The American Journal of Surgery 221 (2021) 538–542

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Original Research Article

Outcomes of cholecystectomy in US veterans with cirrhosis: Predicting outcomes using nomogram

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ARTICLE INFO

Article history:
Received 17 July 2020
Received in revised form
16 November 2020
Accepted 17 December 2020

Keywords:
Cholecystectomy
Veterans
Cirrhosis
Outcomes
Nomogram

ABSTRACT

Background: This study examines the outcomes of open and laparoscopic cholecystectomy (OC/LC) in veterans with cirrhosis and develops a nomogram to predict outcomes.
Methods: We analyzed the Veterans Affairs Surgical Quality Improvement Program to identify all patients with cirrhosis and ascites who underwent cholecystectomy from 2008 to 2015. Univariate and multivariate regression were used to identify predictors of morbidity and mortality. A predictive nomogram was constructed and internally validated.
Results: A total of 349 patients were identified. Overall, complications occurred in 18.7% of patients, and mortality was 3.8%. LC was performed in 58.9%, and 19.2% were preformed emergently. Overall, Model for End-Stage Liver Disease score was an independent factor of morbidity and mortality, while laparoscopic approach had a protective effect on morbidity.
Conclusions: Although cholecystectomy is a high-risk operation in cirrhotic veterans, LC may have favorable outcomes than OC in selected patients. An easy-to-use nomogram to predict morbidity and mortality for cirrhotic patients undergoing cholecystectomy is proposed.

Introduction

The Veteran Affairs healthcare system is the largest single provider for patients with chronic liver disease, taking care of approximately 60,000 veterans with cirrhosis annually, representing a 2-fold increase from 2001 to 2013.[1] Due to higher morbidity and mortality, surgical management of these patients can be challenging, and it is estimated that 10% of those will require a surgical procedure, with cholecystectomy ranking among the most commonly performed.[2] Incidence of gallstones disease is twice as often as in non-cirrhotic patients, and its causality is multifactorial including gallbladder dysmotility, hemolysis and hypersplenism.[3] Laparoscopic cholecystectomy (LC) is proven to be a safe and feasible procedure with clear advantages over open cholecystectomy (OC). However, liver cirrhosis has historically been considered a relative contraindication for LC.[4]

Reported morbidity and mortality following cholecystectomy in cirrhotic patients ranges from 6.6% to 47.3% and 0.88%–8%, respectively.[3,4] Most of the available data is retrospective with small sample size, and a reliable predictive model to estimate postoperative outcomes is yet to be standardized. Using the Veterans Affairs Surgical Quality Improvement Program (VASQIP) database, we compared the outcomes of OC vs. LC in cirrhotic veterans and examined predictors of outcomes to develop a nomogram to predict morbidity and mortality rates.

Methods

Data source and study subjects

The VASQIP database was utilized in our study. VASQIP is a robust database, established in 1991 in 44 veterans affairs medical centers (VAMC), and extended to include 123 centers later on.[5] We inquired this database for patients who underwent

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https://doi.org/10.1016/j.amjsurg.2020.12.031
0002-9610/

Table 1
Patient preoperative characteristics and comorbidities comparing OC vs. LC.

	All (n = 343)	OC (n = 141)	LC (n = 202)	*P*-value
Age (years), mean ± SD	62.7 ± 11.6	63.9 ± 11.5	61.9 ± 11.6	0.103
Sex (male), n (%)	335 (97.7)	137 (97.2)	198 (98.0)	0.630
ASA class, n (%)				**0.006**
1 or 2	35 (10.2)	7 (4.9)	28 (14.0)	
≥ 3	308 (89.2)	134 (95.1)	174 (86.0)	
BMI (kg/m^2), mean ± SD	28.4 ± 5.8	27.4 ± 5.9	29.0 ± 5.1	**0.012**
Obesity (BMI ≥ 30), n (%)	114 (33.2)	34 (25.0)	80 (39.0)	**0.007**
Indication of cholecystectomy, n (%)				**0.011**
Acute cholecystitis	284 (82.8)	121 (86.0)	163 (80.5)	
Symptomatic cholelithiasis	38 (11.1)	8 (5.6)	30 (15.0)	
Others (gallbladder polyps, cholesterolosis or dyskinesia)	21 (6.1)	12 (8.4)	9 (4.5)	
Emergency, n (%)	66 (19.2)	43 (30.8)	23 (11.0)	< **0.001**
Current smoker, n (%)	130 (37.9)	55 (38.5)	75 (37.5)	0.856
Current alcohol use, n (%)	36 (10.5)	14 (9.8)	22 (11.0)	0.719
Independent functional status, n (%)	289 (84.3)	108 (75.5)	182 (90.5)	< **0.001**
Preoperative comorbidities, n (%)				
Esophageal varices	104 (30.3)	27 (18.9)	77 (38.5)	< **0.001**
CHF	13 (3.8)	4 (2.8)	9 (4.5)	0.415
Hypertension on medications	249 (72.6)	96 (68.5)	153 (75.5)	0.154
Diabetes mellitus	109 (32.1)	42 (30.1)	67 (33.0)	0.566
COPD	71 (20.7)	23 (16.1)	48 (24.0)	0.074
Dialysis	8 (2.3)	7 (4.9)	1 (0.5)	**0.008**
Preoperative sepsis, n (%)	45 (13.1)	31 (22.4)	14 (6.9)	< **0.001**
MELD score, mean ± SD	11.1 ± 4.9	12.5 ± 6.3	9.9 ± 3.3	< **0.001**
Mild (≤ 8)	162 (47.2)	62 (43.4)	100 (50.0)	0.224
Moderate (9–16)	128 (37.3)	61 (42.7)	67 (33.5)	
Severe (≥ 17)	53 (15.5)	20 (14.0)	33 (16.5)	
Thrombocytopenia (<150 × 10^9/L), n (%)	125 (36.4)	54 (37.8)	71 (36.4)	0.668

Abbreviations: OC: Open Cholecystectomy; LC: Laparoscopic Cholecystectomy; SD: Standard Deviation; ASA: American Society of Anesthesiologists; BMI: body mass index.; CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; MELD: Model for End-stage Liver Disease.

cholecystectomy between 2008 and 2015 using the following current procedural terminology codes: 47,600, 47,605, 47,610, and 47,612 for OC; 47,562, 47,563 and 47,564 for LC.

Only 6 cases of conversion were identified (conversion rate 3%), due to the small size we decided to exclude this group from the analysis. The diagnosis of liver cirrhosis was identified preoperatively in patients with ascites and/or esophageal varices. Data collection included demographics, preoperative comorbidities, operative details, and 30- and 90-day postoperative outcomes. 30-day morbidity were defined as occurrence of at least one complication within 30 days from the procedure. The VASQIP captures up to 28 different postoperative events as complications. Model for End-stage Liver Disease (MELD) score was calculated using preoperative values of serum total bilirubin, international normalized ratio (INR), and serum creatinine, using the following formula: $11.2 \times \log_e(\text{INR}) + 3.78 \times \log_e(\text{serum bilirubin [mg/dL]}) + 9.57 \times \log_e(\text{serum creatinine [mg/dL]}) + 6.43$.[6] Any patient with a laboratory value < 1 was given one. MELD score was classified into: mild (≤8), moderate (9–16), and severe (≥17), to correlate with Child-Turcotte-Pugh score classes A, B, and C, respectively.[7]

This study was approved by the Institutional Review Board of Wayne State University, Detroit, MI, and due to the retrospective and de-identified nature of the data, patient consent was waived.

Table 2
Unadjusted analysis of operative and postoperative mortality, LOS, and morbidities.

	All (n = 343)	OC (n = 141)	LC (n = 202)	*P*-value
Operation duration (hours), median (25th, and 75th percentiles)	2.1 (1.5, 2.7)	2.3 (1.8, 3.1)	1.7 (1.3, 2.4)	**0.336**
Number of patients received at least one unit of red blood cell intraoperatively, n (%)	34 (9.9)	28 (20.3)	6 (3.0)	< **0.001**
Postoperative LOS (days), median (25th, and 75th percentiles)	5.0 (2.8, 8.0)	7.0 (4.0,12.0)	3.0 (2.0, 5.0)	< **0.001**
30-day mortality, n (%)	13 (3.8)	10 (7.0)	3 (1.5)	**0.009**
90-day mortality, n (%)	24 (7.0)	17 (11.9)	7 (3.5)	**0.003**
Morbidity, n (%)	64 (18.7)	44 (31.5)	20 (9.5)	< **0.001**
Surgical complications, n (%)				
Superficial SSI	10 (2.9)	8 (6.3)	2 (1.0)	**0.002**
Deep SSI	4 (1.2)	3 (2.1)	1 (0.5)	0.174
Organ space SSI	9 (2.6)	5 (3.5)	4 (2.0)	0.393
Reoperation	23 (6.7)	14 (9.8)	9 (4.5)	0.053
Bleeding requiring ≥4 units postoperatively	6 (1.7)	5 (3.5)	1 (0.5)	**0.037**
Medical complications, n (%)				
Pneumonia	5 (1.5)	4 (2.8)	1 (0.5)	0.080
ICU admission	18 (5.2)	14 (9.8)	4 (2.0)	**0.001**
Pulmonary embolism	2 (0.6)	1 (0.7)	1 (0.5)	0.811
Urinary tract infection	8 (2.3)	6 (4.2)	2 (1.0)	0.053
Deep venous thrombosis	3 (0.9)	1 (0.7)	2 (1.0)	0.768

Abbreviations: OC: Open Cholecystectomy; LC: Laparoscopic Cholecystectomy; IQR: Interquartile Range; LOS: Length of Stay; SSI: Surgical Site Infection; ICU: Intensive Care Unit.

Table 3
Multivariate logistic regression for complications and 90-day mortality.

	OR	CI 95%	*P*-value
Complications			
Age	1.0	0.97–1.03	0.840
Gender			
Female	REF		
Male	1.22	0.13–11.79	0.864
Functional status			
Independent	REF		
Partially dependent	2.36	0.98–5.69	0.056
Totally dependent	2.60	0.75–9.01	0.133
Dialysis	0.38	0.04–3.43	0.392
Cardiac comorbidity	2.44	0.80–7.46	0.177
IDDM	1.75	0.83–3.67	0.142
Preoperative sepsis	0.90	0.37–2.19	0.820
Emergency procedure	0.79	0.34–1.80	0.571
MELD	1.10	1.02–1.20	**0.016**
Surgical approach			
Open	REF		
Laparoscopic	0.33	0.17–0.64	**0.001**
90-day mortality			
Age	1.05	1.00–1.10	**0.047**
Functional status			
Independent	REF		
Partially dependent	3.12	0.82–11.90	0.096
Totally dependent	8.22	1.69–40.04	**0.009**
Dialysis	0.31	0.03–3.42	0.340
Cardiac comorbidity	1.01	0.20–5.11	0.993
IDDM	1.70	0.54–5.32	0.363
Preoperative sepsis	0.30	0.06–1.62	0.162
Emergency procedure	0.49	0.12–1.94	0.310
MELD	1.21	1.08–1.35	**0.001**
Surgical approach			
Open	REF		
Laparoscopic	0.43	0.13–1.37	0.152

Abbreviations: OR: Odds Ratios; CI: Confidence Interval; IDDM: Insulin Dependent Diabetes Mellites; MELD: Model for End-stage Liver Disease.

Statistical analysis

The chi-square test was utilized to analyze categorical variables. Two-sided unpaired Student's *t*-test or Mann–Whitney *U* test were used for numerical variables as appropriate. Multivariate logistic regression adjusting for demographics, comorbidities, and other preoperative factors was used to analyze postoperative outcomes. $P < 0.05$ was considered statistically significant.

To construct the nomogram, a list of preoperative variables was selected *a priori,* based on their known or assumed influence on the outcomes. Analyzed variables included: age, MELD score, history of chronic on dialysis preoperatively, history of angina, coronary artery disease or congestive heart failure, functional status, diabetes requiring insulin therapy, elective or emergency procedure, surgical approach (laparoscopic vs. open) and preoperative use of steroids. Univariate analysis was performed with the cofactors more likely to be associated with the outcomes, as described elsewhere,[8] and variables with $P \leq 0.2$ were selected per protocol and inputted into a logistic regression model in order to obtain the parameter estimates for the nomogram. A graphical nomogram was created as described previously.[9]

The internal validation was performed using a calibration method with boots trapping (1000 samples), and a plot was generated to depict the association between the actual outcomes rates and their predicted probability. A receiver operating characteristic (ROC) curve was generated for each nomogram. 95% confidence interval for the area ROC under the curve (AUC) was calculated using the DeLong method. Then, an interactive nomogram (**Supplemental File 1**) to calculate survival and overall complication probability was constructed using the Microsoft Excel 365® (Microsoft Corporation, Redmond, WA). Statistical analyses and nomogram construction were carried out using IBM SPSS 25 and EZR on R Commander 1.38.[10]

Results

A total of 343 patients were included in the analysis, 58.9% cases were performed laparoscopically, whereas 41.1% underwent open approach. Preoperative patients' demographics and comorbidities are listed in Table 1. OC group were sicker with higher proportion of having ASA class $\geq$ III, dependent functional status, and preoperative sepsis with requirement of emergent procedure for acute cholecystitis. Mean MELD score was higher for the OC group, with no significant difference in percentage of patients with MELD $\geq$15 between the two groups (OC 26.5% vs. LC 21.8%, $p = 0.304$). When MELD was divided in mild, moderate or severe, we also did not observe difference between the two groups. LC patients had higher mean BMI and higher incidence of esophageal varices.

As summarized in Table 2, OC had worse outcomes in terms of higher rate of morbidity and mortality, longer LOS, intensive care unit admission, and bleeding requiring blood transfusion either intraoperatively, or postoperatively.

Multivariate logistic regression analysis is shown in Table 3, MELD score was an independent predictor of both morbidity and mortality. Laparoscopic approach has a protective effect on morbidity, and dependent functional status was an independent factor of increased 90-day mortality.

Constructed nomograms were illustrated in Fig. 1, along with their ROC curves. To use the nomogram, locate patient's variable on the left, then mark line from the corresponding axis to the points axis, sum the points then draw line from the total points axis to the estimated rate axis. An easier interactive nomogram is available online as a supplemental file.

Comments

We analyzed outcomes following cholecystectomy in cirrhotic veterans using the VASQIP database. To our knowledge, this is the first study that has used the VASQIP database to address this topic. Our main findings are: (1) OC subgroup were sicker with higher mean MELD score and higher incidence of acute cholecystitis, that require emergency surgery due to preoperative sepsis; (2) MELD score, and dependent functional status, were associated with increased mortality; and (3) an easy-to-use nomograms can estimate 90-day mortality and complication rates with high sensitivity.

In our study, LC was performed at lower rate (58.9%) compared to other studies looked at cholecystectomy in cirrhotic patients with rates ranging between 85 and 90%,[11,12] which may explain our lower conversion rate (3%) compared to what reported previously (4.4–15.7%).[3,4] That could be explained by the preoperative presumption of difficult cholecystectomy in these patients along with coagulopathy, which led to use the open approach primarily instead of attempting a laparoscopic approach initially.

Compared with open cholecystectomy, we demonstrated that LC had favorable outcomes with lower morbidity rate (9.5% LC vs. 31.5% OC, $p < 0.001$), mortality (1.5% LC vs. 7.0% OC, $p = 0.009$), shorter LOS (3.0 days LC vs. 7.0 days OC, $p < 0.001$), and less blood transfusions intraoperatively (3.0% LC vs. 20.3% OC, $p < 0.001$). These findings are consistent with what is reported by Chmielecki et al., as they studied 3240 cirrhotic patients who underwent cholecystectomy between 2003 and 2006 using Nationwide Inpatient Sample database, with higher mortality rate in OC group (8.3% OC vs. 1.3% LC, $p < 0.0001$).[11]

Increased mortality in patients undergoing OC could be explained by pre-selection bias, given that this group was sicker

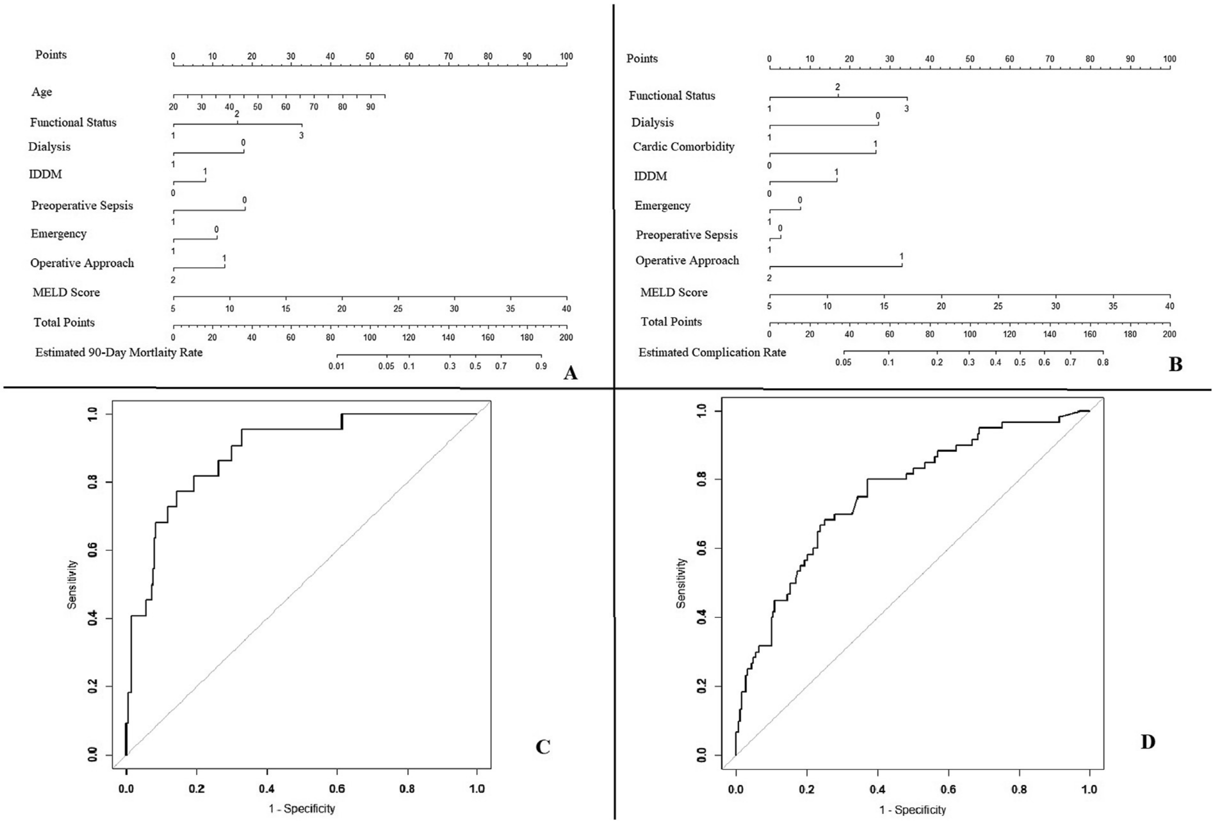

Fig. 1. Nomogram to predict 90-day mortality and complication rates (A and B, respectively). ROC curves for both nomograms were generated (C: 90-day mortality, D: Complication) with AUC 0.89 and 0.76, respectively.

with higher ASA class, perioperative sepsis and higher MELD score. However, the open approach per se has a negative impact on the postoperative outcome as described by Chmielecki et al. who showed higher mortality rate in pure open approach group compared to both total laparoscopic and laparoscopic converted to open cholecystectomy (8.3% OC vs. 1.3% converted vs. 1.4% LC, $p < 0.0001$). This indicates that laparoscopic approach should be tried first, which may aid in dissecting the gallbladder and minimize intraoperative bleeding, especially when dealing with the gallbladder bed which filled with large tortuous blood vessels, in this case laparoscopic subtotal cholecystectomy will be an appropriate alternative to avoid conversion, to avoid the deleterious impact of intraoperative blood transfusion.[3]

Despite the superiority of LC, it is still associated with higher morbidity and mortality in cirrhotic compared to non-cirrhotic.[13] Our analysis shows that MELD score by itself, represented an important predictive factor of higher mortality among cirrhotic. MELD score was shown to be a predictive preoperative tool in cirrhotic patients who are undergoing elective and emergent non-transplant procedures, including: hernia repair, appendectomy, cholecystectomy, hip surgery, and cardiac surgeries.[13,14]

Nomogram represents an emerging tool in the medical field that facilitates risk assessment using a simple graphical method. In this study, calculated AUC for both 90-day mortality and complication rate were 0.89 and 0.76, respectively, indicating the reliability of this tool. To our knowledge, these are the first nomograms to estimate outcomes following cholecystectomy in cirrhotic patients and we were able to translate it into an interactive tool for easier use.

We acknowledge the limitations in our study. As a database analysis, data collection lacked certain pertinent information regarding important preoperative factors that may have affected the surgical approach selection including previous abdominal surgery and the indication of conversion, as well as important post-operative complications, most notably common bile duct injury and decompensated liver failure. Also, given the nature of the VA patient population, which is mainly male and elderly, our findings may not generalize to other patient populations. To confirm this difference on a randomized controlled trial, with a desired power of 80% and alpha of 0.05, the number of patients required each group would be 198. We acknowledge this also represents a limitation, although we do not believe this drawback weaken our results. In addition, per protocol, we opted to do not split our database for validation. Notwithstanding this contributes to preserve the accuracy of our sample data, it certainly limited the external validity of our nomogram. However, as we provide adynamic nomogram calculator, we believe that this will encourage external validation of our findings by other groups, either prospectively or retrospectively, with different population samples.

In conclusion, cholecystectomy in cirrhotic veterans represents a major challenge for the VA surgeon, with worse outcomes compared with non-cirrhotic patients, despite the favorable outcomes using laparoscopic approach in selected patients. We designed an interactive predictive tool to estimate both 90-day mortality and morbidity rates. Further work is needed to validate our tool on a larger and diverse sample prospectively.

Disclaimer

This abstract was accepted as oral presentation at the Midwest Surgical Association Annual meeting 2020, Mackinac Island, MI.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2020.12.031.

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