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Can the degree of fibrosis in the gallbladder wall be predicted by pre-operative routine examinations in chronic cholecystitis? A retrospective analysis

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ABSTRACT

Introduction: Fibrosis caused by chronic inflammation in the gallbladder increases the risk of biliary tract injury. Our aim was to investigate a possible correlation between pre-operative routine examinations and the degree of chronic inflammation.

Materials and Methods: Samples from 74 patients with chronic cholecystitis (CC) were reevaluated to determine the degree of chronic inflammation. The relationship of gallbladder wall thickness and gallbladder stone size in pre-operative abdominal ultrasonography (USG), pre-operative laboratory values, and endoscopic retrograde cholangiopancreatography (ERCP) history with the degree of histopathological chronic inflammation in the gallbladder wall was evaluated. In addition, adhesion of the surrounding tissues to the gallbladder, operation time, hospitalization period, biliary tract injury, and post-operative complications were examined in the context of degree of chronic inflammation.

Results: Grade I CC was detected in 53 (69.8%) and Grade II in 21 (27.6%) patients. While the gallbladder wall was thick (>3 mm) on pre-operative USG in 7 (33.3%) patients with Grade II CC, it was normal in all patients with Grade I (p<0.001). A history of pre-operative ERCP was found in 2 (3.8%) patients in Grade I CC and in 7 (33.7%) patients in Grade II (p=0.002). In univariate and multivariate analysis, gallbladder wall thickness and history of ERCP were found to be significant in predicting the degree of chronic inflammation [(p<0.001 and p=0.002), (p=0.003 and p=0.014), respectively]. In multivariate analysis, an increase in AST value of 1 U/L increases the probability of CC grade II by 1.1 times compared to CC grade I (p=0.019).

Conclusion: Increased gallbladder wall thickness, history of ERCP, and elevated AST value in CC increase the possibility of a high degree of chronic inflammation (fibrosis rate).

Keywords: Chronic cholecystitis, difficult cholecystectomy, endoscopic retrograde cholangiopancreatography, fibrosis, gallbladder wall thickness

Introduction

Gallstones are one of the most common diseases of the gastrointestinal tract. Gallstones present clinically as acute cholecystitis or symptomatic chronic cholecystitis (CC).[1,2] Elevated inflammatory markers and increased gallbladder wall thickness in acute cholecystitis help predict the increased risk of intraoperative bile duct injury and post-

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operative complications.[3] However, this risk is more difficult to predict in CC. In CC, the gallbladder wall is damaged due to stones and chemical reactions in the gallbladder. As a result of the reactions, the inflammatory process begins with the accumulation of neutrophils in the gallbladder wall. The release of cytokines and chemokines at the site of inflammation increases. With the effect of these mediators, the number of fibroblasts and myofibroblasts in the tissue increases.[4] Accumulation of myofibroblasts in the area of inflammation leads to increase in the amount of collagen in the tissue, which, in turn, causes different levels of fibrosis (mild, moderate, and severe) in each patient. Depending on the degree of fibrosis, the tissue becomes scarred and hardened.[1,2,5] Due to this hardening, it becomes difficult to perform the critical view of safety in the Calot's triangle during the gallbladder surgeries and the risk of biliary tract injury increases.[6–9] It is difficult to predict these chronic changes in the pre-operative period.

In laparoscopic cholecystectomy, switching to open surgery due to surgical difficulty does not reduce the risk of dissection difficulty and biliary tract injury.[10] A lot of work has been done and is being done to overcome these difficulties. Although there are predictive studies for intraoperative and post-operative complications without distinguishing between acute and CC, there are only a limited number of studies on CC. Our aim in this study was to examine the relationship between histopathological degree of chronic inflammation in the gallbladder wall and the pre-operative routine examinations.

Materials and Methods

Patient Selection

The study included 74 patients who were diagnosed with CC by histopathological evaluation of cholecystectomy specimens. Demographic, clinical, and radiological data of these patients were obtained from the hospital's electronic database with the approval of the local ethics committee (date: July 13, 2017, meeting no: 5, decision no: 19).

Clinical Evaluation

Patients' age, gender, laboratory values in the pre-operative period [white blood cells ($\times 10^3$/uL), hemoglobin (gr/dL), platelets (PLT) ($\times 10^3$/uL), aspartate aminotransferase (U/L), alanine aminotransferase (U/L), lactate dehydrogenase (U/L), alkaline phosphatase (U/L), gamma-glutamyl transferase (U/L), total bilirubin (mg/dl), direct bilirubin (mg/dl), PLT-lymphocyte ratio, and neutrophil-lymphocyte ratio] were examined. Pre-operative ultrasonography (USG) reports were evaluated and the gallbladder wall thickness was accepted as normal if it was ≤3 mm and thick if it was >3 mm.[11] Gallstone sizes (<1 cm, >1–2 cm, and >2 cm) and history of endoscopic retrograde cholangiopancreatography (ERCP) were recorded. Surgery notes were reviewed. Cases that were completed laparoscopically and converted from laparoscopy to open surgery were recorded. Intraoperative bleeding was considered as bleeding of 100 cc or more. Cases with gallbladder being completely covered by the omentum or surrounding tissues were considered as adhesion.

The patients' demographic, clinical, pre-operative laboratory values, radiological and intraoperative surgery findings, and their relationship with the degree of chronic inflammation in the gallbladder wall were evaluated. Since most of the patients were discharged on the 1st or 2nd post-operative day, the length of hospital stay was not included in the statistical evaluation. No rheumatological disease or corticosteroid use that would affect fibrosis and other chronic inflammation findings was found in any of the patients.

Histopathological Evaluation

Following fixation in neutral buffered formalin, all tissue specimens were embedded in paraffin. The specimens were sectioned, deparaffinized, and subsequently stained with hematoxylin and eosin. A specialist pathologist evaluated histopathological preparations of all patients without knowing the pre-operative clinical, laboratory, and radiological images of the patients. The severity of chronic inflammation was graded as Grades I (Fig. 1a) and II (Fig. 1b). The degree of fibrosis in the gallbladder wall was determined according to the definitions of Sakuramoto et al.[3] (Table 1).

Statistical Analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used in the analyses of the variables. The conformity of the data to the normal distribution was evaluated with the Shapiro–Wilk–Francia test, while the homogeneity of variance was evaluated with the Levene test. In the comparison of two independent groups according to quantitative data, the independent samples t-test was used with Bootstrap results, while the Mann–Whitney U-test was used with Monte Carlo results. Pearson

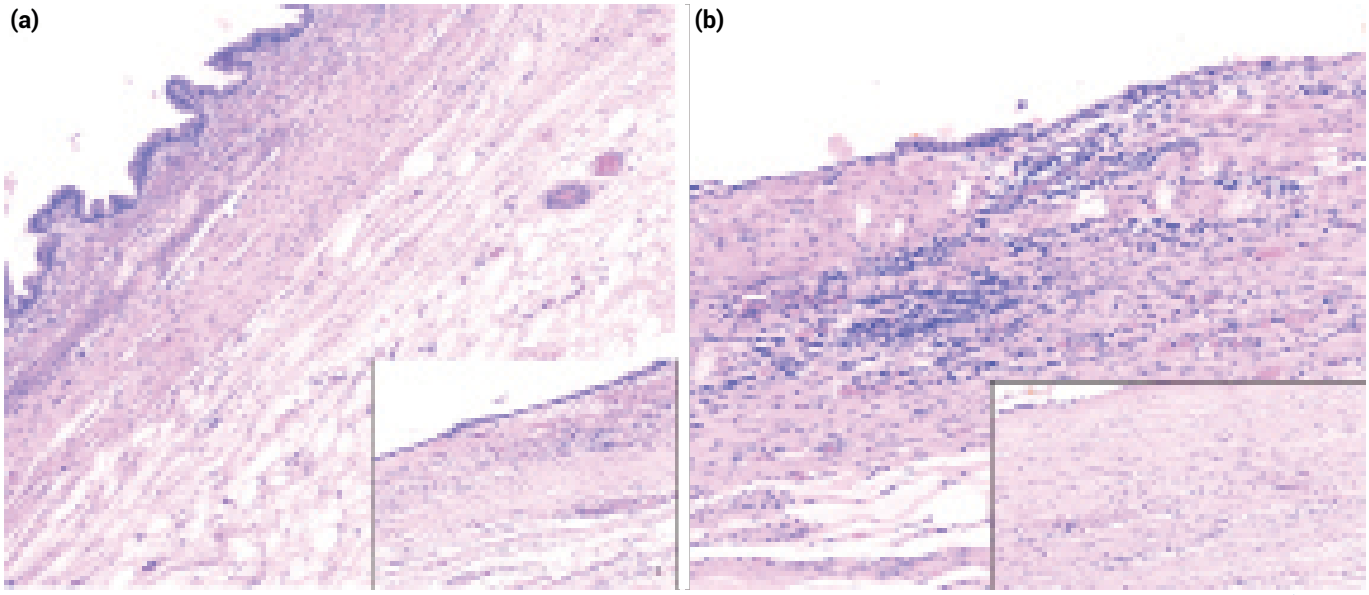

Figure 1. (a) Gallbladder with slight chronic inflammatory cells, inset: Moderate chronic inflammatory cells (H and E, 100×, inset – 100×). **(b)** Gallbladder with moderate chronic inflammatory cells, inset: Fibrosis to muscular layer (H and E, 200×, inset – 200×).

Chi-square, Fisher's exact, and Fisher-Freeman-Holton tests were tested with Monte Carlo Simulation technique while comparing categorical variables and column ratios were compared with each other and expressed according to Benjamini–Hochberg corrected P-value results. Odds ratio (OR) with 95% confidence intervals (CIs) was used to show how many times higher those with a risk factor were than those without. Logistic regression test was used with enter and backward methods to determine the cause-effect relationship between the categorical response variable and the explanatory variables in binary (diatom) and multiple (multinomial) categories. While quantitative variables were expressed as mean (standard deviation) and median (percentile 25/percentile 75) in the tables, categorical variables were shown as n (%). Variables were analyzed at 95% confidence level, and p<0.05 was considered statistically significant.

Results

Grade I CC was detected in 53 (69.8%), Grade II in 21 (27.6%), and Grade III in 2 (2.6%) of 76 patients included in the study. Due to the small number of Grade III CC patients, the study was conducted with 74 patients with Grades I and II CC. There was no significant difference between the two groups in terms of age (50.5±12.6 and 53.5±7.2), respectively, p=0.212. In addition, there was no significant difference between the two grades in terms of gender distribution (41 [77.4%] were female and 12 [22.6%] were male in Group I and 16 [76.2%] were female and 5 [23.8%] were male in Group II (Table 2), [p=0.999]).

In pre-operative abdominal USG, gallbladder wall thickness was normal in all patients with Grade I CC, while it was increased in 7 (33.3%) patients with Grade II. This difference was significant (p<0.001). While 2 (3.8%) patients with Grade I had a history of ERCP, 7 (33.3%) patients with

Table 1. Histological grading of chronic cholecystitis

Grade	Histological findings of chronic cholecystitis
Grade 0 (none):	Those free of chronic findings
Grade I (slight):	Those with slight chronic inflammatory cell invasion and/or with lymph follicle formation
Grade II (moderate):	Those with lymph follicle formation and/or moderate chronic inflammatory cell invasion and/or fibrosis to muscular layer or subserosal layer
Grade III (severe):	Those with lymph follicle formation and/or moderate/severe chronic inflammatory cell invasion and/or fibrosis to muscular layer or subserosal layer and/or fibrosis in com plete layers and destruction of mucosa layer

Table 2. Comparison of demographic, pre-operative laboratory, and radiological findings of patients with Grade I and Grade II chronic cholecystitis in the gallbladder wall with Grade I and Grade II chronic cholecystitis in the gallbladder wall

Histological Grade of Chronic Cholecystitis	Total (n=74)	I (n=53)	II (n=21)	p
Gender, n (%)				0.999[f]
Female	57 (77.0)	41 (77.4)	16 (76.2)	
Male	17 (23.0)	12 (22.6)	5 (23.8)	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Age (years)	51.3 (11.4)	50.5 (12.6)	53.5 (7.2)	0.212[t]
LDH (U/L)	199.5 (46.8)	202.7 (42.3)	189.8 (59.0)	0.437[t]
Wbc (x10^3/uL)	7.7 (1.4)	7.7 (1.4)	7.8 (1.4)	0.868[t]
	Median (q1/q3)	**Median (q1/q3)**	**Median (q1/q3)**	
PLR	105.8 (90.3/138.4)	105.9 (90.3/129.5)	101.5 (90.3/156.8)	0.710[u]
NLR	1.9 (1.6/2.6)	2 (1.7/2.6)	1.8 (1.5/2.3)	0.463[u]
AST (U/L)	22 (18/28)	21.5 (18/26)	22.5 (20/35)	0.282[u]
ALT (U/L)	21 (17/30)	21 (16.5/29)	19 (17/30)	0.972[u]
GGT (U/L)	31 (21/43)	27 (21/42)	34 (23/107)	0.341[u]
ALP (U/L)	88 (71/109)	88 (73/110)	87 (68/102.5)	0.712[u]
Total bilirubin (mg/dl)	0.6 (0.5/0.8)	0.6 (0.5/0.6)	0.7 (0.5/0.9)	0.122[u]
Direct bilirubin (mg/dl)	0.5 (0.2/0.7)	0.7 (0.2/0.7)	0.2 (0.1/0.7)	0.377[u]
Hgb (gr/dL)	13.1 (12.3/14.5)	13.2 (12.3/14.6)	12.8 (12.1/14)	0.323[u]
PLT (x10^3/uL)	262.5 (211/295)	248 (209/294)	267 (244/298)	0.321[u]
Duration of operation (min)	100 (80/130)	95 (75/120)	110 (95/130)	0.169[u]
	n (%)	**n (%)**	**n (%)**	
USG wall thickness				<0.001[f]
Normal (≤3mm)	67 (90.5)	53 (100.0)[B]	14 (66.7)	49.1 (2.6-913.4)[or]
Thick (>3 mm)	7 (9.5)	0 (0.0)	7 (33.3)[A]	
Largest stone size				0.470[ff]
10 mm<	47 (63.5)	35 (66.0)	12 (57.1)	
10-20 mm	21 (28.4)	15 (28.3)	6 (28.6)	
>20 mm	6 (8.1)	3 (5.7)	3 (14.3)	
Type of surgery				0.999[c]
Laparoscopic	41 (55.4)	29 (54.7)	12 (57.1)	
Conversion	33 (44.6)	24 (45.3)	9 (42.9)	
ERCP				0.002[f]
Absent	65 (87.8)	51 (96.2)[B]	14 (66.7)	12.8 (2.4-68.3)[or]
Present	9 (12.2)	2 (3.8)	7 (33.3)[A]	
Perioperative >100 cc bleeding				0.160[f]
Absent	62 (83.8)	42 (79.2)	20 (95.2)	
Present	12 (16.2)	11 (20.8)	1 (4.8)	
Adhesion in the gallbladder				0.439[c]
Absent	35 (47.3)	27 (50.9)	8 (38.1)	
Present	39 (52.7)	26 (49.1)	13 (61.9)	

[t]Independent t Test(Bootstrap); [u]Mann-Whitney U Test(Monte Carlo); [ff]Fisher Freeman Halton (Monte Carlo); [f]Fisher Exact Test (Monte Carlo); [c]Pearson Chi Square Test (Monte Carlot); Post Hoc Test: Benjamini-Hochberg correction; q1: Percentile 25; q3: Percentile 75; [or]Odds Ratio (95% confidence interval); [A]Significant to CCG I group; [B]Significant to CCG II group; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; AST: Aspartate Aminotransferase; ERCP: Endoscopic Retrograde Cholangio Pancreatography; GGT: Gamma glutamyl transferase; Hgb: Hemoglobin; LDH: Lactate Dehydrogenase; NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; PLT: Platelets; USG: Ultrasonography; Wbc: White Blood Cell.

Table 3. Evaluation of the relationship between demographic and preoperative clinical and radiological findings of cases with chronic cholecystitis and the degree of chronic cholecystitis in the gallbladder in univariate and multivariate analysis

Dependent variable: Chronic cholecystitis garde I and II	Univariate*				Multivariate**			
	p	odds ratio	95% CI for odds ratio		p	odds ratio	95% CI for odds ratio	
			Lower	Upper			Lower	Upper
Gender	0.914	0.937	0.284	3.087	-	-	-	-
Age (years)	0.305	1.025	0.978	1.075	-	-	-	-
Wbc (x10^3/uL)	0.618	1.098	0.759	1.589	-	-	-	-
Hgb (gr/dL)	0.248	0.816	0.578	1.153	-	-	-	-
PLT (x10^3/uL)	0.152	1.004	0.998	1.010	-	-	-	-
PLR	0.289	1.006	0.995	1.017	-	-	-	-
NLR	0.338	0.926	0.790	1.084	-	-	-	-
AST (U/L)	**0.036**	1.053	1.003	1.104	0.019	1.072	1.012	1.137
ALT (U/L)	0.327	1.020	0.980	1.062	-	-	-	-
LDH (U/L)	0.370	0.994	0.981	1.007	-	-	-	-
GGT (U/L)	0.108	1.006	0.999	1.013	-	-	-	-
ALP (U/L)	0.645	1.004	0.988	1.020	-	-	-	-
Total bilirubin (mg/dl)	**0.014**	2.259	1.181	4.323	0.068	4.196	0.899	19.585
Direct bilirubin (mg/dl)	0.309	0.399	0.068	2.344	-	-	-	-
USG wall thickness (>3mm)	**<0.001**	3.357	1.848	6.097	**0.002**	18.597	2.883	119.953
Largest stone size	0.479				-	-	-	-
10 mm<	0.225	0.343	0.061	1.933	-	-	-	-
10-20 mm	0.334	0.400	0.062	2.568	-	-	-	-
>20 mm	0.225	2.917	0.517	16.442				
ERCP (present)	**0.003**	12.750	2.379	68.346	**0.014**	10.857	1.620	72.753

Logistic Regression (Method: *Enter; **Backward Stepwise); CI: Confidence interval; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; AST: Aspartate Aminotransferase; ERCP: Endoscopic Retrograde Cholangio Pancreatography; GGT: Gamma glutamyl transferase; Hgb: Hemoglobin; LDH: Lactate Dehydrogenase; NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; PLT: Platelets; USG: Ultrasonography; Wbc: White Blood Cell.

Grade II had such history and this difference was also significant (Table 2), (p=0.002). The demographic and clinical data, pre-operative laboratory values, and radiological findings of the patients are summarized in Table 2.

In the univariate and multivariate analysis, it was determined that the thickness of the gallbladder wall in the preoperative abdominal USG was significant in predicting the increased degree of histological chronic inflammation [OR: 3.357 (95% CI)], [OR: 18,597 (95% CI), respectively] (p<0.001 and p=0.002, respectively). Having a history of ERCP was found to be a predictive marker in determining the increased degree of chronic inflammation in both univariate and multivariate analyses [OR: 12.750 (95% CI)], [OR: 10,857 (95% CI), respectively] (p<0.003 and p=0.014, respectively), (Table 3).

In multivariate analysis, an increase in AST value of 1 U/L increases the probability of CC grade II by 1.1 times compared to CC grade I [OR: 1.072 (95% CI)], (p=0.019), (Table 3).

There was no correlation between the size of the stones in the gallbladder, the rate of intraoperative adhesion, the duration of the operation, the intraoperative bleeding time, the duration of hospital stay, and the degree of chronic inflammation (p>0.05). Univariate and multivariate analysis results are summarized in Table 3. None of

the patients developed intraoperative and post-operative complications.

Discussion

Despite the developments in imaging and surgical instruments used in laparoscopic surgery, the risk of bile duct injury has not changed much in the past 10 years.[8] Many studies have been conducted to estimate the degree of surgical difficulty for acute cholecystitis. However, such studies focusing on CC are limited. In some CC cases, as the degree of inflammation increases, intense fibrosis may occur in the gallbladder wall and Calot's triangle, which leads to tissue hardening and disappearance of dissection margins. This increases the risk of bile duct injury.[6,9] In our study, it was determined that gallbladder wall thickness and ERCP history have predictive value in determining the degree of chronic inflammation in patients with CC.

Barcia[1] emphasized that fibrosis is present in all CC cases and that the degree of fibrosis varies from patient to patient. In their study, Grade I fibrosis was found in 26% of patients, Grade II in 62%, and Grade III in 12% of patients. It has been stated that the different degrees of fibrosis in chronic inflammation depend on genetic and other factors. In addition, chronic inflammation was observed to be prominent in Grade II. In our study, Grade I CC was found in 69.8%, Grade II CC in 27.6%, and Grade III CC in 2.6% of patients.

Gallbladder wall thickness was significantly higher on USG in Grade II CC patients than in Grade I. In the univariate and multivariate analysis, the degree of CC was found to be associated with the gallbladder wall thickness. In the prospective study by Kokoroskos et al.[12] that included 548 (50.4%) patients with acute cholecystitis and 38 (3.5%) patients with CC, a correlation was found between the wall thickness measured in USG and abdominal computed tomography and the wall thickness measured histologically. In the multivariate analysis of the same study, the increase in gallbladder wall thickness was associated with increased risk of biliary tract injury and rate of post-operative complications, as well as prolonged hospital stay. In their retrospective study including 325 elective and 549 emergency cholecystectomy patients, Raman et al.[11] reported that the rate of conversion from laparoscopic cholecystectomy to open and the rate of post-operative complications increased with the increase in gallbladder wall thickness. The multivariate analysis of this study also indicated that increased gallbladder wall thickness was a risk factor in increasing these rates. Both of these large series reported that gallbladder dissection was difficult in patients with thick gallbladder walls (without distinction between acute and CC). Our study, unlike these two studies, was conducted only in CC cases. In addition, our study showed that the increase in gallbladder wall thickness on USG was associated with the increase in the degree of inflammation in CC.Many studies in the literature have reported that an increase in gallbladder wall thickness makes surgical dissection difficult and increases the rate of conversion from laparoscopy to open surgery.[13–16] Numerous studies have also reported that intraoperative and post-operative complication rates increase in acute cholecystitis cases with increased gallbladder wall thickness.[11,16–18] In our study, no difference was found between the rates of conversion from laparoscopic surgery to open surgery between those with normal gallbladder wall thickness and those with increased gallbladder wall thickness. Intraoperative and post-operative complications did not develop in any of the cases. This may be due to the absence of severe cases of chronic inflammation.

In many studies, patients with a history of preoperative ERCP have been found to have a higher rate of difficulty in gallbladder dissection, the rate of transition from laparoscopic surgery to open surgery, and the rate of postoperative complications compared to those without a history of ERCP.[3,19–21] These findings may indicate that chronic inflammation and the degree of fibrosis may be increased in patients with ERCP. In our study, multivariate and univariate analysis showed that CC grade may increase in patients who underwent preoperative ERCP. These findings support our hypothesis.

In our study, according to multivariate analysis, tendency of AST value to increase might indicate higher level of severity of chronic inflammation. The evaluation of these results together with the gallbladder wall thickness may strengthen the predictive value. The limitations of the study are its retrospective design, small number of patients, variation in the time from USG to surgery among patients, and ultrasound being performed by different radiologists.

Conclusion

Increased gallbladder wall thickness and a history of ERCP in the pre-operative period increase the possibility of a high degree of chronic inflammation in the gallbladder wall. When these findings are present, it should be considered that fibrosis caused by chronic inflammation might cause difficulty in gallbladder dissection.

Disclosures

Ethichs Committee Approval: The study was approved by the University of Health Sciences, Izmir Tepecik Training and Research Hospital (Date: 13/07/2017, No: 19).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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