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ORIGINAL ARTICLE

Determinants for symptomatic gallstone disease readmissions – results from a cohort with screen-detected gallstone disease



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KEYWORDS

Cholelithiasis;
Cholecystolithiasis;
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Summary

Aim of the study: Selection of patients for cholecystectomy is hampered by lack of objective criteria. The objectives of this cohort study were to identify if patient, symptoms, or gallstone disease characteristics determined readmission in an unselected cohort with screen-detected gallstone disease and who had experienced a first admission with symptomatic gallstone disease. **Methods:** Data from three random sampled population-based cohorts were used. At baseline, participants were screened with ultrasound and 664 had gallstones of which 84 had a first admission without cholecystectomy performed. A cohort study was performed with follow-up for hospital readmissions beyond 30 days through central registers. Age adjusted Cox regression analyses were performed.

Results: Readmissions occurred in 60.8% and cholecystectomy was eventually performed in 47.7% of patients. Early readmissions were determined by abdominal pain in the epigastrium (Hazard ratio (HR) 3.63, 95% confidence interval (CI) [1.62;8.12]) and of moderate intensity (HR 2.71, 95% CI [1.20;6.16]). Late readmissions were determined by larger gallstone size, especially when above 10 mm (HR 4.11, 95% CI [1.18;14.3]) and inversely determined by age (HR 0.97, 95% CI [0.95;0.998]). In patients with initially uncomplicated gallstone disease, cholecystectomy was inversely determined by age (HR 0.96, 95% CI [0.93;0.98]).

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Conclusion: Once gallstones have become symptomatic and caused hospital admission, a persisting high risk for future readmission exists and half of patients end up having cholecystectomy. Pain in the epigastrium, larger gallstones, and younger age determine readmission. These determinants should be tested in future clinical treatment algorithms for gallstone disease.
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Introduction

“Cholecystectomy is at the moment suitable only for those cases in which the patient and physician have reached the end of their patience” [1] – the challenge in timing of cholecystectomy for symptomatic gallstone disease was already noted by Carl Langenbuch in his report of the first cholecystectomy ever performed in 1882. Screen-detected gallstone disease is common in general populations of developed countries with prevalence of 10–15%, but most gallstones remain “silent” and less than one out of five will develop symptomatic gallstone disease requiring hospital admission [2]. However, when gallstone disease has become symptomatic, a more aggressive history with high risks of hospital readmission and cholecystectomy is reported in cohort studies [3–10]. Only few studies have identified determinants of symptomatic gallstone disease history and not with consistency between studies [5–8,10].

Cholecystectomy is the standard treatment and is recommended for all symptomatic gallstone disease including both uncomplicated and complicated [11]. Laparoscopic cholecystectomy was introduced in many Western countries around the year 1990 and was followed by a boom in cholecystectomy rates and in health-care related costs [12]. Standardized cholecystectomy rates per 1000 patients increased in the following years 20–26% in Denmark and other European countries and 19–59% in the US [13]. Changing indications for laparoscopic cholecystectomy on the part of the surgeon and of the patient have been attributed to this boom [12,13].

Early laparoscopic cholecystectomy within 72 h or same admission is recommended in the presence of complicated gallstone disease such as acute cholecystitis, mild biliary pancreatitis, and after removal of common bile duct stones [11]. The definition of uncomplicated gallstone disease is hampered by its subjective patient-reported nature. Biliary colic has been used in most studies but without a consensus of definition [14]. Recently, hospital admission due to uncomplicated gallstone disease was found associated with pain localized in the epigastrium, duration of hours, intensity of moderate to extreme, and in need of pain medication in persons that were unaware of gallstone disease status [15]. Uncomplicated gallstone disease is the indication for most cholecystectomies performed in the Nordic countries [16]. Observation has been found to cause equal proportions of gallstone disease complications when compared to post-cholecystectomy complications in long-term follow-up of a randomized controlled trial (RCT) and therefore considered feasible for uncomplicated gallstone disease [17]. However, patients referred with asymptomatic gallstone disease to a hospital department based on patient history were re-admitted and had cholecystectomy for both complicated and uncomplicated disease during follow-up in one out of

four cases in a retrospective study [18]. This demonstrates that the selection of patients for cholecystectomy based only on subjective reports from patients is challenging and insufficient.

Knowing what determines future symptomatic gallstone disease readmissions is relevant for health-care providers and individual patients in planning treatment strategies and need of cholecystectomy, especially when gallstone disease is uncomplicated. The purpose of this study was therefore to identify determinants for recurrence of symptomatic gallstone disease in patients with a first episode of symptomatic disease and where gallbladder had been left in situ. The objective was to identify if patient, symptoms, or gallstone disease characteristics determined readmission in a cohort with blinded screen-detected gallstone disease and who had experienced a first admission with symptomatic gallstone disease.

Material and methods

The data in this study comprised three random samples of the general population aged 30–70 years, living in 11 municipalities in the western part of the urban area of Copenhagen, and drawn from the Danish Civil Registration System. The cohorts were part of an international collaboration MONICA (Multinational mONitoring of trends and determinants in Cardiovascular disease) and included MONICA 1 examined 1982–1994, the 1914 cohort examined in 1984, and MONICA 3 examined in 1991–1992. Participants were not informed about gallstone-status or of other benign gallbladder conditions identified by ultrasound examination. This was accepted by the local research-ethics committee to avoid unnecessary treatment and worrying of participants [19]. Informed consent was obtained from each participant before enrolment and all examinations were carried out in accordance with The Declaration of Helsinki.

At baseline examination, participants appeared after 12 h of fasting and underwent a general health examination and had an abdominal ultrasound examination in order to assess gallstone status. Gallstones were defined as acoustic shadows that moved with gravity in a gallbladder lumen. Exceptions from the mobility criteria included if a stone was wedged in the infundibulum of the gallbladder or otherwise impeded by size, septae, or folds [20]. Questionnaires about medical history, abdominal symptoms and lifestyle habits were answered.

The study design is a prospective cohort study where participants with screen-detected gallstones at baseline examination were followed by linkage to the National Patient Registry and The Civil Registration System using the unique personal registration number. The National Patient Registry contains data on hospital admissions and emergency

Table 1 Gallstone disease clinical characteristics at first admission and readmission in the study population.

	ICD 8 ^a	ICD 10 ^a	Surgical intervention code ^b	First admission, n(%)	Readmission, n(%)
Cholecystitis		K80.0 calculus of gallbladder with acute cholecystitis K80.1 calculus of gallbladder with other cholecystitis K81 cholecystitis	KJKA10 cholecystostomy	5(6.0)	3(5.9)
Common bile duct stone	57403 choledocholithiasis	K80.3 calculus of bile duct with cholangitis K80.4 calculus of bile duct with cholecystitis K80.5 Calculus of bile duct without cholangitis or cholecystitis ^c	KJKE12 endoscopic stone extraction from bile duct 47740 choledocholithotomia 48090 extractio calculi ductus choledochi endoscópica KJKE02 endoscopic papillotomia ^d 91050, KUJK12 endoscopic retrograde cholangio-pancreaticography ^d	20(23.8)	7(13.7)
Pancreatitis		K85.9 acute pancreatitis		2(2.4)	0(0)
Uncomplicated gallstone disease	57400 cholecystolithiasis 57409 cholelithiasis	K80.2 calculus of gallbladder without cholecystitis K80.8 other cholelithiasis		57(67.9)	41(80.4)
	Total			84	51

ICD: International Classification of Disease.
^a More diagnose codes according to ICD 10 appeared in the cohort compared to codes from ICD 8 and therefore not all corresponding codes to diagnoses according to ICD10 were reported for ICD 8.
^b The Nordic Classification of Surgical Procedures was used and identified procedure codes included both the current classification system and the five-digit system used before 1996.
^c Only classified as common bile duct stone if a concomitant endoscopic procedure was registered
^d All patients having endoscopic procedures without diagnose codes indicating gallstone disease were controlled for concomitant gastrointestinal cancer diagnoses.

room visits and includes admission diagnose codes according to the International Classification of Disease (ICD 8 or ICD 10—ICD 9 was never used in Denmark) and through surgical intervention codes according to the Nordic Classification of Surgical Procedures [21]. The Danish Central Person Registry contains daily updated information on migration and vital status of the entire nation. Both registers are used frequently in clinical and epidemiological research [21]. Entrance into the study population was defined as the day of the first symptomatic gallstone disease admission. From the first admission, patients were followed prospectively until readmission for symptomatic gallstone disease, death, emigration, or censoring on December 31st 2014, whichever came first. Studies on gallstone disease prevalence [20,22,23], incidence [19,24–26], and clinical follow-up [2,15,27–31] of the cohorts have been published before.

Symptomatic gallstone disease was the definition of both entry-criteria into study population and of readmission. It was defined through primary diagnose codes and surgical intervention codes, either as single codes or in combination. Complicated gallstone disease was defined as diagnoses of cholecystitis, common bile duct stones, or pancreatitis or as

surgical procedures indicating common bile duct stones such as stone extractions, papillotomy, or endoscopic retrograde cholangio-pancreaticography (ERCP). Uncomplicated gallstone disease was defined as a gallbladder stone diagnosis (cholelithiasis or cholecystolithiasis) without concomitant register entries indicating complicated gallstone disease as defined above (Table 1). An admission including a solitary procedure code for ERCP or papillotomy was not included as symptomatic gallstone disease if concomitant admission diagnoses for gastrointestinal cancers were registered.

The main outcome was defined as a readmission with gallstone disease. All admission entries within the same 30 days were considered the same admission and entries beyond 30 days were defined as readmissions. This was due to multiple entries per patient with only days in between which probably reflected wrong diagnosis at initial presentation, i.e. an initial uncomplicated diagnosis with presentation of acute cholecystitis days later. Early readmissions were further defined as occurring at follow-up between one and three months and late readmissions as occurring beyond three months. In Denmark, a patient presenting with uncomplicated gallstone disease at first hospital admission is rarely

treated surgically during the first admission. In most cases, cholecystectomy will be offered within a few months. Further, if patients present a longer symptomatic course of cholecystitis, cholecystectomy will be postponed a few months. Early readmissions would thereby possibly indicate a gallstone disease-related issue from the first admission such as scheduled cholecystectomy or non-sufficient medical treatment and late readmission a recurrence of symptomatic gallstone disease. Subgroup analysis of cholecystectomy readmissions during the entire follow-up in the subgroup of patients with only uncomplicated gallstone disease at first admission were performed in order to explore determinants for need of definitive gallstone disease treatment after just one attack of symptomatic gallstone disease. All analyses were reported adjusted for age at first admission.

Explorative variables included patient, symptoms, and gallstone disease characteristics. Patient characteristics included age at first admission (years), sex, and body mass index (kilograms per square meter), alcohol consumption (units per week), coffee consumption (cups per day), and smoking (never versus past or current). Physical activity level was defined according to Saltin and Grimby into sedentary, mild, moderate, and vigorous activity [32]. The latter three were combined for the purpose of this study. Symptom characteristics were defined as abdominal pain occurring within the past 12 months before baseline examination and included pain localization in the upper abdomen (under right rib, epigastrium, or whole upper abdomen) and pain characteristics including frequency (no pain to monthly versus weekly to daily), duration (no pain to minutes versus hours to days), and intensity (no pain to mild versus moderate to extreme). Functional symptoms were included as complexes that had been identified through symptom cluster analyses

in the same cohort [33] and included two types of dyspepsia defined by upper abdominal pain with either nausea or acid regurgitation. Gallstone ultrasound characteristics measured as baseline examination included gallstone size (<2–5, 6–10, >10 mm) and number of gallstones (1 vs. 2 or more). Characteristics of symptomatic gallstone disease at first admission are defined in the Table 1.

Statistical analyses

Means with standard deviations (SD) and numbers with percentages were reported. Number of readmissions over person years was reported for exposure and reference groups in all analyses. Unadjusted cumulative incidence proportions of readmission with death as the competing event were performed and reported for the year of the last recorded readmission of each analysis. Cox regression analyses adjusted for age at baseline were used for statistical analyses with hazard ratios (HR) and 95% confidence intervals (CI) reported. Significant associations were defined by a 95% CI not including 1. Scaled Schoenfeld residuals were used to test goodness of fit of all analyses. If the assumption of proportional hazards was violated, the specific analysis was left unreported in tables. All statistical analyses were performed with the ‘‘R Studio’’ software (RStudio Inc, Boston, MA) with the ‘‘survival’’ and ‘‘cmprsk’’ packages. Reporting was performed according to the STROCSS Statement.

Results

The three population samples comprised 4847 persons with 77% participation at baseline examination. Of the

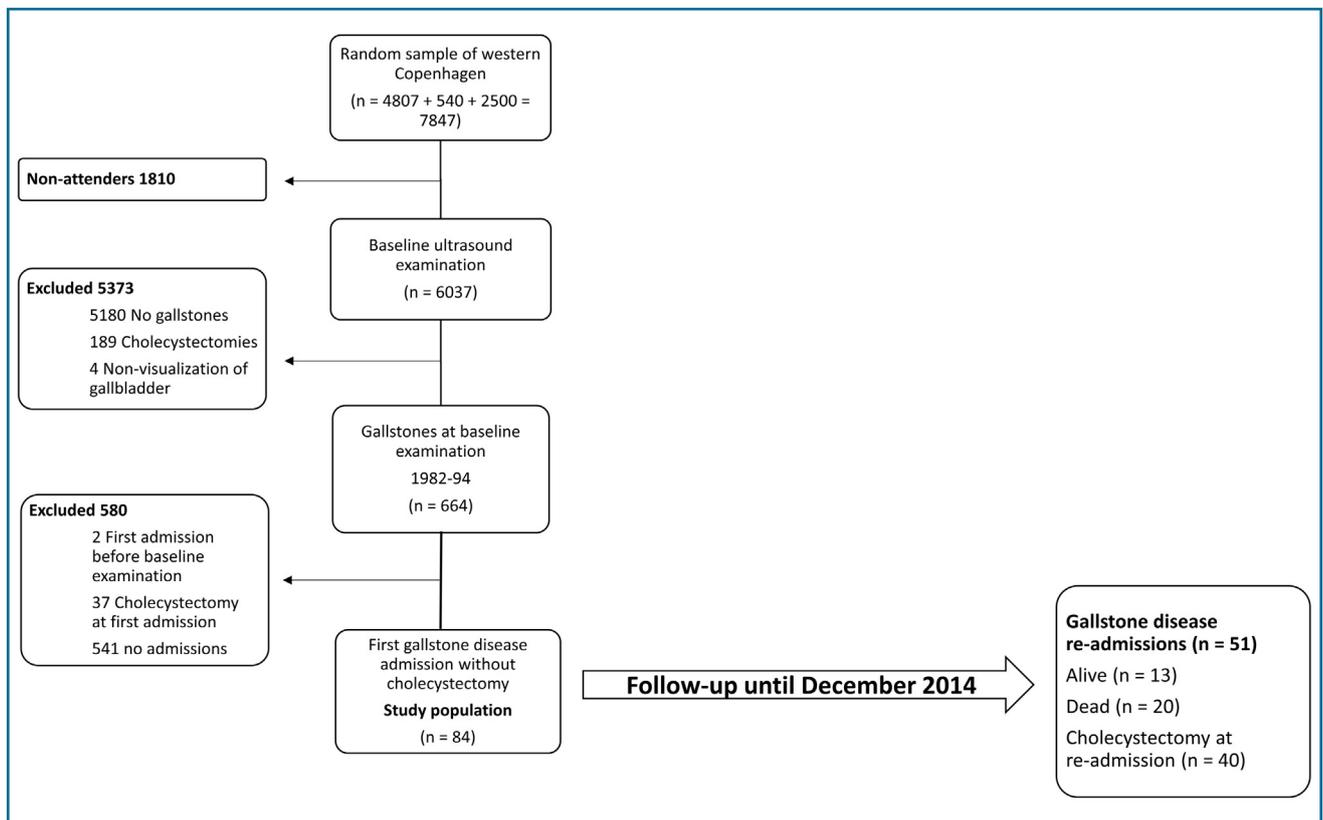


Figure 1. Participant flow and study design.

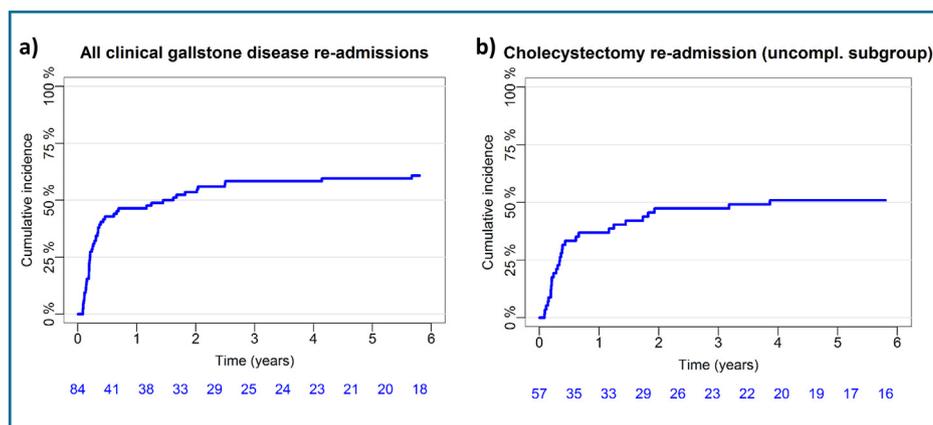


Figure 2. Cumulative incidence proportions of readmissions in study population (a) and of cholecystectomy readmission in subgroup analysis of patients with uncomplicated gallstone disease at first admission (b).

participants that had gallbladders visualized at baseline ultrasound examination, gallstones were identified in 664 (Fig. 1). When following participants gallstones, admission for symptomatic gallstone disease occurred in 123 of which 39 were excluded from further analyses because first admission was before baseline examination ($n=2$) or included a cholecystectomy ($n=37$). The study population thereby included 84 patients with a first symptomatic gallstone disease admission without cholecystectomy. First admission had occurred at mean 11.1 years (SD 7.09) after baseline examination.

During follow-up for outcome in the study population ($n=84$), 51 patients had readmissions recorded (Fig. 1). The study population was followed for mean 3.65 years (SD 5.88) with a range between 0.01 and 23.4 years. None were lost to follow-up. All readmissions occurred within the first six years of follow-up with a readmission cumulative incidence proportion (CIP) 60.8% (Fig. 2). The corresponding competing event (death) CIP was 16.9%. The vast majority of gallstone disease was uncomplicated at both first and readmission (Table 1).

Early readmissions occurred in 24 patients. Of symptom characteristics, abdominal pain, pain localized in epigastrium, and moderate to extreme pain intensity compared with no or mild pain were all associated with early readmission (Table 2). No patient or gallstone disease characteristics were associated with early readmission (Tables 3 and 4).

Late readmission occurred in 27 patients. Of patient characteristics, age was inversely associated with late readmission (Table 3). Of gallstone disease characteristics, larger gallstone size and a size above 10 mm were associated with late readmission (Table 4). No symptom characteristics were associated with late readmissions (Table 2).

In the subgroup analysis of patients with uncomplicated gallstone disease at first admission ($n=57$) and cholecystectomy readmission as outcome, the study population was followed for a period of mean 4.57 years (SD 5.98) and 29 had cholecystectomy readmissions. All occurred within the first four years of follow-up with CIP 50.9% (Fig. 2) and a corresponding competing event (death) CIP 14.0%. In analyses of all variables, only an inverse association for age with cholecystectomy was found (per 1 year, HR 0.96, 95% CI [0.93;0.98]). No other patient, symptom, or gallstone disease characteristics were associated with cholecystectomy readmissions (data not shown).

Discussion

In a population-based cohort with screen-detected gallstone disease and with a first symptomatic gallstone disease admission with mainly uncomplicated disease and where the gallbladder had been left in situ, it was possible to identify determinants for readmission through long-term follow-up. Readmission rates were high and occurred in three out of five patients. Early readmissions were determined by abdominal pain, especially when localized in the epigastrium and when of higher intensity. Late readmissions were determined by younger age and larger gallstone size, especially when gallstone size was above 10 mm. Half of the patients had cholecystectomy performed ultimately. Cholecystectomy was determined by younger age.

A number of previous cohort studies have followed symptomatic gallstone disease patients where cholecystectomy was not performed at initial presentation. In studies performed before the era of laparoscopic surgery, cholecystectomy was performed in 17–51% in patients sampled from a population-based study [9] and in hospital populations [3–7,10]. Studies performed during the era of laparoscopic cholecystectomy report readmissions in 31–41% [34,35] and cholecystectomies in about 30% [36,37] during short follow-up of two years or less. RCTs allocating symptomatic gallstone disease patients to cholecystectomy or observation have also been performed and report that 51% of uncomplicated gallstone disease patients and 33% of acute cholecystitis patients treated expectantly ultimately had cholecystectomy performed [17,38]. The natural history of gallstone disease has recently been reviewed and persisting high risk of readmission or cholecystectomy was found once gallstone disease has become symptomatic [39]. This present study confirms these high proportions of readmission and cholecystectomy in symptomatic gallstone disease patients during long-term follow-up.

In comparison, when performing long-term follow-up of persons with screen-detected gallstone disease sampled from the general population admissions for symptomatic gallstone disease are reported in only 18% [2]. This general low risk of symptomatic gallstone disease in gallstone exosed persons is thereby not comparable to the high risk of symptom recurrence in persons with symptomatic gallstone disease as shown previously and in this present study.

The inverse association with age and late readmission found in this study may be associated with different pain

Table 2 Analyses of symptoms characteristics at baseline as determinants for gallstone disease readmission ($n=84$).

Explorative variable	Unit	n (%) persons in exposure group or mean(SD) for whole study population	Readmissions/ person years or mean(SD) for readmission group	Cumulative readmission incidence proportion at 6 years follow-up	Readmission	
					Age adjusted HR [95% CI]	
					Early ^a	Late ^a
Pain						
localization Abdominal pain within last year	No	41(48.8)	19/191.0	46.3%	ref.	ref.
	Yes	43(51.2)	32/115.6	74.4%	3.25 [1.28;8.20]	1.67 [0.76;3.63]
Under right rib	No	77(91.7)	46/270.2	59.8%	ref.	ref.
	Yes	7(8.30)	5/36.5	71.4%	0.83 [0.19;3.52]	1.07 [0.32;3.56]
Epigastrium	No	63(75.0)	36/237.9	57.2%	ref.	ref.
	Yes	21(25.0)	15/68.7	71.4%	3.63 [1.62;8.12]	0.63 [0.19;2.12]
Whole upper abdomen	No	72(85.7)	42/263.0	58.5%	ref.	ref.
	Yes	12(14.3)	9/44.3	75.0%	1.83 [0.68;4.92]	0.94 [0.33;2.73]
Pain characteristics						
Frequency	No pain/monthly	70(83.3)	42/233.2	60.1%	ref.	ref.
	Weekly/Daily	14(16.7)	9/73.5	64.3%	1.33 [0.50;3.58]	0.78 [0.27;2.29]
Duration	No pain/minutes	53(67.1)	31/200.0	58.6%	ref.	ref.
	Hours/Days	26(32.9)	17/101.8	65.4%	1.20 [0.50;2.86]	1.07 [0.47;2.42]
Intensity	No pain/Mild pain	59(72.0)	31/227.7	52.5%	ref.	ref.
	Moderate/Extreme	23(28.0)	18/78.4	78.3%	2.71 [1.20;6.16]	1.19 [0.50;2.84]
Functional symptoms						
Dyspepsia nausea type	No	69(95.8)	40/246.2	58.1%	ref.	ref.
	Yes	3(4.20)	3/1.4	—	3.81 [0.87;16.7]	2.36 [0.31;18.1]
Dyspepsia regurgitation type	No	81(96.4)	49/300.0	60.6%	ref.	ref.
	Yes	3(3.60)	2/6.6	66.7%	1.25 [0.17;9.25]	1.08 [0.15;7.99]

Bold indicates a significant association; *Italic* indicates $0.05 < P \text{ value} \leq 0.10$.

^a Early readmission was defined as within one to three months follow-up and late readmission was defined as above three months follow-up.

Table 3 Analyses of patient characteristics at baseline as determinants for gallstone disease readmission ($n = 84$).

Explorative variable	Unit	$n(\%)$ persons in exposure group or mean(SD) for whole study population	Readmissions/person years or mean(SD) for readmission group	Cumulative readmission incidence proportion at 6 years follow-up	Readmission	
					Age adjusted HR [95% CI]	
					Early ^a	Late ^a
Physical						
Age at first admission	Per 1 year	63.2(13.0)	59.4(11.9)	—	0.98 [0.95;1.01]	0.97 [0.95;0.998]
Sex	Female	60(71.4)	40/190.2	66.7%	ref.	ref.
	Male	24(28.6)	11/116.5	46.7%	0.58 [0.20;1.70]	0.70 [0.30;1.67]
Body mass index	Per 1 kg/m ²	26.6(4.70)	26.2(4.60)	—	1.02 [0.94;1.11]	0.97 [0.89;1.06]
Lifestyle						
Smoking	Never	23(28.4)	36/227.7	56.5%	ref.	ref.
	Current/Past	58(71.6)	13/76.0	62.3%	0.85 [0.31;2.29]	0.80 [0.32;1.96]
Alcohol consumption	Per 1 unit/week	5.60(7.30)	5.30(6.60)	—	1.01 [0.95;1.07]	0.99 [0.94;1.05]
Coffee consumption	Per 1 cup/day	5.70(3.70)	5.50(3.60)	—	1.00 [0.90;1.11]	0.94 [0.86;1.03]
Physical activity level	Sedentary	22(26.5)	16/45.7	72.7%	ref.	ref.
	Light/Moderate ^b	61(73.5)	35/247.9	57.4%	0.50 [0.22;1.14]	0.65 [0.27;1.56]

Bold indicates a significant association; *Italic* indicates $0.05 < P \text{ value} \leq 0.10$.

^a Early readmission was defined as within one to three months follow-up and late readmission was defined as above three months follow-up.

^b No patients had a vigorous physical activity level at baseline examination.

perception in the younger when compared with the elderly as previously suggested [2] and now also supported by a population-based study were younger age was found associated with being more sensitive to pressure pain [40].

Gallstone size has repeatedly been shown to determine symptomatic gallstone disease in participants with screen-detected gallstone disease sampled from general populations [2,41]. The association of larger gallstones with late readmission may biologically be explained by a higher risk of gallstone impaction in the cystic duct. Gallstone impaction has been attributed symptomatic gallstone disease and cholecystitis by the pioneers of gallstone disease research [42–44].

The association of symptoms with early-readmission including pain localized in the epigastrium and pain of higher intensity is comparable to what is known about incident symptomatic gallstone disease [15]. Symptoms were only found associated with early readmissions and may thereby represent an ongoing gallstone disease such as accumulation of biliary colic or recurrence of cholecystitis. Mechanisms of pain sensation in symptomatic gallstone disease may include the distention of the gallbladder, which has been demonstrated in an experimental study of patients with complicated gallstone disease and percutaneous cholecystostomy tubes [45]. The above-mentioned stone impaction in the cystic duct has also been suggested to cause a

gallbladder distention with activation of visceral sensory neurons and pain sensation [46].

The possible inverse associations for higher physical activity level with early readmission may be explained through increased gallbladder motor function. An increase in plasma cholecystokinin, the hormone stimulating gallbladder contractions, is found during the physiological state of high physical activity [47]. An impaired gallbladder ejection fraction below 40% has been associated with recurrent pain attacks in cohorts of symptomatic gallstone disease during follow-up [48] indicating that increased function should protect from pain development in gallstone disease. However, a high ejection fraction above 60% has also been associated with pain recurrence and the impact of gallbladder motor function in symptomatic gallstone disease is therefore controversial [49].

The present study is unique due to the detailed baseline ultrasound examination of gallstone disease and of other patient and symptom characteristics. Participants were uninformed and thereby unaware of gallstone disease status at baseline when recording self-reported variables such as symptoms causing unbiased data collection. Follow-up was complete and thereby free of selection bias due to attrition. Limitations included the time lag between baseline examination and first admission, which may have caused a change in baseline variables. Number of readmissions was

Table 4 Analyses of gallstone disease characteristics at baseline as determinants for gallstone disease readmission ($n = 84$).

Explorative variable	Unit	$n(\%)$ persons in exposure group or mean(SD) for whole study population	Readmissions/ person years or mean(SD) for readmission group	Cumulative readmission incidence proportion at 6 years follow-up	Readmission	
					Age adjusted HR [95% CI]	
					Early ^a	Late ^a
Gallstone ultrasound characteristics						
Gallstone size	< 2–5 mm	23(28.8)	11/105.4	48.3%	–	ref.
	6–10 mm	25(31.2)	14/101.6	56.0%	–	2.43 [0.62;9.50]
	> 10 mm	32(40.0)	23/77.3	71.9%	–	4.11 [1.18;14.3] 0.019
	<i>P value for trend</i>				–	
Gallstone number	1	37(50.0)	23/115.1	62.4%	ref.	ref.
	≥ 2	37(50.0)	20/144.9	54.1%	0.88 [0.34;2.28]	0.91 [0.42;1.98]
Clinical gallstone disease at first admission						
First admission diagnosis	Uncomplicated gallstone disease	57(67.9)	36/195.2	63.2%	ref.	ref.
	Cholecystitis	5(6.00)	2/9.9	40.0%	0.84 [0.11;6.44]	0.67 [0.09;5.00]
	Common bile duct stone/pancreatitis	22(26.2)	13/101.5	59.1%	1.55 [0.65;3.69]	0.54 [0.20;1.48]
First admission treatment	Non-surgical	65(77.4)	40/206.8	61.5%	ref.	ref.
	Endoscopy	17(20.2)	11/64.7	64.7%	1.45 [0.58;3.67]	0.81 [0.31;2.15]
	Surgical ^b	2(2.40)	0/26.4	–	No events	No events

Bold indicates a significant association; *Italic* indicates $0.05 < P \text{ value} \leq 0.10$.

^a Early readmission was defined as within one to three months follow-up and late readmission was defined as above three months follow-up.

^b Included a cholecystostomy and a choledocholithotomy.

relatively low which possibly may have caused type II error with non-significant associations. Also, the inability to perform multivariable analyses due may possibly have caused residual confounding on some estimates.

This study has identified determinants of symptomatic gallstone readmission, which both confirm previous studies results and has also identified new objective determinants. These objective determinants should be explored further in future prospective clinical trials or RCTs of timing of and patient selection for cholecystectomy in uncomplicated gallstone disease. Evidence of underlying mechanisms of

symptom development when gallstone disease is present is controversial and should be explored further in experimental trials.

Conclusion

Gallstones usually do not cause high-risk symptoms, however once gallstone disease has caused symptomatic disease with hospital admission, a persisting high risk for future readmission exists. Half of patients with initially uncomplicated

disease end up having cholecystectomy. Subjective symptoms of pain localized in the epigastrium and of high intensity determine early readmission. Objective measures of larger gallstones and younger age determine late readmission. Higher physical activity level may be inversely associated to future course of symptomatic gallstone disease. In order to improve selection of patients and timing for cholecystectomy, these determinants should be tested in future clinical treatment algorithms of patients with gallstone disease.

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Disclosure of interest

The authors declare that they have no competing interest.

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