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original article

Early versus delayed approach in cholecystectomy after admission to an emergency department. A multicenter retrospective study

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SUMMARY: **Early versus delayed approach in cholecystectomy after admission to an emergency department. A multicenter retrospective study.**

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Background. *Discussion regarding the timing of cholecystectomy for acute cholecystitis is still ongoing. This study evaluates the outcomes of patients who underwent surgery for acute cholecystitis after emergency admission at St. Orsola University Hospital of Bologna and Umberto I Hospital La Sapienza University of Rome.*

Patients and methods.. *We performed a retrospective study on 464 patients who underwent cholecystectomy for acute cholecystitis. We divided patients in three groups based on the time elapsed between the onset of symptoms and surgery: within 72 hours (Group A), between 72 hours and 6 weeks (Group B) and after 6 weeks (Group C). We performed both univariate and multivariate statistical analysis on the data collected.*

Results. *The best results were in Group C, with significant differences with the others two groups: higher rates of laparoscopic technique (93% of cases), no mortality, better morbidity and shorter hospital stay. On the contrary, no significant differences were observed between Groups A and B: laparoscopic cholecystectomy 67% vs 66%, morbidity (Clavien-Dindo III-IV) 5% vs 5%, mortality 2% vs 1%, hospital stay 6,6 vs 5,6 days. Conversion rate was 11% in Group A, 18% in Group B and 4% in Group C.*

Conclusion. *Our experience shows better results for cholecystectomies performed after 6 weeks from the onset of symptoms, while earlier cholecystectomies have worse outcomes regardless if they are performed before or after 72 hours from the onset of symptoms.*

KEY WORDS: Acute cholecystitis - Timing - Outcome - Emergency department.

Introduction

The general incidence of acute cholecystitis has been reported to be 10%-18% of all patients with symptomatic cholelithiasis and it's the most common gallstone-related complication (1, 2). If not treated, it may be fatal in the short term due to sepsis. In particular, gangrenous and perforated cholecystitis may develop and these complications lead to an increased morbidity and mortality (3).

The international guidelines on acute cholecystitis, the 2013 Tokyo Guidelines (TG13) [**4**-**6**], have been used globally to define the basic criteria for the management of acute cholecystitis (7-9).

The TG13 recommend early laparoscopic cholecystectomy within 72h from the onset of symptoms as the best therapeutic strategy for acute cholecystitis, especially in mild cases. Cholecystectomy performed within 72h decreases hospital stay and costs (10).

Patients with moderate acute cholecystitis, including patients with a duration of symptoms >72h, are likely to be associated with increased difficulty in performing cholecystectomy due to increased inflammation. Gallbladder drainage is recommended in selected cases (moderate/severe acute cholecystitis) as first-line therapy, followed by delayed laparoscopic cholecystectomy 6-8 weeks later (11). The in-

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terval period of medical treatment seems to help the resolution of acute inflammation and improve the safety of surgery (12).

However, other studies report that cholecystectomies performed without interval are just as successful (10).

Therefore, the optimal timing for surgical procedure in case of acute cholecystitis is still controversial, and the discussion regarding potential benefits continues.

The aim of the present study was to analyze the clinical outcomes of laparoscopic cholecystectomy and determine the most appropriate timing for surgery by collecting data from two Italian centers.

Patients and methods

The study was designed as a case-control retrospective, observational multicenter study. Medical records of patients who underwent cholecystectomy for acute cholecystitis between September 2011 and December 2017 were retrospectively reviewed. Records were collected from two centers: "St. Orsola – Malpighi" Hospital - University of Bologna and "Umberto I" Hospital - La Sapienza University of Rome. Patient data was obtained solely from patient's file and collected in an electronic database for each center. All adult patients who underwent cholecystectomy for acute cholecystitis were included. The diagnosis of acute cholecystitis and its severity classification were based on the TG13 criteria (as showed in Table 1) (11).

We collected the data of 464 patients and we divided them into three groups according to the timing of cholecystectomy following the onset of symptoms: Group A within 72 hours, group B between 72 hours and 6 weeks and group C after 6 weeks.

Postoperative complications were classified according to the Clavien-Dindo classification (13). Grade I includes minor complications that do not require any intervention and that can be treated with routine medications like antipyretics, analgesics, diuretics, or physiotherapy. Grade II includes conditions that require major pharmacological intervention, such as respiratory infections, ascites, blood transfusions, and asymptomatic pulmonary embolism. Grade III includes any complication re-

TABLE 1 - TG13 SEVERITY GRADING FOR ACUTE CHOLECYSTITIS.

Grade III (severe) acute cholecystitis

Associated with dysfunction of any of the following organs/systems:

1.	Cardiovascular dysfunction	Hypotension requiring treatment with dopamine > 5microg/Kg per min, or any dose of norepinephrine
2.	Neurological dysfunction	Decreased level of consciousness
3.	Respiratory dysfunction	PaO2/FiO2 ratio <300
4.	Renal dysfunction	Oliguria, creatinine > 2.0 mg/dL
5.	Hepatic dysfunction	PT-INR > 1.5
6.	Hematological dysfunction	Platelet count < 100.000/mm^3

Grade II (moderate) acute cholecystitis

Associated with any one of the following condition:

1. Elevated white blood cell count (>18.000/mm^3)
2. Palpable tender mass in the right upper abdominal quadrant
3. Duration of complains >72h
4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)

Grade I (mild) acute cholecystitis

Does not meet the criteria of Grade III or Grade II acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.

quiring a surgical, endoscopic, or radiological intervention, such as respiratory infections requiring bronchoscopy, pleural effusions requiring drainage, ascites or an abdominal collections requiring percutaneous drainage, and re-operation for abdominal collection, bleeding, or other reasons. Grade IV includes patients with life-threatening complications requiring admission to the Intensive Care Unit, and grade V includes death in the postoperative period. Mortality was evaluated at 90 days.

Clinical and demographical characteristics, comorbidities, complications, lengths of hospital stay, operative times and conversion rates among the three groups were compared.

Statistical analysis was performed using one-way analysis of variance with the Bonferroni correction, Fisher's exact test and $\chi 2$ test. Categorical variables were described as numbers, and continuous variables were described as median and ranges. A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 13.0 (Chicago).

Results

Preoperative characteristics, surgical procedures and postoperative outcomes of the 464 patients included in the study are listed in Table 2. The cohort of patients had a mean age at surgery of 59.3±17.5 [range, 18-102] years. The female to male ratio was 233/231 (1.01). There were 95 patients in Group A (who underwent surgery within 72 hours from the onset of symptoms), 196 in Group B (who underwent surgery between 72 hours and 6 weeks from the onset of symptoms) and 173 in Group C.

Clinical data

The average age of each group ranged from 55.0 years in Group C to 62.9 years in Group A. About 50% of patients were male (n=231). Group B had the largest proportion of male individuals, but no significant differences were observed among three groups. ASA score III-IV were significantly preponderant in Group A and Group B when compared to Group C. Significant difference were recorded among three groups for Cardiovascular disease and Chronic renal failure (CRF); conversely Diabetes, Chronic obstructive pulmonary disease (COPD), Obesity and pre-operative laboratory test results were not significantly different. Regarding case severity, there were 306 mild (grade I) cases (66%), 144 cases moderate (grade II) (31%), and 14 severe (grade III) cases (3%). Statistically significant differences were listened in Table 3.

Intraoperative data

Both open and laparoscopic surgeries were included, with a preponderance of laparoscopic procedures in Group C ($p<0.01$). Group A and Group B had a statistically significant larger number of conversions in comparison with Group C ($p<0.01$).

The overall median operative time was 89.2±42.3 [30-313] minutes. There was a trend toward longer duration of surgeries in Group B; in particular, median operative time was 89.4±40.4 minutes for 95 patients in Group A, 99.1±43.9 minutes for 196 patients in Group B and 77.7±38.8 for patients in Group C; however, the differences were not significant.

Postoperative data

Three patients died in hospital within 90 days after surgery: 2 in Group A, 1 in group B, and none in group C. Neither in-hospital nor 90-days mortality were significantly affected by timing of surgical procedure. Postoperative complications occurred in 52 patients (11%) of our study cohort; these included wound infection in 18 patients; intra-abdominal abscess in 1 patient; bile leakage in 9 patients, heart failure in 3 patients, pneumonia and urinary tract infection in 5 and 1 patients, respectively. No patients had a re-operation. In particular, severe complications (Clavien grade III-IV) were more prevalent in Group A and Group B, and mild complications (Clavien grade I-II) were more prevalent in Group B. However, no significant differences were recorded among the three groups. The overall median hospital stay was 4.9±7.7 [1-69] days and was not significantly affected by the timing of surgery. The median hospital stay was lower in Group C compared to the other two groups, with an average of 3.3 days. The longest median hospital stay was 6.6 days for patients in Group A. The impact of timing on the overall occurrence of complications, postoperative death and discharge at home - in relation to other variables considered in the logistic regression model - is shown in Table 4. No differences in mortality rate were found between the groups, though the power of the study might not be enough high to

TABLE 2 - PATIENT CHARACTERISTICS.

Number of Patients	464
Age (years)*	59.3±17.5 [18-102]
Male sex	231 (50%)
BMI (kg/m²)*	26.4±4.9 [15-50]
ASA Class	
I-II	327 (71%)
III-IV	137 (29%)
Comorbidity	
Cardio-Vascular	218 (47%)
Diabetes	49 (11%)
COPD	45 (10%)
CRF	22 (5%)
Obesity	67 (14%)
Laboratory tests	
WBC (x10^9/L)*	9.54±4.68 [1.90-27.53]
Platelets (x10^9/L)*	246.20±85.11 [22-828]
INR*	1.17±0.50 [0.80-6.52]
Creatinine (mg/dL)*	0.96±0.45 [0.38-5.03]
Amilase (U/L)*	119.98±350.47 [10-4641]
Lipase (U/L)*	188.51±1088.38 [3-12604]
Bilirubine (mg/dL)*	1.18±1.61 [0.14-18.94]
CRP (mg/L)*	8.09±11.17 [0.01-63.26]
Classification of acute cholecystitis [TG13]	
Mild	306 (66%)
Moderate	144 (31%)
Severe	14 (3%)
Emergency Procedure	291 (63%)
Surgical technique	
Open	58 (13%)
Laparoscopic	354 (76%)
Conversion to open	52 (11%)
Operative time (min)*	89.2±42.3 [30-313]
In-hospital mortality	3 (1%)
90-day mortality	3 (1%)
Complication [Clavien-Dindo]	52 (11%)
Grade I-II	34 (7%)
Grade III-IV	18 (4%)
Hospital stay (days)*	4.9±7.7 [1-69]
Discharge at home	426 (92%)

Values in parentheses are percentages unless indicated otherwise; *Values are mean ± SD.

capture statistical significance. Complication rates and rates of discharge at home are shown to be more favourable in Group C in the unadjusted model. However, after adjusting for co-variables, those differences were not found to be statistically significant.

Discussion

Acute cholecystitis is a common disease; although laparoscopic cholecystectomy is accepted as the gold standard of surgical treatment, the timing of surgical intervention is still controversial (14).

TABLE 3 - COMPARISON OF THE PATIENT CHARACTERISTICS AMONG THE GROUPS.

	Group A *Within 3 days from admission*	**Group B** *Surgery after 3 days or more*	**Group C** *After 6 weeks*	**P-value**
Number of Patients	95	196	173	-
Age (years)*	62.9±17.8	61.4±17.8	55.0±16.2	ns
Male sex	46 (48%)	108 (55%)	77 (45%)	**0.05** *BvsC*
BMI (kg/m2)*	26.7±6.1	26.6±4.3	26.1±4.9	ns
ASA Class				
I-II	59 (62%)	122 (62%)	146 (84%)	**<0.01** *BvsC, AvsC*
III-IV	36 (38%)	74 (38%)	27 (16%)	
Comorbidity				
Cardio-Vascular	47 (50%)	104 (53%)	67 (39%)	**0.01** *BvsC*
Diabetes	13 (14%)	23 (12%)	13 (8%)	ns
COPD	10 (11%)	24 (12%)	11 (6%)	ns
CRF	3 (3%)	15 (8%)	4 (2%)	**<0.01** *AvsB, BvsC*
Obesity	15 (16%)	31 (16%)	21 (12%)	ns
Laboratory tests				
WBC (x10^9/L)*	10.9±5.6	10.8±4.9	7.32±2.7	ns
Platelets (x10^9/L)*	254.0±83.2	248.1±98.3	239.7±68.5	ns
INR*	1.2±0.5	1.3±0.7	1.1±0.2	ns
Creatinine (mg/dL)*	1.0±0.6	1.0±0.5	0.9±0.2	ns
Amilase (U/L)*	133.7±517.3	149.5±368.4	69.3±48.5	ns
Lipase (U/L)*	240.8±1312.9	329.8±1489.5	38.4±34.0	ns
Bilirubine (mg/dL)*	1.3±2.2	1.5±1.8	0.7±0.6	ns
CRP (mg/L)*	8.8±10.4	9.3±11.5	3.0±9.92	ns
Classification of acute cholecystitis [TG13]				
Mild	64 (67%)	101 (52%)	141 (81%)	**<0.01** *AvsB, AvsC, BvsC*
Moderate	30 (32%)	83 (42%)	31 (18%)	**<0.01** *AvsC, BvsC*
Severe	1 (1%)	12 (6%)	1 (1%)	**<0.01** *BvsC*
Operation				
Open	22 (23%)	30 (15%)	6 (3%)	**0.01** *AvsC, BvsC*
Laparoscopic	63 (66%)	131 (67%)	160 (93%)	**<0.01** *AvsC, BvsC*
Conversion to open	10 (11%)	35 (18%)	7 (4%)	**<0.01** *AvsC, BvsC*
Duration of procedure (min)*	89.4±40.4	99.1±43.9	77.7±38.8	ns
In-hospital mortality	2 (2%)	1 (1%)	0	ns
90-day mortality	2 (2%)	1 (1%)	0	ns
Complication [Clavien-Dindo]	10 (10%)	31 (16%)	11 (6%)	**< 0.01** *BvsC*
Grade I-II	5 (5%)	21 (11%)	8 (4%)	ns
Grade III-IV	5 (5%)	10 (5%)	3 (2%)	
Hospital stay (days)*	6.6±9.8	5.6±8.5	3.3±4.4	ns
Discharge at home	80 (84%)	174 (89%)	172 (99%)	**< 0.01** *AvsC, BvsC*

Values in parentheses are percentages unless indicated otherwise; *Values are mean ± SD.

According to SAGES (Society of American Gastrointestinal and Endoscopic Surgeons), the rates of conversions and complications in delayed cholecystectomies are not significantly different from those

TABLE 4 - LOGISTIC REGRESSION MODEL EXPLORING THE RELATIONSHIP BETWEEN TIMING TO SURGERY, COMPLICATIONS, IN-HOSPITAL MORTALITY AND 30-DAY MORTALITY.

		Unadjusted Model		Adjusted for co-variables	
	No. of patients	Odds ratio [CI 95%]	P-value	Odds ratio [CI 95%]	P-value
Complications					
Group A	10 (10%)	0.618 [0.289-1.322]	0.215	0.390 [0.156-1.972]	0.053
Group B	31 (16%)	1.00	-	1.00	-
Group C	11 (6%)	0.340 [0.165-0.699]	0.003	0.624 [0.279-1.392]	0.249
In-hospital mortality					
Group A	2 (2%)	4.108 [0.368-45.880]	0.251	2.989 [0.449-5.711]	0.142
Group B	1 (1%)	1.00	-	1.00	-
Group C	0	N/A	N/A	N/A	N/A
Discharge at Home					
Group A	80 (84%)	0.588 [0.263-1.315]	0.196	0.686 [0.238-1.979]	0.486
Group B	174 (89%)	1.00	-	1.00	-
Group C	172 (99%)	15.529 [2.029-118.857]	0.008	5.089 [0.600-43.186]	0.136

The adjusted model accounts for the possible impact of the co-variables: sex, presence of hypertension, presence of CRF, ASA score, Laparoscopic procedure and grade of cholecystitis. Patients of Group B (Surgery after 3 days and before 6 weeks) represented the reference group.

of early cholecystectomies. However, hospitalization-related medical expenses might be lower in early cholecystectomy (15). Conversely, while it does recommend surgical intervention, the EAES (European Association for Endoscopic Surgery) does not specify the timing of the operation (16).

The TG13 guidelines suggest an algorithm of management of acute cholecystitis based on overall clinical severity. Early cholecystectomy is recommended in mild or medium cases, while percutaneous drainage of the gallbladder with subsequent delayed cholecystectomy should be preferred in severe cholecystitis (17, 18).

Therefore, management of acute cholecystitis depends on the preferences of doctors as well as local factors, with early cholecystectomy rates ranging from 55% of cases in Australia to just 11% in the UK (19). In addition, the department the patient is initially admitted to can strongly influence subsequent management, with patients admitted to internal medicine departments being more likely to be treated conservatively.

This tendency is reflected in our study, with most patients belonging to group B having been admitted to internal medicine wards where they were unsuccessfully managed conservatively. However, this delay did not impact overall outcomes.

No statistically significant difference was found with regard to the mean ages among the groups in our cohort of people. The mean age was lower in Group C. Hershkovitz et al. (20) showed a significant age difference between early and delayed laparoscopic cholecystectomy groups, in particular the mean age of the early group was found to be significantly lower. This could be explained by the bias toward interval surgical procedure for more fragile patients with advanced age. On the other hands, Saber and Hokkam (21) found no difference in mean ages between similar groups. For our cohort of study, the mean of age was lower in groups with cholecystectomy performed after 6 weeks. This was due to our tendency to treat younger and less fragile patients conservatively whenever possible. In our study, the prevalence of comorbidities was not significantly different among the groups, except for cardiovascular disease and chronic kidney disease, which were significantly more prevalent in group B. Overall prevalence of comorbidities was higher in groups A and B when compared to group C, highlighting once more the tendency to delay the surgery for less frail patients. In the study performed by Ohta (16) comorbidities were significantly more prevalent in the group of patients treated with delayed cholecystectomy (> 6 weeks) compared with those treated with early cholecystectomy.

Conclusions

In conclusion, the lack of consensus regarding the timing of cholecystectomy for acute cholecystitis remains an important issue. There is an ongoing worldwide discussion about the modern concept of cholecystectomy being performed within 24 hours since hospital admission.

Our experience shows a trend towards better results for cholecystectomies performed after 6 weeks from the onset of symptoms, while earlier cholecystectomies have similar outcomes regardless if they are performed before or after 72 hours from the onset of symptoms. Therefore, the choice of timing does not seem to impact postoperative outcomes. More prospective, randomized studies will be required to confirm our results.

Conflict of interest/Financial support and sponsorship
None.

References

1. Attili AF, Carulli N, Roda E, et al. Epidemiology of gallstone disease in Italy: prevalence data of the Multicenter Italian Study on Cholelithiasis (M.I.COL.). Am J Epidemiol. 1995;141:158-165.
2. Halldestam I, Enell E-L, Kullman E, et al. Development of symptoms and complications in individuals with asymptomatic gallstones. Br J Surg. 2008;91:734-738.
3. Ausania F, Guzman Suarez S, Alvarez Garcia H, et al. Gallbladder perforation: morbidity, mortality and preoperative risk prediction. Surg Endosc. 2015;29:955-960. Doi: 10.1007/s00464-014-3765-6.
4. Takada T, Strasberg SM, Solomkin JS, et al. TG13: Updated Tokyo Guidelines for the management of acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2013;20:1-7. Doi: 10.1007/s00534-012-0566-y.
5. Yamashita Y, Takada T, Strasberg SM, et al. TG13 surgical management of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2013;20:89-96.
6. Miura F, Takada T, Strasberg SM, et al. TG13 flowchart for the management of acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2013;20:47-54.
7. Asai K, Watanabe M, Kusachi S, et al. Risk factors for conversion of laparoscopic cholecystectomy to open surgery associated with the severity characteristics according to the Tokyo guidelines. Surg Today. 2014;44:2300-2304.
8. Ambe PC, Christ H, Wassenberg D. Does the Tokyo guidelines predict the extent of gallbladder inflammation in patients with acute cholecystitis? A single center retrospective analysis. BMC Gastroenterol. 2015;15:142-150.
9. Paul Wright G, Stilwell K, Johnson J, et al. Predicting length of stay and conversion to open cholecystectomy for acute cholecystitis using the 2013 Tokyo Guidelines in a US population. J Hepatobiliary Pancreat Sci. 2015;22:795-801.
10. Gurusamy K, Samraj K, Gluud C, et al. Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Br J Surg. 2010;97:141-150.
11. Yokoe M, Takada T, Strasberg SM, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2013;20:35-46.
12. Chang TC, Lin MT, Wu MH, et al. Evaluation of early versus delayed laparoscopic cholecystectomy in the treatment of acute cholecystitis. Hepatogastroenterology. 2009;56:26-28.
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications. A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-213.
14. Agrawal R, Sood KC, Agarwal B. Evaluation of early versus delayed laparoscopic cholecistectomy in acute cholecistitis. Surg Res Pract. 2015:349801.
15. Low JK, Barrow P, Owera A, et al. Timing of laparoscopic cholecystectomy for acute cholecystitis: evidence to support early interval surgery. Am Surg. 2007;73:1188-1192.
16. Ohta M, Iwashita Y, Yada K. Operative timing of laparoscopic cholecystectomy for acute cholecystitis in a Japanese institute. JSLS. 2012;16:65-71.
17. Hirota M, Takada T, Kawarada Y. Diagnostic criteria and severity assessment of acute cholecystitis: Tokyo Guidelines. Hepatobiliary Pancreat Surg. 2007;14:78-82.
18. Koo KP, Thirlby RC. Laparoscopic cholecystectomy in acute cholecystitis: What is the optimal time for operation? Arch Surg. 1996;131:540-544.
19. Lujan JA, Parrilla P, Robles R, et al. Laparoscopic Cholecystectomy Vs Open Cholecystectomy in the treatment of acute cholecystitis: a prospective study. Arch Surg. 1998;133:173-175.
20. Hershkovitz Y, Kais H, Halevy A, et al. Interval laparoscopic cholecystectomy: what is the best timing for surgery? Isr Med Assoc J. 2016;18:10-12.
21. Saber A, Hokkam EN. Operative outcome and patient satisfaction in early and delayed laparoscopic cholecystectomy for acute cholecystitis. Minim Invasive Surg. 2014;2014:162643. doi: 10.1155/2014/162643.