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The impact of cirrhosis and MELD score on postoperative morbidity and mortality among patients selected for liver resection

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ABSTRACT

Background: Independent associations between chronic liver disease, MELD, and postoperative outcomes among patients selected for liver resection have not been completely established. We hypothesized independent associations between MELD, cirrhosis, and postoperative mortality.
Methods: Patient-level data from the targeted hepatectomy module and ACS NSQIP PUF during 2014–2015 were merged. Multivariable regression models with interaction effect between MELD and liver texture (normal, congested/fatty, cirrhotic) tested the independent effects of covariates on mortality and morbidity.
Results: 3,530 patients were included, of whom 668 patients (19%) had cirrhosis. ACS NSQIP defined mortality (3.9%vs1.1%) and morbidity (23.5%vs15.8%) were higher in patients with cirrhosis (both $p < 0.001$). In multivariable models, cirrhosis (OR = 2.24; 95%CI:1.16–4.34, p = 0.016) and MELD (OR = 1.10; 95%CI:1.03–1.18, p = 0.007) were independently associated with mortality. MELD (OR = 1.04; 95%CI:1.002–1.08, p = 0.038) was associated with postoperative morbidity.
Conclusions: Higher MELD and presence of cirrhosis have an independent negative effect on mortality after liver resection. MELD could be used to estimate postoperative risk in patients with and without cirrhosis.

Introduction

Patient selection criteria continue to be important in liver surgery. A number of factors such as extent of resection and planned future liver remnant have been associated with postoperative morbidity and mortality.[1–3] Presence of underlying chronic liver disease such as steatosis, fibrosis, or cirrhosis has also been associated with postoperative outcomes.[4] Stratification of risk among patients with cirrhosis has been particularly challenging and a number of studies have provided evidence linking greater liver disease scores, such as Model for End-Stage Liver Disease (MELD) score, with worse patient-specific outcomes.[5]

MELD score was initially developed as an alternative to Child-Pugh-Turcotte score to predict mortality of patients with cirrhosis who had transjugular intrahepatic portosystemic shunts and a separate cohort of patients with chronic liver disease awaiting liver transplantation.[6,7] Subsequent studies established utility of MELD in predicting mortality among patients with cirrhosis selected for resection.[5,8] Interestingly, other contemporaneous studies demonstrated lack of association between MELD score and mortality after liver resection among patients without cirrhosis.[9,10]

MELD score remains an attractive preoperative tool for assessment of postoperative outcomes after liver surgery. It relies on objective, readily available data, which can be directly compared between patient populations. Given published equipoise surrounding utility of the MELD score among patients with varying degrees of underlying liver disease, we aimed to estimate independent effects of MELD score and chronic liver disease on postoperative morbidity and mortality.

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Methods

Patient selection and variable definitions

All patients ≥18 years who had a liver resection between 2014 and 2015 were abstracted from The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Participant Use File (PUF). ACS NSQIP is a de-identified, independently collected, Health Insurance Portability and Accountability Act (HIPAA) compliant dataset that includes patient-level data from a nationwide cohort of participating hospitals. An additional hepatectomy-specific targeted module was released in 2014 and available subsequently. Patient data abstracted from the ACS NSQIP PUF were merged with data from the targeted dataset for use in this retrospective cohort study. The University of Virginia Institutional Review Board has designated the ACS NSQIP PUF and targeted datasets as a publicly available de-identified data exempt from formal IRB review.

Patients with reported liver texture variable as reported in the hepatectomy targeted dataset were included in this study. Liver texture was categorized as normal, congested/fatty, and cirrhotic. Sodium adjusted MELD score was calculated from serum creatinine, bilirubin, international normalized ratio, and sodium.[11] Extent of liver resection was categorized according to the Current Procedural Terminology (CPT) classification as minor (partial hepatectomy: 47120) or major (right, left, or trisectionsectomy: 47130, 47125, 47122, respectively). Other demographic and clinical variables included age, sex, and American Society of Anesthesiologists (ASA) class. The ACS NSQIP estimated probabilities of morbidity and mortality were calculated for each patient and used in model development for overall adjustment for differences in morbidity and mortality risk. ACS NSQIP calculates these estimated probabilities for both morbidity and mortality using hierarchical regression models that account for multiple patient-level factors and represents the probability that an individual will experience a mortality or morbidity based on these factors.[12] Importantly, the ACS NSQIP probabilities of morbidity and mortality can be publicly reported and viewed with the ACS NSQIP risk calculator (http://www.riskcalculator.facs.org/RiskCalculator/) and statistically adjust for important clinical covariates which are included in these models including extent of liver resection (as defined by CPT code), age range, ASA class, functional status, and selected comorbid conditions.

Outcome measures

Primary outcome measure was ACS NSQIP mortality defined as any death occurring within 30 days following the date of surgery or in-hospital mortality. Secondary outcome was defined as ACS NSQIP defined overall morbidity. Composite overall morbidity was defined as the occurrence of any of the following events: surgical site infection, wound disruption, pneumonia, unplanned intubation, pulmonary embolism, > 48 h ventilator requirement, renal failure, urinary tract infection, stroke or cerebral vascular accident, cardiac arrest, myocardial infarction, deep venous thrombosis, or systematic sepsis. Posthepatectomy liver failure (PHLF) was also included as an outcome measure but was not included as a dependent variable in multivariable analyses given lack of corresponding ACS NSQIP estimated probability of PHLF. PHLF was reported in the hepatectomy targeted dataset according to the International Study Group for Liver Surgery definition[13] and categorized as present or absent.

Statistical analysis

Differences in distribution of categorical variables were assessed using chi-square or Fisher's exact text, where appropriate, and reported as frequencies with percentages; continuous variables were reported as median with interquartile range (IQR) and compared using the Wilcoxon rank-sum test.

Two separate multivariable analyses were performed to test the associations between clinically relevant covariates and outcome measures. Each multivariable model included MELD (included as a continuous variable), categorized liver texture, and adjustment for clinically relevant baseline risk characteristics using the logit of ACS NSQIP probability of mortality (for mortality model) and the logit of ACS NSQIP probability of morbidity (for morbidity model). Additional interaction terms between liver texture and MELD were included in both multivariable models to estimate independent effects of these two covariates; both of these interaction terms were subsequently removed prior to fitting the final models due to their lack of significance. Separate Receiver Operating Curves (ROC) with Area Under the Curve (AUC) estimates were developed from both models to demonstrate goodness of fit of the regression models. All data management and statistical analysis was performed using SAS 9.4(Cary, North Carolina).

Results

A total of 3,530 adult patients with reported liver texture had liver resection during the study period. Liver texture was reported as normal in 1,887 patients, congested/fatty in 975 patients, and cirrhotic in 668 patients. Demographic and clinical variables are reported by liver texture in Table 1. Among patients included in the study, those with cirrhosis were less likely to have major hepatectomy than patients with congested/fatty or normal liver (28.9% vs 37.9% vs 37.1, respectively, $p < 0.001$) and were more likely to have higher ASA classes ($p < 0.001$) than patients with normal liver. ACS NSQIP probabilities or morbidity and mortality varied significantly between the three patient groups (Table 1).

ACS NSQIP defined 30-day or inpatient mortality occurred in 3.9% of patients with cirrhosis, 1.7% of patients with congested/fatty liver and 1.1% of patients with normal liver parenchyma ($p < 0.001$). In the multivariable model, both cirrhosis (OR = 2.24; 95% CI: 1.16–4.34, $p = 0.016$) and MELD (OR = 1.10; 95% CI: 1.03–1.18; $p = 0.007$) were independently associated with postoperative mortality (Table 2). ROC curves derived from the mortality models demonstrate an overall high predictive value with calculated AUC = 0.844 for patients with normal liver (Fig. 1A), AUC = 0.735 for patients with congested/fatty liver (Fig. 1B), and AUC = 0.792 for patients with cirrhotic liver (Fig. 1C).

ACS NSQIP defined composite morbidity occurred in 23.5% of patients with cirrhosis, 21.0% of patients with congested/fatty liver and 15.8% of patients with normal liver parenchyma ($p < 0.001$). In the multivariable model, MELD (OR = 1.04; 95% CI: 1.002–1.08; $p = 0.038$) was independently associated with postoperative morbidity (Table 3). Presence of cirrhosis or congested/fatty liver did not have an independent effect of postoperative morbidity. Both mortality and morbidity multivariate models initially included interaction terms between liver texture and MELD; these were not significant in any model (all $p > 0.50$) and were removed in order to fit models only containing main effects. PHLF occurred in 9.1% of patients with cirrhosis, 6.5% of patients with congested/fatty liver and 4.7% of patients with normal liver parenchyma ($p < 0.001$).

Discussion

This multi-institutional ACS NSQIP study includes data from 3,530 patients who had liver resection after implementation of targeted hepatectomy data collection. Current analysis demonstrates that both cirrhosis and MELD score have significant

Table 1
Clinical characteristics of study population.

	Normal (n = 1887)	Congested/Fatty (n = 975)	Cirrhotic (n = 668)	P = value
Age	58 (47–68)	60 (50–68)	63 (57–70)	<0.001
Male sex	793 (42.0)	499 (51.2)	486 (72.8)	<0.001
ASA				<0.001
Class 1	84 (4.5)	3 (0.3)	3 (0.4)	
Class 2	517 (27.5)	203 (20.9)	126 (18.9)	
Class 3	1179 (62.7)	688 (70.8)	464 (69.6)	
Class 4/5	100 (5.3)	78 (8.0)	74 (11.1)	
Hepatectomy				<0.001
Major	700 (37.1)	370 (37.9)	193 (28.9)	
Minor	1187 (62.9)	605 (62.1)	475 (71.1)	
MELD	7 (6-8)	7 (6-8)	7 (6-9)	<0.001
PHLF	88 (4.7)	63 (6.5)	61 (9.1)	<0.001
Any morbidity	298 (15.8)	205 (21.0)	157 (23.5)	<0.001
Mortality	21 (1.1)	17 (1.7)	26 (3.9)	<0.001
ACS NSQIP Prob of Morbidity	14.6 (11.1–20.3)	17.5 (13.2–23.9)	18.2 (13.6–24.2)	<0.001
ACS NSQIP Prob of Mortality	0.8 (0.3–1.8)	1.1 (0.5–2.5)	1.1 (0.5–2.1)	<0.001

ACS NSQIP: American College of Surgeons National Surgical Quality Improvement Program; ASA: American Society of Anesthesiologists; MELD: Model for End-Stage Liver Disease; PHLF: posthepatectomy liver failure.

independent negative impact on postoperative mortality. In addition, MELD score has significant independent impact on postoperative morbidity. Historically, characterization of liver texture was not included in ACS NSQIP and has also not been a part of any other national registry database. As such, previous studies evaluating potential associations between cirrhosis, MELD, and postoperative outcomes have relied on institutional data collection. A linked ACS NSQIP – institutional study published prior to introduction of targeted hepatectomy variable collection did not demonstrate statistically significant association between cirrhosis and mortality.[4] This previously published study was limited by either 1) lack of statistical power to establish association, or 2) was limited to a single institution selection bias whereas only a small proportion of patients with cirrhosis were selected for resection.

With improvements in patient selection, operative technique, and perioperative care, the overall rate of postoperative mortality among patients selected for liver resection in the current era is low. A number of single institution studies have reported no cases of postoperative deaths after liver resection in patients with and without cirrhosis.[14,15] Multi-institutional and registry studies with broad inclusion criteria report a higher proportion of postoperative mortality, ranging from 1 to 5%, dependent on patients age, diagnosis, and other patient-specific comorbid criteria.[16–19] Postoperative mortality is even greater for patients with perihilar cholangiocarcinoma selected for combined liver and bile duct resection and ranges between 8 and 10% at high-volume referral centers.[20–22] As such evaluation of clinical factors associated with mortality after liver resection remains important.

Association between cirrhosis and postoperative outcomes has been established extensively in both liver-specific and non-liver operations. Mortality is higher in patients with cirrhosis selected for bariatric surgery,[23] cardiac surgery,[24] and general non-hepatic abdominal surgery.[25] Similarly associations between MELD score in patients with cirrhosis and mortality among non-liver surgery patients have also been established.[26] One of the most interesting findings of this study describes associations between MELD and mortality even among patients selected for liver resection who did not have cirrhosis. While interquartile range for MELD was higher among patients with cirrhosis, 75% of patients with normal liver parenchyma had MELD scores between 6 and 8. Associations between greater MELD and outcome measures (including mortality and morbidity) are likely a factor of associated preoperative end organ insufficiency such as chronic kidney disease, coagulopathy, or liver dysfunction (possibly from inadequate biliary drainage). Despite robust ACS NSQIP data collection, with only 1.1% postoperative mortality among patients with normal liver parenchyma, the specifics of possible effects of individual underlying preoperative comorbid conditions on MELD among patients with normal liver would be difficult to establish and would not alter model outcomes.

The ACS NSQIP probabilities of mortality and morbidity are particularly useful in establishment of baseline preoperative risk and statistical adjustment within multivariable models. These probabilities are calculated by ACS NSQIP for each individual patient using hierarchical regression models that account for multiple patient-level factors[12] and allow for robust and clinically meaningful adjustment for preoperative covariates such as age, ASA class, functional status, extent of resection, and others. As can be seen from the magnitude of effect (represented by odds ratios), these probabilities have significant statistical weight in both mortality and morbidity models. However, even after adjustment for ACS NSQIP probability of mortality, both cirrhosis and MELD score were independently associated with mortality in patients selected for liver resection and MELD score was independently associated with morbidity. Importantly, neither of these two variables are included among the patient-level factors used in calculating ACS NSQIP probabilities of mortality and morbidity.

Although this study describes robust analyses demonstrating statistically significant and clinically meaningful effects or MELD score and cirrhosis on patient outcomes, two potential limitations are notable. First, only patients selected for liver resection are included in the study. As surgical outcomes after liver resection continue to improve, robust series testing associations between patient-specific covariates and mortality and morbidity will require greater number of patients. Second, only patients with reported liver texture were included in this study. Statistical imputation of liver texture using other existing patient factors would not meaningful discern between patient populations, would predispose to

Table 2
Multivariable mortality model.

	OR	95% CI	p-value
Liver Parenchyma			
Normal	Ref		
Congested/Fatty	1.20	0.59–2.46	0.615
Cirrhotic	2.24	1.16–4.34	0.016
MELD (increase = 1)	1.10	1.03–1.18	0.007
ACS NSQIP probability of mortality (incr = 0.1)	2.37	1.84–3.07	<0.001

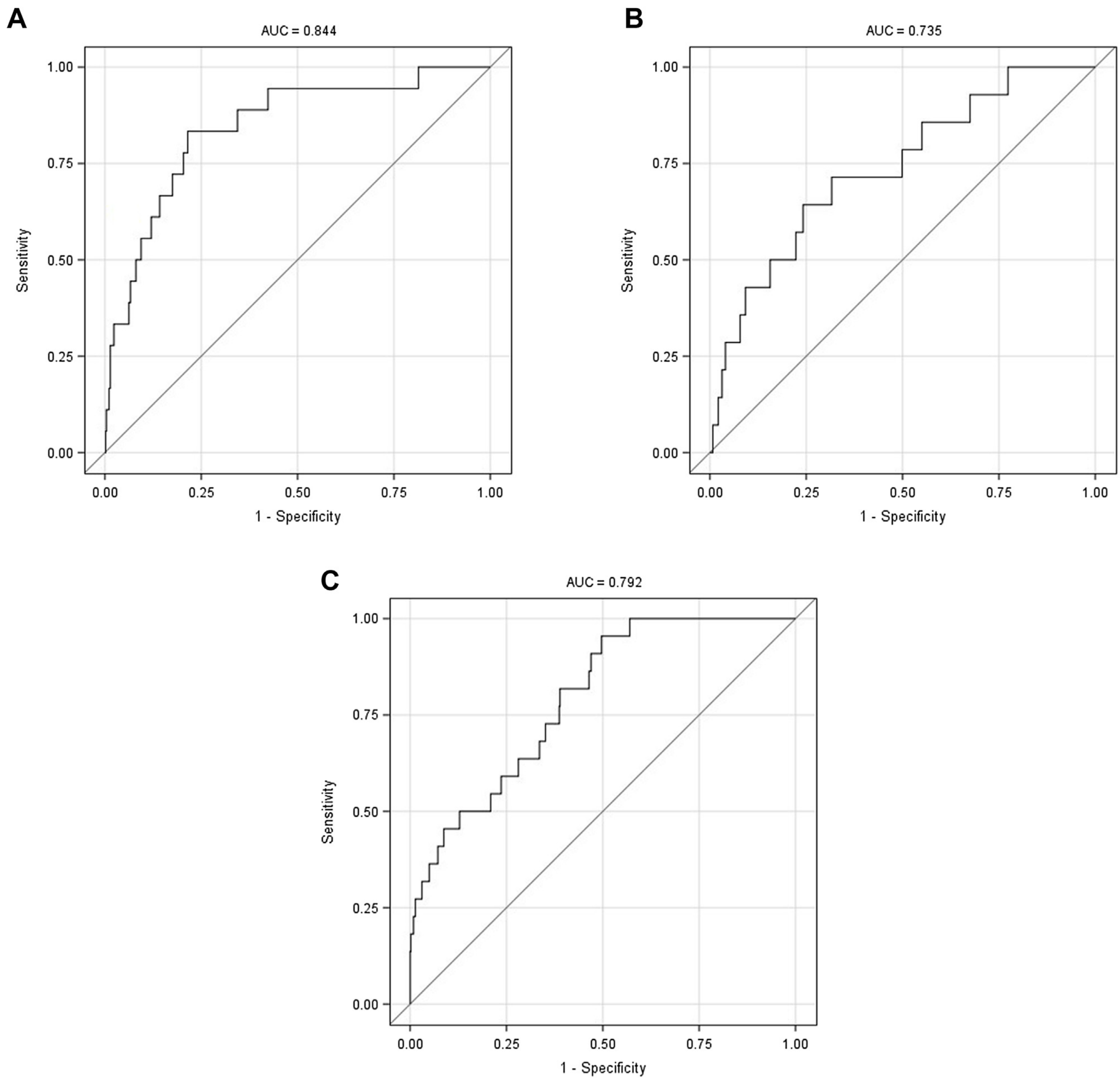

Fig. 1. ROC curves derived from the mortality models for patients with normal liver (1A), congested/fatty liver (1B), and cirrhotic liver (1C).

information bias and was not used in this study. Despite these limitations, present data demonstrate significant independent associations between cirrhosis and mortality and increasing MELD and mortality in patients selected for liver resection.

In conclusion, both cirrhosis and MELD score are associated with postoperative mortality after liver resection. MELD score is also associated with postoperative morbidity. MELD score could be used to estimate postoperative risk in patients with and without cirrhosis.

Table 3
Multivariable morbidity model.

	OR	95% CI	p-value
Liver Parenchyma			
Normal	Ref		
Congested/Fatty	1.20	0.96–1.50	0.108
Cirrhotic	1.19	0.94–1.52	0.150
MELD (increase = 1)	1.04	1.002–1.08	0.038
ACS NSQIP probability of morbidity (incr = 1)	3.08	2.56–3.71	<0.001

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References

1. Abdalla EK, Denys A, Chevalier P, Nemr RA, Vauthey J-N. Total and segmental liver volume variations: implications for liver surgery. *Surgery*. 2004

Apr;135(4):404–410.

2. Ferrero A, Viganò L, Polastri R, et al. Postoperative liver dysfunction and future remnant liver: where is the limit? Results of a prospective study. *World J Surg*. 2007 Aug;31(8):1643–1651.
3. Regimbeau J-M, Kianmanesh R, Farges O, Dondero F, Sauvanet A, Belghiti J. Extent of liver resection influences the outcome in patients with cirrhosis and small hepatocellular carcinoma. *Surgery*. 2002 Mar;131(3):311–317.
4. Zaydfudim VM, Kerwin MJ, Turrentine FE, Bauer TW, Adams RB, Stukenborg GJ. The impact of chronic liver disease on the risk assessment of ACS NSQIP morbidity and mortality after hepatic resection. *Surgery*. 2016 May;159(5):1308–1315.
5. Cucchetti A, Ercolani G, Vivarelli M, et al. Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. *Liver Transplant*. 2006 Jun;12(6):966–971.
6. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology*. 2003 Jan;124(1):91–96.
7. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*. 2000 Apr;31(4):864–871.
8. Teh SH, Christein J, Donohue J, et al. Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: model of End-Stage Liver Disease (MELD) score predicts perioperative mortality. *J Gastrointest Surg*. 2005 Dec;9(9):1207–1215. discussion 1215.
9. Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. *Ann Surg*. 2006 Mar;243(3):373–379.
10. Teh SH, Sheppard BC, Schwartz J, Orloff SL. Model for End-stage Liver Disease score fails to predict perioperative outcome after hepatic resection for hepatocellular carcinoma in patients without cirrhosis. *Am J Surg*. 2008 May;195(5):697–701.
11. Biggins SW, Kim WR, Terrault NA, et al. Evidence-based incorporation of serum sodium concentration into MELD. *Gastroenterology*. 2006 May;130(6):1652–1660.
12. Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *J Am Coll Surg*. 2013 Nov;217(5):833–842.e1.
13. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the international study group of liver surgery (ISGLS). *Surgery*. 2011 May;149(5):713–724.
14. Torzilli G, Makuuchi M, Inoue K, et al. No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? A prospective analysis of our approach. *Arch Surg*. 1999 Sep;134(9):984–992.
15. Fan ST, Lo CM, Liu CL, et al. Hepatectomy for hepatocellular carcinoma: toward zero hospital deaths. *Ann Surg*. 1999 Mar;229(3):322–330.
16. Aloia TA, Fahy BN, Fischer CP, et al. Predicting poor outcome following hepatectomy: analysis of 2313 hepatectomies in the NSQIP database. *HPB*. 2009 Sep;11(6):510–515.
17. Tzeng C-WD, Cooper AB, Vauthey J-N, Curley SA, Aloia TA. Predictors of morbidity and mortality after hepatectomy in elderly patients: analysis of 7621 NSQIP patients. *HPB*. 2014 May;16(5):459–468.
18. Newhook TE, LaPar DJ, Lindberg JM, Bauer TW, Adams RB, Zaydfudim VM. Morbidity and mortality of hepatectomy for benign liver tumors. *Am J Surg*. 2016 Jan;211(1):102–108.
19. Zaydfudim VM, Stukenborg GJ. Effects of patient factors on inpatient mortality after complex liver, pancreatic and gastric resections. *BJS Open*. 2017 Dec;1(6):191–201.
20. Matsuo K, Rocha FG, Ito K, et al. The Blumgart preoperative staging system for hilar cholangiocarcinoma: analysis of resectability and outcomes in 380 patients. *J Am Coll Surg*. 2012 Sep;215(3):343–355.
21. Wiggers JK, Groot Koerkamp B, Cieslak KP, et al. Postoperative mortality after liver resection for perihilar cholangiocarcinoma: development of a risk score and importance of biliary drainage of the future liver remnant. *J Am Coll Surg*. 2016 Apr 5;223(2):321–331.e1.
22. Franken LC, Schreuder AM, Roos E, et al. Morbidity and mortality after major liver resection in patients with perihilar cholangiocarcinoma: a systematic review and meta-analysis. *Surgery*. 2019 May;165(5):918–928.
23. Jan A, Narwaria M, Mahawar KK. A systematic review of bariatric surgery in patients with liver cirrhosis. *Obes Surg*. 2015 Aug;25(8):1518–1526.
24. Jacob KA, Hjortnaes J, Kranenburg G, de Heer F, Kluin J. Mortality after cardiac surgery in patients with liver cirrhosis classified by the Child-Pugh score. *Interact Cardiovasc Thorac Surg*. 2015 Apr;20(4):520–530.
25. Hickman L, Tanner L, Christein J, Vickers S. Non-hepatic abdominal surgery in patients with cirrhotic liver disease. *J Gastrointest Surg*. 2019 Mar;23(3):634–642.
26. Northup PG, Wanamaker RC, Lee VD, Adams RB, Berg CL. Model for End-Stage Liver Disease (MELD) predicts nontransplant surgical mortality in patients with cirrhosis. *Ann Surg*. 2005 Aug;242(2):244–251.