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Original Article

Risk Factors Affecting Complications in Patients with Gallbladder Inflammation Due to Gallstones Following Initial Antibiotic Treatment

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Abstract

Background: In 2019, the COVID-19 pandemic limited the timing of surgery in patients with acute calculous cholecystitis (AC), resulting in delayed laparoscopic cholecystectomy (LC) operations for more than three months, according to the FSSA Clinical guide to surgical prioritization during the Coronavirus pandemic, 2022.

Objective: This study aimed to identify the risk factors for gallstone-related complications, including recurrent cholecystitis, cholecystitis with cholangitis, and CBD stone-related complications, within 90 days after conservative treatment for AC.

Materials and Methods: From June 2019 to June 2021, retrospective medical records from a single-center tertiary care hospital were reviewed. A total of 184 patients, aged over 18 years, who were admitted with AC grade I-II according to the Tokyo Guidelines 2018 and treated with conservative therapy were included. Patients with severe cholecystitis, cholangitis, or choledocholithiasis were excluded. Data including age, sex, comorbidities, laboratory results, and imaging findings were collected. Multivariable binary regression was performed to identify risk factors for gallstone-related complications, with results presented as risk ratios (RR) and 95% confidence intervals. Gallstone-related complications were defined as recurrent cholecystitis, cholangitis, choledocholithiasis, and pancreatitis.

Results: Among the 184 patients, thirty-two (17.4%) experienced gallstone-related complications within 90 days after receiving conservation treatment for AC. The risk factors identified were white blood cell counts ≥ 12,000 cells/mL (Adj. RR 2.63, 95% CI 1.35-5.14, $p = 0.005$), gallbladder wall thickness ≥ 10 mm (Adj. RR 3.01, 95% CI 2.01-4.50, $p < 0.001$), and serum bicarbonate < 22 mmol/L (Adj. RR 0.38, 95% CI 0.17-0.87, $p = 0.022$). The model predicted gallstone-related complications with an accuracy of 67% (area under the ROC curve = 0.669).

Conclusion: In the context of delayed surgery for acute cholecystitis, patients with a white blood cell count of less than 12,000 cells/mL, gallbladder wall thickness of less than 10 mm, and bicarbonate levels of 22 mmol/L or higher may be suitable candidates for delayed laparoscopic cholecystectomy. However, concerns regarding gallstone-related complications remain. Definitive treatment should be provided based on the available clinical circumstances.

Keywords: Acute calculous cholecystitis, COVID-19, Gallstones, Laparoscopic cholecystectomy

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Introduction

Acute cholecystitis is associated with gallstones in 95% of cases. Treatment for cholecystitis includes antibiotics and cholecystectomy, which can be performed either as an open surgery or laparoscopic cholecystectomy (LC). Laparoscopic cholecystectomy is the primary treatment method.[1] according to the Tokyo Guidelines 2018. The treatment of acute cholecystitis depends on the severity of the inflammation. The appropriate timing for surgery is divided into early LC, performed within 72 hours of inflammation, and delayed LC, conducted 6-10 weeks after the inflammation.[2]

During the COVID-19 pandemic, surgeries have been delayed more than usual. According to the guidelines of the Federation of Surgical Specialty Associations (FSSA) in the UK, cholecystectomy after acute cholecystitis is categorized as non-urgent surgery, and it is recommended to postpone the procedure for more than 90 days.[3]

The rate of hospital readmission due to complications from gallstones while waiting for laparoscopic cholecystectomy was found to be 28.5%, according to the research by Cheruvu CV, et al. Complications include cholecystitis, gallbladder perforation, cholangitis, and pancreatitis.[4]

The important consequences of developing complications after conservative treatment of acute cholecystitis are increased hospital stays, increased medical costs, and increased morbidity or mortality.[4]

According to research by Loozen C, et al., surgical treatment was successful in 87% of patients with gallbladder disease and 96% of patients with mild gallbladder disease, with a recurrence rate of 20%.[5] The recurrence rate among patients treated with antibiotics alone, with an average age of 62.2 years, was 13.7%. The recurrence rate in patients who received only antibiotic treatment was low.[6] However, in elderly patients with an average age of 80.4 ± 7.2 years, the recurrence rate was 58%, with a possibility of recurrence within two years.[7]

Research Objectives

This research aims to explore the risk factors contributing to gallstone complications and the complications arising from gallstones following cholecystitis after conservative treatment, including recurrent cholecystitis, cholecystitis with cholangitis, and CBD stone-related complications over 90 days.

Materials and Methods

Research Design and Sample Group

The research design was a retrospective cohort study. It involved selecting patients with mild to moderate acute cholecystitis (Grade I-II) who were admitted for inpatient treatment at Nakornping Hospital between June 1, 2019, and June 1, 2021, as shown in Figure 1.

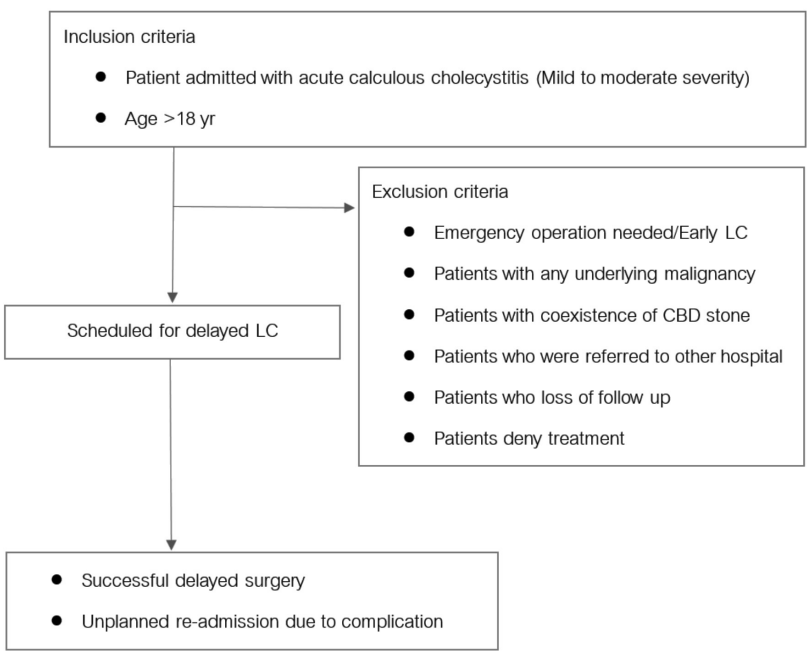

Figure 1 Research implementation plan

Research Location: Nakornping Hospital

Inclusion Criteria

1. Acute calculous cholecystitis
2. Age over 18 years.
3. Patients diagnosed with mild to moderate acute cholecystitis according to the Tokyo Guidelines 2018.
4. Patients scheduled for cholecystectomy at Nakornping Hospital.

Exclusion Criteria

1. Patients with a pre-existing cancer diagnosis.
2. Patients with common bile duct stones identified during initial treatment.
3. Patients referred back to other hospitals.
4. Patients who cannot be followed up.
5. Patients who refused treatment.

The research design was a retrospective cohort study. We included patients over 18 years old diagnosed with mild to moderate acute calculous cholecystitis[8] admitted to the Surgical department, Nakornping Hospital, Chiangmai, during the COVID-19 pandemic between 1 June 2019 and 1 June 2021. After admission, intravenous antibiotics; ceftriazone 2 grams intravenous once daily; metronidazole 500 mg intravenous every 8 hours for 7 - 10 days; then switch to oral antibiotics for 7 days; and general supportive care was given to all patients as a standard treatment. Response to aforementioned treatments was reevaluated on a daily basis. Patients could be discharged when clinical improvement based on stable vital signs, ameliorated abdominal signs, and symptoms were observed. Then, patients would be scheduled for elective LC in the next six to eight weeks. However, the schedules might be extended due to limited resources during the pandemic.

We excluded patients who underwent early LC, as it is also considered to be the first-line treatment for cases of mild form acute calculous cholecystitis.[8] We also excluded patients with pre-existing cancer, coexisting bile duct stones, LC done in other hospitals, loss follow-up, and patients who denied treatment protocol as listed above.

Sample size estimation and key measurements

Based on the calculation for sample size, a total of 162 patients is required when setting α (Type I error) at 0.05 and β (Type II error) at 0.2. Using the calculation for two independent proportions based on gallbladder wall thickness, the minimum sample size required is 162 patients. According to the research by T. Miyata et al. (2021),[9] factors affecting the occurrence of complications include age, white blood cell count (> 13,500/ul), C-reactive protein (CRP), serum albumin level, and gallbladder wall thickness (≥ 5 mm).

Proportion in group 1 (P1) = 0.45, proportion in group 2 (P2) = 0.189, ratio (r) = 5.0, (with ratio 1:5), the sample size for group 1 = 27, and group 2 = 135, adding 20% loss follow-up or completed that sample size for group 1 was 32 and group 2 was 162.

Data analysis

Comparisons of general clinical characteristics are analyzed using Student's *t*-test. Group comparisons and continuous variable cases are generalized linear models: extension to the binomial family resulted in risk ratio; we used risk ratio used to causal relationship analysis to explain the probability of events occurring in the exposed group over the non-exposed group analyzed using Fisher's exact test. Predictive complication factors are analyzed using univariable binary regression, adjusting for confounding factors using multivariable binary regression. The results are presented as adjusted risk ratios, with statistical significance set at 0.05. Data analysis is performed using STATA version 14.0.

Results

From a review of medical records for patients with Grade I-II acute cholecystitis who were admitted to Nakornping Hospital between June 1, 2019, and June 1, 2021, a total of 339 patients met the criteria. After excluding 155 patients who did not meet the criteria, 184 patients were included in the study. Among these, 152 patients were scheduled for surgery as planned, and 32 patients required hospitalization due to complications from gallstones, as shown in Figure 2.

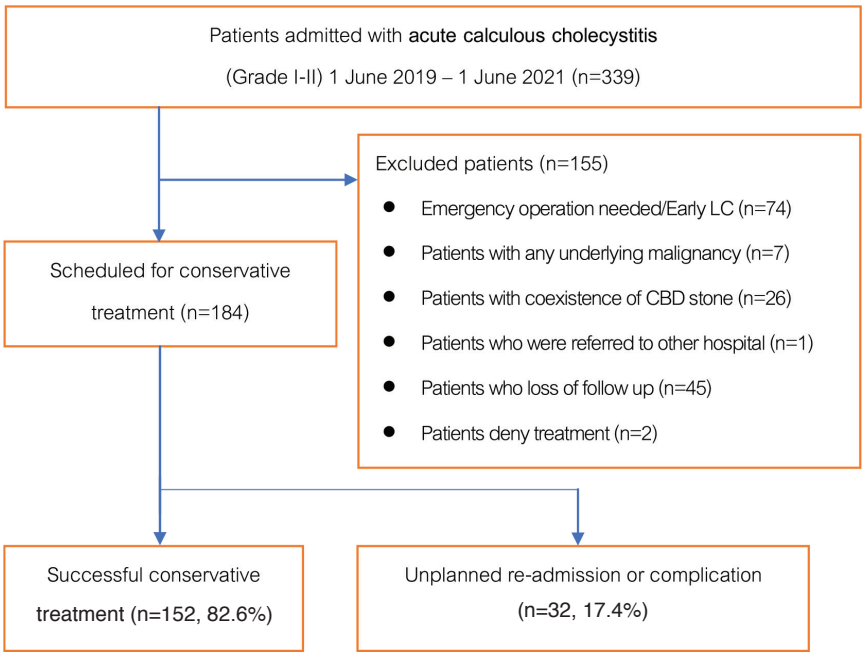

Figure 2 Research implementation plan

Basic Clinical Characteristics

The average age of the patients who were able to undergo surgery as scheduled was 57.08 ± 16.19 years. The average age of the patients who experienced complications before surgery was 56.66 ± 20.72 years. As shown in Table 1, there were no significant differences between the two groups in terms of age, sex, weight, height, body mass index, or pre-existing conditions.

Table 1 Comparison of basic patient characteristics

Patient Characteristics	Gallstone-related complications		
	Yes n = 32, (%)	No n = 152, (%)	*p*-value
Age (years), mean ± SD	56.66 ± 20.72	57.08 ± 16.19	0.701
Age			0.593
< 60	19 (59.38)	78 (51.32)	
≥ 60	13 (40.62)	74 (48.68)	
Sex			0.515
Male	15 (48.88)	69 (45.39)	
Female	17 (53.12)	83 (54.61)	
Weight (kg), mean ± SD	64.72 ± 19.75	64.57 ± 14.51	0.956
Height (metre)	1.61 ± 0.95	1.60 ± 0.95	0.957
BMI (kg/m^2)	24.77 ± 5.26	24.93 ± 5.26	0.874
Diabetes mellitus (DM)			0.210
Yes	3 (9.38)	31 (20.39)	
No	29 (90.62)	121 (79.61)	
Hypertension (HTN)			0.843
Yes	12 (37.50)	63 (41.45)	
No	20 (62.50)	89 (58.55)	
Thalassemia			0.580
Yes	1 (3.12)	7 (4.61)	
No	31 (96.88)	145 (95.39)	
Chronic kidney disease (CKD) stage 3-5			0.378
Yes	2 (6.25)	21 (13.82)	
No	30 (93.75)	131 (86.18)	

Primary Outcome

Single factors that significantly affect the occurrence of complications from gallstones include White Blood Cells (WBC) and Lymphocytes. In the group with WBC ≥ 12,000 cells/ml, 65.63% (21 patients) experienced complications, compared to 34.38% (11 patients) in the WBC < 12,000 cells/ml group, with a statistically significant difference ($p = 0.020$). Additionally, the average Lymphocyte percentage in the group with complications was 11.48 ± 7.82%, compared to 15.56 ± 10.47% in the group without complications ($p = 0.038$),

An imaging study measured the GB wall thickness by ultrasound in 142 patients and by CT scan in 42 patients, as shown in Table 2.

Table 2 Results of the primary outcome

Factors	Gallstone-related complications (n =184)		
	Yes, n = 32 Mean ± SD	No, n = 152 Mean ± SD	*p*-value
Clinical symptoms			
Body temperature (°C)	36.97 ± 0.67	37.02 ± 0.75	0.727
Onset of symptoms (hours)	34.71 ± 31.82	42.90 ± 39.01	0.268
Laboratory studies			
Hb (g/dL)	13.26 ± 2.25	12.89 ± 2.02	0.357
WBC (cells/μL), (%)			0.020
< 12,000	11 (34.38)	87 (57.24)	
≥ 12000	21 (65.63)	65 (42.76)	
Neutrophil	81.94 ± 10.68	77.62 ± 12.30	0.067
Lymphocyte	11.48 ± 7.82	15.56 ± 10.47	0.038
Plt (/uL)	264,719 ± 63,652	261,069 ± 82,596	0.828
Laboratory studies			
BUN (mg/dL)	12.37 ± 4.50	13.97 ± 9.32	0.383
Cr (mg/dL)	0.94 ± 0.29	1.11 ± 1.36	0.558
Sodium (mmol/L)	138.13 ± 3.19	137.41 ± 3.20	0.228
< 140 n, (%)	23 (76.67)	132 (85.71)	
≥ 140 n, (%)	7 (23.33)	22 (14.29)	
Chloride (mmol/L)	103.91 ± 4.38	103.80 ± 4.20	0.894
Bicarbonate (mmol/L)			0.095
< 22 n, (%)	6 (20.00)	57 (37.01)	
22-28 n, (%)	23 (76.67)	86 (55.85)	
> 28 n, (%)	1 (3.33)	11 (7.14)	
Potassium (mmol/L)	3.75 ± 0.39	3.85 ± 0.50	0.289
Albumin (g/dL)	4.02 ± 0.60	3.95 ± 0.56	0.256
Globulin (g/dL)	3.31 ± 0.54	3.25 ± 0.57	0.588
AST (U/L)	100.17 ± 177.54	86.45 ± 187.40	0.731
ALT (U/L)	75 ± 110.68	64.35 ± 107.93	0.642
ALP (U/L)	122.53 ± 90.05	109.48 ± 67.92	0.325
Total bilirubin (mg/dL)	1.35 ± 1.39	1.38 ± 2.67	0.961
Direct bilirubin (mg/dL)	0.79 ± 1.05	0.82 ± 2.05	0.941
Imaging findings			
Gallbladder (GB) wall thickness			0.092
< 10mm n, (%)	27 (87.10)	146 (95.42)	
≥ 10mm n, (%)	4 (12.90)	7 (4.58)	
Diagnosis by CT n, (%)			0.589
Yes n, (%)	7 (22.58)	35 (22.88)	
No n, (%)	24 (77.42)	118 (77.12)	
Gallstones			0.419
Few (1-4) n, (%)	15 (50.00)	92 (59.74)	
Many (≥ 5) n, (%)	15 (50.00)	62 (40.26)	
Severity in Tokyo guidelines			0.541
Grade I n, (%)	23 (71.88)	99 (65.13)	
Grade II n, (%)	9 (28.12)	53 (34.87)	

When factors with a *p*-value < 0.2 were analyzed using Univariable analysis to calculate the risk ratio, statistically significant factors were identified. For WBC ≥ 12,000 cells/ml, the risk ratio was 1.53 (1.12-2.10) with a p-value of 0.023, and for Lymphocytes, the risk ratio was 0.96 (0.92-1.00) with a *p*-value of 0.038, as shown in Table 3.

Table 3 Risk ratio of key variables from univariable analysis

Univariable analysis	Risk ratio	*p*-value
WBC ≥ 12000 cells/μL	1.53 (1.12-2.10)	0.023
Neutrophil	1.03 (1.00-1.06)	0.067
Lymphocyte	0.96 (0.92-1.00)	0.038
Bicarbonate < 22 mmol/L	0.45 (0.19-1.03)	0.600
GB wall thickness ≥ 10 mm	2.22 (0.95-5.22)	0.067

When these factors were analyzed for Adjusted Risk Ratio (Adj. Risk Ratio) using Multivariable binary regression, factors significantly increasing the risk of complications included WBC ≥ 12,000 cells/ml with an adjusted risk ratio of 2.63 (1.35-5.14) and a *p*-value of 0.005, and Gallbladder wall thickness ≥ 10 mm with an adjusted risk ratio of 3.01 (2.01-4.50) and a *p*-value of < 0.001. Conversely, a factor that reduced the risk of complications was Bicarbonate < 22 mmol/L, with an adjusted risk ratio of 0.38 (0.17-0.87) and a *p*-value of 0.022, as shown in Table 4.

Table 4 Adjusted risk ratio of key variables from multivariable analysis

Multivariable analysis	Adjusted risk ratio	*p*-value
WBC ≥ 12000 cells/μL	2.63 (1.35-5.14)	0.005
GB wall thickness ≥ 10 mm	3.01 (2.01-4.50)	< 0.001
Bicarbonate < 22 mmol/L	0.38 (0.17-0.87)	0.022

Secondary Outcome

Among the total of 184 patients in the study, 32 patients (17.4%) experienced complications. These were categorized as follows: recurrent cholecystitis in 10 patients (31.25%), cholecystitis with cholangitis in 4 patients (12.50%), and CBD stone-related complications in 18 patients (56.25%), as shown in Table 5.

Table 5 Results of the secondary outcome

Gallstone-related complication ≤ 90 days	Number of patients n = 32 (%)
Recurrent cholecystitis	10 (31.25)
Cholecystitis with cholangitis	4 (12.50)
CBD stone-related complications	
Cholangitis	6 (18.75)
CBD stone	8 (25.00)
Gallstone pancreatitis	4 (12.50)

Discussion

Acute calculous cholecystitis is one of the most common acute abdomen conditions. Tokyo Guidelines 2018 recommends early LC as the first line treatment for cases of mild form acute calculous cholecystitis, while in moderate form, it can also be managed with intravenous antibiotics and general supportive care, followed with elective LC. Unfortunately, some patients develop gallstone-related complications while waiting for the surgery.

Miyata, et al. found that 20 out of 168 patients with moderate and severe (grade II and III) acute calculous cholecystitis developed acute cholangitis and/or cholecystitis while waiting for surgery. Pre-operative parameters were analyzed, including white blood cell counts, C-reactive protein levels, albumin levels, gallbladder wall thickening (> 5 mm), incarcerated gallbladder neck stones, and peri gallbladder abscess. Compared with our study, similar results are observed, such as white blood cell counts (> 13,500/mL and ≥ 12,000/mL, respectively) and gallbladder wall thickening (> 5mm and > 10 mm, respectively) associated with increased risk of complication while waiting for surgery.

Several studies also demonstrated factors affecting the risk of complications while waiting for surgery. Barak, et al. showed the factors that affected the failure of conservative treatment of AC were age > 70 years, and DM distended gallbladder > 5 cm.[9]

According to the guidelines, elective LC should be scheduled 6-10 weeks after the attack. Our study demonstrates that, in order to avoid gallstone-related complications while waiting for the surgery, patients with WBC ≥ 12,000/ml, gallbladder wall thickness ≥ 10 mm, and bicarbonate > 22 mmol/L should be considered to be the first priority group, and operative scheduled should not be postponed.

However, this study has limitations due to the inability to collect additional data on C-reactive protein, stone incarceration, and lactic acid. Moreover, the study expresses moderate prediction performance, with a ROC of 67% (Figure 3). Therefore, further randomized controlled trials are recommended for additional, comprehensive data to enhance the accuracy of predictive parameters.

In this study, WBC ≥ 12,000 cells/ml, Gallbladder wall thickness, and Bicarbonate < 22 mmol/L were identified as factors that increase the risk of complications. Compared to previous research, the factors that affected the failure of Conservative Treatment of AC were age > 70 years and DM distended gallbladder > 5 cm.[10] Among those treated with antibiotics for acute cholecystitis (AC), the recurrence rate was 13.7, with a higher recurrence rate within 100 days after AC.[6]

This study is a retrospective cohort study, which avoids selection bias but has limitations due to the inability to collect additional data such as C-reactive protein, stone incarceration, and lactic acid. Moreover, the study had only moderate prediction performance, with an ROC of 67%. Therefore, further research using randomized controlled trials is recommended to include additional data and enhance predictive accuracy, as shown in Figure 3.

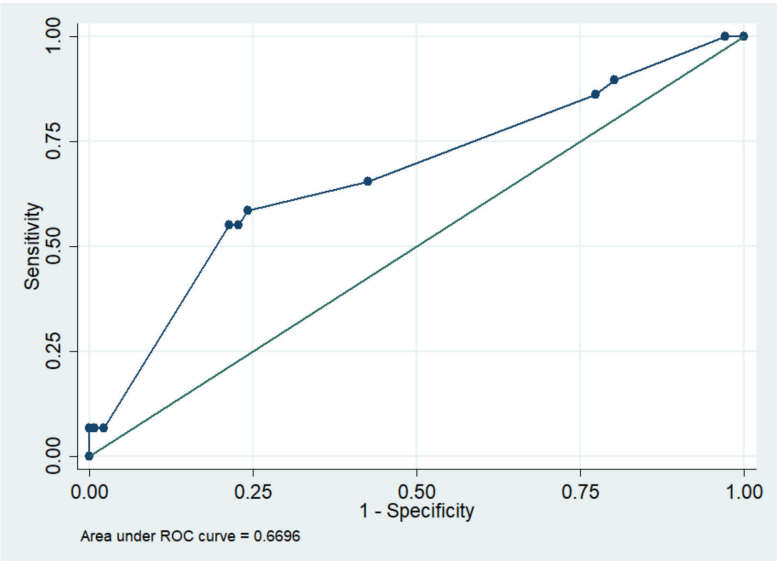

Figure 3 Receiver operating characteristic curve (ROC) derived from the post-estimation probability of gallstone-related complications. The Y-axis shows fractions of true positives, while the X-axis demonstrates false positives of the correspondent prediction from multivariable analysis.

This study found that the factors associated with the above studies were persistently elevated WBC (> 15,000) and gallbladder wall thickening, indicating severe AC inflammation, affecting AC treatment; therefore, follow-up should be performed in this group. However, in cases where surgical limitations arise, patients with risk factors such as WBC ≥ 12,000 cells/ml, Gallbladder wall thickness ≥ 10 mm, and Bicarbonate < 22 mmol/L may benefit from earlier surgery compared to those without risk factors, potentially reducing the likelihood of complications.

Conclusion

In the context of delayed surgery for acute cholecystitis, patients with a white blood cell count of less than 12,000 cells/mL, gallbladder wall thickness of less than 10 mm, and bicarbonate levels of 22 mmol/L or higher may be suitable candidates for delayed laparoscopic cholecystectomy. However, concerns regarding gallstone-related complications remain. Definitive treatment should be provided based on the available clinical circumstances.

REFERENCES

1. Brunicardi FC, Andersen DK, Billiar TR, et al. Schwartz's Principles of Surgery. 11th ed. New York: McGraw-Hill, 2019.
2. Okamoto K, Suzuki K, Takada T, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2018;25(1):55-72. doi: 10.1002/jhbp.516. Erratum in: J Hepatobiliary Pancreat Sci. 2019 Nov;26(11):534. doi: 10.1002/jhbp.686.
3. Federation of Surgical Specialty Associations. Clinical Guide to Surgical Prioritisation During the Coronavirus Pandemic; 26 January - 26 March 2021. [Cited 2021 Sep 1]. Available from: https://fssa.org.uk/covid-19_documents.aspx
4. Cheruvu CV, Eyre-Brook IA. Consequences of prolonged wait before gallbladder surgery. Ann R Coll Surg Engl. 2002;84(1):20-2.
5. Loozen CS, Oor JE, van Ramshorst B, et al. Conservative treatment of acute cholecystitis: a systematic review and pooled analysis. Surg Endosc. 2017;31(2):504-15. doi: 10.1007/s00464-016-5011-x.
6. Wang CH, Chou HC, Liu KL, et al. Long-term outcome of patients with acute cholecystitis receiving antibiotic treatment: a retrospective cohort study. World J Surg. 2014;38(2):347-54. doi: 10.1007/s00268-013-2311-3.
7. Mora-Guzmán I, Di Martino M, Bonito AC, et al. Conservative Management of Gallstone Disease in the Elderly Population: Outcomes and Recurrence. Scand J Surg. 2020;109(3):205-10. doi: 10.1177/1457496919832147.
8. Okamoto K, Suzuki K, Takada T, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2018;25(1):55-72. doi: 10.1002/jhbp.516.
9. Miyata T, Matsui D, Fujiwara Y, et al. Predictive factors for developing acute cholangitis and/or cholecystitis in patients undergoing delayed cholecystectomy: A retrospective study. Asian J Surg. 2021;44(1):280-5. doi: 10.1016/j.asjsur.2020.07.002.
10. Barak O, Elazary R, Appelbaum L, et al. Conservative treatment for acute cholecystitis: clinical and radiographic predictors of failure. Isr Med Assoc J. 2009;11(12):739-43.