2021</td>
<td>N/A</td>
<td>92.5%</td>
<td>48 (18.7%)</td>
<td>83 (7.9%)</td>
<td>68 (26.5%)</td>
<td>65 (25.3%)</td>
<td>43.6%</td>
<td>47.1%</td>
</tr>
<tr>
<td>Murphy 2021</td>
<td>N/A</td>
<td>N/A</td>
<td>6/72–08%</td>
<td>0.0319</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Çiyiltepe 2021</td>
<td>N/A</td>
<td>N/A</td>
<td>6/72–08%</td>
<td>0.0319</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Somuncu 2021</td>
<td>N/A</td>
<td>N/A</td>
<td>6/72–08%</td>
<td>0.0319</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Çakır 2021</td>
<td>N/A</td>
<td>N/A</td>
<td>6/72–08%</td>
<td>0.0319</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Matías–García 2021</td>
<td>N/A</td>
<td>N/A</td>
<td>6/72–08%</td>
<td>0.0319</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Baglaenko 2021</td>
<td>N/A</td>
<td>N/A</td>
<td>6/72–08%</td>
<td>0.0319</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Valles 2021</td>
<td>N/A</td>
<td>N/A</td>
<td>6/72–08%</td>
<td>0.0319</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Reviews and Meta-Analyses (PRISMA) guideline [10]. All cross-sectional, cohort and case-control studies evaluating the possible management options of acute cholecystitis during the COVID-19 pandemic were included. Case series, letters to editors, case reports, and reviews were excluded. Diagnostic criteria for acute gallbladder inflammation should have been defined in the article, and the disease should have been confirmed by ultrasound or histological examination.
Study Selection

After excluding the duplicate articles, the titles and abstracts of the articles were independently reviewed by two reviewers (M.S. and F.P.) to assess the relevance of the publications. Then, the full text of the articles was reviewed in order to evaluate the studies regarding the inclusion criteria.

The remaining articles were reviewed using a cross-reference search to identify studies that might have been overlooked. If the approaches or results were ambiguous, the authors would contact them for further explanation. General characteristics (first author's name, year and country of publication, sample size, duration of the study, and study design), as well as study information (prevalence of AC, prevalence of COVID-19 among AC-suspected patients, prevalence of different management methods, grading of AC, co-morbidities, and follow-up time) were collected. As there was not enough data for meta-analysis of the outcome measures of each type of management in the included studies, these measurements are only discussed in the systematic review section.

Statistical analysis

Perioperative risk factors were considered as the proportion of the event and its 95% confidence interval. In comparative studies, the data related to the one group which was eligible for our study was considered. Using the Stata statistical software 14, the estimated pooled rates were calculated. Funnel plot and I² index were applied for evaluating the heterogeneity between the studies. A high I² index was suggestive of a high heterogeneity.

Quality Assessment

The Hoy tool designed by Hoy et al. was implemented for evaluating the risk of bias and quality of the methodology [11]. This scale consists of 10 items assessing the study quality based on external and internal validity. The risk of bias was evaluated by two independent researchers and in case of any disagreement, the opinion of the third researcher was considered as the final decision.

RESULTS

Study selection

Fig. 1 illustrates the selection process of this paper according to the PRISMA statement. A total number of 743 references were identified by electronic search. Ninety-four duplicate articles were excluded, and the titles and abstracts of other related articles were reviewed; 325 articles were excluded due to the reasons mentioned in Fig. 1. Eight studies were found to meet the inclusion criteria and were used in the final analysis. Both authors (M.S. and F.P.) fully agreed on the requirements for inclusion of the studies.

Characteristics of the Included Studies

The general characteristics of 8 included studies are shown in Tab. I. Among 8 studies, 7 were conducted retrospectively, while one study used a combined retrospective-prospective design. The prevalence of COVID-19 among our included
Meta-analysis of the prevalence of different comorbidities

The most prevalent comorbidity observed among patients was arterial hypertension with a prevalence of 38% (95% CI: 34–43, I²: 94.2%), followed by diabetes 30% (95% CI: 24–36, I²: 89.1%), cardiovascular disorders 28% (95% CI: 23–32, I²: 92%), and lung diseases 15% (95% CI: 11–18, I²: 74.3%) (Tab. II.).

Meta-analysis of the prevalence of different severity levels of acute cholecystitis

Most of the included patients were classified as grade 1, 58% (95% CI: 44–53, I²: 92%), based on Tokyo guidelines. The prevalence of grade 2 and 3 among our patients was 44% (95% CI: 39–49, I²: 29.5%), and 15% (95% CI: 11–18, I²: 96.1%), respectively (Tab. II.).

Quality Assessment

Tab. III. shows the quality of the articles that is calculated using a checklist which includes 10 criteria. Based on these 10 criteria,
The number of patients seeking surgical treatments as well as the number of surgical operations has decreased during the COVID-19 pandemic, globally [12–16]. This can be explained by several reasons, including the fear of being exposed to COVID-19 infection and trying to lower the burden on healthcare providers [17, 18]. Our study indicated a total prevalence of 44% and 15% for patients presenting with grade 2 and 3 AC, respectively. Among our included studies, Valles et al. reported a 48.7% decrease in the admission rate of patients presenting with acute cholecystitis in the period during the COVID-19 pandemic [19] as compared to the same period the year before, while Murphy et al. indicated a 63% increase in the corresponding rate [20]. However, Garcia et al. found no significant difference in the admission rate due to cholecystitis before and during the pandemic [21]. Valles et al. showed no significant difference in the severity of the disease between patients referring during the pandemic and patients who were referred before the pandemic [19]. In situations such as the current pandemic, the priority has been given to preventive protocols in order to limit the spread of the COVID-19 infection and provide an optimal level of protection to the hospital personnel [22]. Patients who present with abdominal pathologies requiring emergency surgery can be the major source of nosocomial infection spread [23]. However, the emergency surgery indications should not differ between the infected and non-infected patients [24]. Acute cholecystitis caused by a gallstone is responsible for a huge number of emergency referrals and laparoscopic cholecystectomy remains the treatment of choice in these patients [25]. However, a number of studies indicated that surgical smoke decline was documented for abdominal pain referrals. The number of patients seeking surgical treatments as well as the number of surgical operations has decreased during the COVID-19 pandemic, globally [12–16]. This can be explained by several reasons, including the fear of being exposed to COVID-19 infection and trying to lower the burden on healthcare providers [17, 18]. Our study indicated a total prevalence of 44% and 15% for patients presenting with grade 2 and 3 AC, respectively. Among our included studies, Valles et al. reported a 48.7% decrease in the admission rate of patients presenting with acute cholecystitis in the period during the COVID-19 pandemic [19] as compared to the same period the year before, while Murphy et al. indicated a 63% increase in the corresponding rate [20]. However, Garcia et al. found no significant difference in the admission rate due to cholecystitis before and during the pandemic [21]. Valles et al. showed no significant difference in the severity of the disease between patients referring during the pandemic and patients who were referred before the pandemic [19]. In situations such as the current pandemic, the priority has been given to preventive protocols in order to limit the spread of the COVID-19 infection and provide an optimal level of protection to the hospital personnel [22]. Patients who present with abdominal pathologies requiring emergency surgery can be the major source of nosocomial infection spread [23]. However, the emergency surgery indications should not differ between the infected and non-infected patients [24]. Acute cholecystitis caused by a gallstone is responsible for a huge number of emergency referrals and laparoscopic cholecystectomy remains the treatment of choice in these patients [25]. However, a number of studies indicated that surgical smoke

**Country**

The prevalence of COVID-19 among cholecystitis patients was 54%, 22%, and 22% in Turkey, Spain, and Ireland respectively, based on 7 included studies (Fig. 5.). As the study which was from Russia included only COVID-19 patients, we could not evaluate this measure in that study.

**Egger’s Plot of publication bias**

The Egger’s plot provided in Fig. 4., demonstrated no indication of publication bias. The size of circles is representative of the weight of studies (the bigger the circle, the higher the sample size). Our meta-regression results showed no significant association between the COVID-19 prevalence and male-to-female ratio as well as patients’ age (Fig. 2., 3.).

**DISCUSSION**

After the WHO declared the COVID-19 pandemic, a 42% decrease in the emergency department applications was reported by The National Syndromic Surveillance Program (NSSP), while the highest articles were scored and then classified into three different quality groups, including: good quality (score higher than 7), average quality (score 4–7), and poor quality (score below 4). Only one study had average quality, and the other seven studies were average.

![Fig. 5. Acute cholecystitis during the COVID-19 pandemic by country.](image-url)
can contain many toxic components as well as be able to transmit certain viruses (HIV, hepatitis B virus) to the surgical team [26, 27]. The overall prevalence of COVID-19 among patients suspected for AC was calculated to be 82%. A recent article regarding surgical team protection indicated the presence of COVID-19 virus in blood, peritoneal fluid, feces, nasopharyngeal swab and gastrointestinal tissues. On the other hand, it is possible for the virus to be transmitted through aerosols produced by high-speed surgical equipment such as energy devices and carbon dioxide insufflation devices during laparoscopic procedures. Due to the longer operation time of laparoscopy as well as higher exposure of the personnel to the virus, it was suggested that, during the pandemic, laparoscopy might not be the optimal way of management for cholecystitis, especially in cases suspected of COVID-19 [28, 29]. The most common management based on our meta-analysis was non-surgical, with a prevalence of 54.4% followed by cholecystectomy (35%) and PC (19%). Laparoscopy was evaluated only by one of our included studies. Somuncu et al. in their study comparing the efficacy of laparoscopic cholecystectomy (LC) with percutaneous cholecystostomy (PC) during the pandemic, demonstrated that LC is not recommended and PC can be a suitable alternative being performed safely [30]. Çiyiltepe et al. suggested percutaneous cholecystostomy as the method of choice for managing patients with cholecystitis during the COVID-19 pandemic in order to lower the risk of infection in both patients and health care providers [31]. On the other hand, Çakır et al. in their study on elderly COVID-19 patients presenting with acute cholecystitis, indicated PC as a safe alternative which can be performed under local anesthesia in high-risk patients [32]. On the other hand, our study indicated a rate of 54.4% for non-surgical management of AC. Caballero et al. in their study demonstrated that the rates of non-surgical management, conservative management failure, length of hospital stay, and morbidity increased significantly during the COVID-19 pandemic [33]. However, Banglaeaco et al. reported that there was no significant difference in the rate of complication and mortality among COVID-19 AC patients and non-COVID patients undergoing early cholecystectomy [34]. Our study had several limitations. Firstly, out of 8 studies included only one had a prospective design and the remaining articles were retrospective. Secondly, there was limited data regarding the efficacy of each type of management as well as outcome measures. And finally, we did not consider cases of acalculous cholecystitis in this article as there were few case reports published about it.

**CONCLUSION**

Considering the fact that, due to the current pandemic, the number of patients referring with higher grades is assumed to be increased, early cholecystectomy remains the best management option for AC patients. However, LC seems not to be the most favorable option since it is associated with a relatively higher risk of contamination with COVID-19. PC can also be considered as a temporary and safe method in high-risk patients which might enable us to protect both patients and healthcare providers.

**REFERENCES**


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