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ORIGINAL SCIENTIFIC REPORT

Severity of Acute Cholecystitis and Risk of Iatrogenic Bile Duct Injury During Cholecystectomy, a Population-Based Case–Control Study

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Abstract

Background Acute cholecystitis is a common complication to gallstone disease. The relation between the severity of acute cholecystitis and risk of bile duct injury during cholecystectomy has not yet been addressed and is the main focus of this study.

Methods All cases with iatrogenic bile duct injury during cholecystectomy, within the Lake Mälaren region, Sweden, were identified through ICD procedure codes for biliary reconstruction within the Swedish Inpatient Register and matched to non-injured cholecystectomized controls. Information regarding perioperative variables was collected through medical record review.

Results After review, 158 cases and 623 controls remained for analyses. Adjusted risk of bile duct injury was doubled among patients with acute cholecystitis (OR 1.97 95 % CI 1.05–3.72), whereas a mild acute cholecystitis (Tokyo grade I) did not affect the risk of bile duct injury (OR 0.96 95 % CI 0.41–2.25), a moderate (Tokyo grade II) more than doubled the risk (OR 2.41 95 % CI 1.21–4.80). Severe cholecystitis (Tokyo grade III) had a close to significant eightfold increase in risk (OR 8.43 95 % CI 0.97–72.9). The intention to use intraoperative cholangiography reduced injury risk by 52 % (OR 0.48, 95 % CI 0.29–0.81).

Conclusions Patients with on-going acute cholecystitis had twice the risk of sustaining a biliary lesion compared to patients without acute cholecystitis. There was a relation between the Tokyo guidelines severity grading of acute cholecystitis and injury risk and the intention to use intraoperative cholangiography halved the risk of reconstructed bile duct injury during cholecystectomy.

Introduction

Acute cholecystitis is a common complication to gallstone disease [1]. Early cholecystectomy within 1 week of symptom onset is considered safe and often favorable compared to delayed surgery [2–5]. However, patients with acute cholecystitis are a very heterogeneous group, and previous research does not provide convincing knowledge regarding how the severity of cholecystitis influences the risk of severe complications.

One of the challenges in the treatment of acute cholecystitis is where to draw the line between emergency cholecystectomy and conservative management. The

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Tokyo Guidelines [6] for severity assessment of acute cholangitis and cholecystitis offer a consensus definition and severity scoring for these conditions. The relation between different severity grades of acute cholecystitis and risk of bile duct injury during cholecystectomy has not yet been addressed and is one of the main focuses of this study. Using a population-based case–control design, analyzing risk factors for bile duct injury, we hypothesize that severe forms of acute cholecystitis may be associated with increased risk of iatrogenic bile duct injury during cholecystectomy.

Materials and methods

Identification of cases and controls

Using the Swedish Inpatient Registry, cases with potential iatrogenic bile duct injuries were defined as having an international classification of diseases (ICD) procedure code for biliary reconstruction within 1 year after cholecystectomy. To avoid other causes for biliary reconstruction, patients with a concomitant cancer diagnosis within 2 years of the index event or a diagnosis code representing a few benign conditions potentially treated with biliary reconstruction were excluded. This methodology has previously been described in detail [7–9].

The study was limited to persons 15 years or older with a cholecystectomy performed between the years of 1990 and 2005. For practical purposes concerning medical record review, only cases and controls within the geographically restricted area of the five Counties of the Lake Mälaren Valley in central eastern Sweden were included. This area constitutes approximately 1/3 of the Swedish population including the capital, Stockholm. All 30 hospitals performing cholecystectomies within this area were included.

Control patients were defined as cholecystectomies without reconstructive biliary events and matched to cases on gender, age, and year of cholecystectomy and randomly sampled to a case-to-control ratio of 1:3.

Data collection

After obtaining consent, patient- and procedure-related data were collected through a retrospective review of medical records.

The duration of symptomatic gallstone disease was estimated either from information available in the admission records or, if missing, from a possible previous gallstone diagnosis in the Inpatient register. The diagnosis of acute cholecystitis was made according to the 2013 revision of the Tokyo Guidelines for acute cholecystitis [6] (TG13). Patients with acute cholecystitis were subsequently graded according to the TG13 severity assessment into mild (Grade I), moderate (Grade II), or severe (Grade III). Patients with an ICD diagnosis code of acute cholecystitis within the Swedish Inpatient Registry, prior to the hospital stay involving cholecystectomy, were classified as having a history of former acute cholecystitis. A history of pancreatitis was similarly defined using ICD codes, whereas information on present acute pancreatitis was obtained from the medical records. Comorbidity was analyzed using the Deyo modification of the Charlson comorbidity index [10]. Information of intraoperative cholangiography was obtained from the cholecystectomy report. The intention to perform intraoperative cholangiography was defined as a successful or attempted cholangiography. In a subgroup of cholecystectomies, it was evident that the intraoperative cholangiography was performed only to confirm a suspected bile duct injury after division and clipping of the presumed cystic duct. These cases were ordered into the *no intention* of intraoperative cholangiography group.

Statistics

Statistical analyses were performed using STATA 11 software. Risk factors for iatrogenic bile duct injury were analyzed using multivariate logistic regression, controlling for the matched variables. Risk factors were tested univariately and multivariately adjusting for possible confounders and presented as an odds ratio for bile duct injury with 95 % confidence interval. Due to significant collinearity between acute cholecystitis and emergency operation, these variables were analyzed in separate models, and only acute cholecystitis was used for confounder adjustment. CRP was only available in a subset of patients and thus not used for confounder adjustment. The models were tested for effect modification and finally assessed using Spearman's goodness of fit. A p value <0.05 was considered to be significant.

Results

Using the ICD procedure code methodology, 232 possible reconstructed iatrogenic bile duct injury cases were identified and 696 cholecystectomy controls were selected. In accordance with the ethical approval, informed consent was sent out to living participants and 38 (10 cases and 28 controls) denied review. After review, 50 potential bile duct injury cases were found to be wrongly classified as bile duct injuries and thus excluded. Furthermore, 14 potential cases and 45 controls were either inaccessible (due to deletion of patient records) or lacked sufficient

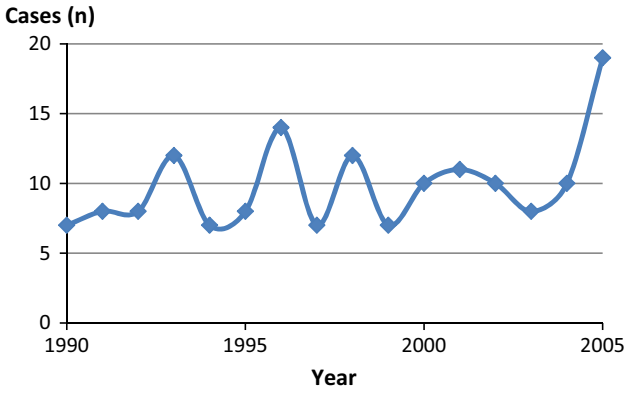

Fig. 1 Distribution of bile duct injury cases

Table 1 Causes of non-inclusion

	Cases ($N = 232$)	Controls ($N = 696$)
No approval	10	28
Destroyed medical records	4	15
Incomplete medical records[a]	10	30
Misclassification of bile duct injury cases	50	N/A
Remaining for analysis	158	623

N/A not applicable

[a] Not sufficient information in records regarding surgery or complications

information regarding surgery, injury extent, or complications and were therefore excluded. The remaining 158 cases were evenly distributed over the time period (Fig. 1) and classified according to the Hannover classification of bile duct injuries [11]. The reasons for non-retrievable records are listed in Table 1.

Of the 158 reconstructed bile duct injury cases, 10.8 % ($N = 17$) were complete transections of the common bile duct or common hepatic duct. 15.8 % ($N = 25$) of the injuries were transections or major tangential injuries to bile ducts above the hepatic confluence. A majority, 68.9 % ($N = 109$), of the injuries consisted of lateral incomplete lesions to the common bile duct or common hepatic duct. Nine injuries (6 %) had a preoperatively discovered concomitant vascular injury to the right hepatic artery. A majority, 80 %, of the injuries were discovered during cholecystectomy with the remaining discovered at a median of 7 days post cholecystectomy (range 1–250 days). A detailed description of bile duct injury pattern, classified according to the Hannover classification, is presented in Table 2.

The controls were matched to cases on age, gender, and year of cholecystectomy and thus similar regarding these variables. A detailed frequency distribution of cases and controls on analyzed variables is displayed in Table 3.

Table 2 Distribution of bile duct injuries according to the Hannover classification

Hannover classification	*N* (with vascular injury)
Peripheral leakage	
A1—cystic duct leak	2
A2—leak in the gallbladder bed	0
Biliary tract occlusion	
B1—incomplete	3
B2—complete	0
Tangential injury	
C1—lesion <5 mm	73 (1)
C2—lesion >5 mm below hepatic confluence	34 (1)
C3—extensive lesion at hepatic confluence	2
C4—extensive lesion above hepatic confluence	11 (2)
Complete transection	
D1—without defect below hepatic confluence	6
D2—with defect below hepatic confluence	7 (2)
D3—at hepatic confluence	4 (1)
D4—above hepatic confluence	14 (2)
Late stenosis	
E1—main bile duct, short <5 mm	0
E2—main bile duct, >5 mm	2
E3—at hepatic confluence	0
E4—above hepatic confluence	0
Total	158 (7)

Risk factors for bile duct injury

Patients' BMI, the presence of common bile duct stones or pancreatitis were not significantly correlated to bile duct injury risk, whereas comorbidity, length of symptomatic gallstone disease, and a present or past acute cholecystitis increased the risk (Table 4).

Among the bile duct injury cases, 25.6 % ($n = 40$) had on-going acute cholecystitis. The corresponding figure among controls was 16.9 % ($n = 104$). The severity distribution of acute cholecystitis among cases and controls, according to the Tokyo guidelines (TG13), is presented in Table 5. Regarding the few cases meeting the criteria of severe acute cholecystitis, all of them ($N = 4$) had preoperative renal dysfunction with elevated creatinine >2.0 mg/dl.

Increased severity of acute cholecystitis was associated with a corresponding increase in injury risk, whereas a mild acute cholecystitis (Tokyo grade I) did not significantly increase the risk of injury (OR 0.96 95 % CI 0.41–2.25), a moderate cholecystitis (Tokyo grade II) more than doubled the risk (OR 2.41 95 % CI 1.21–4.80). Additionally, a trend toward even higher risk was seen among the most severe cases of acute cholecystitis (OR 8.43 95 % CI 0.97–72.9).

Table 3 Characteristics of cases and controls

	Cases ($N = 158$)	Controls ($N = 623$)
Gender[a]		
Male (%)	75 (47 %)	309 (50 %)
Female (%)	83 (53 %)	314 (50 %)
Age[a], mean (SD)	58.6 (16.5)	61.3 (15.7)
BMI, mean (SD)	27.2 (4.40)	26.3 (4.19)
Comorbidity (Charlson index)		
0	84 (53 %)	435 (70 %)
1	30 (19 %)	103 (17 %)
2	44 (28 %)	85 (13 %)
Years with gallstone disease		
>1 years (%)	46 (29 %)	253 (41 %)
1–5 years (%)	52 (33 %)	239 (38 %)
>5 years (%)	44 (28 %)	92 (15 %)
Missing data	16	39
Cholecystectomy		
Laparoscopic (%)	130 (82 %)	499 (80 %)
Open (%)	28 (18 %)	124 (20 %)
Emergency (%)	61 (39 %)	166 (27 %)
Planned (%)	97 (61 %)	457 (73 %)
Acute cholecystitis (%)	40 (25 %)	104 (17 %)
CRP[b], mean (SD)	163 (91)	121 (95)
CRP < 10	1 (3 %)	4 (5 %)
CRP 10–100	12 (30 %)	45 (48 %)
CRP > 100	27 (67 %)	44 (47 %)
Acute cholecystitis in the medical history (%)	40 (25 %)	92 (15 %)
Acute pancreatitis (%)	3 (2 %)	15 (2 %)
Acute pancreatitis in the medical history (%)	16 (10 %)	60 (10 %)
Common bile duct stones (%)	21 (13 %)	87 (14 %)
Intraoperative cholangiography (IOC)		
No (%)	30 (19 %)	184 (29 %)
Yes (%)	120 (76 %)	410 (66 %)
Attempted, but failed (%)	8 (5 %)	29 (5 %)
To confirm BDI[c] (%)	29 (18 %)	N/A
IOC intention to do[d] (%)	99 (62 %)	439 (70 %)

N/A not applicable

[a] Matching variables

[b] CRP among patients with acute cholecystitis

[c] IOC (to confirm BDI) after complete division of suspected cystic duct

[d] Intention to do IOC consists of performed IOC and attempted but failed IOC but not cases where IOC was used to confirm BDI

Within the acute cholecystitis group, C-reactive protein (CRP) showed a linear trend with an increase in injury risk corresponding to the level of CRP elevation.

Intraoperative cholangiography was used in 76 % ($N = 120$) of the bile duct injury cases and in 70 % ($N = 410$) of the uneventful control cholecystectomies. However, in 18 % ($N = 29$) of the bile duct injury cases, the cholangiography was performed specifically to confirm a bile duct injury after complete division or clipping of the suspected cystic duct and thus not primarily intended. Subsequently, 62 % ($N = 99$) of the cases had an original intention of intraoperative cholangiography, resulting in a 52 % adjusted reduction in the risk of iatrogenic bile duct injury when intraoperative cholangiography was intended (OR 0.48 95 % CI 0.29–0.81). Suboptimal cholangiography technique or misinterpretations were not found as causes of bile duct injury among cases.

Table 4 Estimated risk of reconstructed bile duct injury (expressed as odds ratios) during cholecystectomy

	Crude OR (95 % CI)	Adjusted[a] OR (95 % CI)
Gender	*	*
Age	*	*
BMI		
Underweight (BMI < 18.5)	1.21 (0.13–11.2)	1.67 (0.16–18.0)
Normal (BMI 18.5–25) (ref)	1.0 (ref)	1.0 (ref)
Overweight (25–30)	1.25 (0.78–2.02)	1.25 (0.73–2.12)
Obese (BMI > 30)	1.73 (0.98–3.06)	1.53 (0.82–2.88)
Comorbidity (Charlson index)		
0 (ref)	1.0 (ref)	1.0 (ref)
1	1.90 (0.72–1.49)	1.70 (0.85–3.38)
2	3.77 (2.33–6.08)	3.71 (1.96–7.01)
Years with gallstone disease		
<1 years (ref)	1.0 (ref)	1.0 (ref)
1–5 years	1.21 (0.78–1.88)	1.24 (0.70–2.21)
>5 years	2.96 (1.80–4.88)	2.88 (1.51–5.48)
Cholecystectomy		
Laparoscopic (ref)	1.0 (ref)	1.0 (ref)
Open	0.95 (0.60–1.51)	0.93 (0.47–1.84)
Planned (ref)	1.0 (ref)	1.0 (ref)
Emergency	1.88 (1.29–2.74)	2.62 (1.46–4.72)
Acute cholecystitis		
No (ref)	1.0 (ref)	1.0 (ref)
Yes	1.94 (1.25–2.99)	1.97 (1.05–3.72)
Tokyo grade I (mild)	1.22 (0.63–2.33)	0.96 (0.41–2.25)
Tokyo grade II (moderate)	2.59 (1.51–4.43)	2.41 (1.21–4.80)
Tokyo grade III (severe)	5.26 (0.72–38.58)	8.43 (0.97–72.9)
CRP < 10 (ref)	1.0 (ref)	1.0 (ref)
CRP 10–100	2.24 (0.24–20.84)	1.49 (0.10–21.48)
CRP 100–200	4.72 (0.50–45.55)	4.12 (0.27–62.26)
CPR > 200	6.40 (0.67–60.44)	7.04 (0.47–104.78)
Acute cholecystitis in the medical history	2.12 (1.38–3.26)	3.63 (2.00–6.57)
Acute pancreatitis	0.83 (0.24–2.92)	1.76 (0.41–7.52)
Acute pancreatitis in the medical history	1.09 (0.61–1.96)	1.13 (0.50–2.59)
Common bile duct stones	0.99 (0.59–1.66)	0.79 (0.39–1.61)
Intraoperative cholangiography		
No intention	1.0 (ref)	1.0 (ref)
Intention to do	0.68 (0.47–0.99)	0.48 (0.29–0.81)

* Matching variables

[a] Adjusted for variables in Table 3

Discussion

This population-based case–control study examines risk factors for severe, surgically reconstructed bile duct injury at cholecystectomy, with emphasis on the influence of the severity of acute cholecystitis. Patients with on-going acute cholecystitis had twice the risk of sustaining a biliary lesion compared to patients without acute cholecystitis. There was a relation between the Tokyo guidelines severity grade of acute cholecystitis and the risk of injury. The intention to use intraoperative cholangiography halved the risk of reconstructed bile duct injury during cholecystectomy.

A case–control study offers advantages in research concerning rare outcomes, such as iatrogenic bile duct injury. When detailed information regarding the surgical procedure or patient characteristics are lacking in registers, a case–control study with review of medical records is often the only cost-effective solution. The study base, with

Table 5 Severity assessment according to the 2013 Tokyo guidelines

Tokyo grade for acute cholecystitis	Cases	Controls
Mild (grade I)	13	53
Does not meet the criteria of grade II or III		
Moderate (grade II)	25	49
Associated with any one of the following conditions:		
1. Elevated WBC count (> 18 000/mm3)		
2. Palpable tender mass in the right upper abdominal quadrant		
3. Duration of complaints > 72 h		
4. Marked local inflammation		
Severe (grade III)	2	2
Associated with dysfunction of any one of the following organs/systems		
1. Cardiovascular dysfunction (Hypotension requiring treatment with dopamine <5 mikrog/kg per min, or any dose of norepinephrine		
2. Neurological dysfunction (decreased level of consciousness)		
3. Respiratory dysfunction (PaO_2/FiO_2 ratio <300)		
4. Renal dysfunction (oliguria, creatinine >2.0 mg/dl (>180 umol/L))		
5. Hepatic dysfunction (PT-INR >1.5)		
6. Hematological dysfunction (platelet count <100 000/mm3)		

all cholecystectomies performed in the area of eastern middle part of Sweden 1990–2005, allows for identification of a relatively large number of reconstructed bile duct injury cases despite the rareness of this dreaded complication. One may raise concerns about the data not being that recent, with the last included patients from 2005. The delay can partly be explained by the need to wait 2 years before data extraction to allow for the exclusion of malignant causes of biliary reconstruction in combination with a time consuming manual record review at 30 different participating hospitals. However, cases and controls were evenly distributed over the years and a sub analysis with dichotomization of the time period did not alter the main results significantly comparing the last 8 years to the previous years (data not shown). This variable was not included in the main analyses due to a significant loss of power. It is thus reasonable to believe that the results are most relevant to today's surgeons handling patients with complicated gallstone disease.

The Tokyo guidelines on classification and management of acute cholecystitis are based on expert reviews of the available scientific literature. However, the recommendations regarding optimal treatment according to severity grade were based upon the general opinions of professionals due to the lack of published high quality data [12]. In these recommendations, early laparoscopic cholecystectomy is advocated for mild (Grade I) acute cholecystitis. Moderate (Grade II) cholecystitis cases are recommended to undergo cholecystectomy at experienced centers, but early drainage and delayed cholecystectomy are recommended if the patient has severe local inflammation. For severe (Grade III) cases, early drainage is the preferred treatment.

Even though these recommendations are supported by other authors [13, 14], the timeliness of the guidelines has been questioned and voices were raised for the safety of cholecystectomy even in severe cases of acute cholecystitis [15]. Borzellino et al. [16] concluded in a systematic review and meta-analysis that laparoscopic cholecystectomy may be acceptable in cases of severe acute cholecystitis although with a significant higher overall postoperative complication rate. In the only study addressing bile duct injury and different severity grades of acute cholecystitis, Navez et al. [17] report no different rates of bile duct injuries comparing pathology findings of acute edematous cholecystitis to cholecystitis with empyema or gangrenous cholecystitis. However, the correlation between pathology findings and Tokyo grading in patients with acute cholecystitis is unclear. Acute cholecystitis per se has been established as a risk factor for bile duct injury in previous population-based research [18], and the present results support this with a close to doubled injury rate. More importantly, the risk of severe bile duct injury is not different in patients with mild (Grade I) cholecystitis compared to non-cholecystitis patients emphasizing the safety of cholecystectomy in this group. The increased bile duct injury risk in moderate to severe cholecystitis cases does not necessarily implicate a conservative regime but points out the need for a more precarious approach with a thorough preoperative analysis of the patient's risk factors and an experienced surgeon using a safe technique. The results furthermore support the non-

surgical management for patients with severe forms of acute cholecystitis as the risk of severe surgery-related complications is increased.

Patients with severe comorbidity and a longer history of symptomatic gallstone disease were factors that apart from acute cholecystitis were associated with an increased bile duct injury risk in this study. Symptomatic gallstone disease for more than 5 years prior to the cholecystectomy more than doubled the risk of bile duct injury compared to patients with less than 1 year of symptom duration, probably explained by a higher frequency of chronic cholecystitis when symptomatic years are added. It is however important to keep in mind that since surgeons causing bile duct injuries are likely to emphasize difficult circumstances like chronic cholecystitis, this information is sensitive to bias.

CRP was analyzed among patients with acute cholecystitis as an indicator of severity. The point estimates suggest a an association, but as CRP was not routinely used during the early years of this study, the vast number of missing values hampers the precision of these analyses. CRP has been shown to predict the histopathological severity of acute cholecystitis [19] and might work as a readily available predictor for hazardous surgery.

In this study, the intention to use intraoperative cholangiography was associated with a reduced risk of bile duct injury. Although the vast majority of previous data favors the use of intraoperative cholangiography [9, 18, 20–24] the issue is still a matter of debate as a potential major source of bias, the different reasons for performing intraoperative cholangiography, are usually not controlled for [25]. Failed cholangiography attempts are often caused by difficult circumstances, such as inflammation or bleeding where bile duct injuries also tend to be more frequent. The majority of registry-based research identifies cholangiography usage with procedure codes without the possibility to detect failed attempts. Moreover, some surgeons only use intraoperative cholangiography to confirm and evaluate the extent of a suspected injury causing an apparent high incidence of injuries in the cholangiography group. In this study, the thorough review of surgical reports made it possible to both identify failed attempts for cholangiography as well as operations where it was used solitarily for bile duct injury confirmation, after division and clipping of a misinterpreted bile duct.

In conclusion, the main finding of this study is the association between the severity of cholecystitis and iatrogenic bile duct injury, stressing the need of a differentiated treatment algorithm for the very heterogeneous group of patients with acute cholecystitis. The results support the Tokyo Guidelines treatment recommendations advocating early cholecystectomy for mild and moderate forms of acute cholecystitis, whereas a conservative approach with drainage should be strongly considered for patients with severe acute cholecystitis.

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Compliance with Ethical Standard

Conflict of interest The authors disclose no conflicts of interest

Ethics The study was approved by the Regional Research Ethics Committee of Stockholm, reference number 04-139/3

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