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ORIGINAL ARTICLE

Predicting a 'difficult cholecystectomy' after mild gallstone pancreatitis

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Abstract

Background: Cholecystectomy after gallstone pancreatitis may be technically demanding. The aim of this study was to investigate risk factors for a difficult cholecystectomy after mild pancreatitis.

Methods: This was a prospective study within a randomized controlled trial on the timing of cholecystectomy after mild gallstone pancreatitis. Difficulty of cholecystectomy was scored on a 0 to 10 visual analogue scale (VAS) by the senior attending surgeon. The primary outcome 'difficult cholecystectomy' was defined by presence of one or more of the following features: a VAS score $\geq$ 8, duration of surgery > 75 minutes, conversion or subtotal cholecystectomy.

Results: 249 patients were included in the primary analysis. A difficult cholecystectomy occurred in 82 patients (33%). In the 'same-admission cholecystectomy' group 29 of 112 cholecystectomies were difficult (26%) versus 49 of 127 patients (39%) who underwent surgery after 2 weeks (p = 0.037). After multivariable analysis, male sex (OR 1.80, 95% confidence interval [CI] 1.04–3.13; p = 0.037), prior sphincterotomy (OR 1.79, 95% CI 1.01–3.16; p = 0.046), and delaying cholecystectomy for at least two weeks (OR 1.81, 95% CI 1.04–3.16; p = 0.036) were independent predictors of a difficult cholecystectomy.

Conclusion: Surgeons should anticipate a difficult cholecystectomy after mild gallstone pancreatitis in case of male sex, prior sphincterotomy and delayed cholecystectomy.

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Introduction

Early cholecystectomy is the treatment of choice in complicated gallstone disease such as cholecystitis or gallstone pancreatitis.[1–3] As most cholecystectomies are performed electively for symptomatic cholelithiasis, this procedure is one of the cornerstones of surgical trainee programs.[4] In recent years a shift in treatment strategies for complicated gallstone disease has taken place.[5–7] Current guidelines now advocate early cholecystectomy in acute cholecystitis and mild gallstone pancreatitis.[1–3,7,8] In coming years, increasing numbers of cholecystectomies will be performed as acute or semi-acute care procedures. Accordingly, it is vital to anticipate in which patients cholecystectomy is likely to be difficult.[9] Cholecystectomy in patients at high risk for surgical complications, including bile duct injuries, can then be assigned to or supervised by gastrointestinal surgeons with laparoscopic expertise, rather than less experienced surgeons or unsupervised surgical trainees.[10]

Studies in cohorts of unselected patients have identified several risk factors for technical difficulty of cholecystectomy. Among these are male sex, previous endoscopic sphincterotomy, increasing age and inflammation of the gallbladder or pancreas.[11−14] One population based study found an odds ratio of 3.2 for bile duct injury in 30 211 cholecystectomies after gallstone pancreatitis.[15]

Only three studies have focused on the difficulty of cholecystectomy after mild gallstone pancreatitis. Two of these are small case series including less than 25 patients, the third was a retrospective study which also included patients with severe pancreatitis.[16−18] Other studies which assessed outcome of cholecystectomy after pancreatitis have not described the difficulty of these procedures.[19,20] As the rationale for delaying cholecystectomy after mild gallstone pancreatitis has traditionally been the concern for technical difficulties and increased risk of bile duct injury and other complications, the aim of this study was to investigate the risk factors for a 'difficult cholecystectomy' after mild gallstone pancreatitis.[21]

Methods

Study design

This was a prospective study carried out during the previously published multicentre randomized PONCHO trial.[8] In brief, 266 adult patients with mild gallstone pancreatitis from 23 Dutch centres were randomized 24−48 h before anticipated discharge. Patients with moderately severe or severe pancreatitis (i.e. documented organ failure (persisting for more than 48 h), pancreatic necrosis with peripancreatic fluid collections), chronic pancreatitis or alcohol abuse were not eligible for participation. Patients were randomized to either cholecystectomy within 3 days ('same-admission cholecystectomy') or discharge and cholecystectomy after 25−30 days ('interval cholecystectomy'). Patients were followed for 6 months after surgery for the occurrence of acute readmission for gallstone related complications (recurrent pancreatitis, cholangitis, choledocholithiasis requiring endoscopic retrograde cholangiopancreatography or simple gallstone colic) or mortality. Clinical, radiological and surgical data were prospectively collected on patient record forms and source material and entered into the trial database. Surgical data included the experience with laparoscopic surgery of the team, operating time, the presence of adhesions and the reason for conversion or subtotal cholecystectomy. Difficulty of cholecystectomy was scored immediately after surgery by the most experienced attending surgeon on a 0−10 visual analogue scale (10 being most difficult; VAS). Additionally, the forms included questions regarding the difficulty of dissection, dichotomized as 'easy' or 'difficult', and the presence or absence of dense adhesions in the dissection area. Surgical complications such as bile duct injuries and bleeds are described but not statistically analysed, due to their low incidence. As this study focuses on the intraoperative findings as described by the surgeon and the subjective difficulty of dissection, postoperative complications such as wound infections were not part of this analysis.

Intraoperative cholangiography (IOC) was not part of the PONCHO study protocol and left to the discretion of the surgeon. The procedure was applied regularly in only one of the participating hospitals. When performed, the attending surgeon was asked to complete an additional form, including cholangiography time and the presence of bile duct stones.

Variables, data sources and measurements

The primary outcome of this study was a 'difficult cholecystectomy', as defined by a VAS score of 8 or higher (75th percentile), duration of surgery beyond 75 min (75th percentile; excluding IOC time), conversion or subtotal cholecystectomy. In a secondary analysis, the individual components of this combined outcome measure were investigated. Predictive factors assessed were sex, age, body mass index (BMI), significant comorbidity (defined as ASA class III), a history of prior biliary colic, a history of upper abdominal surgery, endoscopic sphincterotomy before surgery, the number of days between sphincterotomy and cholecystectomy and the interval between pancreatitis onset and cholecystectomy. For practical applicability, the latter was tested both as a continuous variable and dichotomized in 'cholecystectomy within or after 2 weeks of admission'. This arbitrary cut-off value was chosen as cholecystectomy within this period should be possible for virtually all patients with mild pancreatitis.

Statistical analysis

Analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk NY). The relationship between the predictive factors and the combined endpoint was first explored through univariable logistic regression analysis. Factors with a *p*-value less than 0.2 were then selected for a multivariable logistic regression model. The final multivariable model was internally validated using 5000 bootstrap resamples and a nomogram of the model was designed. Risks are presented as odds ratios (OR) with 95% confidence interval (CI). Additionally, the predictive value of the variables on the individual components of the combined endpoint was explored. A sensitivity analysis was performed, excluding patients in which the most experienced member of the surgical team had performed 100 or less laparoscopic cholecystectomies. This cut-off value was designated by the surgeons involved in the design of the PONCHO trial as a reasonable measurement of experience in the field. A subgroup analysis was also performed for predictive factors in the patients who underwent same-admission cholecystectomy. Differences in the dichotomous outcomes 'difficult dissection' and the presence or absence of adhesions were tested through the χ^2 or Mann−Whitney U test, as appropriate.

Results

Of the 266 patients originally randomized in the PONCHO trial, two were excluded from the present study. In one patient the amylase levels on admission did not exceed three times the upper limit of normal required for the diagnosis acute pancreatitis, leading to exclusion by the adjudication committee; the other patient ultimately refused cholecystectomy. Baseline characteristics of the 264 included patients can be found in Table 1. Difficulty VAS scores were recorded in 259 patients (98%), with a difficult cholecystectomy (i.e. the combined endpoint) in 82 out of 249 patients (33%).

The median VAS for difficulty of cholecystectomy was 6 (interquartile range [IQR] 4–7, Table 1). A primary open cholecystectomy was performed in 6 patients (2%); these patients were not included in the analysis predicting conversion or subtotal cholecystectomy. Laparoscopy was converted in nine patients (3%), two of which were completed as subtotal cholecystectomies. A third subtotal cholecystectomy was completed laparoscopically. Duration of surgery was recorded in 250 patients (95%) with a median of 60 min (IQR 43–75 min). In 60 patients the duration of surgery exceeded 75 min (24%).

Intraoperative cholangiography was successful in 16 of 17 patients, and took a median of 14 min (range 9–45). In five patients, operating time was well below 75 min regardless of IOC (up to 60 min *including* IOC). In five other patients, operating time was well over 75 min, regardless of IOC (80–171 min *excluding* IOC). In three patients, duration of operation was within 5 min of the 75 min cut-off value when IOC time was excluded.

In only one of the 17 patients in whom IOC was performed a filling defect was seen, which was treated conservatively.

In two patients, a cystic duct leakage was discovered several days after surgery. Difficulty of surgery was scored '9' in one of these patients with a duration of cholecystectomy of 80 min. In the other patient difficulty was scored '2' with an unknown duration of surgery. Two other patients underwent a re-intervention for bleeding; in one patient difficulty of surgery was scored '8', with a duration of 80 min, in the other it was scored '4' with a duration of 35 min.

Table 2 presents the results from the uni- and multivariable analyses using the combined endpoint as the outcome. As a continuous variable, the number of days between admission and cholecystectomy was predictive of a difficult cholecystectomy with an OR of 1.02 per day delay (95% CI 1.00–1.04; $p = 0.022$). The internal validation of the model with 5000 bootstrap resamples yielded no new insights. Presence of all risk factors (i.e. a male patient who had undergone sphincterotomy and delayed cholecystectomy) resulted in an overall chance of a difficult cholecystectomy of 55%; this chance was 18% in absence of these factors. The positive and negative predictive values of all risk factors are presented in Table 5.

Table 1 Baseline characteristics

	Patients (N = 264)
Demographics and history	
Age; median (IQR)	53 (40–66)
Male sex; *N* (%)	104 (39)
Body mass index; median (IQR)	28 (25–31)
Morbidly obese (BMI ≥ 40); *N* (%)	13 (5)
ASA classification; *N* (%)	
Class 1	94 (36)
Class 2	149 (55)
Class 3	25 (10)
Prior biliary colic; *N* (%)	74 (28)
History of upper abdominal surgery	15 (6)
Preoperative features	
Prior endoscopic sphincterotomy; *N* (%)	81 (31)
Complications during ERCP[a]	8 (9)
Number of days between sphincterotomy and cholecystectomy; median (IQR)	21 (7–32)
Duration of pancreatitis[b] in days; median (IQR)	5 (3–8)
Days from pancreatitis onset to cholecystectomy; median (IQR)	22 (7–33)
Cholecystectomy delayed until 2 weeks after admission; *N* (%)	145 (55)
Surgical characteristics	
Difficulty of cholecystectomy[c]; median (IQR)	6 (4–7)
VAS ≥ 8; *N* (%)	44 (17)
Conversion[d]; *N* (%)	9 (3)
Subtotal cholecystectomy	3 (1)
Duration of surgery in minutes[e]; median (IQR)	60 (43–75)
>75 min; *N* (%)	60 (24)

IQR, interquartile range; ASA, American Society for Anesthesiology; ERCP, endoscopic retrograde Cholangio-Pancreatography; CT, computed tomography; CTSI, computed tomography severity index; VAS, visual analogue scale.

[a] 5 bleeds and 3 perforations in 88 patients who underwent ERCP.

[b] Calculated as the number of days between admission and randomization in the PONCHO trial.

[c] Case record forms were received from 259 patients.

[d] Excluding 6 patients in whom a primary open cholecystectomy was performed.

[e] Duration of surgery was reported in 250 patients.

The rate of difficult cholecystectomy in those patients who underwent cholecystectomy before discharge (i.e. within 3 days after randomization) was 26% (29/112 patients) versus 39% (49/127 patients) in those patients who underwent surgery after 2 weeks ($p = 0.0037$).

Sensitivity and subgroup analyses

After excluding less experienced teams, 238 cholecystectomies (90%) remained in which the experience exceeded 100 cholecystectomies. Excluding 11 patients with missing variables, 69

Table 2 Univariable and multivariable analysis with sensitivity analysis on the combined endpoint

Predictor	All cases (*N* = 249)				Surgical experience > 100 laparoscopic cholecystectomies (*N* = 227)	
	Univariable analysis		Multivariable analysis		Univariable analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.01 (0.99–1.03)	0.312			1.01 (0.99–1.03)	0.422
Male Sex	1.75 (1.02–3.00)	0.042	1.88 (1.08–3.27)	0.025	1.52 (0.85–2.72)	0.154
Morbidly obese (BMI ≥ 40)	1.81 (0.59–5.55)	0.303			2.05 (0.66–6.36)	0.211
ASA class 3	1.52 (0.64–3.58)	0.341			1.26 (0.48–3.31)	0.640
Prior biliary colic	1.06 (0.58–1.93)	0.855			1.17 (0.62–2.19)	0.635
History of upper abdominal surgery	1.39 (0.48–4.04)	0.549			1.69 (0.52–5.51)	0.388
Endoscopic sphincterotomy prior to cholecystectomy	1.77 (1.02–3.09)	0.044	1.77 (1.00–3.13)	0.050	1.61 (0.89–2.92)	0.114
Days between sphincterotomy and cholecystectomy	1.02 (0.99–1.05)	0.269			1.01 (0.97–1.04)	0.684
Cholecystectomy after 2 weeks of admission	1.81 (1.05–3.11)	0.034	1.81 (1.04–3.16)	0.036	1.16 (0.90–2.88)	0.105

out of 227 patients (30%) had difficult cholecystectomies in this subgroup. No predictive factors could be identified through uni- or multivariable analysis on the combined endpoint (Table 3). The odds ratio per day between admission and cholecystectomy was similar in this group, but failed to show statistical significance (OR 1.02, 95% CI 1.00–1.05; $p = 0.051$).

Table 3 Uni- and multivariable sensitivity analysis of individual components of the combined endpoint

Predictor	VAS difficulty ≥ 8				Conversion or subtotal cholecystectomy				Duration of surgery > 75 min	
	(*N* = 234)				(*N* = 238)				(*N* = 223)	
	Univariable		Multivariable		Univariable		Multivariable		Univariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.02 (1.00–1.04)	0.096	1.03 (1.00–1.05)	0.037	1.08 (1.02–1.13)	0.008	1.07 (1.01–1.13)	0.019	1.00 (0.98–1.02)	0.952
Male Sex	1.77 (0.89–3.84)	0.101			6.27 (1.27–30.87)	0.024	4.38 (0.87–22.14)	0.074	1.12 (0.58–2.16)	0.747
Morbidly obese (BMI ≥ 40)	3.21 (0.99–10.38)	0.051	5.56 (1.55–20.00)	0.008	1.00 (0.99–1.00)	0.999			2.55 (0.79–8.18)	0.117
ASA class 3	1.13 (0.36–3.54)	0.840			1.29 (0.15–10.82)	0.816			1.73 (0.63–4.76)	0.293
Prior biliary colic	0.95 (0.45–2.03)	0.896			0.72 (0.15–3.58)	0.691			1.54 (0.77–3.07)	0.223
History of upper abdominal surgery	1.62 (0.42–6.28)	0.483			2.70 (0.31–23.72)	0.370			1.29 (0.34–4.96)	0.713
Endoscopic sphincterotomy prior to cholecystectomy	2.79 (1.40–5.56)	0.003	3.28 (1.58–6.80)	0.001	0.26 (0.03–2.13)	0.211			1.12 (0.60–2.36)	0.609
Days between sphincterotomy and cholecystectomy	1.02 (0.98–1.05)	0.426			1.06 (0.92–1.23)	0.422			0.99 (0.96–1.04)	0.808
Cholecystectomy after 2 weeks of admission	2.03 (0.990–4.14)	0.053	2.09 (0.98–4.46)	0.055	1.09 (0.28–4.15)	0.905			1.30 (0.68–2.50)	0.426

In the subgroup analysis performed on patients who underwent cholecystectomy before discharge, only male sex was predictive of a difficult cholecystectomy (OR 2.42, 95% CI 1.02–5.72, $p = 0.045$; Table 4). No multivariable model could be designed.

Discussion

In this prospective study within a multicentre randomized trial, male sex, previous endoscopic sphincterotomy and delaying cholecystectomy for more than two weeks predicted a difficult cholecystectomy after mild gallstone pancreatitis. When all factors are present this risk increased from 18% to 55%. The risk of a difficult cholecystectomy was 26% in the same-admission group versus 39% when surgery was delayed for more than 2 weeks after discharge. When only analysing procedures performed by experienced surgeons no risk factors were identified for the combined endpoint.

The PONCHO trial and several retrospective studies have demonstrated the superiority of same admission cholecystectomy over interval cholecystectomy for mild gallstone pancreatitis in terms of the risk of recurrent pancreatitis.[5,8,18–20] These studies were largely performed to convince the surgical community to abandon interval cholecystectomy, which has been the approach preferred by many according to international reports.[22,23] This strategy was advocated in the early 90s, when early cholecystectomy after acute pancreatitis was associated with high conversion rates. Moreover, as a result of concerns of bile duct injury, mild gallstone pancreatitis and acute cholecystitis were generally considered a contraindication for early cholecystectomy.[20,24,25] As experience and proficiency with laparoscopic surgery increased, indications have shifted.[26] Cholecystectomy during the same admission for mild pancreatitis became

Table 4 Univariable subgroup analysis of the combined endpoint

Predictor	VAS difficulty ≥ 8 ($N = 112$) OR (95% CI)	*p*
Age	1.01 (0.98–1.03)	0.676
Male Sex	2.42 (1.02–5.72)	0.045
Morbidly obese (BMI ≥ 40)	1.16 (0.21–6.31)	0.88
ASA class 3	1.08 (0.28–4.39)	0.912
Prior biliary colic	1.33 (0.53–3.37)	0.549
History of upper abdominal surgery	1.16 (0.21–6.31)	0.867
Endoscopic sphincterotomy prior to cholecystectomy	1.25 (0.50–3.19)	0.639
Days between sphincterotomy and cholecystectomy	0.96 (0.77–1.19)	0.695

Table 5 Positive and negative predictive values of the risk factors

Risk factor	Positive predictive value	Negative predictive value
Male sex	41% (33–48)	72% (67–76)
Previous sphincterotomy	41% (33–51)	71% (67–75)
Surgery after 2 weeks	39% (34–44)	74 (67–80)
Male sex and sphincterotomy	61% (43–76)	71% (68–73)
Sphincterotomy and after 2 weeks	48% (36–60)	71% (68–74)
Male sex and after 2 weeks	46% (34–58)	70% (67–73)
All three factors	72% (50–87)	70% (68–72)

Data are percentages with 95% confidence interval.

standard in some centres, but the majority of the surgical community continues to delay cholecystectomy.[27,28] This can be explained in part because interval surgery has distinct logistical advantages, but also due to the lingering doubt regarding the safety of early cholecystectomy. Studies addressing the safety of cholecystectomy have largely refrained to conversion and general surgical complications such as wound infections, as more specific complications like bile duct injury are relatively rare.[29] Neither conversion nor complication rates differed between the two strategies in any of these studies.[5,16,19,20,23,30,31]

The present study is the largest cohort to date focussing on technical difficulty of cholecystectomy in mild gallstone pancreatitis. The finding of male sex as a risk factor for difficult cholecystectomy is in line with data from several reports on cholecystectomy in unselected cohorts, among which a systematic review including 109 studies, in which male patients were at a significantly higher risk of conversion.[11,14,32,33] A clear anatomical explanation for this phenomenon is lacking but could be related the amount of intra-abdominal fat in males. Likewise, previous endoscopic sphincterotomy has been shown to increase difficulty of laparoscopic cholecystectomy.[12,13] It is difficult to understand why this is an independent risk factor because it raises the question why an uncomplicated sphincterotomy has an effect of Calot's triangle and any impact on the critical view of safety. It has been hypothesized that this is the result of scarring of the hepatoduodenal ligament due to bacterial colonization and low-grade inflammation of the common bile duct, which can be seen after sphincterotomy.[34,35] In the current cohort however, the ERCP's were performed relatively short before cholecystectomy in most patients. This raises the question whether scarring can occur within a short time frame. Furthermore, in contrast with the belief that cholecystectomy in the early post-acute phase of pancreatitis would be technically more demanding, the current results rather indicate the opposite.[36] Although it was impossible to determine what the exact mechanism behind this effect is in the current study, previous investigators found more dense adhesions and difficult dissection of Calot's triangle in delayed cholecystectomy.[16,18]

From a clinical point of view, this means that many patients do not have to be assigned to specialized surgeons but can be operated on by trainees, provided an experienced surgeon is present for supervision whereas patients with one or more risk-factors should potentially be operated by more experienced teams.[13,28]

This study has some limitations. First, technical 'difficulty' is, by definition, a subjective term. Quantifying and dichotomizing these outcomes is therefore inherently arbitrary. We believe that by combining the prospectively registered perceived difficulty (VAS score), conversion, need for subtotal cholecystectomy and duration of the procedure, we have succeeded in providing a reasonable representation of the most difficult cholecystectomies. Second, although the cohort was relatively large, the absolute number of bile duct injuries is very low. Much larger studies with many thousands of patients would, however, be required to assess the impact of 'difficult cholecystectomy' on this complication.

In conclusion, risk factors for a difficult cholecystectomy after mild gallstone pancreatitis were male sex, prior sphincterotomy and delaying cholecystectomy until after 2 weeks after initial admission. Although the overall risk of conversion and bile duct injury was low, surgeons should anticipate a more challenging cholecystectomy in this patient group and perform surgery during the same admission.

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Conflict of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2018.10.015.