

## Гистологическая классификация степени тяжести острого холецистита: хирургические последствия

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## Histology-based classification of acute cholecystitis severity: Surgical Implications

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### Реферат

**Цель.** Современные классификации острого холецистита (ОХ) не учитывают степень выраженности гистологического воспаления желчного пузыря.

Нами проведена оценка взаимосвязи между гистологическим воспалением желчного пузыря, риском конверсии лапароскопической холецистэктомии (КЛХ) в открытую операцию (и тяжестью периоперационных осложнений), а также разработана гистологическая классификация степени тяжести ОХ.

**Материалы и методы.** Ретроспективное когортное исследование основано на клинических наблюдениях за 1762 пациентами, которым была выполнена лапароскопическая холецистэктомия. Из них у 472 пациентов диагноз ОХ был подтвержден при гистологическом исследовании.

**Результаты.** У пациентов с активным хроническим холециститом и с острым отечным холециститом риск КЛХ был выше более чем в пять раз по сравнению с пациентами с нормальным желчным пузырем и с хроническим холециститом: отношение шансов (ОШ) = 5,1; 95% доверительный интервал (ДИ) 3,5-7,6;  $p < 0,00005$ . Пациенты с острым некротическим холециститом имели 10-кратное увеличение риска КЛХ (ОШ = 10,9; 95% ДИ 6,1-19,1;  $p < 0,00005$ ). Пациенты с острым гангренозным и гнойным холециститом имели более чем 11-кратное увеличение риска КЛХ (ОШ = 11,9; 95% ДИ 6,8-20,5;  $p < 0,00005$ ). Пациенты с перихолецистическим абсцессом или перфорацией желчного пузыря имели в 25-кратное увеличение риска КЛХ (ОШ = 25,2; 95% ДИ 5,2 - 129,2;  $p < 0,00005$ ). Пациенты с умеренно тяжелой степенью гистологического воспаления желчного пузыря имели в два раза выше риск КЛХ, чем пациенты с легкой степенью гистологического воспаления (ОШ = 2,0; 95% ДИ 1,3-3,1;  $p = 0,003$ ), них была большей продолжительность операции и более высокая частота и тяжесть периоперационных осложнений.

**Выводы.** Повышение степени тяжести гистологического воспаления желчного пузыря соответствует большему риску КЛХ, увеличению частоты и тяжести периоперационных осложнений.

**Ключевые слова:** лапароскопическая холецистэктомия; острый холецистит; классификация.

### Abstract

**Objective.** Current classifications of acute cholecystitis (AC) severity do not relate clinical to histological severity of AC. The aims of our study were to assess the relationship between histologic gallbladder inflammation, risk of CTO and severity of perioperative complications, and to propose a histology-based clinical classification for AC severity.

**Materials and methods.** This was a retrospective cohort study of 1762 patients who had laparoscopic cholecystectomy (LC), 472 of whom had AC confirmed on histological examination.

**Results:** Patients with active chronic cholecystitis and those with acute edematous cholecystitis had more than a five-fold increase in odds of CTO compared with patients with normal gallbladders and those with chronic cholecystitis, (OR = 5.1; 95% CI, 3.5 – 7.6;  $p < 0.00005$ ). Patients with acute necrotizing cholecystitis had a ten-fold increase in CTO odds (OR = 10.9; 95% CI, 6.1 – 19.1;  $p < 0.00005$ ). Patients with acute gangrenous and suppurative cholecystitis had more than 11-fold increase in CTO odds (OR = 11.9; 95% CI, 6.8 – 20.5;  $p < 0.00005$ ) and those with pericholecystic abscess or gallbladder perforation had 25 times higher odds of CTO (OR = 25.2; 95% CI, 5.2 – 129.2;  $p < 0.00005$ ). Patients with moderate-severe AC have twice the risk of CTO that patients in the mild group have (OR=2.0; 95% CI: 1.3-3.1;  $p = 0.003$ ), longer durations of surgery and higher rates and severity of perioperative complications.

**Conclusion.** Increasing severity of histologic gallbladder inflammation corresponds with greater risk of CTO, higher rates and severity of perioperative complications.

**Keywords:** laparoscopic cholecystectomy; acute cholecystitis; classification

## Introduction

The prevalence of cholelithiasis in an adult Western population is estimated to be around 15% to 20% [1]. In the USA, this means that approximately 12 million people aged between 20 and 74 years have gallstones [1]. Annually 1% to 2% of these people will develop right upper quadrant pain and present to hospital [2, 3]. Twenty percent of these patients will be diagnosed with acute cholecystitis (AC), which, in elderly and very sick patients, is associated with 2-3% mortality [4, 5].

Laparoscopic cholecystectomy (LC) is now the "gold standard" surgical procedure for treating symptomatic gallbladder stone disease including AC [6]. To predict potential difficulties during LC, the 2007 and updated 2013 and 2018 Tokyo guidelines (TG07/TG13/TG18) were developed based on clinical and bio-inflammatory indicators of gallbladder inflammation [7-9]. According to TG13/TG18 criteria, LC should be a straight forward and safe operation in patients with mild AC, whereas in patients with moderate-severe AC, minimally invasive surgery can be difficult and more risky [8]. However, TG13/TG18 guidelines for AC do not use an objective measure of surgical difficulty such as CTO in the classification of severity. Also, TG13/TG18 grades of AC severity lack gallbladder histological correlates [8, 9]. Ambe et al. questioned the accuracy of the TG13 severity grades in predicting the surgical complexity of LC and concluded that TG13 grades tended to underestimate the severity of gallbladder inflammation in mild AC and overestimate the difficulty of LC in patients with moderate AC [10]. In addition, these grading systems have not considered histologic active chronic cholecystitis (aka acute on chronic cholecystitis) as a variant of AC.

In a large multicentre retrospective study conducted in Japan and Taiwan that involved 5459 consecutive patients who underwent cholecystectomy, acute on chronic cholecystitis was the most common (36%-22%) histologic variant of AC [11].

Our clinical ability to predict the severity of gallbladder inflammation and operative difficulty is based on patients' history of illness, vital signs, physical examination, laboratory blood tests, and imaging studies such as abdominal ultrasound, computed tomography and magnetic resonance imaging [12-17]. These scans can show gallbladder wall thickening, pericholecystic fluid and pericholecystic abscesses among other manifestations of gallbladder inflammation [12].

Recently, in the same group of AC patients that are in the current study, we showed that inflammatory biomarkers including C-reactive protein (CRP) and neutrophil-to-lymphocyte ratio (NLR) were associated with severity of histological gallbladder inflammation [18, 19]. CRP is an acute phase protein produced by the liver in response to increased secretion of the cytokine interleukin-6 by macrophages in infection, inflammation, and injury [20]. Concentrations of CRP and NLR rise proportionally with increasing histologic severity of AC [18, 19]. In predicting the severity of gallbladder inflammation, these findings can help clinicians to formulate the most effective management strategy. However, there are no studies demonstrating the relationship between histological findings and surgical risk in patients with AC.

Our study hypothesis was that the severity of histologic gallbladder inflammation corresponds with the clinical severity of AC and surgical difficulty. The aim of our study was two-fold; firstly, to assess the relationship between histologic gallbladder inflammation, risk of CTO and severity of peri-operative complications. Secondly, we aimed to establish a histology-based clinical classification for AC severity.

## Methods

This was a retrospective cohort study of 1959 patients who underwent cholecystectomy at a tertiary referral hospital in New Zealand between May 2004 and June 2009. Patients were excluded if they had open liver resection with cholecystectomy, open cholecystectomy (OC), conversion to open surgery for common bile duct (CBD) exploration or gallbladder cancer. Clinical data were derived from patients' electronic outpatient clinic visits, hospital discharge summaries, operation notes, blood tests, radiological reports and histology reports. Primary end-point of outcome was histologic classification of excised gallbladders.

In our review the following morphological features were used for the histological classification of cholecystitis:

Chronic cholecystitis: thickening of the gallbladder wall due to fibrosis and muscular hyperplasia, a chronic interstitial inflammatory cell infiltrate, epithelial lined sinuses and metaplastic epithelial changes.

Active chronic cholecystitis: as for chronic cholecystitis but with additional neutrophilic mucosal infiltrates.

Acute edematous cholecystitis: vascular congestion and dilatation in the gallbladder wall, accompanied by interstitial and subserosal edema with scattered areas of interstitial haemorrhage.

Acute necrotizing cholecystitis: as for edematous cholecystitis but with an acute inflammatory response and/or necrosis mostly confined to the mucosa.

Acute gangrenous cholecystitis: extensive replacement of the mucosa and muscularis propria by necrotic debris, neutrophils and granulation tissue.

Acute suppurative cholecystitis: areas of tissue necrosis and suppuration extending beyond the mucosa into the gallbladder wall.

Complicated AC: Any AC with accompanying pericholecystic abscess or gallbladder perforation that was walled off by peritoneal or omental tissues. Gallbladder perforation was characterized by transmural extension of gangrenous or suppurative cholecystitis with spill over of the exudate onto the serosal surface.

The secondary points of outcome for this study were rate of conversion of laparoscopic cholecystectomy to open surgery (CTO), which was used as a proxy measure of surgical difficulty of LC, major bile duct injury, bowel injury, duration of surgery and the rate and severity of peri-operative complications. Major bile duct injury corresponds to type D and E of the Strasberg's classification [21]. Peri-operative complications were graded according to the Clavien-Dindo classification into non-life-threatening (Clavien-Dindo grades I-III)

and life-threatening complications (Clavien-Dindo grades IV and V) [22].

Based on severity and depth of histologic gallbladder inflammation, patients were divided into 5 groups. Patients with normal gallbladders and those with chronic cholecystitis were used as the reference groups. Patients with active chronic and acute edematous cholecystitis were grouped together because they had minimal evidence of acute inflammation. Patients with acute necrotizing cholecystitis had established inflammation that was confined mainly to the mucosa. Patients with acute gangrenous and suppurative cholecystitis had acute inflammation involving the entire gallbladder wall. In patients with pericholecystic abscess and gallbladder perforation, inflammation extended through the gallbladder wall.

A subgroup analysis was performed to assess the relationship between each histologic classification and CTO. Patients with low odds of CTO were assigned to the mild AC group, whereas patients with more advanced acute inflammatory gallbladder histologic findings and higher risk of CTO were allocated to the moderate-severe AC group.

This study was registered by Our Institutional Research Office as an audit (RM080712419).

*Statistical analysis*

Statistical analysis was performed with Stata/SE (version 13) software package (StataCorp LP, College Station, TX, USA). Continuous variables were analysed with the skewness and kurtosis test for the normality of data distribution. Continuous variables were expressed as median and range and analysed with the two-sample Wilcoxon rank-sum test if they had non normal distribution and as mean and standard deviation for normally distributed data. Categorical variables were presented as an absolute number and percentage (%) and analysed using chi-square test. Logistic regression was used to estimate adjusted and unadjusted odds ratio of CTO. P-values less than 0.05 were accepted as statistically significant.

**Results**

Of the 1959 patients identified over the 5 years, 197 were excluded. The remaining 1762 patients who met the eligibility criteria were included in this study. Patients' demographic and clinical characteristics are presented in *Table 1*.

Among the 1762 patients who underwent LC there were 185 (10.5%) patients who had CTO. Eighteen (1%) patients had concomitant laparoscopic procedures performed including seven gastric bypass, six funduplications, two had liver cysts de-roofed and one each had gastric resection, appendectomy and inguinal hernia repair. Twenty eight (1.6%) LC patients also had paraumbilical, epigastric or anterior abdominal wall incisional hernia repair with sutures using an open technique and 8 (0.5%) patients had open mesh repair of paraumbilical, unilateral inguinal or anterior abdominal wall incisional hernia.

*Relationship between histologic severity of gallbladder inflammation and CTO*

Analysis of the relationship between histologic severity of gallbladder inflammation and CTO demonstrated a sta-

**Table 1. Overall characteristics of the study patients**

Characteristics	Study patients, N=1762, n (%)
Age (median, range), years	52 (15-93)
Gender, n (%)	
Male	707 (43.7)
Female	992 (56.3)
Ethnicity, n (%)	
Caucasian	1301 (73.8)
Maori	130 (7.4)
Pacific Islander	81 (4.6)
Asian	132 (7.5)
Others§	118 (6.7)
Admission type	
Elective	883 (50.1)
Acute	879 (49.9)
Cholelithiasis	1642 (93.2)
Comorbidities	
Hypertension	454 (25.8)
TIA/stroke	44 (2.5)
Angina	101 (5.7)
Previous MI	83 (4.7)
Cardiac arrhythmia	87 (4.9)
Heart failure	35 (2.0)
Diabetes mellitus	171 (9.7)
Previous abdominal operation, n (%)	373 (21.2)
Number of previous abdominal operations (median,range)	1 (1 – 5)
ASA score, n (%)	
I	555 (31.5)
II	891 (50.6)
III	297 (16.9)
IV	18 (1.0)
V	1 (0.1)
Abbreviations.	ASA score, American Society of Anesthesiologists score. § includes Indians, Africans and 1 patients with an unidentified response.

tistically significant association (Pearson  $\chi^2$  (6) = 208.172,  $p < 0.0005$ ) (*Table 2*).

Patients with histologically normal gallbladders and those with chronic cholecystitis had similar low risks of CTO (OR = 2.1; 95% CI, 0.6-18.8,  $p = 0.269$ ). Patients with active chronic cholecystitis demonstrated more than a five-fold increase in risk of CTO compared with patients with chronic cholecystitis (OR = 5.3; 95% CI, 3.4-8.1,  $p < 0.00005$ ).

A subgroup analysis of the 472 patients with AC including those with active chronic cholecystitis showed that patients with histologic findings of acute edematous cholecystitis and those with active chronic cholecystitis had similar risks of CTO (OR = 1.3, 95% CI, 0.6 – 2.7;  $p = 0.46$ ), whereas patients with histologic findings of acute necrotizing, gangrenous and suppurative cholecystitis, acute cholecystitis with gallbladder perforation and biliary peritonitis or pericholecystic abscess had statistically higher risks of CTO, (OR = 2.5; 95% CI, 1.1 – 5.8;  $p = 0.012$ ; OR = 2.8; 95% CI, 1.3 – 6.2;  $p = 0.005$ ; OR = 5.9; 95% CI, 1.1 – 32.9;  $p = 0.008$ ), respectively (*Table 3*).

**Table 2. Conversion rate for each histologic classification**

Gallbladder histopathology	CTO rate (%)
Normal gallbladder/gallbladder polyp/papillary hyperplasia/gallbladder adenomyosis	2/87 (2.3)
Chronic cholecystitis	59/1203 (4.9)
Acute oedematous cholecystitis	14/80 (17.5)
Active chronic cholecystitis	48/225 (21.3)
Acute necrotizing cholecystitis	27/77 (35.1)
Acute gangrenous/suppurative cholecystitis‡	30/81 (37.0)
Pericholecystic abscess/acute cholecystitis with gallbladder perforation	5/9 (55.6)
Abbreviation.	CTO, conversion of laparoscopic cholecystectomy to open surgery. ‡ includes one case of gallbladder torsion.

*Relationship between the depth and severity of AC and CTO*

We have shown that patients with active chronic cholecystitis and those with acute edematous cholecystitis had more than a five-fold increase in risk of CTO than patients with either normal gallbladders or those with chronic cholecystitis (OR = 5.1; 95% CI, 3.5 – 7.6; p < 0.00005). We showed a ten-fold increase in patients with acute necrotizing cholecystitis (OR = 10.9; 95% CI, 6.1 – 19.1; p < 0.00005), more than 11-fold increase in those with acute gangrenous and suppurative cholecystitis (OR = 11.9; 95% CI, 6.8 – 20.5; p < 0.00005) and those with pericholecystic abscess and gallbladder perforation had 25 times higher odds of CTO (OR = 25.2; 95% CI, 5.2 – 129.2; p < 0.00005) (Table 4).

Patients with acute necrotizing cholecystitis had more than twice the risk of CTO as those patients who had active chronic and acute edematous cholecystitis, (OR = 2.1; 95% CI, 0.5 – 2.2; p = 0.006). Those with acute gangrenous or suppurative cholecystitis and those with pericholecystic abscess and gallbladder perforation also had more than twice the risk of CTO (OR = 2.3; 95% CI, 1.3-4.0; p = 0.002) and 4.9 times the

risk of CTO (95% CI, 1.01 – 25.3; p = 0.011), respectively (Table 4). The risk of CTO was similar for patients with acute necrotizing, acute gangrenous and suppurative cholecystitis and those with either pericholecystic abscess formation or gallbladder perforation.

*Histology-based clinical classification of AC*

Based on the histologic findings of AC and similar risk of CTO, patients with acute oedematous cholecystitis and those with active chronic cholecystitis comprised the mild AC category. In contrast, patients with acute necrotizing, gangrenous/suppurative cholecystitis, AC with gallbladder perforation, biliary peritonitis or pericholecystic abscess had significantly higher risk of CTO and were grouped into the histologically moderate-severe AC category. Demographic and clinical characteristics of patients within each grade of AC are presented in Table 5.

These two groups were unbalanced on variables of age, gender, hospital admission type, angina, diabetes mellitus and the American Association of Anaesthesiology score. After adjusting for these variables, those patients in the moderate-severe histologic categories demonstrated a two-fold increase in risk of CTO compared with those in the mild category (adjusted OR=2.0; 95% CI: 1.3-3.1; p = 0.003). Patients with moderate-severe AC also had longer durations of surgery (median 130 min, range: 70 – 320 min) than patients with mild AC (median 106 min, range 42 – 255 min) (p < 0.005). In addition, there were different rates and severity of peri-operative of complications.

Sixty five (38.9%) patients with histologic moderate-severe AC and 72 (23.6%) patients with mild AC developed peri-operative complications (p < 0.0005). 10 of 65 (15.4%) patients with moderate-severe AC developed life-threatening peri-operative complications (ASA score IVa-V) with one death, whereas only 3 of 72 (4.2%) patients in the mild group, had life-threatening complications but with no fatalities (Pearson chi<sup>2</sup> (1) = 5.005, p = 0.025). Seven (4.2%) patients from the moderate-severe AC group and 2 (0.7%) patients from the mild AC group developed major bile duct injury (chi<sup>2</sup> (1)=7.21; p = 0.007). Intraoperative bowel injury was also more common in the moderate-severe AC group. Three (1.8%) patients from

**Table 3. Conversion of laparoscopic cholecystectomy to open surgery in each histologic classification of acute cholecystitis**

Gallbladder histopathology	CTO rate, (%)	OR	95% CI	P-value*
Acute oedematous cholecystitis	14/80 (17.5)	1	–	–
Active chronic cholecystitis	48/225 (21.3)	1.3	0.6–2.7	0.46
Acute necrotizing cholecystitis	27/77 (35.1)	2.5	1.1–5.8	0.012
Acute gangrenous/suppurative cholecystitis‡	30/81 (37.0)	2.8	1.3–6.2	0.005
Acute cholecystitis with gallbladder perforation and biliary peritonitis/pericholecystic abscess	5/9 (55.6)	5.9	1.1–32.9	0.008
Abbreviations.	CTO, conversion of laparoscopic cholecystectomy to open surgery; OR, odds ratio; CI, confidence interval. ‡ includes one case of gallbladder torsion.			

Table 4. Association between the depth and histological severity of gallbladder inflammation and CTO

Histologic severity of gallbladder inflammation	OR1	95% CI	P-value1	OR2	95% CI	P-value2	OR3	95% CI	P-value3	OR4	95% CI	P-value4
Normal gallbladder and chronic cholecystitis	1	--	--									
Active chronic cholecystitis and acute oedematous cholecystitis	5.1	3.5–7.6	<0.00005	1	--	--						
Acute necrotizing cholecystitis	10.9	6.1–19.1	<0.00005	2.1	1.2–3.8	0.006	1	--	--			
Acute gangrenous and suppurative cholecystitis*	11.9	6.8–20.5	<0.00005	2.3	1.3–4.0	0.002	1.1	0.5–2.2	0.796	1	--	--
Pericholecystic abscess and gallbladder perforation	25.2	5.2–129.2	<0.00005	4.9	1.01–25.3	0.011	2.3	0.5–12.6	0.229	2.1	0.4–11.5	0.28

Abbreviations. CTO, conversion of laparoscopic cholecystectomy to open surgery; OR, odds ratio; CI, confidence interval.  
\* – includes one case of gallbladder torsion

the moderate-severe AC group and no patients from the mild AC group suffered intraoperative bowel injury ( $\chi^2(1)=5.51$ ;  $p=0.019$ ).

### Discussion

For the first time we have demonstrated an association between histologic severity of gallbladder inflammation and surgical risk in patients with AC. We have previously shown how these histologic categories can be predicted with increasing levels and number of raised inflammatory markers [18, 19]. Therefore, preoperative inflammatory markers can help to establish clinical severity of patients presenting with AC and thereby predict surgical difficulty. Recently, Moloney et al. also demonstrated that patients with preoperative NLR greater than 3 had longer durations of surgery, higher rates of CTO and prolonged lengths of hospital stay [14].

Since LC was introduced into clinical practice in the late 1980's, it has surpassed conventional OC as the procedure of choice in the surgical management of gallbladder disease [5]. The main limitations of LC are; lack of a 3-dimensional view, a narrow field of laparoscopic vision, insufficient tactile sensation due to manipulation with long laparoscopic instruments and difficulties with instruments placement and maneuvering [23]. These limitations predispose patients undergoing LC to potential organ injury, especially in AC [24, 25]. To prevent such injury, safety CTO is advised [26].

An attempt to predict more difficult LC on the basis of AC severity was first made in TG07 [7]. However, neither TG07, TG13 nor TG18 criteria provide objective measures of surgical difficulty such as CTO. Also, some of the individual TG13/TG18 severity grading criteria have been shown to be inaccurate in predicting surgical difficulty. Asai et al. showed that elevation in WCC ( $>18.0 \times 10^9/L$ ) did not predict risk of CTO [16]. AC patients with WCC  $> 18.0 \times 10^9/L$  had a similar CTO risk as those with WCC  $\leq 18.0 \times 10^9/L$  (OR = 1.1; 95% CI: 0.3 - 3.3;  $p=0.511$ ).

The relationship between TG13 severity grades and gallbladder histologic inflammation was investigated by P. Ambe et al. [10]. They found more than 40% of their patients who were classified as Grade 1 by TG13 criteria had histologic evidence of either acute necrotizing or gangrenous cholecystitis with complicated perioperative courses. The authors concluded that the TG13 severity grades of AC criteria tended to underestimate the severity of gallbladder inflammation in patients with mild AC and overestimate the difficulty of LC in patients with moderate AC [10].

Our study differed from that of Ambe et al. in several ways. Firstly, we excluded patients who underwent CTO for exploration of CBD and used CTO as a proxy of surgical difficulty during LC. Secondly, we assessed the relationship between different histologic gallbladder pathology and CTO and found active chronic cholecystitis to have a higher rate of CT compared to patients with chronic cholecystitis and a similar CTO rate to acute edematous cholecystitis. Thirdly, we have shown that histology-based severity of AC is not only associated with increase in the rate of CTO, but also with major bile duct and bowel injury during LC.

Importantly, we have grouped patients with different histologic severity of AC according to their CTO rate into mild and moderate-severe AC. Mild AC included patients with active chronic cholecystitis and acute edematous cholecystitis. Patients with acute necrotizing, gangrenous, or suppurative cholecystitis, and those with pericholecystic abscess or gallbladder perforation had more severe histologic features of gallbladder inflammation and higher rates of CTO, therefore, they were included in the moderate-severe AC category. We have demonstrated that patients in the moderate-severe group not only had higher odds of CTO, but also had longer durations of surgery and increased rates and severity of peri-operative

**Table 5. Characteristics of patients with histologic mild and moderate-severe acute cholecystitis**

Characteristics	Histologic Mild AC, N=305, n (%)	Moderate-severe AC, N=167, n (%)	P-value
Age (median, range), years	55 (18-92)	61 (17-91)	0.0121
Gender, n (%)			
Male	143 (46.9)	102 (61.1)	
Female	162 (53.1)	65 (38.9)	0.003
Ethnicity, n (%)			
Caucasian	237 (77.7)	131 (78.4)	
Maori	19 (6.2)	7 (4.2)	
Pacific Islander	15 (4.9)	6 (3.6)	
Asian	18 (5.9)	9 (5.4)	
Others§	16 (5.3)	14 (8.4)	0.563
Admission type, n (%)			
Elective	48 (15.7)	1 (0.6)	
Acute	257 (84.3)	166 (99.4)	< 0.0005
Cholelithiasis	285 (93.4)	154 (92.2)	0.617
Comorbidities, n (%)			
Hypertension	95 (31.2)	61 (36.5)	0.235
TIA/stroke	11 (3.6)	4 (2.4)	0.473
Angina	20 (6.6)	16 (9.6)	0.0237
Previous MI	18 (5.9)	14 (8.4)	0.305
Cardiac arrhythmia	17 (5.6)	8 (4.8)	0.716
Heart failure	8 (2.6)	4 (2.4)	0.881
Diabetes mellitus	28 (9.2)	30 (18.0)	0.005
Previous abdominal operation, n (%)	58 (19.0)	26 (15.6)	0.349
Number of previous abdominal operations (median, range)	1 (1-2)	1 (1-4)	0.53
ASA score, n (%)			
I	86 (28.2)	28 (16.8)	
II	159 (52.1)	81 (48.5)	
III	55 (18.0)	51 (30.5)	
IV	5 (1.6)	6 (3.6)	
V	0 (0)	1 (0.6)	0.002
Abbreviations.	AC, acute cholecystitis; TIA, transient ischaemic attack; ASA score, American Society of Anesthesiologists score; MI, myocardial infarction.		

complications including major injury to bile ducts and bowel. Based on these findings, we propose a histology-based clinical classification for AC.

It has been previously shown that inflammatory markers such as NLR and CRP can discriminate between these histology-based severity grades of AC [18, 19]. NLR cut off values of greater than 4.17 (95% CI: 3.76-4.58) were found to distinguish between the histologic mild and moderate-severe categories that we have proposed. NLR areas under the receiver operating characteristic curves in moderate-severe AC was 98% (95% CI, 96%-100%) [19].

In a prospective study, Micic et al. demonstrated that NLR  $\geq 4.18$  predicted severe AC defined as gallbladder inflammation, empyema, acute gangrenous cholecystitis and AC with gallbladder perforation, adhesions and difficulty in dissecting the Calot's triangle with 78.3% sensitivity and 74.3% specificity [13]. This means that in AC patients with NLR of 4.18 or above concerns are raised for increased surgical risks. Patients with raised CRP and NLR should have a higher priori-

ty for urgent LC than patients in the histology-based mild AC category [27]. More accurate prediction of clinical severity of AC using the histology-based approach should not only help with anticipation of surgical complexity, but also with management decisions that can include conservative versus surgical treatment in high-risk patients, prioritization of patients for surgery, allocation of surgical expertise for patients with moderate-severe AC, intensive care or high dependency unit bed occupancy booking and the choice and duration of antimicrobial medication.

Importantly, TG18 guidelines do not consider the histologic group of active chronic cholecystitis as a clinical variant of AC. These patients frequently have recurrent acute presentations with either cholecystitis or biliary colic. The risk of CTO in patients with active chronic cholecystitis was more than 5 times higher than for patients with chronic cholecystitis. We believe that patients with AC who are surgical candidates should benefit from LC being performed soon after their first episode of AC either as an acute or elective procedure.

Our study is limited by its retrospective nature. Further prospective studies will enable more detail regarding clinical presentation and timing for patients in each of these groups.

In conclusion, increasing severity of histologic gallbladder inflammation corresponds with greater risk of CTO and higher rates and severity of postoperative complications. Patients with active chronic cholecystitis and acute edematous cholecystitis correspond to clinically mild AC and those with acute necrotizing, gangrenous, suppurative cholecystitis, pericholecystic abscess and AC with gallbladder perforation comprise clinically severe AC.

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