Retrospective Study
Which octogenarian patients are at higher risk after cholecystectomy for symptomatic gallstone disease? A single center cohort study.

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Abstract
BACKGROUND
Incidence of gallstones in those aged≥ 80 is as high as 38-53%. The decision-making process to select those oldest old patients who could benefit from cholecystectomy is challenging.

AIM
To assess the risk of morbidity of the “oldest-old” patients treated with cholecystectomy in order to provide useful data that could help surgeons in the decision-making process leading to surgery in this population.

METHODS
A retrospective study was conducted between 2010 and 2019. Perioperative variables were collected and compared between patients who had postoperative complications. A model was created and tested to predict severe postoperative morbidity.
RESULTS
269 patients were included in the study (193 complicated). The 9.7% of complications were grade 3 or 4 according to the Clavien-Dindo classification. Bilirubin levels were lower in patients who did not have any postoperative complications. American Society of Anesthesiologists scale 4 patients, performing a choledocholithotomy and bilirubin levels were associated with Clavien-Dindo>2 complications (p<0.001). The decision curve analysis showed that the proposed model had a higher net benefit than the treating all/none options between threshold probabilities of 11 and 32% of developing a severe complication.

CONCLUSION
Patients with American Society of Anesthesiologists scale 4, higher level of bilirubin and need of choledocholithotomy are at the highest risk of a severely complicated postoperative course. Alternative endoscopic or percutaneous treatments should be considered in this subgroup of octogenarians.

Key Words: Cholecystitis; Gallstones; Choledocholithotomy; Elderly; Post-operative complications

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Core Tip: The incidence of gallstone disease is high in octogenarian patients. There are no contraindications in performing cholecystectomy in this population, however, they may be at higher risk of complications. Herein, we will analyze perioperative variables to understand their impact on postoperative courses. Then, we will construct a model in order to help in the selection of patients aged >80 years who need cholecystectomy.
INTRODUCTION

Extended life expectancy, coupled with the increased incidence of gallstones with aging, progressively leads to more elderly patients being evaluated for possible surgery for symptomatic gallstones [1,2]. The incidence of gallstones in those aged 80 or over is as high as 38-53%, and it could increase up to 80% for patients over 90 years of age [3-5]. After an initial episode of biliary colic, 20-40% of patients will experience recurrent episodes [6,7]. Within one year, 14% of patients will develop acute cholecystitis, 5% biliary acute pancreatitis (BAP) and 5% choledocholithiasis [8,9]. Acute Cholecystitis (AC) is the sixth most common gastrointestinal disease encountered in the emergency department and the second most common cause of hospital admission in the USA [10]. With the aid of modern perioperative care and laparoscopic surgery, patients between 65 and 80 years of age are now thought to have operative risks comparable to the younger population [5]. To date, the outcomes regarding the safety of cholecystectomy performed in older patients are controversial [11-13].

Age itself is one of the critical factors influencing mortality and morbidity after cholecystectomy [14,15]. The greater burden of comorbidities in elderly patients leads to reduced physiological reserve and increased susceptibility to perioperative complications [16]. Outcomes can vary widely, depending on the clinical presentation and whether the procedure is performed electively or as an emergency. Increasing age has previously been identified as a factor which significantly reduces the likelihood of emergency and elective cholecystectomy being undertaken [12]. One of the reasons quoted for this choice was the reduced life expectancy of this group of patients. The decision about the most appropriate treatment for these patients is always challenging for the surgeon, regardless of the pattern of onset.

The purpose of this study is to assess the risks in terms of morbidity of the octogenarian patients treated with cholecystectomy for symptomatic cholelithiasis (biliary colic, AC,
BAP) in order to provide useful data that could help surgeons in the decision process leading to both emergency and elective surgery in this particular population.

**MATERIALS AND METHODS**

A single center retrospective cohort study was conducted on patients who underwent cholecystectomy for symptomatic cholelithiasis between September 2010 and October 2019. Exclusion criteria were age<80 years and cholecystectomies performed during other surgical procedures. Data were extracted from a retrospective institutional review board-approved database (C.E.ROM. prot. 3238/2019; I.5/263) on hepatobiliary pancreatic surgery.

Diagnosis of cholelithiasis was performed based on imaging studies: ultrasound (US), computed tomography (CT) and/or magnetic resonance (MR). AC was diagnosed and graded according to the Tokyo Guidelines (TG18)[17]. Postoperative complications were defined according to the Clavien-Dindo classification[18]. The analyzed variables included patients- age, sex, American Society of Anesthesiologists scale (ASA), Body Mass Index (BMI), Charlson comorbidity index (CCI) [19], comorbidity, prior abdominal surgery, laboratory test, radiological imaging, Endoscopic Retrograde Cholangio-Pancreatography (ERCP), diagnosis at admission in urgency; disease- cholelithiasis, cholangitis, AC, TG 18 score; and operation-related- timing, admission surgery interval, surgical approach, associated procedures, operative time, afternoon or night procedure, post-operative complication according to Clavien-Dindo classification, length of hospital stay, supported discharge, mortality.

**Indications and procedures**

Candidates for elective cholecystectomy were those patients with previous history of cholecystitis, biliary colic and/or biliary pancreatitis in the absence of biliary tract lithiasis. In case of choledocholithiasis in the preoperative work-up, in either election or emergency setting patients were referred for preoperative or intraoperative ERCP. Postoperative ERCP was indicated solely in case of choledocholithiasis diagnosed during intraoperative cholangiography in absence of contraindications for endoscopic
treatment. The indications for choledocholithotomy were the failure to resolve choleodochal lithiasis endoscopically or percutaneously (including by intraoperative Rendez-vous) and Mirizzi’s syndrome type 2.

The laparoscopic approach was performed with the patient placed in the French position. The first 10-12 mm trocar is inserted with an open technique in peri-umbilical area to achieve a 11 mmHg pneumoperitoneum. The other three trocars are positioned under direct vision in the epigastrium (5mm), 1 Laterally in the right flank (5mm) and 1 medially in the left flank (10 or 5 mm). In case of open conversion, access with a right subcostal laparotomy was preferred. Antibiotic prophylaxis with 3rd gen cephalosporins was administered in all patients. In case of AC a combination of antibiotics was used and continued based on clinical grounds.

In urgency and elective settings the open approach was indicated in high risk patients who had previous gastric surgery or repeated open abdominal surgery, in patients who need a surgical clearance of the common bile duct, in case of anesthetic contraindications to laparoscopy and in case of patient refusal to laparoscopy.

**Statistical analysis**

Data were analyzed using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015). Continuous variables were shown as median and interquartile range (IQR) while categorical data were presented as numbers and percentages. Differences between complicated and uncomplicated patients were analyzed with the Mann-Whitney U test for continuous variables and with the Chi square or Fisher exact tests for the categorical ones.

Logistic regression analyses were performed to investigate the predictors of complications and major complications. The variables who displayed a p<0.05 at multivariable analysis for Clavien-Dindo<2 complications were merged in a model and its accuracy was assessed with a receiver operating characteristic (ROC) curve analysis to calculate the Area Under the curve (AUC).
Decision curve analysis (DCA) was constructed using STATA version 15 (STATA Corp., Texas, USA). DCA allowed the calculation of a clinical benefit for the prediction model in comparison with default strategies of operating all or no patient. The DCA graph has on the y-axis the “net benefit” and on the x-axis the “threshold probability” ($P_t$).

The net benefit could be calculated as follows: $Net=(TP/n-FP/n)(Pt/1-Pt)$. $TP$ and the $FP$ are the number of patients with true- and false-positive results, respectively; $n$ was the total number of patients, and $P_t$ is the threshold probability of Clavien-Dindo≥2 complications. Thus, the “decision curve” resulted from plotting the net benefit against the threshold probability and, in this study, it was used to test the utility of the constructed model in influencing the indication of performing or not the cholecystectomy in the given population. Each graph showed a curve representing the proposed model, one about performing cholecystectomy on all patients (treat all) and one about treating all patients with conservative treatment (treat none).

The study was reviewed by our expert biostatistician Leonardo Solaini, MD.

**RESULTS**

Overall, 269 patients (179 urgent vs 90 elective cholecystectomies) were included in the analysis. Patients’ characteristics are shown in Table 1. Overall, 193 (71.7%) patients had a complicated postoperative course [Table 2]. ASA score was significantly higher in the patients who had postoperative complications ($P = 0.002$). Median leukocyte (12850 versus 9300, $P = 0.009$) and platelets (272000 vs 197000, $p<0.0001$) counts at admission were higher in the complicated group. Bilirubin levels were lower in patients who did not have any postoperative complications ($0.82 vs 1.11, P = 0.011$). The open approach (23.8 vs 13.0%) was more common in the group who had postoperative complications ($P = 0.012$). The complicated group had more intraoperative cholangiography (46.1 vs 65.3%). The uncomplicated group had more cholecystectomies which were performed during afternoon/night (31.6 vs 48.2%, $P = 0.014$).
The 9.7% (n = 26) of complications were grade 3 or 4 according to the Clavien-Dindo classification. The in-hospital mortality rate was 1.5% (n = 4) while the 90-days mortality rate was 3.9% (n = 7). The three patients who died after discharge but within 90 days of surgery had had a postoperative course with Clavien-Dindo grade <3 (Table 2). All cases of postoperative deaths occurred after open or converted urgent cholecystectomy.

At 24 mo follow-up, 195 were alive (85.9%) while 32 (14.1%) died for unrelated causes. For 23 (8.8%) patients last follow-up was at 90 days. At multivariable analysis, performing an intraoperative cholangiography (2.99, 1.43-6.24; P = 0.003), the diagnosis of cholangitis at admission (12.7, 1.61-100.1; P = 0.016), platelets count (1.00, 1.00-1.01; P = 0.0008), the laparoscopic approach (0.10, 0.02-0.46; P = 0.003) were significantly associated with postoperative complications (Table 3).

ASA 4 patients (12.6, 4.27-37.3; <0.0001), performing a choledocholithotomy (10.2 (2.04-51.1; 0.005) and bilirubin levels (1.4, 1.33-1.75; 0.002) were significantly associated with Clavien-Dindo>2 complications (Table 4) for the whole population.

The ROC curve analysis showed that the model including the three variables to predict Clavien-Dindo>2 complications had an AUC of 0.79 (0.73-0.85) (Figure 1).

The decision curve analysis is shown in Figure 2. According to the graph, the treating all strategy may be harmful in terms of Clavien-Dindo>2 complications in patients with threshold probabilities >13%. The proposed model showed a higher Net benefit than the treating all/none options between threshold probabilities of 11 and 32% of developing a Clavien-Dindo>2 complication.

**DISCUSSION**

Even though gallstones increase with aging, older patients are less likely to undergo cholecystectomy [1,22]. In fact, it has been estimated that less than a quarter of elderly patients who meet the criteria for elective cholecystectomy undergo surgery [1,22]. This is because increasing age is a negative predictor after cholecystectomy, due to the higher perceived surgical risks, especially after hospitalization for complications of gallstones.
In this clinical arena, the availability of a tool to support the surgeon in his decision making is of utmost importance.

Cholecystectomy for symptomatic gallstone disease is associated with a high postoperative complication rate in octogenarians. However, it must be highlighted that only 9.7% of patients had a severe complication, indicating that cholecystectomy could remain a treatment option in this population. In line with this assumption, the NICE 2014\(^2\) and TG18\(^3\) guidelines did not suggest an age cut-off to surgically treat symptomatic gallstone disease or cholecystitis.

Other reports showed similar high morbidity rates ranging between 14.7% and 51% \(^{24-27}\).

Only 3 studies with populations with similar characteristics reported complications graded according to the Clavien-Dindo classification and all found that the majority of complications were Clavien-Dindo grade 1-2 characteristics \(^{28-30}\).

The feasibility of cholecystectomy in octogenarians was evaluated in different studies that confirmed its safety, but in the investigated “all comers” groups the surgical treatment in an elective setting always represented more than half of the cases\(^{28}\). Differently, the population analyzed in this study was characterized by a limited number of patients (33.5%) treated electively with cholecystectomy.

In addition, according to our analysis, cholecystectomy seemed to be associated with acceptable safety parameters in moderate-severe acute cholecystitis. As such, 90-days mortality in our cohort was 2.6%. This is similar to what has been reported by the two largest single-center studies which showed in-hospital mortality ranging between 4% to 4.8% \(^{28,31}\). This was also confirmed by a recent systematic review comparing the outcomes of patients with 65-79 Vs ≥80 years which showed a mortality rate of 0 - 4.6% in the older age group\(^5\).

A severely complicated postoperative course, may have a dramatic impact on the elderly patients who may not return to their previous level of activity \(^{32}\).

Our analysis could find those factors which could help in predicting those patients at risk of having a severely complicated postoperative course.
According to the decision curve analysis our model may be of use in selecting those elderly patients at the lowest risk of severe complications for whom cholecystectomy should be performed. We found that ASA 4 patients with elevated bilirubin levels and in need of choledocholithotomy had the highest risk of developing a Clavien-Dindo>2 complication. The risk of a Clavien-Dindo>2 complication was nearly 80% for this subgroup of patients. This may indicate the need of considering alternative non-operative approaches for this subgroup of patients, preferring endoscopic/percutaneous options.

Our paper appears to be the first in the literature to document a statistically significant correlation between the use of choledocholithotomy and complications.[33,34] This may be due to the fact that our analysis focused on a very select population of patients with >80 years of age. This finding may suggest considering a surgical-endoscopic 'rendezvous' procedure as an alternative to choledocholithotomy.[35]. However, additional studies on this approach on the oldest-old populations are warranted to confirm this hypothesis.

The limitations of this study are linked to its retrospective nature whose outcomes may be confounded by selection bias. As such, the cohort may include the fittest patients, for whom a definitive treatment like cholecystectomy may not represent a major risk. In addition, we could not provide data on frailty which may be another factor to consider when dealing with the oldest-old patients. This might have helped in creating an even more accurate model in predicting patients at risk for severe postoperative complications following cholecystectomy for gallstone disease. Finally, since the study is based on a surgical database, we could not consider those patients treated only with percutaneous/endoscopic procedures which might be considered a treatment option for a subpopulation of octogenarians.

**CONCLUSION**
ASA 4 patients with higher levels of bilirubin at admission who may need a choledocholithotomy are at the highest risk of a severely complicated postoperative course. These factors should be included in the decision-making process in defining the ideal elderly patients to be submitted to cholecystectomy for cholelithiasis in either an emergency or elective setting.
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