DOI: 10.14744/cm.2024.85856
Comprehensive Medicine 2024;16(3):147-156

RESEARCH ARTICLE

The Efficacy of Percutaneous Cholecystostomy in Patients with Acute Cholecystitis Before and During the COVID-19 Pandemic: Is the Percutaneous Cholecystostomy Procedure Safe for Patients and Healthcare Professionals in Pandemic Conditions?

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ABSTRACT

Objective: Our aim is to demonstrate the effectiveness of percutaneous cholecystostomy (PC) in the treatment of patients with acute cholecystitis (AC) before and during the COVID-19 pandemic and to show that it is a safe procedure for healthcare professionals and patients.

Materials and Methods: Demographic, clinical and laboratory data, technical success of PC, clinical response to treatment, duration of hospital stay, of patients with AK who applied to our hospital and underwent PC procedure in a total of 24 months before and during the pandemic, one-month post-procedure observation, and complications were compared.

Results: PC was applied to a total of 124 patients in the pre-pandemic period (52) and pandemic period (72) examined in the study. The median age was 73.5 (25–93) in the pre-pandemic period, and 64 (23–90) in the pandemic period, and the difference between these was found to be significant (p=0.004). Clinical improvement due to PC was detected in 43 (86%) patients in the pre-pandemic period, and in 61 (84.7%) patients in the pandemic period, no significant differences were detected between the two groups (p=1.000). The day of hospitalization median value was 3 (1–18) days in pandemic period, and 3 (1-30) days in the pandemic period, and no significant differences were detected between the groups (p=0.794).

Conclusion: PC treatment in patients with AC during the pandemic and pre-pandemic periods is effective and safe for both the patient and the healthcare professionals who perform the procedure.

Keywords: Acute cholecystitis, COVID-19, percutaneous cholecystostomy

How to cite this article: Topal Ü, Dağıstanlı S, Boşat Sönmez M, Sönmez S. The Efficacy of Percutaneous Cholecystostomy in Patients with Acute Cholecystitis Before and During the COVID-19 Pandemic: Is the Percutaneous Cholecystostomy Procedure Safe for Patients and Healthcare Professionals in Pandemic Conditions? CM 2024;16(3):147-156

INTRODUCTION

The Coronavirus Disease (COVID-19), which broke out in Wuhan, China in November 2019, continues to pose a great threat to public health and healthcare professionals all over the world. The course of the pandemic was prolonged due to multiple infection waves.[1,2] The pandemic caused an extraordinary patient load in healthcare centers.[3] Several surgical societies published recommendations to manage the effects of the COVID-19 pandemic, especially regarding surgical clinical practices.[1,4–6] Acute Cholecystitis (AC) is an acute inflammatory disease of the gallbladder, and the most appropriate treatment is Laparoscopic Cholecystectomy (LC).[7,8] However, viruses that are transmitted by blood during LC and other abdominal surgery were shown to be present in the smoke produced by the

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Received date: 31.03.2024
Revised date: 20.04.2024
Accepted date: 01.07.2024
Online date: 01.08.2024

Comprehensive Medicine published by Kare Media.
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electrocautery. There is not enough data on the absence of this virus in surgical smoke because Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) RNA was detected in the peritoneal cavity.[9–11] Percutaneous Cholecystostomy (PC) is the alternative treatment option for patients who cannot undergo surgery because of the higher AC prevalence, the mortality of COVID-19 with morbidity in elderly patients, increased number of patients during the pandemic period, and the occupancy of Intensive Care Units (ICU).[7,12,13] The purpose of the present study was to show that PC therapy is safe and effective both for patients and for healthcare professionals who perform the procedure, in patients with AC, which can be seen at any age before and during the COVID-19 pandemic.

MATERIALS and METHODS

This single-center retrospective study that was conducted following the ethical standards of the Declaration of Helsinki was approved by the local ethics committee and written informed consent was waived (KAEK/2021.05.155). The study included patients with AC who applied to various services of our hospital and did not respond to antibiotic treatment before the pandemic (1 March 2019–28 February 2020) and during the pandemic (1 March 2020–28 February 2021) who underwent PC procedure over a 24-month period by using the Interventional Radiology (IR) Quality Assurance Database and electronic medical records. The demographic data, clinical and laboratory data (fever, pain, C-Reactive Protein (CRP), and White Blood Cell (WBC) before PC and 3 days after the procedure, technical success of PC, complications, clinical treatment response evaluation, length of hospital stay, and postprocedural one-month observation results of the patients were compared. The culture results obtained in the PC process were noted along with the presence of stones or sludge in the Gallbladder (GB). It was recorded whether cholecystectomy was performed within 1 month after the PC procedure. It was recorded that the procedure was successful, with clinical improvement (fever returning to normal, pain disappearing) and WBC values returning to normal within three days.

The Polymerase Chain Reaction (PCR) test results were recorded during the pandemic period, COVID-19.

The oral intake of the patients with AC and/or COVID-19 and AC who applied to our hospital before and during the pandemic period was discontinued after hospitalization, and their treatment with intravenous antibiotics was initiated by the relevant clinical specialist physicians. The patients with AC who did not improve between 1 and 5 days after the treatment were sent to the IR department with the request of PC procedure, which was performed at the bedside for patients who developed AC during the follow-up due to COVID-19 in the Intensive Care Unit. Patients with severe coagulopathy or who did not give informed consent, who came to our unit for PC from external centers and returned to their centers immediately after the procedure were excluded from the study. Pre-pandemic and COVID-19 negative patients were treated after standard surgical preparations. COVID-19 PCR test-positive patients were treated by wearing personal protective equipment (water-resistant and virus-resistant overalls, N95 masks, bones, protective glasses or visors, sterile gloves).

Patients with non-complicated AC before and during the pandemic, and complicated cases such as those with pericholecystic liver abscess, bilioma, ruptured AC, necrotizing AC, emphysematous AC, metastatic AC, and AC caused by autoimmune hepatitis were also included in the study.

The AC diagnosis was made with right upper quadrant pain or tenderness, fever and heightened WBC, wall thickening and hydrops in GB, and pericholecystic fluid in Computed Tomography (CT) - Ultrasonography Imaging (US).

The PC procedure was performed under local anesthesia with US and/or transhepatic GB puncture that had an 18-gauge needle under the guidance of scope in patients who had chronic calculous cholecystitis, and 8–10 cc samples were taken for culture and cytology. Then, the guide wire was sent through the needle into the GB lumen with the Seldinger technique. The needle was removed and the tract was widened with dilators. Over the guide wire (8 or 10 Franch), the pigtail drainage catheter was inserted in the GB lumen, locked and fixed to the skin; and its end was attached to the drainage bag for free drainage. Samples were taken after GB puncture in patients with calculous AC. The GB was made opaque by administering less contrast material than the sample taken. The drainage catheter was placed in the GB lumen under the guidance of fluoroscopy with the Seldinger Technique. The transperitoneal route was used in patients who had bleeding disorders. The PC procedure was performed by experienced interventional radiologists.

The catheter removal was made after tract maturation and following the confirmation of cystic duct patency with scope (i.e., by administering contrast substance through the catheter) for clinical and laboratory improvement in patients who were not operated on.

Statistical Analysis

Statistical analyses were made by using SPSS version 21 software (Armonk, New York: IBM Corp). The conformity of the variables

Table 1. The comparison of patient characteristics for PC procedure applied in prepandemic and pandemic period

Characteristics	Prepandemic period (52)		Pandemic period (72)		p
	n	%	n	%	
Age[1]	73.5 (25–93)		64 (23–90)		0.004[b]
Gender					0.506[a]
Male	22	42.3	36	50	
Female	30	57.7	36	50	
CRP (mg/L) admission value[1]	194.5 (76.5–309.5)		127 (65.2–290.5)		0.328[b]
WBC (×10³/µl) admission value[1]	14 (9.2–19.7)		12.9 (9.5–17.7)		0.347[b]
Acute cholecystitis type					0.696[a]
Acalculous cholecystitis	14	26.9	16	22.2	
Calculous cholecystitis	36	69.2	56	77.8	
Bile culture result					0.309[a]
Positive	17	68	18	51	
Negative	8	32	17	49	

[a]: Pearson-Chi-Square Test; [b]: Mann Whitney U test; [1]: Median (Minimum-Maximum). PC: Percutaneous cholecystostomy; CRP: C-reaktif protein; WBC: White blood cell

to normal distribution was evaluated with Kolmogorov Smirnov and Shapiro Wilk Test, Q-Q plots, and histogram graphs. As a result of the analyses, normally distributed variables were shown as mean ± standard deviation, and non-normally distributed variables were shown as median (minimum-maximum). The categorical data were presented with frequency (percentage). The comparison of two groups was made with Mann Whitney U Test in continuous data as the data were not normally distributed. The categorical data were compared with Pearson Chi-Square Test when the number of observations was sufficient, and with Fisher's Exact Test when the number of observations was insufficient. The correlation between the continuous data was evaluated with the Pearson Correlation Test for those with normal distribution and with the Spearman Correlation Test for those who were not normally distributed. The relations between categorical data were examined with the Phi Correlation Test; $p<0.05$ was considered significant.

RESULTS

Demographic Characteristics of All Patients

PC was applied to a total of 124 patients, 52 in the prepandemic period, and to 72 patients in pandemic period in the study. The median age was found to be 73.5 (25–93) in the prepandemic period, 64 (23–90) in the pandemic period, and the difference was statistically significant (p=0.004). A total of 22 (42.3%) of the patients in the prepandemic period were male, 30 (57.7%) were female, and 36 (50%) were female in the pandemic period, 36 (50%) were male. No statistically significant differences were detected between the two groups (p=0.506) (Table 1).

At first presentation, the median value of CRP (mg/L) was found to be 194.5 (76.5–309.5) in the prepandemic period, and 127 (65.2–290.5) in the pandemic period, and statistically significant differences were detected between the groups (p=0.328). WBC (x10³/µl) first presentation median value was 14 (9.2–19.7) in the prepandemic period, and 12.9 (9.5–17.7) in the pandemic period, and no statistically significant differences were detected between the groups (p=0.347) (Table 1).

A total of 14 (26.9%) of the patients had acalculous cholecystitis, and 38 (73.1%) had calculous cholecystitis in the prepandemic period; and 16 (22.2%) of the patients had acalculous cholecystitis, and 56 (77.8%) had calculous cholecystitis in the pandemic period. No statistically significant differences were detected between the groups (p=0.696).

The result was positive in 17 (68%) patients and negative in 8 (32%) patients whose bile culture was taken in the prepandemic period; and the result was positive in 18 (51%) and negative in 17 (49%) in the pandemic period. No statistically significant differences were detected between the groups (p=0.309) (Table 1).

The Comparison of Pandemic and Prepandemic Groups and Evaluation of Results

The clinical improvement in 72 hours due to PC was observed in 43 (86%) patients, but not in 7 (14%) patients in the prepan-

Table 2. Comparison of technical success-complications of prepandemic and pandemic period PC procedure and evaluation of the treatment response

Characteristics	Prepandemic period (52)		Pandemic period (72)		p
	n	%	n	%	
72-hour clinical recovery due to PC procedure					
No	7/50	14	11/72	15.3	1.000[a]
Yes	43/50	86	61/72	84.7	
Duration of hospitalization (days)[1]	3 (1–18)		3 (1–30)		0.794[a]
Technical success of PC procedure					
No					
Yes	52/52	100	72/72	100	-
PC complications					1.000[c]
No	48/51	94.2	68/72	94.4	
Yes	3/51	5.8	4/72	5.6	
LC					1.000[c]
No	48/52	92.3	67/72	93.1	
Yes	4/52	7.7	5/72	6.9	

[a]: Pearson-Chi-Square Test; [b]: Mann Whitney U-Test; [c]: Fisher's Exact Test. [1]: Median (Minimum-Maximum). PC: Percutaneus cholesiststomy; LC: laparoscopic cholecystectomy

demic period, and was observed in 61 (84.7%) patients due to PC procedure in 72 hours, and not in 11 (15.3%) patients in the pandemic period, and no statistically significant differences were detected between the groups (p=1.000) (Table 2).

The median value for the duration of hospital stay was found to be 3 (1–18) days in the prepandemic period, and 3 (1–30) days in the pandemic period, and no statistically significant differences were detected between the groups (p=0.794) (Table 2).

PC complication was detected in 3 (5.8%) patients in the prepandemic period, and in 4 (5.6%) patients in the pandemic period, and no statistically significant differences were detected between the groups (p=1.000) (Table 2).

The number of patients with LC was 4 (7.7%), and the number of patients without LC was 48 (92.3%) in the pre-pandemic period. The number of patients with LC was 5 (6.9%), the number of patients without LC was 67 (93.1%) in the pandemic period, and no statistically significant differences were detected between these two groups (p=1.000) (Table 2).

The Characteristics of Patients in the Pandemic Period, PC Technical Success-Complications, and Comparison of Response to Treatment according to the PCR Test Results

When Table 3 is examined, there is a comparison of the technical success complications of the PC procedure and the response to treatment of the patient groups that had positive (12) and negative (60) PCR test results in the pandemic period. The median age of those who had positive PCR test results was 60.5 (34–90), the median age of those with negative PCR test results was 64 (23–90) years, and no statistically significant differences were detected between the groups (p=0.786). Also, 7 (58.3%) patients with positive PCR test results were male, 5 (41.7%) were female, and 29 (48.3%) of those who had negative PCR test results were male, and 31 (51%, 7) were female, and no statistically significant differences were detected between the groups (p=0.752) (Table 3).

The number of patients who had positive PCR test results and acalculous cholecystitis was 5 (41.7%), and the number of patients with calculous cholecystitis was 7 (58.3%). The number of patients with acalculous cholecystitis was 11 (18.3%), and the number of patients with calculous cholecystitis was 49 (81.7%) in the patients who had negative PCR test results, and no statistically significant differences were detected between the groups (p=0.122) (Table 3).

The number of patients who had clinical improvement in 72 hours due to PC procedure was 11 (91.7%), and the number of patients without clinical improvement was 1 (8.3%) in the patients with positive PCR test results. The number of patients who had clinical improvement in 72 hours due to PC pro-

Table 3. Comparison of the characteristics of the patients with the technical success of PC procedure-complications and the response to the treatment with the pcr test results in the pandemic period

Characteristics	PCR test result positive		PCR test result negative		p
	n	%	n	%	
Total patient count	12		60		
Age[1]	60.5 (34–90)		64 (23–90)		0.786[b]
Gender					0.752[a]
Male	7	58.3	29	48.3	
Female	5	41.7	31	51.7	
AC type					0.122[c]
Acalculous cholecystitis	5	41.7	11	18.3	
Calculous cholecystitis	7	58.3	49	81.7	
Biliary culture result					
Positive	0		18	58	–
Negative	4	33	13	42	
72-hour clinical recovery due to PC procedure					0.677[c]
No	1	8.3	10	16.7	
Yes	11	91.7	50	83.3	
Mean day of hospitalization (day range)[1]	3 (2–4.5)		3 (3–6)		0.191[b]
Technical success of PC procedure					
No	0	0	0	0	
Yes	12	100	60	100	–
PC complications					0.526[c]
No	11	91.7	57	95	
Yes	1	8.3	3	5	

[a]: Chi-Square Test; [b]: Mann Whitney U-Test; [c]: Fisher's Exact Test; [1]: Median (Minimum-Maximum). PC: Percutaneus cholesiststomy; PCR: Polymerase chain reaction; AC: Acute cholecystitis

cedure was 50 (83.3%), and the number of patients without clinical improvement was 10 (16.7%) in the patients with negative PCR test results, and no statistically significant differences were detected between the groups (p=0.677) (Table 3).

The median length of hospital stay was found to be 3 (2–4.5) days in patients who had positive PCR test results, and the median value was 3 (3–6) days in patients who had negative PCR test results, and no statistically significant differences were detected between the groups (p=0.191). PCR complication was detected in 1 (8.3%) of the patients who had positive PCR test results, and PCR complication was not detected in 11 (91.7%), and 3 (5%) patients who had negative PCR test results had PC complications, 57 (95%) did not have any complications, and no statistically significant differences were detected between the groups (p=0.526) (Table 3).

A total of 11 patients who had positive PCR test results and positive PC procedure success and 1 patient who had negative PCR test results were detected in the pandemic period. The mean duration of hospital stays of the patients who had positive PC procedure success was 4.18±4.99, and the duration of hospitalization of the patients who had negative procedure success was 7 days. Technical success was achieved in PC procedure in both groups. Complications were detected in 1 (9.1%) of the patients who had positive PC procedure success, but not in 10 patients (90.9%). No complications were detected in the patient whose PC procedure success was negative. A total of 2 (18.2%) patients who had positive PC procedure success had LC, and 9 (88.8%) did not have LC. No LC was detected in the patients who had negative PC procedure success (Table 4).

The number of patients with AC increased at a rate of 38% in the pandemic period when compared to the previous period. Patients with AC were more complicated (e.g. ruptured AC, emphysematous AC, pericholecystic abscess, bilioma) in the pandemic period. PC was also applied to patients with com-

Table 4. Evaluation of technical success-complications and treatment responses of patients with positive PCR test results in pandemic period according to the success of PC procedure

Characteristics	Success of procedure positive*		Success of procedure negative	
	n	%	n	%
Number of total patients	11		1	
Day of hospitalization[1]	4.18±4.99		7	
Technical success of PC procedure				
No				
Yes	11	100	1	100
PC complications				
No	10/11	90.9		
Yes	1/11	9.1	1	100
LC				
No	9/11	81.8	1	100
Yes	2/11	18.2		

*: 72-hour clinical recovery due to PC procedure; [1]: Mean±standard deviation. PC: Percutaneus cholesiststomy; LC: Laparoscopic cholecystectomy

plicated AC, and the response to the treatment was dramatic. However, the hospitalization period of these patients was found to be longer than 7 days (Fig. 1-5).

PC was also applied to the patient with the diagnosis of advanced pancreatic cancer and AC who metastasized to the GB causing perforation during the follow-up. The catheter of this patient was not removed, and it was decided to change every 2 months.

A separate catheter was placed in both the GB and the abscess cavity in the liver for patients with AC and accompanying liver abscess who applied during the pandemic period. Dramatic improvements were detected in the first few days in clinical and laboratory findings (Fig. 2-5).

DISCUSSION

COVID-19, which emerged in Wuhan, China in November 2019, still continues to threaten the entire world. It is the most important public healthcare issue faced by healthcare professionals struggling with it. It was reported that the risk of contracting COVID-19 in healthcare employees was 7% higher than in the normal population.[14–16] Strategies were developed to decrease infection risks. Unnecessary aerosol-generating procedures were avoided as much as possible to protect healthcare employees.[3,6,8,12,13] AC is an acute inflammatory disease of the GB requiring immediate treat-

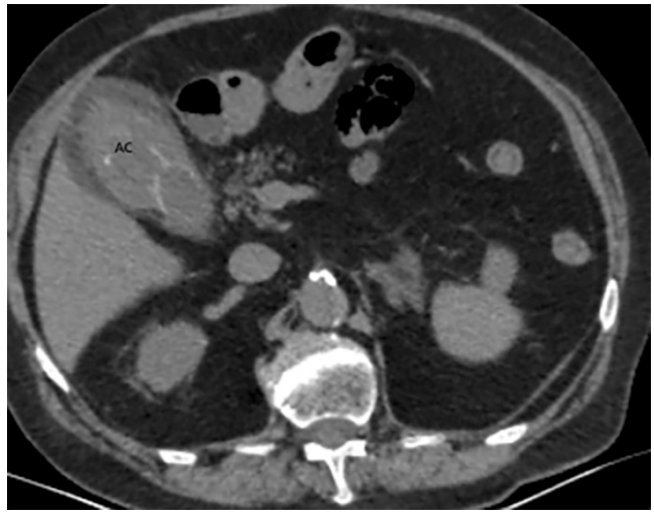

Figure 1. 89-year-old female patient who presented with COVID-19 pneumonia during the pandemic period. COVID-19 pneumonia findings, ground glass opacity consolidation, and pleural effusion are observed (not shown here). Non-contrast axial abdomen CT. Acute cholecystitis developed while treated for pneumonia. Percutaneous cholecystostomy was performed without complications in the Intensive Care Unit by wearing personal protective equipment and accompanied by bedside US

CT: Computed tomography; US: Ultrasonography

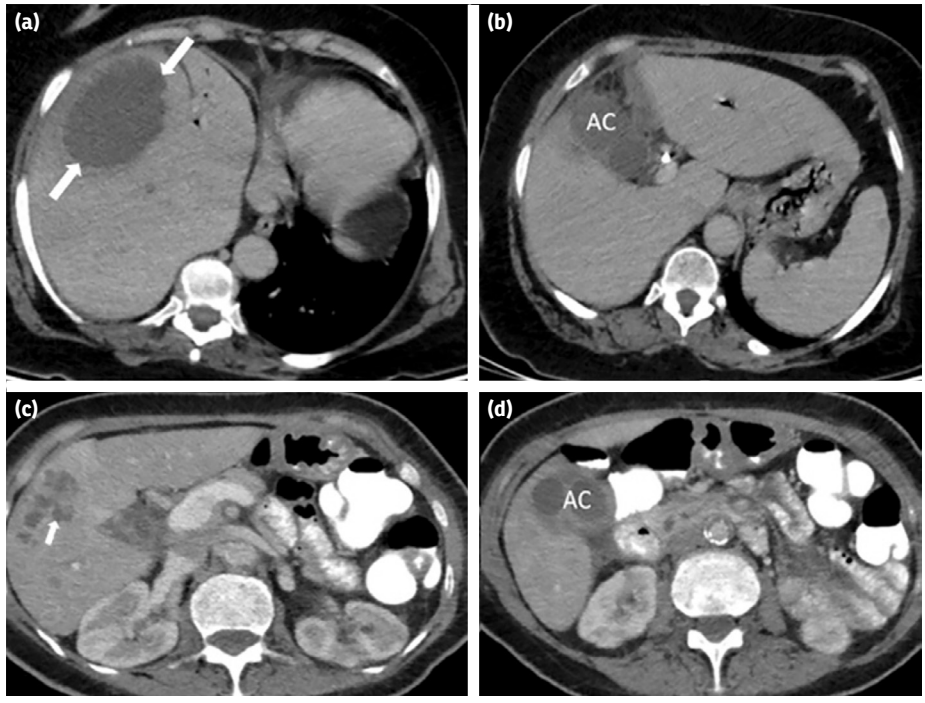

Figure 2. (a, b) Contrast-enhanced axial abdomen CT. COVID-19-positive patient with acute cholecystitis and unilocular liver abscess (arrows) adjacent to the gall bladder in pandemic period. A 10F drainage catheter was placed to the gall bladder and the abscess cavity separately. **(c, d)** Contrast-enhanced axial abdomen CT. Prepandemic period. Acute cholecystitis and multilocular liver abscess (arrow) adjacent to the gall bladder. Percutaneous cholecystostomy was performed. The multilocular abscess in the liver responded to antibiotherapy

CT: Computed tomography

ment. Although the most appropriate treatment is LC, it is already known that viruses transmitted by the blood during abdominal surgeries exist in the smoke produced by electrocautery. There is insufficient data on the absence of SARS-CoV-2 in surgical smoke because SARS-Cov-2 RNA was detected in the peritoneal cavity. A quality evacuation filter system that prevents the risk of infecting the surgical team during abdominal gas evacuation impermeable to viruses may not be available in every healthcare center. For these reasons, a cautious approach is needed in the COVID-19 pandemic process until more data are available.[9–11]

All health centers have faced an extraordinary patient load due to the COVID-19 pandemic. In particular, some surgical communities support procedures to delay or treat some cases with minimally invasive methods.[6,8] During the pandemic process, increased emergency patient burden IR was observed in our center, whether infected or not, when compared to the previous year.[12]

Although Minilaparotomic Cholecystectomy (MC), which is a surgical technique for AC, was shown to provide an excellent alternative to LC, it may not be available in all healthcare centers.[17] The patients who have surgically high-risk with AC may not be candidates for surgery. The effectiveness of PC was proven in the period before the pandemic.[18–21] In the present study, it was shown that PC carries minimal risk for healthcare staff during the pandemic period, and is effective and safe for patients who are not suitable for surgery.[22]

Although there are studies which show that LC can be preferred for AC even in the COVID-19 pandemic, this method may not be applicable in every center and in every patient because of the reasons mentioned above.[9,11,23] It was also shown in the present study that PC is an inexpensive and bedside treatment, safe for healthcare staff, and an effective and safe treatment method for patients.

Although the effectiveness of emergency LC was reported in patients with AC before the pandemic, the rate of con-

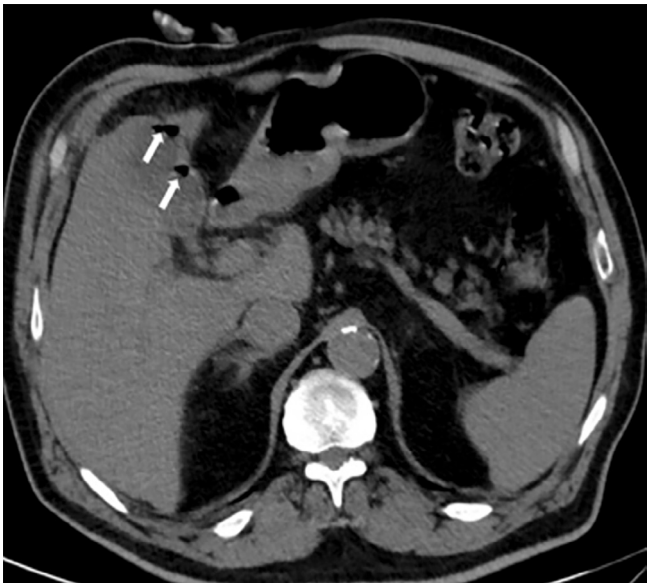

Figure 3. Emphysematous acute cholecystitis. Axial unenhanced abdomen CT. Air densities (arrows) in the gallbladder lumen in patient who presented in the prepandemic period with upper-right quadrant pain, tenderness, and elevated WBC

CT: Computed tomography, WBC: White blood cell

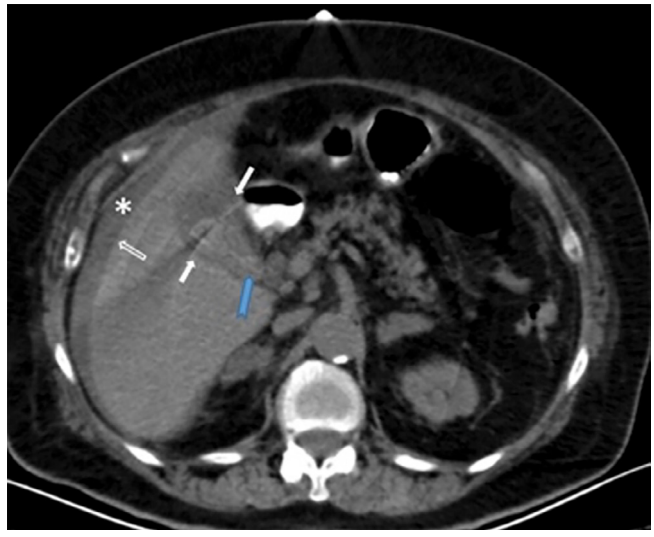

Figure 4. Axial unenhanced abdomen CT. Pandemic period. A COVID-19-positive patient who presented with the diagnosis of ruptured acute cholecystitis perihepatic bilioma. Catheters were placed to the gall bladder and the bilioma separately. Ruptured acute cholecystitis (arrows), stone in the gall bladder lumen (blue arrow), perihepatic bilioma (star, hollow arrow)

CT: Computed tomography

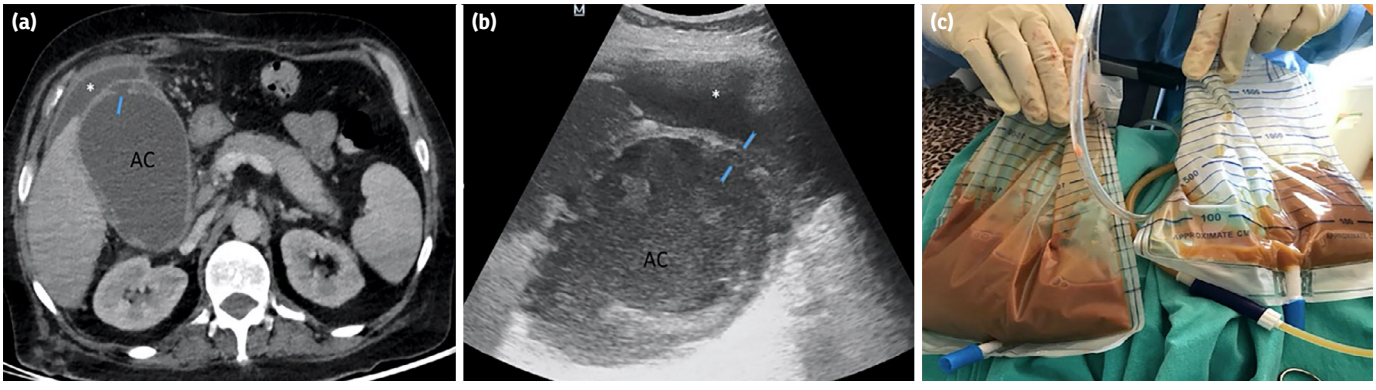

Figure 5. A patient who presented during the pandemic period with the diagnosis of polymerase chain reaction negative, perforated AC, and pericholecystic abscess. **(a)** contrast-enhanced abdominal CT, **(b)** ultrasonographic imaging. Defect secondary to the perforation in the gallbladder wall (blue arrows). Pericholecystic abscess (*). Drainage catheters placed separately in the gallbladder and pericholecystic abscess area are observed. **(c)** Drainage catheters placed separately in the gallbladder and pericholecystic abscess area are observed

AC: Acute cholecystitis; CT: Computed tomography

version to open surgery was high.[23–26] The morbidity and mortality rates of emergency cholecystectomy in patients who have high surgical risk and comorbid diseases were found to be higher than in PC.[27]

It was reported in the study that was conducted by Borzellino et al.[20] that acute attacks were resolved after an average of 1.8 days in AC patients treated with PC, and the technical success was found to be high. In the present study, the tech-

nical success was found to be 100% in both periods. The clinical success rate was found to be 86% in the prepandemic period and 84.7% in the pandemic period.

While the prevalence of PC-related mortality was found to be 0–3% in the literature, and the rate of minor complications was shown to be 4–18%.[21,28] No mortality was detected in any of the patients in the present study after PC. PC-related complications were found to be far below the complication rates in the literature in our center (5.8% in the prepandemic period and 5.6% in the pandemic period). We associated this with the experience of our center.

In a 20-year literature review conducted by Crucitti et al.[29] It was reported that large, prospective, randomized studies are required comparing PC with cholecystectomy in patients with high surgical risks and moderate-to-severe AC In the present study, PC was also used in the treatment of patients with ruptured AC, emphysematous AC, complicated AC accompanied by pericholecystic, intrahepatic abscess, bilioma, and who had high surgical risks, and a dramatic response was obtained (Fig. 2-5).

In a study that was conducted by Aroori et al.,[30] it was shown that PC was a useful procedure in patients who had severe AC in their study, which excluded patients who had malignancy and who were not suitable for surgery. In the present study, PC was also applied to a patient who had advanced-stage pancreatic cancer, developed metastasis to the gallbladder and had perforated gallbladder, and success was achieved.

The limitations of the present study were that there was a postoperative follow-up of 1 month, the number of COVID-19 patients was low, and it was a retrospective study. Also, the number of cancer patients was low.

CONCLUSION

Although many guidelines emphasize that LC can be performed at the first admission to hospital in patients with AC with non-delayed low morbidity, elective surgery is a clinical situation, which can be postponed in the AC COVID-19 pandemic. PC must be used effectively due to aerosol formation during LC, and if necessary, extended indications (e.g. younger patients with low ASA) must be expanded until better evidence is found in the pandemic process. PC is a safe and effective treatment method for the patient and the healthcare staff, and employees who perform the procedure whether they have mild, severe, complicated or comorbid disease that can be seen at any age especially in patients who had AC during the COVID-19 pandemic.

Disclosures

Ethics Committee Approval: The study was approved by the Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (No: 2021.05.155, Date: 06/05/2021).

Authorship Contributions: Concept: Ü.T., S.D., S.S.; Design: Ü.T.; Supervision: Ü.T., S.S., S.D., M.B.S.; Materials: Ü.T.; Data Collection or Processing: Ü.T.; Analysis or Interpretation: Ü.T.; Literature Search: Ü.T.; Writing: Ü.T., S.S., S.D., M.B.S.; Critical review: Ü.T., S.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Informed Consent: Written informed consent was obtained from all patients.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study received no financial support.

Peer-review: Externally peer reviewed.

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