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Risk Factors for Difficult Laparoscopic Cholecystectomy in Acute Cholecystitis

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ABSTRACT

Background and Objectives: Factors that contribute to difficult laparoscopic cholecystectomy (LC) in acute cholecystitis (AC) that would affect the performance of early surgery remain unclear. The purpose of this study was to identify such risk factors.

Methods: One hundred fifty-four patients who underwent LC for AC were retrospectively analyzed. The patients were categorized into early surgery and delayed surgery. Factors predicting difficult LC were analyzed for each group. The operation time, bleeding, and cases of difficult laparoscopic surgery (CDLS)/conversion rate were analyzed as an index of difficulty. Analyses of patients in the early group were especially focused on 3 consecutive histopathological phases: edematous cholecystitis (E), necrotizing cholecystitis (N), suppurative/subacute cholecystitis (S).

Results: In the early group, the CDLS/conversion rate was highest in necrotizing cholecystitis. Its rate was significantly higher than that of the other 2 histopathological types (N 27.9% vs E and S 7.4%; $P = .037$). In the delayed-surgery group, a higher white blood cell (WBC) count and older age showed significant correlations with the CDLS/conversion rate ($P = .034$ and $P = .004$).

Conclusion: In early surgery, histopathologic necrotizing cholecystitis is a risk factor for difficult LC in AC. A higher WBC count and older age are risk factors for delayed surgery.

Key Words: Acute cholecystitis, Difficult laparoscopic cholecystectomy, Histopathologic necrotizing cholecystitis, Laparoscopic cholecystectomy, Operative timing.

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INTRODUCTION

Delayed laparoscopic cholecystitis (LC) has been preferred for acute cholecystitis in the past, out of fear of a higher complication rate because of increased local inflammation and difficulty in dissection of Calot's triangle.[1,2] Recent analyses are in favor of early surgery, which seems to be feasible and safe, and it offers both medical and socioeconomic benefits compared with delayed-interval surgery.[3–7] As a result, delayed surgery is now chosen under certain situations, such as a prolonged time from onset to presentation, patient's comorbidity and age, and emergency medical system in each hospital, among other reasons. LC for AC is surgery with a high degree of surgical difficulty, and surgeons sometimes encounter difficult cases that require conversion. Although some risk factors for these cases have been analyzed,[8–10] comprehensive analyses related to the performance of early surgery have been inadequate. The status of the gallbladder differs between early surgery and delayed surgery. That is, early surgery is an operation done during a progressive inflammatory process, while delayed surgery is performed after inflammation has subsided. In addition, in early surgery, the edematous status of the gallbladder wall affects the difficulty of LC.[11] In early surgery, both the stages of cholecystitis and the edematous status can be confirmed from histopathological findings.[12,13] Therefore, histopathological analyses are sure to be indispensable for this analysis. However, few previous reports have referred to histopathological findings for this purpose. The present study therefore evaluated the difficulty in performing LC in patients with AC, separately for early surgery and delayed surgery, with special focus on early surgery and on the histopathological findings.

MATERIALS AND METHODS

A retrospective analysis of patients who underwent LC for AC at Steel Memorial Muroran Hospital from April 2007 through December 2013 was performed. Patients with recurrent AC were excluded from the study. The patients were categorized into 2 groups according to the interval between surgery and symptom onset (early surgery, ≤240 hours; delayed surgery, >240 hours). Patients who had coexisting common bile duct stones or severe comorbidi-

ties or who were receiving anticoagulant agents were excluded from early surgery. Since 2009, patients over 75 years of age were all scheduled for delayed-interval surgery because of the need for a detailed preoperative medical check. In principle, cholecystectomy was performed laparoscopically whether the operation was early or delayed. Patients who had undergone upper abdominal surgery previously were excluded from undergoing LC. LC for AC was performed in 154 patients during the study period. All 154 cholecystectomy procedures were performed by experienced surgeons using the 4-port method. A case of difficult laparoscopic surgery (CDLS) was defined as any case with operation time ≥3 hours and/or bleeding volume ≥300 mL. Time to operation was defined as the time from symptom onset to the time of operation. In converted cases, the extent of dissection before conversion was classified as minimal, some, and extensive dissection, according to a previous report.[14]

The early group comprised 70 patients who underwent surgery ≤240 hours after symptom onset, while the delayed group comprised 84 patients who underwent surgery >240 hours after symptom onset.

The 70 patients in the early group were divided by histopathological findings into 3 consecutive phases according to the classification published by Muto et al.[12]: edematous cholecystitis (E); necrotizing cholecystitis (N); and suppurative/subacute cholecystitis (S). Moreover, the edematous status of the gallbladder wall was assessed in these cases as an indicator of the ease of dissection. An experienced pathologist confirmed the histopathological features of all cases.

CT findings, including air in the gallbladder wall or lumen, intraluminal membranes, hemorrhage into the lumen, irregular or absent gallbladder wall, pericholecystic abscess, and lack of gallbladder wall enhancement, were reported as findings suggesting necrotizing cholecystitis.[15] The rates of these CT findings were compared with the histopathological diagnosis of necrotizing cholecystitis.

Finally, the 70 patients in the early group were divided into 8 subgroups based on performance of surgery with cutoffs of 24, 48, 72, and 96 hours from symptom onset for comparison of clinical results in ultra-early stages. Group 1 comprised patients who underwent cholecystectomy at ≤24 hours, group 2 at >24 hours but ≤240 hours, group 3 at ≤48 hours, group 4 at >48 hours but ≤240 hours, group 5 at ≤72 hours, group 6 at >72 hours but ≤240 hours, group 7 at ≤96 hours, and group 8 at >96 hours but ≤240 h. Group 1 was compared to group 2, group 3 to group 4, group 5 to group 6, and group 7 to group 8, with respect to the association between clinical factors including histopathological classification and CDLS with or without conversion.

Statistical analysis

Statflex version 6 software (Artech Co., Ltd., Osaka, Japan) was used for all statistical analyses. The χ^2 and Fisher's exact test were used for categorical variables, and Student's *t* test was used for continuous variables. Differences reaching $P < .05$ were significant. Multiple comparisons were performed with the Tukey-Kramer test.

RESULTS

The characteristics of the 154 participants are shown in Table 1. The median age at the time of surgery was 63 years (range, 21–88 years), and 34.4% of the patients were women. Seventy patients (45.5%) underwent early surgery, and 84 (54.5%) underwent delayed surgery. CDLS (+) with/without conversion (+) was encountered in 29 patients (18.8%, conversion rate 8.4%). There were no differences in the CDLS (+) with/without conversion (+) rate between early surgery and delayed surgery (20% vs 17.9%). The reasons for CDLS (+) or conversion (+) included inflammation (11 cases), adhesions (1 case), bleeding (1 case), and bile leakage from the liver bed (1 case) in early surgery and inflammation (8 cases), adhesions (6 cases), and bleeding (1 case) in delayed surgery. In converted cases, dissection before conversion was extensive (3 cases) or minimal (2 cases) in early surgery, whereas it was minimal (8 cases) and some (1 case) in delayed surgery.

Table 2 shows a comparison of the characteristics between the CDLS (+) with/without conversion (+) and the CDLS (−) and conversion (−) subgroups in the early surgery group. No significant differences between the 2 groups were seen in terms of sex ratio, age, white blood cell (WBC) count, C-reactive protein (CRP) level, time to operation, postoperative complication rate, and total hospital stay.

However, with regard to the histopathological classification according to Muto et al,[12] the CDLS (+) with/without conversion (+) rate was highest in necrotizing cholecystitis and was significantly higher than the rate of the other 2 histopathological types (N 27.9% vs E and S 7.4%; $P = .037$).

The breakdown of the 3 consecutive phases of AC in early surgery is shown in Table 3, with edematous cholecystitis (E) in 14 cases (20%), necrotizing cholecystitis (N) in 43

Table 1.
Summary of Patient Characteristics (n = 154)

Characteristic	Data	*P*
Female, n (%) of patients	53 (34.4)	
Median age (years)	63 (21–88)	
Median operation time (minutes)	114.5 (43–293)	
Median bleeding (mL)	7 (3–850)	
Postoperative complications	11 (7.1%)	
Median hospital stay (days)	12 (3–85)	
Operative timing, n (%)		
Early surgery	70 (45.5)	
Delayed surgery	84 (54.5)	
CDLS (+) with/without conversion (+), n (%)	29 (15/14) (18.8)	
Early surgery	14 (10/4) (20)	0.735
Delayed surgery	15 (6/9) (17.9)	
Reason for CDLS (+) and/or conversion (+), n		
Early surgery		
Inflammation	11	
Adhesion	1	
Bleeding	1	
Bile leakage	1	
Delayed surgery		
Inflammation	8	
Adhesion	6	
Bleeding	1	
Extent of dissection before conversion		
Early surgery (n = 5)		
Minimal	2	
Some	0	
Extensive	3	
Delayed surgery (n = 9)		
Minimal	8	
Some	1	
Extensive	0	

n = 154.

(61.4%), and suppurative/subacute cholecystitis (S) in 13 (18.6%). Edema in the gallbladder wall, which is an indicator of the ease of dissection, remained at the same level in all phases of AC. Edematous cholecystitis had the shortest interval between surgery and symptom onset (time to operation) (E vs N, $P = .038$; E vs S; $P = .017$). With regard to the surgical results, edematous cholecystitis showed the most favorable outcome in the 3 consecutive histological phases, with shorter operation time (E vs N, $P < .001$; E vs S, 0.018) and less bleeding (E vs N, $P = .047$; E vs S, $P = .088$) compared with the other 2 histopathological groups. In contrast, necrotizing cholecystitis was associated with a longer operative time than the other 2 histopathological groups (N vs E, $P < .001$; N vs S, $P = .014$) and more

Table 2.
Clinical Features of Patients With CDLS (+) With/Without Conversion (+) Undergoing Early Surgery

Feature	CDLS (+) and/or conversion (+) (n = 14)	CDLS (−) and conversion (−) (n = 56)	P
Female, n (%)	3 (21.4)	23 (41.1)	.174
Median age (years)	60 (41–74)	61 (21–88)	.581
WBC (n/μL)	15175 (9340–25500)	11885 (2860–22830)	.12
CRP (mg/dL)	12.6 (0.09–40.8)	7 (0–38.7)	.117
Median time to operation (days)	3 (1–7)	3 (1–9)	.902
Median operation time (minutes)	213.5 (111–293)	102.5 (59–176)	<.001
Median bleeding (mL)	235 (3–820)	7 (3–200)	<.001
Complications	1 (7.1%)	4 (7.1%)	1.000
	Urinary tract infection	Wound infection	
		Prolonged fever	
		Bile leakage	
		Duodenal ulcer perforation	
Histological classification	N 12 (27.9%)	N 31 (82.1%)	.037
	E and S 2 (7.4%)	E and S 25 (92.6%)	
Median hospital stay (days)	7 (4–23)	7 (3–23)	0.65

bleeding (N vs E, P = .047), and the CDLS (+) with/without conversion (+) rate was 27.9%, representing the worst rate for the 3 histopathological phases.

Table 3 also shows the preoperative features of necrotizing cholecystitis. Significantly higher WBC count (N vs E, P < .001; N vs S, P = .001) and elevated CRP level (N vs E, P = .011) were seen in necrotizing cholecystitis compared to the other 2 histopathological groups. CT findings reported as characteristic of necrotizing cholecystitis were positive for 34.9% of necrotizing cholecystitis cases, whereas they were positive for 3.7% of the other 2 histopathological groups (false-positive).

The breakdown of the 3 types of acute cholecystitis on days 1, 2, 3, and 4, and on days 5–10 is shown listed in Table 4. Edematous cholecystitis, for which the operative outcomes were most favorable, occurred at the beginning of AC, distributed about 30% of patients on days 1 and 2, declined to the 10% range on days 3 and 4, and then declined to none on days 5–10. On the other hand, necrotizing cholecystitis, which had the worst operative outcomes, had developed from edematous cholecystitis to a considerable degree on days 1 and 2 and was distributed over ~50% of patients. Suppurative/subacute cholecystitis was found in a small fraction of patients during the first 5 days, whereas it was present in >50% of patients from 5 to 10 days.

Table 5 shows a comparison of clinical results in the ultra-early stages. No significant differences were seen in the 10-day surgical results, including the CDLS (+) with/without conversion (+) rate.

Table 6 shows a comparison of the characteristics between the CDLS (+) with/without conversion (+)and the CDLS (–) and conversion (–) subgroups in the delayed-surgery group. A significantly higher age (P = .004) and a tendency for a larger proportion of men (P = .074) were seen in the CDLS (+) with/without conversion (+) group; there was a significant difference between elderly men (≥75 years) and other patients of CDLS (+) with/without conversion (+) rate (44.4% vs 10.6%, respectively; P = .003). There was a significant difference in WBC counts (P = .034) and a tendency to higher CRP (P = .052). After surgery, there were more frequent complications in the CDLS (+) with/without conversion (+) group than in the CDLS (−) and conversion (−) group (P = .008).

DISCUSSION

LC for AC is a procedure with a rather high degree of surgical difficulty, and surgeons sometimes encounter difficult cases, some of which need conversion. Risk factors for difficulty have been reported to include old age, male sex, and high CRP level.[8–10] However, comprehensive

Table 3.
Histopathological Classification and Clinical Features

Feature	Edematous Cholecystitis (E) (n = 14)	Necrotizing Cholecystitis (N) (n = 43)	Suppurative/Subacute Cholecystitis (S) (n = 13)				
Edematous layer, n (%)	14 (100)	43 (100)	13 (100)				
Median time points from the onset (days)	2 (1–4)	3 (1–7)	3 (1–9)	p	E	N	S
				E		.038	.017
				N			.167
Median operative time (minutes)	76.5 (59–225)	128 (59–293)	102 (64–256)	p	E	N	S
				E		<.001	.018
				N			.014
Median bleeding (mL)	5 (3–120)	7 (3–820)	7 (3–676)	p	E	N	S
				E		.047	.088
				N			.907
CDLS with/without conversion	1 (0/1) (7.1%)	12 (9/3) (27.9%)	1 (0/1) (7.7%)	p	E	N	S
				E		.103	.741
				N			.125
Complications	14 (100%)	43 (100%)	13 (100%)	p	E	N	S
				E		.566	.098
				N			.076
WBC (range)	14720 (2860–25500)		10730 (7040–16280)	p	E	N	S
				E		<.001	.884
				N			.001
CRP (range)	10.7 (0.06–40.81)		5.7 (0–30.52)	p	E	N	S
				E		.011	.166
				N			.322
CT findings*	15 (34.9%)		1 (3.7%)	Sensitivity 34.9%, Specificity 96.3%			

*Intraluminal membranes, hemorrhage into the lumen, and irregular or absent wall, pericholecystic abscess.

Table 4.
Breakdown of the 3 Types of AC in Early Surgery

Pathology, n (%)	Day 1 (n = 9)	Day 2 (n = 17)	Day 3 (n = 28)	Day 4 (n = 6)	Days 5–10 (n = 10)
E	3 (33.3)	6 (35.3)	4 (14.3)	1 (16.7)	0
N	5 (55.6)	9 (52.9)	19 (67.9)	5 (83.3)	5 (50)
S	1 (11.1)	2 (11.8)	5 (17.9)	0	5 (50)

analyses relating to the appropriateness of early surgery remain insufficient. There should be risk factors specific to each operative timing because early surgery is performed during a progressive inflammatory process, but few reports have analyzed risk factors by operative timing. It is of great significance to analyze AC cases from such a perspective and to explore risk factors that can act as a warning.

Table 5.
Surgical Results in the Ultra-early Stage

Result	Day 1 (n = 9)	Days 2–10 (n = 61)	*P*	Days 1–2 (n = 26)	Day 3–10 (n = 44)	*P*
Median operative time (minutes)	115 (59–233)	111 (59–293)	.868	103.5 (59–256)	115.5 (59–293)	.34
Median bleeding (mL)	5 (3–200)	7 (3–820)	.435	7 (3–676)	7 (3–820)	.410
CDLS (+) and/or conversion (+)	2 (22.2%)	12 (19.7%)	.578	5 (19.2%)	9 (20.5%)	.902
	Days 1–3 (n = 54)	**Days 4–10 (n = 16)**	***P***	**Days 1–4 (n = 60)**	**Days 5–10 (n = 10)**	***P***
Median operative time (minutes)	105.5 (59–293)	121 (64–215)	.327	106.5 (59–293)	115.5 (64–180)	.551
Median bleeding (mL)	7 (3–676)	7 (5–820)	.168	7 (3–676)	13.5 (5–820)	.098
CDLS (+) and/or conversion (+)	11 (20.4%)	3 (18.8%)	.599	13 (21.7%)	1 (10%)	.357

Table 6.
Clinical Features of patients with CDLS With/Without Conversion Undergoing Delayed Surgery

Feature	CDLS (+) and/or conversion (+) (n = 15)	CDLS (−) and conversion (−) (n = 69)	*P*
Female, n (%)	2 (13.3)	25 (36.2)	.074
Median age (years)	76 (55–86)	66 (23–85)	.004
Elderly men (≥75 years), n (%)	8 (44.4%)	10 (55.6%)	.003
Others, n (%)	7 (10.6%)	59 (89.4%)	
WBC (n/μL)	13360 (8470–36670)	11200 (2770–29240)	.034
CRP (mg/dL)	15.6 (2.8–38.5)	11.7 (0–38.6)	.052
Median time to operation (days)	34 (15–86)	38 (12–236)	.829
Median operative time (minutes)	200 (99–292)	102 (43–178)	<.001
Median bleeding (mL)	320 (5–850)	5 (3–200)	<.001
Complications	4 (26.7%)	2 (2.9%)	.008
	Wound dehiscence 1	Wound infection 1	
	Wound infection 3	Prolonged fever 1	
Median hospital stay (days)	37 (16–85)	20 (5–53)	<.001

Of course, surgeons consider conversion to maintain the safety of the patient during surgery. Continuing with laparoscopic surgery, despite increases in bleeding and operative time, can be dangerous and may lead to a higher risk of intraoperative complications such as bile duct injury. In such cases, it is often safer to consider conversion to open surgery.

Therefore, cases of laparoscopic cholecystectomy that resulted in more than a certain amount of bleeding and operative time (CDLS) were also analyzed and regarded in the same light as conversion. Surgeons in our institute had a policy of completing surgery laparoscopically as much as possible and thought that CDLS was acceptable. However, we should have considered conversion in some cases of CDLS to maintain the safety of the patient. Moreover, median operative time and bleeding were 218 min and 330 mL in the conversion cases, respectively. Preferably, time to conversion should be as short as possible. Surgeons should predict conversion in high-risk patients before surgery and make decisions for conversion swiftly when necessary.

The period of 10 days may be too long, considering the trends of the timing of early surgery in recent reports,[8,16–18] However, AC progresses from edematous cholecystitis through necrotizing cholecystitis to suppurative/subacute cholecystitis within about 10 days.[11,12] That is the reason why cases with operations performed within 10 d were regarded as "early surgery."

The present histopathological findings confirmed that edematous cholecystitis showed the most favorable outcome in the 3 consecutive histological phases. On the other hand, necrotizing cholecystitis had the worst operative results and was associated with the highest CLDS (+) with/without conversion (+) rate. Therefore, the concept of optimal surgery in which LC is performed within the phase of edematous cholecystitis, before proceeding to necrotizing cholecystitis, may emerge. However, no differences in surgical results, including CDLS (+) with/without conversion (+) rate, were seen at any cutoff point, even during the ultra-early stage. The reason for this is that a significant proportion of necrotizing cholecystitis cases develop rapidly from edematous cholecystitis and make surgery difficult, even in the earliest stage. Moreover, a minimum amount of time is needed from symptom onset to the start of surgery in patients with AC. In our hospital, urgent surgery after a routine preoperative screening test is mandatory, and the process from patient referral to the diagnosis and surgery is usually rapid enough. Nonetheless, the median time point from onset to surgery was 3 days. Therefore, emergent surgery mainly targeting edematous cholecystitis is virtually impossible. Clearly, we assume that other reports preferring early cholecystectomy dealt with not only edematous cholecystitis, but also necrotizing and suppurative/subacute cholecystitis.

Given that a mixed difficulty level is a matter of course in early surgery, being aware of the presence of necrotizing cholecystitis before surgery is important to prepare for potentially worse operative outcomes. Although computed tomographic (CT) findings[15] were useful in diagnosing necrotizing cholecystitis, they had lower sensitivity (sensitivity: 34.9%, specificity: 96.3%). In the present data, higher WBC count and elevated CRP level were indication for CT. A more sensitive screening test mirroring histopathological necrotizing cholecystitis is needed.

Another important element is the time course of edematous change in the gallbladder wall, by which the dissection is made markedly easier in early surgery.[4,5,11] However, no reports have actually clarified how long these edematous changes last. In the present histopathological analysis, it was consistently preserved around 10 days, regardless of histopathological type, with various degrees of surgical difficulty, which could at least guarantee the feasibility of surgery in this period. On the other hand, the CDLS/conversion rate for necrotizing cholecystitis did not reach a significant level in multiple comparisons, probably because of the small sample size. That is a limitation in this study, but accrual of additional cases could reveal a significant difference in the CDLS/conversion rate between histopathological types.

In the delayed-surgery group, a higher WBC count and older age showed significant correlations with the CDLS/conversion rate. Although there was no difference in the CLDS and conversion rate between early and delayed surgery, the conversion rate was higher in delayed surgery (10.7%) than in early surgery (5.7%). Moreover, in conversion cases, the extent of dissection before conversion was greater in early surgery. The reasons could be the elimination of the edematous layer and tighter fibrotic adhesion in delayed surgery compared with early surgery. Of course, early surgery offers socioeconomic benefits compared with delayed-interval surgery, moreover, we believe that early surgery has an advantage over delayed surgery in ease of dissection. Therefore, we should perform the operation in patients with AC as early as possible.

CONCLUSION

There were different risk factors associated with difficult LC in AC between early and delayed surgery. Histopathological progression to necrotizing cholecystitis was a risk factor for difficulty in early surgery, whereas a higher WBC count and older age were the risk factors in delayed surgery. To some extent, necrotizing cholecystitis may be detectable from particular CT findings, WBC count, and CRP level. Surgeons predict conversion in these high risk patients and thereby maintain the safety of the operation in AC patients.

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