BMJ Open Gastroenterology

Relapse in gallstone disease after non-operative management of acute cholecystitis: a population-based study

Louise Helenius,[1] Fredrik Linder,[2,3] Erik Osterman [2,3,4]

To cite: Helenius L, Linder F, Osterman E. Relapse in gallstone disease after non-operative management of acute cholecystitis: a population-based study. *BMJ Open Gastroenterol* 2025;**12**:e001680. doi:10.1136/bmjgast-2024-001680

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjgast-2024-001680).

Received 14 November 2024
Accepted 3 March 2025

[1]Department of Surgery, Gävle sjukhus, Gavle, Sweden
[2]Department of Surgery, Uppsala University Hospital, Uppsala, Region Uppsala, Sweden
[3]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden
[4]Centre for Research and Development, Region Gävleborg, Gävle, Sweden

Correspondence to
Dr Erik Osterman;
erik.osterman@igp.uu.se

ABSTRACT

Objective Non-operative management (NOM) of acute cholecystitis (ACC) may be preferable in patients with advanced inflammation, long duration of symptoms or severe comorbidities. This study aims to investigate time to recurrence and patient factors predicting relapse in gallstone complications after NOM.

Methods Records of 1634 patients treated for ACC at three Swedish centres between 2017 and 2020 were analysed, with 909 managed non-operatively. Data were linked to the National Gallstone Surgery registry for those who later underwent surgery. The time to relapse of gallstone complications was calculated and Cox proportional hazards regression was used to analyse new gallstone complications and adjust for multiple variables.

Results Of the 909 non-operatively managed patients, 348 patients suffered a new gallstone complication. The median time to recurrence was 82 days. Of those who recurred, 27% did so within 30 days, 17% between 31 and 60 days, 27% between 61 days and 6 months, 16% between 6 months and 1 year and 13% later than 1 year. Younger patients with their first gallstone complication had a lower risk of new complications compared with those with previous gallstone complications. In older individuals, there was no difference in the risk of relapse regardless of previous gallstone complications, but they were more likely to be readmitted than younger patients.

Conclusion Delayed cholecystectomy should be prioritised for younger patients with a history of gallstone disease if early cholecystectomy is not feasible. Delayed cholecystectomy should be scheduled without a prior outpatient clinic visit to minimise delays.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous gallstone complications, duration of percutaneous cholecystostomy, cancer, young age, comorbidities, inflammation and small stones are known risk factors of recurrence after non-operative management for cholecystitis.

WHAT THIS STUDY ADDS

⇒ The risk factors above are based on small studies, patients treated with cholecystostomy tubes or administrative data. This study found that recurrences occurred earlier than previous research indicated and confirmed previous gallstone complications and young age as risk factors for recurrence. Elderly and comorbid patients had increased risks of readmission regardless of recurrence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ It reaffirms the value of early cholecystectomy. If delayed cholecystectomy is chosen, those with previous gallstone complications should be prioritised, especially if they are young, if a reduction of recurrent gallstone disease is the goal.

INTRODUCTION

Acute cholecystitis (ACC) is a common complication in patients with cholecystolithiasis and is the first clinical presentation in 10%–15% of patients with symptomatic cholecystolithiasis.[1] The management can be either operative or non-operative, with or without drainage of the gallbladder. Operative management by early cholecystectomy (EC), preferably laparoscopically, is recommended by international guidelines.[2 3] EC is beneficial as it shortens the length of stay, as well as prevents future complications (eg, recurrent cholecystitis, pancreatitis, cholangitis).[4–6] Non-operative management (NOM) may be beneficial in patients with severe inflammation (as indicated by clinical status or laboratory tests),[7–13] in whom surgery is expected to be technically difficult with an increased risk of intraoperative complications (eg, long time between symptom onset and diagnosis)[14 15]; in these cases, the recommendation is delayed elective cholecystectomy (DC). NOM is also the preferred choice in severely comorbid patients, in whom the operative risks are too high.[2 3]

Previous research has shown that in patients who did not undergo surgical removal of the gallbladder when admitted for ACC, the risk of gallstone complications was 14%, 19% and 29% at 6 weeks, 12 weeks and 1 year after discharge, respectively.[16] A study from 2018 showed that 20% of patients who did not undergo EC at the time of index

cholecystitis suffered recurrent disease within 2 years of discharge.[17]

Several risk factors for new gallstone complications have previously been identified, including earlier gallstone complications,[17 18] duration of percutaneous cholecystostomy,[19] cancer,[19] young age,[16] comorbidities,[20] inflammation[18] and size of stones[21 22] (small stones increasing risk of recurrence). However, there is a lack of consensus among the studies.[19 23] Furthermore, several studies only investigated the risk of recurrence after cholecystostomy tube placement,[18 20] or in a limited number of patients.[18 20–23] Knowing which patients have a high risk of relapse may help guide the planning of DC after NOM of ACC as patients with repeated gallstone complications have an increased risk of a difficult DC, with more complications, prolonged postoperative stays and readmissions.[24]

This study aimed to investigate the group of patients who received NOM for their ACC and determine risk factors for relapse in gallstone disease as well as try to establish the timeline in which relapses frequently occur.

METHODS

Study design and setting

This is a retrospective study on patients who were treated for ACC during the period 2017–2020 at three Swedish hospitals: Gävle Hospital, Hudiksvall Hospital and Uppsala University Hospital. Electronic patient records were requested from Region Gävleborg and Region Uppsala for all patients who had received the diagnosis of ACC (ICD10-SE K80.0, K80.1, K81.0-K81.9) during the study period; these data were then screened and patients who fulfilled the diagnostic criteria for ACC (based on the Tokyo guidelines[2]) criteria and no other diagnosis explaining the symptoms, for example, cholangitis or pancreatitis, were included in the study. These data were then supplemented by data from the national Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography, Gallriks, as described previously.[25] The manuscript was prepared according to the REporting of studies Conducted using Observational Routinely collected Data checklist (available in online supplemental file 2).

Variables

The exposure was NOM. The primary outcome was any new gallstone complication after NOM at index cholecystitis assessed from patient records (cholecystitis, cholangitis, pancreatitis, gallstone ileus, perforation, abscess, sepsis, fistula, choledocholithiasis). Patients readmitted with resurgence of symptoms and increased inflammatory labs after discharge were treated as recurrent cholecystitis; however, no distinction between failure of treatment or recurrence could be made since this was not documented in the electronic patient records. Time to recurrent gallstone disease was calculated from the date of diagnosis at the index cholecystitis. Covariates of interest were basic demographics, including sex, age and body mass index (BMI). Age was divided based on quartiles into four age groups: 18–50, 51–66, 67–77 and older than 77. The perioperative risk was determined based on the American Society of Anesthesiologist Classification (ASA)[26] and comorbidities were recorded according to the Charlson Comorbidity Index (CCI).[27] The severity grading of ACC was made based on the Tokyo guidelines.[28] Previous gallstone complications and the time since that previous complication were recorded. Previous gallstone complications were defined as previously described but included gallstone colic.

Statistical analysis

Power analysis for the Wilcoxon rank-sum test and χ^2 test with 4 degrees of freedom with an effect size of 0.3 (for Wilcox rank-sum test a small-medium effect and for the χ^2 test a medium effect)[29 30] with 95% power and α 0.05, gave a required sample size of at least 854 and 207 patients. This determined the number of years to include in the study. Baseline demographics were tabulated for NOM patients. Categorical variables were tested with the χ^2 test and continuous variables were tested with the Kruskal-Wallis test to assess for differences between groups. Logistic regression was used to assess the risk of readmission and to adjust for multiple variables. Cox proportional hazards regression was used to analyse new gallstone complications, adjust for multiple variables and censor for surgery and death. Covariates with OR/HR of <0.9 or >1.1 and p of ≤0.1 were included in multivariable analysis. Exploratory analysis of the interaction between age and previous gallstone disease was performed based on previous reports.[16–18] Kaplan-Meier curves were drawn for the outcome of recurrent gallstone disease stratified by age group and previous cholecystolithiasis and without previous cholecystolithiasis. Analysis was performed using Jamovi V.2.3 (The Jamovi Project, 2023) and R V.4.2.2 (R Core Team (2022)). Analysis was done using complete cases on an analysis-by-analysis basis, excluding patients with missing data. P values <0.05 were deemed statistically significant.

RESULTS

Of the 1634 patients included in the study (figure 1), 725 (44.3%) underwent early surgery (EC) at the time of index cholecystitis, while 909 (55.6%) underwent initial NOM. In total, 97 (5.9%) patients were treated with cholecystostomy, 3 (3.0%) of which required surgery before discharge; the remaining 94 (98.9%) were included in the NOM group, since this group did not differ significantly from the patients undergoing NOM without drainage of the gallbladder regarding sex, age and comorbidities. 17 (1.8%) patients in the NOM group died during their index cholecystitis. 239 (26.3%) patients who presented with index ACC during the study period had had previous gallstone disease; 96 (40.2%) had less than 3 months before index, 30 (12.6%) 3–6

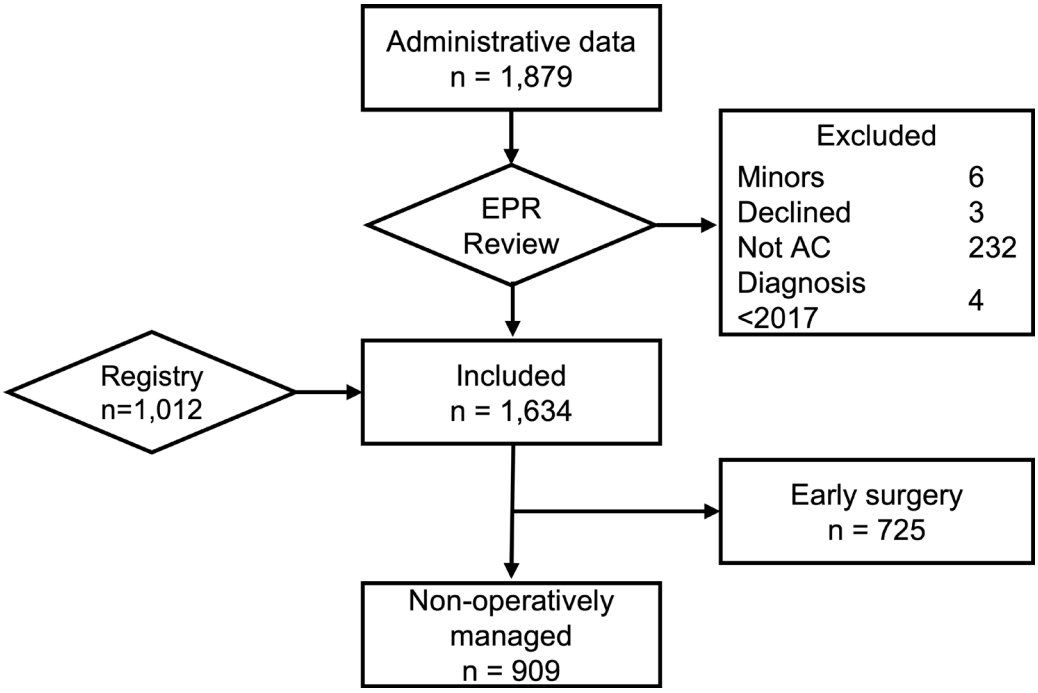

Figure 1 Patient flow chart. All patients with a registered diagnosis of acute cholecystitis (ACC) were screened. Patients not fulfilling the inclusion criteria were excluded, data supplemented by registry data and then separated into a cohort of patients having early surgery (EC) and non-operatively managed (NOM).

months before, 30 (12.6%) 6–12 months before, 64 (26.8%) 1–5 years before and 19 (7.9%) over 5 years ago.

NOM versus surgery

The NOM group was older and more comorbid than the EC group. There was no difference in sex or BMI between the groups (online supplemental table 1). Patients with CCI>3 or ASA 3 were mainly treated with NOM. There was a longer time between the onset of symptoms until contact with a hospital and diagnosis in the NOM group compared with the EC group (online supplemental table 2). Patients in the NOM group had higher peak C reactive protein (CRP) measured during the index cholecystitis (median 185 vs 152 mg/L).

Readmission

In the NOM group, 145 (16.0%) patients required readmission within 30 days of discharge at index (table 1). Most patients requiring readmission were patients older than 77 and comorbid. The OR of readmission within 30 days of discharge (table 2) increases with increasing age; 0.81 (95% CI 0.40–1.62) at 51–66 years of age; 1.51 (95% CI 0.84–2.80) at 67–76 years of age; and 1.7 (95% CI 0.99–3.06) over 77 years of age. The OR of readmission increased with increasing ASA score as well; 1.55 (95% CI 0.79–3.35) for ASA 2; 1.99 (95% CI 1.03–4.27) for ASA 3 and 3.32 (95% CI 1.51–7.77) for ASA 4.

Recurrent gallstone complications

348 (38.3%) patients in the NOM group suffered a new gallstone complication. Sex was not a risk factor for recurrent disease. In the age group 18–50, 62 (42.4%) suffered recurrence, which is slightly higher than for the other age groups, although not statistically significant. Time to recurrent gallstone complication was calculated from the index date of diagnosis. The median time to a new complication was 82 days. Of the 299 patients with data on when the recurrence occurred, 81 (27.1%) had their recurrence within 30 days from diagnosis of index AC; 49 (16.4%) between 31 and 60 days; 81 (27.1%) between 61 days and 6 months; 49 (16.4%) between 6 months and 1 year; and 39 (13.0%) recurrence later than 1 year.

There was no difference in time (p 0.72) to new gallstone complication between those who had suffered previous gallstone disease (median time 69 days, mean 160.2±194.5, min: 1, max: 921) and those without previous stone disease (median time 86 days, mean 166.4±235.7, min: 2, max: 1608). The risk of new complications was lower in young patients (<67 years old) with their first gallstone complication compared with those with a previous gallstone complication (online supplemental table 3, figure 2 and online supplemental figure 1). In older individuals, there was no difference in the risk regardless of previous stones or not.

Delayed cholecystectomy

Of 892 patients who underwent NOM at index cholecystitis and were discharged alive, 351 (39.3%) were not planned for any follow-up at all when discharged, 133 (14.9%) were planned for DC, 167 (18.7%) were followed up at the outpatient clinic and at that time put up for DC and 214 (24.0%) were followed up at the outpatient clinic with the decision not to undergo DC. For 10 patients, these data were missing. The median time to follow-up at the outpatient clinic, from the date of diagnosis, was

Table 1 Demographics of non-operatively managed (NOM) group in three Swedish hospitals 2017–2020

		Total NOM	30-day readmission			New gallstone complication			Later surgery		
		N	N	%/SD	P value	N	%/SD	P value	N	%/SD	P value
	Total	909	145	16.0%		348	38.3%		362	39.8%	
Sex	Male	484	81	16.7%	0.400	184	38.0%	0.984	172	35.5%	0.008
	Female	425	64	15.1%		164	38.6%		190	44.7%	
Age	18–50	146	16	11.0%	0.022	62	42.5%	0.172	99	67.8%	<0.001
	51–66	177	19	10.7%		69	39.0%		99	55.9%	
	67–76	234	42	17.9%		83	35.5%		121	51.7%	
	>77	352	68	19.3%		134	38.1%		43	12.2%	
	Mean (SD)	69.7 (16.6)	72.4	±15.8		69.7	±15.9		60.6	±15.2	
	Median	73.4	76			73.3			63.9		
ASA class	1–2	461	60	13.0%	0.003	169	36.7%	0.326	263	57.0%	<0.001
	3	363	63	17.4%		149	41.0%		94	25.9%	
	4–5	85	22	25.9%		30	35.3%		5	5.9%	
	Mean (SD)	2.5 (2.8)	2.67	±0.817		2.55	±0.781		2.09	±0.708	
	Median	2	3			3			2		
CCI	0	115	14	12.2%	0.002	49	42.6%	0.044	78	67.8%	<0.001
	1–2	158	16	10.1%		66	41.8%		111	70.3%	
	3–4	238	32	13.4%		76	31.9%		123	51.7%	
	5–6	231	47	20.3%		85	36.8%		40	17.3%	
	>7	167	36	21.6%		72	43.1%		10	6.0%	
	Mean (SD)	4.1 (2.8)	4.86	±2.92		4.32	±3.09		2.41	±1.93	
	Median	4	5			4			2		
BMI (kg/m^2)	Mean (SD)	28.2 (5.9)	27.7	5.4	0.593	28	5.9	0.721	29	5.6	<0.001
	Median	27.4	27.7			27			28.1		
	Missing	89	4			63			18		
Previous gallstone disease											
	Stones on previous radiology	198	34	17.2%	0.680	85	42.9%	0.164	85	42.9%	0.360
	Previous complication	239	34	14.2%	0.328	116	48.5%	<0.001	117	49.0%	0.001
	Cholecystitis	39	9	23.1%	0.222	23	59.0%	0.005	12	30.8%	0.248
	Cholangitis	15	2	13.3%	0.822	6	40.0%	0.937	6	40.0%	0.963
	Pancreatitis	22	5	22.7%	0.361	11	50.0%	0.413	8	36.4%	0.814
	Pain	173	28	16.2%	0.902	93	53.8%	<0.001	101	58.4%	<0.001
	Other	6	1	16.7%	0.991	4	66.7%	0.164	4	66.7%	0.192
	Planned surgery	15	3	20.0%	0.565	9	60.0%	0.503	11	73.3%	0.075

Stratified by readmissions, new complications and later surgery.
χ^2 test is used for categorical variables. The Kruskal-Wallis test is used for continuous variables.
ASA, American Society of Anesthesiologists physical status classification; BMI, body mass index (kg/m^2); CCI, Charlson Comorbidity Index; NOM, non-operative management.

Table 2 Logistic regression for risk of readmission within 30 days from index cholecystitis in patients non-operatively managed for cholecystitis in three Swedish hospitals 2017–2020

Factor		Number	OR	95% CI	P value
Univariable					
Sex		909			
	Male		–	–	
	Female		0.88	0.62–1.26	0.5
Age		909			
	18–50		–	–	
	51–66		0.81	0.40–1.62	0.5
	67–76		1.51	0.84–2.80	0.2
	>77		1.7	0.99–3.06	0.062
ASA class		909			
	1		–	–	
	2		1.55	0.79–3.35	0.2
	3		1.99	1.03–4.27	0.055
	4		3.32	1.51–7.77	0.004
CCI		909	1.12	1.05–1.19	<0.001
BMI (kg/m^2)		831	0.98	0.95–1.01	0.2
Previous stone disease		909			
	No		–	–	
	Yes		0.84	0.54–1.25	0.4
BMI (kg/m^2)		831			
	<25		–	–	
	25–35		0.94	0.64–1.41	0.8
	>35		0.74	0.37–1.40	0.4
CCI		909			
	0		–	–	
	1–2		0.81	0.38–1.76	0.6
	3–4		1.12	0.58–2.25	0.7
	5–6		1.84	0.99–3.62	0.063
	>7		1.98	1.03–3.98	0.045
Multivariable		909			
Age	18–50		–	–	
	51–66		0.68	0.33–1.41	0.3
	67–76		1.22	0.65–2.36	0.5
	>77		1.29	0.70–2.47	0.4
ASA class	1		–	–	
	2		1.4	0.68–3.12	0.4
	3		1.66	0.79–3.79	0.2
	4		2.77	1.17–6.92	0.024

ASA, American Society of Anesthesiologist physical status classification; BMI, body mass index (kg/m^2); CCI, Charlson Comorbidity Index.

45 days (mean 66.7±78.6, min: 0, max: 730). The median time from diagnosis of ACC at index until delayed cholecystectomy was 130 days. Of the 384 (43.0%) who later underwent surgery, 282 (73.4%) had elective surgery and 72 (18.8%) required emergency surgery, 30 (7.8%) patients had DC after their recurrence. The median time to DC for those who were planned for it at discharge was 98 days (mean 128.2±109.3, min: 7, max: 778); for those who were put up for DC at follow-up at the outpatient clinic the median wait time was 166 days (mean 192.7±135.7, min: 24, max: 635). Table 3 shows the distribution of follow-up based on ASA score for patients under 67 years of age. 171 (54.5%) patients were planned for DC after their index cholecystitis in this age group, 155 (49.3%) patients later underwent DC. 10 of 171 (5.8%) patients had emergency surgery before DC. 11 (13.6%) patients not scheduled for follow-up were operated with DC and 10 (12.3%) had emergency surgery after a second gallstone complication.

DISCUSSION

A total of 909 patients underwent NOM over 4 years. Based on earlier research, young patients with a history of gallstone disease were assumed[16–18] to be at an increased risk of recurrence, which was confirmed. There was no increased risk of recurrence based on comorbidities[20] or inflammation[18] as previously reported. The size of stones[21 22] was not reported in the ultrasonography reports and could thus not be assessed. Comorbid patients had an increased risk of readmission within 30 days. The reasons for readmission were not documented in the data but older and comorbid patients were at an increased risk. Multiple reasons are conceivable, for example, failure of treatment, relapse, worsening of comorbidities, failure of home care or a lack of assisted living facilities.

Although earlier studies have found that recurrence tends to occur 1 year or later[16] after NOM of ACC, many recurrences occurred earlier in this study, even within 60 days, earlier than most patients had DC or were followed up at the outpatient clinic. It was assumed that patients under the age of 67 would be planned for DC at discharge if NOM; however, a surprisingly large cohort of these patients were not planned for DC. Data were not collected on why these patients were not planned for DC, but it may have come down to patients' choices or resources.

A large proportion of patients was treated with NOM compared with international studies.[31] Although there are reasons as to why one would opt for NOM, such as the inflammation was too severe (high grade of ACC) or too low (low grade of ACC), comorbidities, patients' choice or in-hospital resources. There was no obvious reason supporting NOM as the choice of treatment in such a large proportion of the population; many younger patients with low CCI and ASA scores underwent NOM. The time from symptom onset until diagnosis was 1 day longer for those who underwent NOM compared with

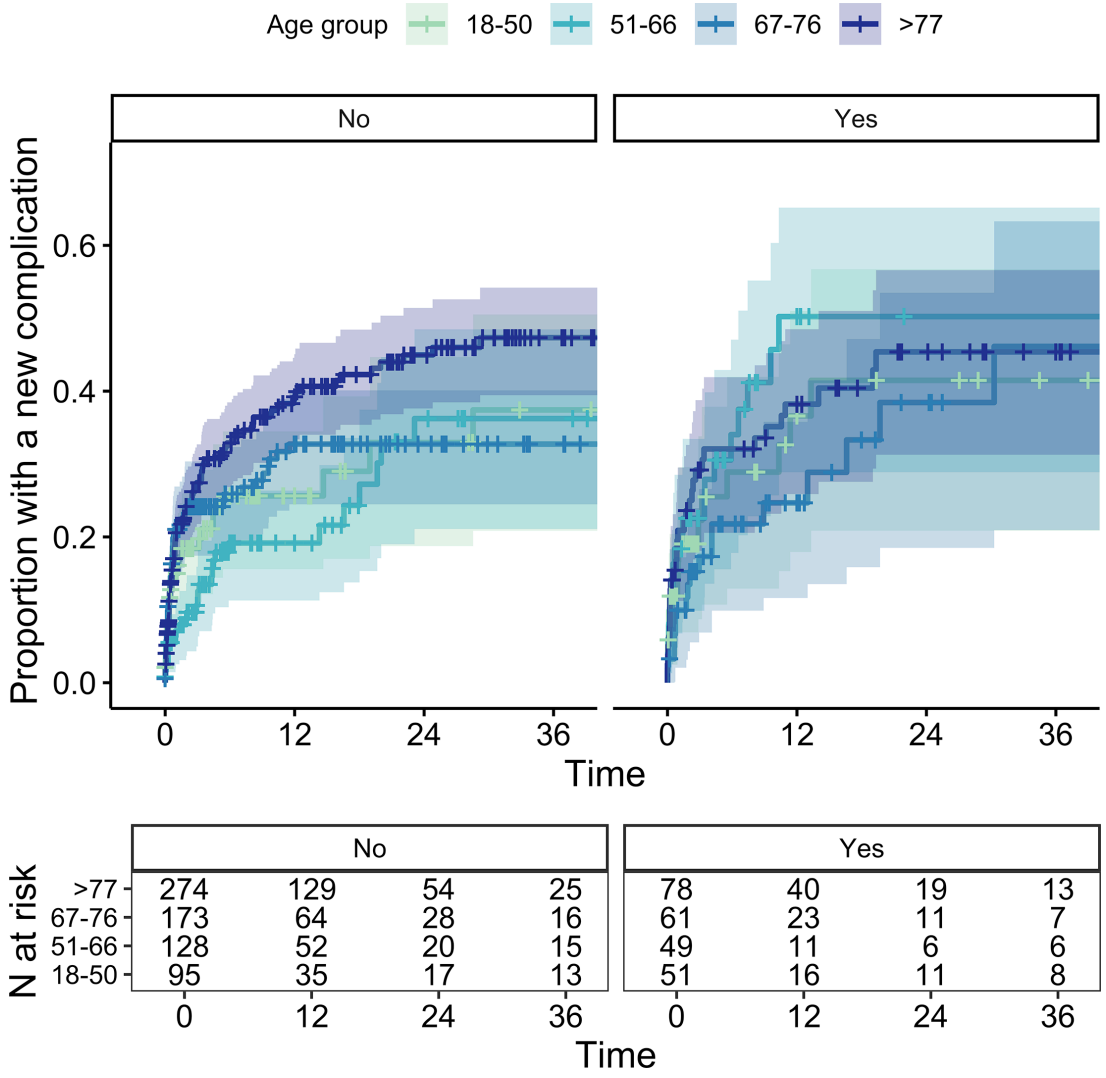

Figure 2 Cumulative incidence of gallstone complications after non-operative management in three Swedish hospitals 2017–2020 by age group for patients without (no) and with (yes) previous gallstone complications.

the surgery group and CRP was higher among the NOM which may be explained by disease progression from symptom onset until first contact. At the three hospitals, local practice was to manage patients non-operatively with >5 days of symptoms, severe comorbidities or where previous surgery made EC unsafe. The Swedish healthcare system is organised around a single-payer universal access model, and contrary to elsewhere, there is no economic incentive to delay cholecystectomy,[32] rather the opposite is true as delayed cholecystectomy is more expensive.

Strengths and limitations

Compared with previous research on risk factors for new gallstone complications, this was a large study, in which all patients who received the diagnosis of ACC at

Table 3 ASA class and follow-up of 314 patients under 67 years having initial non-operative management for cholecystitis in three Swedish hospitals 2017–2020

	Total	DC as follow-up	Outpatient clinic and DC	Outpatient clinic no DC	No follow-up
ASA class 1–2	227 (72.3%)	67 (29.5%)	76 (33.5%)	34 (15.0%)	50 (22.0%)
ASA class 3	71 (22.6%)	13 (18.3%)	15 (21.1%)	21 (29.6%)	22 (31.0%)
ASA class 4–5	16 (5.1%)	0	0	7 (43.8%)	9 (56.3%)

DC as follow-up: determined at discharge, outpatient clinic and DC: DC decided at outpatient clinic visit. Outpatient clinic no DC: visited outpatient clinic, opted against DC. Column percentage for total, row percentages for follow-up categories.
ASA, American Society of Anesthesiologist physical status classification; DC, delayed cholecystectomy.

the three centres over 4 years were included. Including patients at three centres of different sizes and academic levels increases generalisability. The study design included a retrospective evaluation of EPR data which limits the possible variables to what is registered. The largest study on recurrences used administrative data,[6] while this study included data on comorbidities, grade of cholecystitis, blood work, and previous complications. There was a long wait time for DC, which allows us to follow the 'natural' course of the disease over the first few weeks and even months as the median time to DC was 3 months for patients planned from the ward, and even longer if evaluation at the outpatient clinic was performed first.

Due to the short time period of the study, it is not possible to determine the long-term risk of recurrence, here, those who presented with index ACC in 2017 were followed for a longer time than those who presented in 2020. The risk of recurrence could not be investigated for the size of stones, which has been presented as a risk factor in other studies,[21 22] since this was not readily and routinely documented.

Another consideration is the SARS-CoV-2 pandemic that occurred from the beginning of 2020; although only five patients in the study tested positive for COVID-19 (all treated by NOM),[33] the presence of the pandemic demanded a prioritisation of resources. This could have affected treatment choices; however, previous evaluation of the material shows that the number of emergency cholecystectomies increased during the pandemic and the pandemic does not in itself seem to be a reason to opt for NOM.[33 34]

Clinical implications

Guidelines and previous research support EC, especially as patients with no, or few comorbidities have a low risk of perioperative and postoperative complications compared with their risk of a new gallstone complication before DC.[25] The risk of complications is, compared with EC, lower in DC patients who do not recur,[25] but higher in patients with repeated gallstone complications with an increased risk of a difficult DC, complications, prolonged postoperative stays and readmissions.[24] In addition, patients NOM had a high risk of readmission, especially if comorbid.

As the wait times for DC and the risk of recurrence are high early after discharge, an increased rate of EC would, based on previous research and current guidelines, be beneficial both for patients and the healthcare system in Sweden.[35–38] If forced to manage patients with DC, for example, in the case of limited resources (such as war, pandemic, staffing shortages), knowing which patients have an elevated risk of relapse may help guide the prioritisation of EC and DC after NOM. In the current cohort, patients waited far too long before DC and an inexplicably low proportion of otherwise healthy patients were discharged with their gallbladders in situ.

CONCLUSION

Guidelines recommend EC in most patients, and the healthcare system should strive towards this. DC could be prioritised in younger patients with a history of gallstone disease if EC is impossible and if recurrences are the only metric, however, readmission and recurrences among elderly patients must be factored in. DC should be planned as follow-up for patients who are candidates, with the informed consent process before discharge and without prior outpatient clinic visit, to minimise the wait time for DC. This, of course, must be individualised, as some patients may at the time of discharge be too sick to be planned for DC; in these cases, follow-up at the outpatient clinic may be necessary before decision of whether to operate or not can be made, though this delays DC.

X Erik Osterman @osterik

Acknowledgements Thanks to the EPR and analysis departments at Region Gävleborg and Region Uppsala for their help with identifying the population from ICD codes. Thanks to the surgeons and administrators reporting to Gallriks for making the study possible. Thanks to Anders Blomberg and Jennie Wickenberg for discussions regarding the design of the study. Thanks to Christina Larsson, Sofia Jakobsson and Tamali Majumder for helping with the collection of data.

Contributors EO and FL contributed to the conception and design of the study. LH and EO acquired the data with the support of FL. LH and EO performed analysis and interpretation of data. LH, EO and FL drafted the article. All authors revised it critically for important intellectual content. All authors approved the final version to be published. EO is the guarantor of the manuscript.

Funding The research was funded by the Centre for Research and Development, Gävleborg Region grant numbers CFUG-965514, CFUG-965517. EO and LH were funded by Region Gävleborg, grant number—NA. FL was financed by grants from the Swedish state under the agreement between the Swedish Government and the Uppsala County Council (ALF), grant number—NA. Open access funding from Uppsala University, grant number—NA.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The study was approved by the Swedish Ethical Review Authority, dnr 2021-00862. Patients with data from Gallriks had consented to be included in the registry for research purposes, for patients not included in Gallriks the Swedish Ethical Review Authority waived the requirement of consent since the study was retrospective and without intervention or risk to the patients. Waived by ethics board since retrospective collection of data, small intrusion of privacy.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. The data are not publicly available due to information that could compromise the privacy of research participants. The registry data that support the findings of this study are available from Gallriks (https://www.ucr.uu.se/gallriks/). Restrictions apply to the availability of these data why the authors cannot share them. EPR data are however available from the corresponding author upon reasonable request and ethics approval.

ORCID iD

Erik Osterman http://orcid.org/0000-0003-1621-7872

REFERENCES

1 Pisano M, Allievi N, Gurusamy K, *et al*. 2020 World Society of Emergency Surgery updated guidelines for the diagnosis and treatment of acute calculus cholecystitis. *World J Emerg Surg* 2020;15:61.
2 Okamoto K, Suzuki K, Takada T, *et al*. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. *J Hepato Biliary Pancreat* 2018;25:55–72.
3 Ansaloni L, Pisano M, Coccolini F, *et al*. 2016 WSES guidelines on acute calculous cholecystitis. *World J Emerg Surg* 2016;11:25.
4 Bagepally BS, Haridoss M, Sasidharan A, *et al*. Systematic review and meta-analysis of gallstone disease treatment outcomes in early cholecystectomy versus conservative management/delayed cholecystectomy. *BMJ Open Gastroenterol* 2021;8:e000675.
5 Cao AM, Eslick GD, Cox MR. Early laparoscopic cholecystectomy is superior to delayed acute cholecystitis: a meta-analysis of case-control studies. *Surg Endosc* 2016;30:1172–82.
6 de Mestral C, Rotstein OD, Laupacis A, *et al*. Comparative operative outcomes of early and delayed cholecystectomy for acute cholecystitis: a population-based propensity score analysis. *Ann Surg* 2014;259:10–5.
7 Nassar AHM, Hodson J, Ng HJ, *et al*. Predicting the difficult laparoscopic cholecystectomy: development and validation of a pre-operative risk score using an objective operative difficulty grading system. *Surg Endosc* 2020;34:4549–61.
8 Wu T, Luo M, Guo Y, *et al*. Role of procalcitonin as a predictor in difficult laparoscopic cholecystectomy for acute cholecystitis case: A retrospective study based on the TG18 criteria. *Sci Rep* 2019;9:10976.
9 Wennmacker SZ, Bhimani N, van Dijk AH, *et al*. Predicting operative difficulty of laparoscopic cholecystectomy in patients with acute biliary presentations. *ANZ J Surg* 2019;89:1451–6.
10 Ng HJ, Ahmed Z, Khan KS, *et al*. C-reactive protein level as a predictor of difficult emergency laparoscopic cholecystectomy. *BJS Open* 2019;3:641–5.
11 Gregory GC, Kuzman M, Sivaraj J, *et al*. C-reactive Protein is an Independent Predictor of Difficult Emergency Cholecystectomy. *Cureus* 2019;11:e4573.
12 Maehira H, Kawasaki M, Itoh A, *et al*. Prediction of difficult laparoscopic cholecystectomy for acute cholecystitis. *J Surg Res* 2017;216:143–8.
13 Gupta N, Ranjan G, Arora MP, *et al*. Validation of a scoring system to predict difficult laparoscopic cholecystectomy. *Int J Surg* 2013;11:1002–6.
14 Mora-Guzmán I, Di Martino M, Gancedo Quintana A, *et al*. Laparoscopic Cholecystectomy for Acute Cholecystitis: Is the Surgery Still Safe beyond the 7-Day Barrier? *J Gastrointest Surg* 2020;24:1827–32.
15 Blohm M, Österberg J, Sandblom G, *et al*. The Sooner, the Better? The Importance of Optimal Timing of Cholecystectomy in Acute Cholecystitis: Data from the National Swedish Registry for Gallstone Surgery, GallRiks. *J Gastrointest Surg* 2017;21:33–40.
16 de Mestral C, Rotstein OD, Laupacis A, *et al*. A population-based analysis of the clinical course of 10,304 patients with acute cholecystitis, discharged without cholecystectomy. *J Trauma Acute Care Surg* 2013;74:26–30; .
17 Escartín A, González M, Pinillos A, *et al*. Failure to perform index cholecystectomy during acute cholecystitis results in significant morbidity for patients who present with recurrence. *HPB (Oxford)* 2019;21:876–82.
18 Tuncer K, Kilinc Tuncer G, Çalık B. Factors affecting the recurrence of acute cholecystitis after treatment with percutaneous cholecystostomy. *BMC Surg* 2023;23:143.
19 Park JK, Yang J-I, Wi JW, *et al*. Long-term outcome and recurrence factors after percutaneous cholecystostomy as a definitive treatment for acute cholecystitis. *J Gastroenterol Hepatol* 2019;34:784–90.
20 Do YA, Yoon CJ, Lee JH, *et al*. Percutaneous cholecystostomy as a definitive treatment for acute acalculous cholecystitis: clinical outcomes and risk factors for recurrent cholecystitis. *Br J Radiol* 2023;96:20220943.
21 Thornton DJA, Robertson A, Alexander DJ. Patients awaiting laparoscopic cholecystectomy--can preoperative complications be predicted? *Ann R Coll Surg Engl* 2004;86:87–90.
22 Kim SB, Kim TN, Chung HH, *et al*. Small Gallstone Size and Delayed Cholecystectomy Increase the Risk of Recurrent Pancreatobiliary Complications After Resolved Acute Biliary Pancreatitis. *Dig Dis Sci* 2017;62:777–83.
23 Wang C-H, Wu C-Y, Yang JC-T, *et al*. Long-Term Outcomes of Patients with Acute Cholecystitis after Successful Percutaneous Cholecystostomy Treatment and the Risk Factors for Recurrence: A Decade Experience at a Single Center. *PLoS One* 2016;11:e0148017.
24 Lucocq J, Scollay J, Patil P. Elective laparoscopic cholecystectomy: recurrent biliary admissions predispose to difficult cholecystectomy. *Surg Endosc* 2022;36:6403–9.
25 Osterman E, Helenius L, Larsson C, *et al*. Surgery for acute cholecystitis in severely comorbid patients: a population-based study on acute cholecystitis. *BMC Gastroenterol* 2022;22:371.
26 Horvath B, Kloesel B, Todd MM, *et al*. The Evolution, Current Value, and Future of the American Society of Anesthesiologists Physical Status Classification System. *Anesthesiology* 2021;135:904–19.
27 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
28 Hirota M, Takada T, Kawarada Y, *et al*. Diagnostic criteria and severity assessment of acute cholecystitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg* 2007;14:78–82.
29 Sawilowsky SS. New Effect Size Rules of Thumb. *J Mod App Stat Meth* 2009;8:597–9.
30 Kim H-Y. Statistical notes for clinical researchers: Chi-squared test and Fisher's exact test. *Restor Dent Endod* 2017;42:152–5.
31 Gallaher JR, Charles A. Acute Cholecystitis. *JAMA* 2022;327:965.
32 Fehring L, Brinkmann H, Hohenstein S, *et al*. Timely cholecystectomy: important factors to improve guideline adherence and patient treatment. *BMJ Open Gastroenterol* 2024;11:e001439.
33 Osterman E, Jakobsson S, Larsson C, *et al*. Effect of the COVID-19 pandemic on the care for acute cholecystitis: a Swedish multicentre retrospective cohort study. *BMJ Open* 2023;13:e078407.
34 Sandblom G, Österberg J, Rogmark P, *et al*. Impact of the COVID-19 pandemic on the management of gallstone surgery: A Swedish population-based study. *Scand J Surg* 2022;111:14574969211070389.
35 Wani H, Meher S, Srinivasulu U, *et al*. Laparoscopic cholecystectomy for acute cholecystitis: Any time is a good time. *Ann Hepatobiliary Pancreat Surg* 2023;27:271–6.
36 Gurusamy KS, Davidson C, Gluud C, *et al*. Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. *Cochrane Database Syst Rev* 2013;CD005440.
37 Hartwig W, Büchler MW. Acute cholecystitis: early versus delayed surgery. *Adv Surg* 2014;48:155–64.
38 Gutt CN, Encke J, Köninger J, *et al*. Acute cholecystitis: early versus delayed cholecystectomy, a multicenter randomized trial (ACDC study, NCT00447304). *Ann Surg* 2013;258:385–93.