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Outcome after cholecystectomy in the elderly

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ABSTRACT

Background: Cholecystectomy is considered the standard treatment for acute cholecystitis and symptomatic gallstones. An increasing number of frail elderly patients are being referred for this surgical treatment. A better understanding of surgical outcome in the elderly is needed to improve quality of care.
Methods: A retrospective analysis of 565 patients who underwent cholecystectomy was performed. Focus of the analyses was on postoperative complications and its predictors.
Results: The study population was divided in two cohorts; aged <70. More complications were found in patients aged ≥70 years. More elderly patients were admitted to the intensive care, respectively 4.0% and 14.1% ($P = 0.045$). Hospital mortality was 6% in patients aged ≥70 years vs 0.6% in patients <70.
Conclusion: In elderly patients, the complication and mortality rate following cholecystectomy is higher than previously reported. For high-risk patients aged ≥70 with cholecystitis, alternative therapies should be considered as a bridge to surgery or definite treatment.

Introduction

Cholecystectomy is considered the golden standard for patients with acute cholecystitis or symptomatic gallstones. However, surgical treatment is frequently subject of debate in patients with major comorbidities and in the elderly.[1,2] In our ageing population, an increasing number of frail elderly patients are being referred for gallbladder surgery for acute cholecystitis, symptomatic gallstones, after biliary pancreatitis, cholangitis or gallbladder polyposis. Advanced age is frequently associated with significant comorbidity and limited functional reserves.[3] Recent data suggests a turning point after which mortality increases fast at an advanced age after cholecystectomy.[3] The question is whether age alone is predictive for worse outcomes following gallbladder surgery or if other predictors such as pre-operative comorbidities are of equal significance. To date, only a few studies have focused on the outcome of (laparoscopic) cholecystectomy in elderly patients.[4–12]

Although cholecystectomy has become common surgical practice for both cholecystitis and symptomatic gallstone disease, it can still be associated with severe morbidity and even mortality. For acute cholecystitis, less invasive alternatives, e.g. percutaneous gallbladder drainage or follow-up with adequate antibiotic treatment, are frequently applied.[13,14] Although the incidence of acute cholecystitis in patients aged ≥70 years is higher than in their younger counterparts, it is unsure whether this elderly patient group can potentially benefit from the described alternative therapies, either as definite treatment or as a bridge to surgery. A better understanding of the postoperative course in elderly patients requiring a cholecystectomy and factors influencing the outcome will contribute to the decision making whether a cholecystectomy is the treatment of choice or whether a nonoperative approach should be considered. The aim of the current study was to investigate the postoperative outcome in patients ≥70 years undergoing a cholecystectomy, with emphasis on postoperative complications and its predictors.

Materials and methods

Study design and participants

All patients aged ≥18 years who underwent an elective or emergency cholecystectomy in our tertiary university hospital between January 2009 and January 2016 were included. Indications for surgery were acute cholecystitis, symptomatic gallstones, biliary pancreatitis, cholangitis or gallbladder polyposis. Patients

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who previously underwent percutaneous gallbladder drainage were excluded from this study.

Clinical data selection included: Endoscopic Retrograde Cholangiopancreatography (ERCP) prior to surgery (yes/no), indication for cholecystectomy (symptomatic gallstones, acute cholecystitis (right upper quadrant pain, fever, and leukocytosis> 15×10^9/l), emergency surgery (acute cholecystitis requiring surgery within 24–48 h, at the discretion of the surgeon, depending on clinical symptoms, y/n), biliary pancreatitis or gallbladder polyposis (y/n), perioperative sepsis (y/n), type of procedure (laparoscopic or open surgery), conversion rates (n, %), use of antibiotics (y/n), and intraoperative cholangiography (IOC) (y/n). Indications for preoperative ERCP included cholangitis, biliary pancreatitis, persisting jaundice or the presence of common bile duct stones on the ultrasound. An intraoperative cholangiogram was performed routinely in patients with complicated gallstone disease. Indications for a postoperative ERCP included retained stones, bile leakage and/or cholestasis.

Additionally, gender, Body Mass Index (BMI), American Society of Anesthesiologists score (ASA), and intoxications were collected. Comorbidity was determined by the age-adjusted Charlson Comorbidity Index (CCI), based on the medical history. Laboratory results collected included preoperative predictors such as hemoglobin levels (mmol/l), Leucocytes (10^9/L), C - reactive protein levels (mg/l), impaired renal function classified as an estimated glomerular filtration rate (eGFR) < 30 ml/min x 1.73m2, and elevated bilirubin levels (>5 mmol/L).

Postoperative complications after cholecystectomy

Postoperative complications were registered and recalculated using the Comprehensive Complication Index (CCI). The CCI summarizes all postoperative complications with respect to their severity, according to the Clavien-Dindo classification of surgical complications.[15,16] Complications are assessed by scoring patients based on 19 pre-defined comorbidities that are in turn weighed by their severity. The CCI takes the quantity of appearance of each complication into account, using a specific calculation that yields a score from 0 to 100, thereby giving a very detailed assessment for every patient.

Patient data were processed and electronically stored according to the declaration of Helsinki - Ethical principles for medical research involving human subjects.

Outcome measures

The primary outcome was the incidence of postoperative complications. Secondary outcomes were hospital length of stay (HLOS), ICU admittance and in-hospital and 1-year mortality.

Statistical analysis

Data was analyzed using SPSS for Windows, version 22.0 (SPSS Inc, Chicago, III). Categorical variables were analyzed by means of the χ^2 test and presented as numbers (percentages) or presented as mean ± standard deviation (SD). Continuous variables were tested with the Student *t*-test for normal distribution, Pearson's correlation for the association of quantitative variables and the Mann-Whitney *U* test for skewed distribution and presented as median ± interquartile range [IQR]. To determine possible risk factors for complications a binary logistic regression analysis was performed. Covariates with trend-significant effects ($P < 0.10$) on the univariate analysis were selected for multivariate analysis. A backward selection was applied, i.e. starting with a multivariate model (containing the variables that were selected in the univariate analysis) followed by eliminating the least significant variables step-by-step until all *P*-values were <0.05. Estimates of the effects were reported with corresponding 95% confidence intervals (CI).

Results

A total of 565 patients were included for analysis. The study population was stratified and distributed in two cohorts aged <70 ($n = 473$, 83.7%) and ≥70 years ($n = 92$, 16.38%). The mean age of the entire population was 54 ± 16 years. Patients in the ≥70 years group had higher ASA scores (≥3) compared to the younger patients, respectively 18.6% and 23.9% ($P = 0.038$) (Table 1). At the time of surgery 34.7% of patients aged <70 years suffered from acute cholecystitis, compared to 57.6% of the patients aged ≥70 years ($P < 0.001$). In the patient cohort aged <70 years 32.3% of patients underwent emergency surgery, compared to 51.1% of the patients aged ≥70 years ($P < 0.001$), (Fig. 1). However similar conversion rates were found (14.7% versus 18.5%, $P = 0.271$) with insufficient 'critical view of safety' as the main reason for conversion (22.2% versus 10.5%, $P = 0.760$).

Incidence and predictors of complications after cholecystectomy

To calculate the incidence of postoperative complications, the CCI sore was used to compare the complication rate between both groups. Univariate and multivariate analysis were performed to define predictors of a high CCI. In patients aged <70 the mean CCI was 3.8 (range 0–88.6, SD 10.41) and 9.3 (range 0–47.3, SD 14.32) in the patients aged ≥ 70 years ($P < 0.001$). In the unadjusted univariate analysis, the following variables appeared to be predictors for a higher CCI score; age ≥70 years ($P < 0.001$), emergency surgery ($P < 0.001$), conversion to laparotomy ($P = 0.019$), preoperative sepsis ($P = 0.001$) and elevated pre-operative C-reactive protein ($P = 0.040$). In the adjusted multivariate analysis age >70 (OR 2.64; 95% CI 1.44–4.84) laparotomy (OR 3.31; 95% CI 1.72–6.38), emergency surgery (OR 0.34; 95% CI 0.18–0.63) and conversion to open surgery (OR 3.31; 95% CI 1.72–6.38) ($P = 0.019$) were statistically significant predictors for an increase in CCI (Table 2).

General organ comorbidity was calculated by using the Charlson comorbidity score. In patients aged <70 the mean Charlson comorbidity score was 0.9 (range 0–10, SD 1.6) and 2.2 (range 0–9, SD 2.0) in the patients aged ≥ 70 years ($P < 0.001$) (Table 4).

Secondary outcomes

The median hospital length of stay (HLOS) was 3 [IQR 2–6] days for patients aged < 70 years and 6 [IQR 3–10] days for patients aged ≥ 70 years ($P < 0.001$). ICU admittance was lower in favor of the younger cohort (respectively 4% and 14.1%, $P < 0.001$). In-hospital mortality was lower in patients aged <70 years (0.6% versus 6.5%, $P = 0.026$). One-year mortality was 4.0%, versus 23% in the patients aged ≥70 years ($P = 0.074$).

A separate analysis for elective cholecystectomy shows that there is no significant difference in median HLOS [IQR 2–5] in patients < 70 years and patients > 70 years [IQR 2–7] ($P = 0.315$).

Similarly ICU admittance (respectively 2.8% and 6.8%, $P = 0.321$), in-hospital mortality (respectively 0.3% versus 4.5%, $P = 0.727$) and one year mortality (respectively 2.8% and 15.9%, $P = 0.024$) showed no significant difference between the two age groups.

All secondary outcomes are presented in Tables 3a and 3b.

Discussion

In this study we show that cholecystectomy in elderly patients is associated with a higher complication rate (CCI), an increased

Table 1
Baseline characteristics and perioperative factors.

Variable	Patients <70 (n = 473)	Patients ≥ 70 (n = 92)	P*
Recipient characteristics			
Age (years)	49 ± 13.4	77 ± 5.2	
Male sex, n (%)	198 (41.5)	48 (54.5)	0.073
BMI (kg/m^2)			
Mean (SD)	28.8 (7.0)	27.65 (5.0)	
≥25	256 (55.6)	52 (56.5)	0.226
ASA-classification			
Median [IQR]	2.0[2-3]	2.4[2–4]	<0.001
≤2	269 (56.9)	32 (34.8)	0.027
≥3	88 (18.6)	22 (23.9)	0.027
Charlson comorbidity index			
Mean [SD]	0.9 (1.6)	2.2 (2.0)	<0.001
Sepsis postoperative	19 (4)	7 (8.0)	0.194
Intoxication			
Smoking (yes)	143 (30.0)	12 (13.6)	0.004
Alcohol (yes)	154 (32.3)	22 (25.0)	0.699
Preoperative predictors			
Hemoglobin level (mmol/l); <8.0	206 (43.6)	41 (50)	0.015
C-reactive protein (mg/l); >5	229 (48.4)	33 (69.1)	0.008
Impaired renal function	62 (13.1)	13 (14.1)	0.262
Bilirubine, median [IQR]	14[9–22]	12[6–20]	0.173
ERCP prior to surgery (yes)	21 (22.8)	105 (18.3)	0.050
Cholecystitis (yes)	219 (38.2)	53 (57.6)	<0.001
Symptomatic gallstones	246 (43.5)	24 (26.1)	<0.001
Biliary pancreatitis and gallbladder polyposis	35 (6.1)	4 (4.3)	0.422
Elective surgery	316 (66.2)	44 (7.8)	<0.001
Emergency surgery	160 (33.5)	48 (51.1)	<0.001
Laparoscopic procedure	431 (90.4)	72 (81.8)	<0.001
Primary open procedure	64 (11.2)	19 (20.7)	<0.001
Conversion to open procedure	67 (14.0)	17 (19.3)	0.271
Intraoperative cholangiogram (IOC)	237 (50.1)	37 (40.2)	0.072
IOC abnormal	42 (8.9)	8 (8.7)	0.819
Postoperative ERCP (yes)	27 (7.4)	7 (16.3)	0.019
Prescription of antibiotics Median	0 [0–1]	1 [0–7]	
Preoperative	83 (17.4)	24 (27.3)	0.042
Peroperative	129 (27.0)	26 (29.5)	0.815
Postoperative	79 (16.6)	26 (29.5)	0.031
Follow-up mean (SD)	819 [490]	710 [508]	0.008

Values are means ± (SD), medians [IQR], or numbers (%).
BMI Body Mass Index Kg/m2.
ASA American Society if Anesthesiologist score.
Charlson Morbidity Index weighted index ranging from 0 to 19 indicating comorbidities.
Impaired renal function defined as eGFR <30 ml/min x 173m^2.
ERCP Endoscopic retrograde cholangiopancreatography.
Follow-up in days.

hospital length of stay (HLOS), higher rate of ICU admittance and an increased mortality. We found a higher incidence of complications in the elderly patients than previously reported.[17] We identified several preoperative predictors for the development of complications after cholecystectomy that should be taken under consideration while considering surgery. Most importantly we show that more pre-operative factors than age alone are predictors for postoperative complications in accordance with Vilches et al.[18,28] Pre-operative factors connected to cholecystitis such as sepsis and elevated CRP as well as perioperative factors as emergency surgery and conversion to an open procedure were all significant predictors for postoperative complications. Complications were accompanied by a significantly longer HLOS and a higher ICU admittance rate in the elderly. In the literature, postoperative

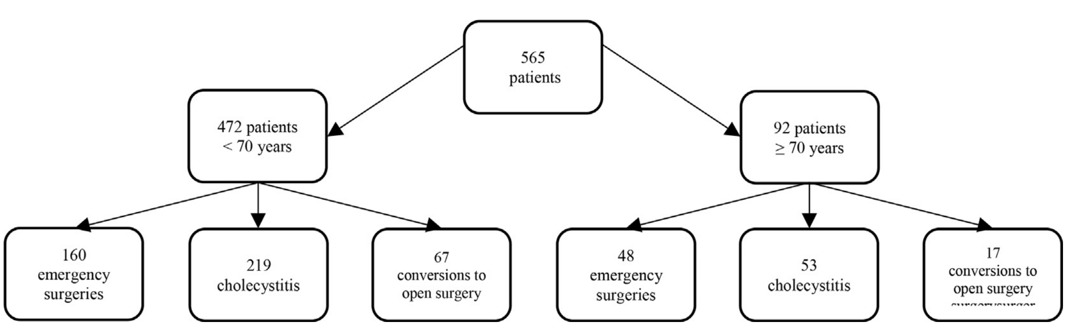

Fig. 1 Flowchart of included patients..

Table 2
Predictors for development of postoperative complications: univariate and multivariate regression analysis.

Variable	Univariate unadjusted analysis	P	Multivariate adjusted analysis	P
	Odds Ratio (95% CI)		Odds Ratio (95% CI)	
Age				
<70	1.00		1.00	0.04
≥70	3.30 (2.02–5.39)	<0.001	2.64 (1.44–4.84)	
Gender				
Female	1.00			
Male	0.68 (0.45–1.04)	0.008		
BMI				
<25	1.00			
≥25	1.71 (1.02–2.88)	0.042		
ASA-classification				
≤2	1.00			
≥3	2.57 (1.47–4.52)	0.001		
Type of procedure				
Elective	1.00		1.00	
Emergency	2.40 (1.56–3.68)	<0.001	0.34 (0.18–0.63)	0.03
Laparoscopic procedure	1.00		1.00	
Primary open procedure	2.85 (1.62–4.99)	<0.001	3.31 (1.72–6.38)	0.02
Conversion to open procedure	3.18 (1.92–5.28)	<0.001		
Intraoperative cholangiography (IOC)				
Normal	1.00			
Abnormal	1.11 (0.54–2.26)	0.93		
Indication				
Symptomatic gallstones	1.00			
Cholecystitis	3.63 (2.13–6.19)	<0.001		
Biliary pancreatitis and gallbladder polyposis	2.04 (0.92–4.43)	0.76		
Preoperative sepsis				
No	1.00		1.00	
Yes	8.65 (3.84–19.52)	<0.001	46.3 (10.4–206.7)	0.001
Preoperative hemoglobin level (mmol/l)				
≥8.0	1.00			
<8.0	0.74 (0.47–1.18)	0.25		
Preoperative renal impairment				
No	1.00			
Yes	0.48 (0.15–1.47)	0.19		
Preoperative C-reactive protein (mg/l)				
≤5	1.00		1.00	
>5	0.58 (0.33–1.03)	0.08	0.29 (0.17–0.50)	0.04
Preoperative leucocyte count (10ˆ9/l)				
≤15	1.00			
>15	0.43 (0.22–0.82)	0.02		
Smoking				
No	1.00			
Yes	0.65 (0.35–1.22)	0.23		
Alcohol				
No	1.00			
Yes	0.90 (0.50–1.62)	0.83		

CI confidence interval of 95%.
Preoperative renal impairment defined as eGFR <30 ml/min x 173 m^2.

mortality after (laparoscopic) cholecystectomy in elderly patients (≥65 years) is reported to be 0.8–3%. In addition, in patients ≥80 years, the postoperative mortality rate increases to more than 6%.[1,7,10–12] More importantly, the mortality rates are mostly attributed to cardiac, respiratory and septic complications, even though the comorbidity burden is generally low in these studies.[1,4,13] We found an in-hospital mortality rate of 6% in the elderly group, which is in line with current literature.

Table 3a
Primary and secondary outcome variables stratified by age cohort in both elective and emergency patients.

Variable	Total (%)	Patients < 70	Patients ≥ 70	P
N	565 (100.0)	473 (83.7)	92 (16.3)	
Hospital Length of Stay	4[2–7]	3[2–6]	6[3–10]	<0.001
Intensive Care				
Admittance	32 (5.6)	19 (4.0)	13 (14.1)	<0.001
Length of stay	1[1–4]	2[1–7]	1[1–4]	0.749
Mortality				
In-hospital mortality	9 (1.6)	3 (0.6)	6 (6.5)	0.026
1-year	39 (6.9)	19 (4.0)	22 (23.4)	0.074

Values are means ± (SD), medians [IQR], or numbers (%).

Table 3b
Primary and secondary outcome variables stratified by age cohort in elective patients.

Variable	Total (%)	Patients < 70	Patients ≥ 70	P
N	360 (100.0)	316 (66.2)	44 (7.8)	
Hospital Length of Stay	5 [2-5]	5 [2-5]	5 [2-7]	0.315
Intensive Care				
Admittance	32 (5.6)	9 (2.8)	3 (6.8)	0.321
Length of stay	1 [0–3]	0 [0–3]	0 [0–2]	0.321
Mortality				
In-hospital mortality	3 (0.8)	1 (0.3)	2 (4.5)	0.727
1-year	16 (4.4)	9 (2.8)	7 (15.9)	0.024

Data are number of patients (%) or mean (standard deviation).
Intensive care admittance number of patients admitted.
Hospital length of stay & Intensive care unit in days in Median [IQR].

Table 4
Charlson comorbidity index.

Comorbidity	Total	Patients <70	Patients ≥70	*P*
Myocardial infarct	17 (3.0)	11 (2.3)	6 (6.8)	0.109
Congestive heart failure	76 (13.5)	47 (8.9)	29 (33)	<0.001
Peripheral vascular disease	25 (4.4)	20 (4.2)	5 (5.7)	0.896
Dementia	2 (0.4)	2 (100)	0	0.449
Chronic obstructive pulmonary disease	54 (9.6)	45 (9.4)	9 (10.2)	0.822
Connective tissue disease	42 (7.4)	36 (7.5)	6 (6.8)	0.781
Peptic ulcer	14 (2.5)	12 (2.5)	2 (2.3)	0.861
Diabetes	57 (10.1)	39(8.2)	18 (20.5)	0.008
Hemiplegia	6 (1.1)	4 (0.8)	2 (2.3)	0.556
Renal disease	28 (5.0)	22 (4.6)	6 (6.8)	0.446
Malignancy	77 (13.6)	55 (11.5)	22 (25.0)	0.007
AIDS	7 (1.2)	7 (1.5)	0 (0)	0.008
Cerebrovascular disease/Transient ischemia attack	24 (4.2)	14 (2.9)	10 (11.4)	0.017

The outcomes in the published studies are difficult to interpret because there is a selection bias leading surgeons to select the healthiest patients for a cholecystectomy and high-risk patients (dementia, non-ambulatory, cardiovascular disease, and acute clinical decompensated) for percutaneous gallbladder drainage. This is similarly reflected in the higher incidence of cholecystitis as operation indication in the elderly compared to patient <70.

In patients ≥80 years incidence of conversion from laparoscopic to open surgery is high and occurs in 25.3% of the patients undergoing cholecystectomy.[2,7] In order to decrease the risk of emergency surgery, alternative therapies, in order to avoid cholecystectomy, have been explored and successfully applied.[24–27] Examples are percutaneous gallbladder drainage and endoscopic placement of a lumen-apposing metal stent.

Percutaneous gallbladder drainage supplemented with antibiotics has proven to be safe as a treatment for high-risk elderly patients (≥70). After drainage only minor complications occur and cholecystitis only reoccurs in 4% of the patients.[13,19] With these complication and mortality rates of respectively 4.1% and 1.4% there is clearly much to gain in this vulnerable patient group.[20] Percutaneous gallbladder drainage is most frequently applied as an alternative to cholecystectomy and has emerged as a safe and reliable therapy in the acute setting. In addition, Lin. et al. described that compared to emergent cholecystectomy in high-risk elderly patients percutaneous drainage resulted in a reduced hospital stay ($P = 0.002$) and morbidity rate ($P = 0.013$).[19] Because of concerns for recurrent cholecystitis in most cases percutaneous gallbladder drainage is considered a bridge to surgery. A comparison of emergency cholecystectomy to percutaneous cholecystostomy for calculous cholecystitis in critically ill patients favored cholecystectomy in terms of mortality and complications.[21] The CHOCOLATE trail in which high risk patients are randomized to laparoscopic cholecystectomy or percutaneous cholecystostomy will likely further contribute to the decision making whether a cholecystectomy is the treatment of choice or whether a nonoperative approach should be considered.[22]

Another non-surgical option for cholecystitis is endoscopic placement of a lumen-apposing metal stent. The technique is described to be successful in 98% of the patients undergoing the endoscopic stenting. During the procedure, a cholecystoenteric fistula is created and therefore endoscopic stenting should be reserved only for patients who are not eligible for future cholecystectomy.[23]

We acknowledge limitations of the current study. First, the fact that the University medical Center Groningen (UMCG) is a university-based tertiary referral hospital, leads to a condensation of more complex patients and procedures compared to secondary care centers. Morbidity and mortality rates may therefore be higher than expected in a general population. Second, we found a significantly higher incidence of cholecystitis in the elderly: 57.6% versus 34.7% ($P < 0.001$). Although preoperative sepsis and emergency surgery were added to the adjusted model, we cannot rule out that this difference in some way has influenced our results. However, demographic variation between the cohorts does not explain this difference in outcome and therefore this finding might be interesting to focus on in the future. Third, we performed a retrospective analysis from a prospectively collected database whereby selection bias and missing data may have occurred. Fourth, even though we support the selected use of percutaneous gallbladder drainage in frail elderly patients, that data was not collected and reported in the present study.

In conclusion, this study shows that in elderly patients the risk of complications and mortality after cholecystectomy is higher than previously reported. Considering the high incidence of cholecystitis in the elderly, and the significantly higher rate of complications in the acute setting, further research should be done to determine whether the indication for cholecystectomy in the elective setting should be expanded for elderly patients.

Conflicts of interest

None.

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