A simple scoring system to estimate perioperative mortality following liver resection for primary liver malignancy—the Hepatectomy Risk Score (HeRS)

Dimitrios Moris[#], Brian I. Shaw[#], Cecilia Ong, Ashton Connor, Mariya L. Samoylova, Samuel J. Kesseli, Nader Abraham, Jared Gloria, Robin Schmitz, Zachary W. Fitch, Bryan M. Clary, Andrew S. Barbas

Department of Surgery, Duke University Medical Center, Durham, NC, USA

Contributions: (I) Conception and design: D Moris, BI Shaw, C Ong, A Connor, BM Clary, AS Barbas; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Dimitrios Moris MD, MSc, PhD, DUMC. Department of Surgery, Duke University Medical Center, Durham, NC 27710, USA. Email: dimitrios.moris@duke.edu.

Background: Selection of the optimal treatment modality for primary liver cancers remains complex, balancing patient condition, liver function, and extent of disease. In individuals with preserved liver function, liver resection remains the primary approach for treatment with curative intent but may be associated with significant mortality. The purpose of this study was to establish a simple scoring system based on Model for End-stage Liver Disease (MELD) and extent of resection to guide risk assessment for liver resections.

Methods: The 2005–2015 NSQIP database was queried for patients undergoing liver resection for primary liver malignancy. We first developed a model that incorporated the extent of resection (1 point for major hepatectomy) and a MELD-Na score category of low (MELD-Na =6, 1 point), medium (MELD-Na =7–10, 2 points) or high (MELD-Na >10, 3 points) with a score range of 1–4, called the Hepatic Resection Risk Score (HeRS). We tested the predictive value of this model on the dataset using logistic regression. We next developed an optimal multivariable model using backwards sequential selection of variables under logistic regression. We performed K-fold cross validation on both models. Receiver operating characteristics were plotted and the optimal sensitivity and specificity for each model were calculated to obtain positive and negative predictive values.

Results: A total of 4,510 patients were included. HeRS was associated with increased odds of 30-day mortality [HeRS =2: OR =3.23 (1.16–8.99), P=0.025; HeRS =3: OR =6.54 (2.39–17.90), P<0.001; HeRS =4: OR =13.69 (4.90–38.22), P<0.001]. The AUC for this model was 0.66. The AUC for the optimal multivariable model was higher at 0.76. Under K-fold cross validation, the positive predictive value (PPV) and negative predictive value (NPV) of these two models were similar at PPV =6.4% and NPV =97.7% for the HeRS only model and PPV =8.4% and NPV =98.1% for the optimal multivariable model.

Conclusions: The HeRS offers a simple heuristic for estimating 30-day mortality after resection of primary liver malignancy. More complicated models offer better performance but at the expense of being more difficult to integrate into clinical practice.

Keywords: Hepatocellular carcinoma (HCC); cholangiocarcinoma; liver resection; Model for End-stage Liver Disease (MELD); outcomes

Introduction

Primary liver cancer is currently the second most common cause of cancer-related death worldwide (1,2). It demonstrates the greatest increase in both mortality and morbidity in the United States during the past 2 decades (3,4). Primary liver cancer comprises a heterogeneous group of malignant tumors with different histological features and prognosis that range from hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) to mixed hepatocellular cholangiocarcinoma (HCC-CCA), fibrolamellar HCC (FLC), and the pediatric neoplasm hepatoblastoma (5).

HCC accounts for over 70% of primary liver malignancies with over 750,000 new cases and nearly equal number of cancer-related deaths each year (6,7). Surgery, in the form of either liver resection or transplantation, remains the mainstay of treatment for patients with resectable HCC (8-10). Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver malignancy and its incidence and mortality are increasing worldwide and in the US (11-13). Surgical resection is the mainstay for treatment of resectable iCCA (14) with liver transplantation remaining controversial (15).

Safety of elective hepatectomies for primary liver malignancies in patients with or without cirrhosis has increased significantly during the last decades but mortality of such procedures is still estimated between 3% and 14% (16,17). A key determinant of "resectability" is the anticipated volume of the future liver remnant; for patients without hepatic dysfunction, a remnant volume of >25% or >250 mL/m^2 is typically recommended (18,19). However, patients with pre-existing liver disease have less hepatic reserve, and prediction of postoperative liver decompensation remains difficult (20). Post-hepatectomy liver failure is the most severe complication, with a reported mortality as high as 50% (21,22). Moreover, it is the leading cause of prolonged hospitalization, increased costs, and poor long-term outcomes in patients undergoing surgical procedure.

The Model for End-stage Liver Disease (MELD) has been shown to reflect hepatocellular reserve and mortality risk in patients with cirrhosis and has been used to stratify end-stage liver disease patients for liver transplantation organ allocation (23,24). In patients with cirrhosis, the preoperative MELD score has been shown to be a strong predictor of both perioperative mortality and long-term survival for patients undergoing hepatic resection for HCC (21,25).

In the current era of multidisciplinary patient care, selection of the optimal treatment modality for primary liver cancers remains complex, balancing patient condition, liver function, and extent of disease. To date, several systems have been proposed to inform prognosis and guide treatment decisions for patients with HCC (26-29). Of interest, there are only a few prognostic tools available for patients with ICC (30,31). In addition, most of these tools rely on factors known only after surgery as only a few models have utilized exclusively preoperative factors to stratify early and late postoperative outcomes (31,32).

The purpose of this study was to establish a simple scoring system based on MELD sodium (MELD-Na), which is currently used for organ allocation in liver transplantation, and extent of resection to guide risk assessment for liver resection of primary liver malignancies. We present the following article in accordance with the STARD reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2020.03.12/rc).

Methods

Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board (IRB#Pro00103324) and informed consent was taken from individual participants where applicable.

Cohort definition

Data from the National Surgical Quality Improvement Project (NSQIP) were extracted for the years 2005–2015. Patients with a post-operative diagnosis of code 155.* ("Malignant neoplasm of liver and intrahepatic bile ducts"), who underwent one of four well defined procedures (CPT 47120—hepatectomy, resection of liver; partial lobectomy, CPT 47125—hepatectomy, resection of liver, total left lobectomy; CPT 47122—hepatectomy, resection of the liver, trisegmentectomy; and 47130—hepatectomy, resection of the liver, total right lobectomy) were included in our analysis. Patients who were missing outcome data, missing lab values needed to calculate the MELD-Na in the 30 days prior to surgery (INR, Total Bilirubin, Creatinine, and Sodium), who underwent emergency surgery, or were missing variables needed for our multivariable analyses were excluded.

Of note, a substantial portion of patients in this cohort were coded with a diagnosis code of 155.1, which is
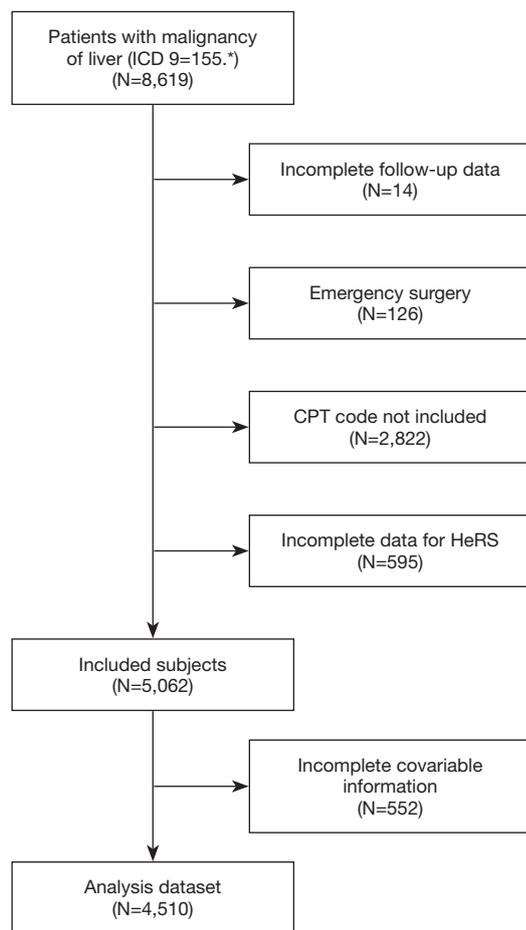
Figure 1 Patient flow chart. Patients were initially identified by a post-operative diagnosis of liver cancer as defined by ICD-9 code 155. All 155 subcodes were included. Patients were excluded if they did not undergo one of four known hepatectomy codes (CPT =47120, 4712, 47122, and 47130). Patients were also excluded if they did not have data for any one of the following variables: age, sex, BMI, ASA class >2, functional status other than independent, smoker within 1 year of surgery, dyspnea (on exertion or at rest), ascites at the time of surgery, weight loss >10% in last 6 months, platelet count <100, albumin at time of surgery, history of COPD, history of HTN, and history of insulin dependent diabetes. CPT, current procedural terminology.

specifically "Malignant neoplasm of the intrahepatic bile ducts" (n=984, 21%; Table S1). Because cholangiocarcinoma is thought to be different than HCC, a sensitivity analysis for all below analyses using only those patients with a diagnosis of 155.0 ("Malignant neoplasm of the liver, primary"), which is essentially HCC only, was also completed.

Development of HeRS

The HeRS was defined *a priori* to include MELD-Na and the extent of hepatic resection. Hepatic resection was considered "major" if the patient underwent a procedure associated with CPT codes 47122 (trisegmentectomy) or 47130 (right hepatectomy); "minor" hepatectomies were defined by CPT codes 47120 (partial hepatectomy) or 47125 (left hepatectomy). The MELD-Na was defined *a priori* as low if it was 6 (no evidence of disease). Patients with abnormal MELD-Na scores (7 or greater) were stratified into two groups for optimal sensitivity and specificity for mortality using the Youden index (33). A cutoff of 10 was determined using this method. A patient was assigned a score of 1 or 0 for a major or a minor hepatectomy, respectively, and a score of 1 (MELD-Na =6), 2 (MELD-Na 7–10), or 3 (MELD-Na >10) for their MELD-Na category. The HeRS was calculated by first determining the patients MELD-Na categorization (1, 2, or 3) and then adding one if the patient had undergone a major hepatectomy. The minimum value for the HeRS was defined as 1 and the maximum 4.

Statistical analysis

Descriptive statistics were summarized for the cohort. 30-day mortality was compared among HeRS groups using chi-squared. Simple logistic regression and Firth logistic regression for 30-day mortality was performed with HeRS as the predictor variable and receiver operating characteristics (ROC) curves plotted. In order to interrogate what residual risk was not captured by the HeRS, other presumed predictors of perioperative mortality were included in a multivariable logistic regression model with the HeRS. Sequential stepwise backwards selection with a cutoff of P<0.05 was performed to find the optimal model which included the HeRS. K-fold cross validation was used to avoid overfitting when determining receiver operating characteristics of both the univariate model with HeRS alone and the optimal multivariable model. The Youden index was again used to define the cutoff for maximum sensitivity and specificity of this model to determine positive- and negative-predictive value (PPV and NPV). All statistical analyses were performed in STATA 15 (College Station, TX).

Results

Cohort definition and demographics

A total of 8,619 patients were identified in the NSQIP

Table 1 Patient demographics and characteristics

Variables	HeRS =1	HeRS =2	HeRS =3	HeRS =4	Total cohort
Total, n [%]	476 [10]	1,877 [42]	1,676 [37]	481 [11]	4,510
Age, years, median [Q1–Q3]	63 [55–70]	64 [56–71]	64 [57–72]	66 [57–73]	64 [56–71]
Sex, female, n [%]	268 [56]	744 [40]	568 [34]	151 [31]	1731 [38]
Race, n [%]					
American Indian or Alaskan Native	1 [1]	6 [1]	8 [1]	2 [1]	17 [1]
Asian	44 [9]	183 [10]	136 [8]	38 [8]	401 [9]
Black or African American	40 [8]	189 [10]	160 [9]	35 [8]	424 [9]
Native Hawaiian or Pacific Islander	1 [1]	9 [1]	3 [1]	3 [1]	16 [1]
White	321 [67]	1,246 [66]	1,141 [68]	320 [66]	3,028 [67]
Other	28 [6]	106 [6]	82 [5]	31 [6]	247 [6]
Unknown	41 [9]	138 [7]	146 [9]	52 [11]	377 [8]
BMI, median [Q1–Q3]	27 [24–31]	27 [24–31]	27 [24–31]	26 [23–30]	27 [24–31]
ASA class ≥3, n [%]	348 [73]	1,474 [79]	1,365 [81]	405 [82]	3,592 [80]
Dependent functional status, n [%]	1 [1]	24 [1]	21 [1]	7 [1]	53 [1]
Smoker, w/in 1 year, n [%]	102 [21]	410 [22]	367 [22]	88 [18]	967 [21]
Dyspnea on exertion or at rest, n [%]	41 [9]	153 [8]	153 [9]	33 [7]	380 [8]
Ascites, n [%]	0 [0]	32 [2]	43 [3]	19 [4]	94 [2]
>10% weight loss, n [%]	17 [4]	68 [4]	118 [7]	62 [13]	265 [6]
Platelets <100, n [%]	7 [1]	105 [6]	102 [6]	15 [3]	229 [5]
Pre-op albumin, median [Q1–Q3]	4.2 [3.8–4.5]	4 [3.7–4.3]	3.9 [3.4–4.2]	3.6 [3.1–4]	3.9 [3.5–4.3]
Steroid use, n [%]	15 [3]	46 [3]	55 [3]	13 [3]	129 [3]
History of COPD, n [%]	25 [5]	105 [6]	96 [6]	24 [5]	250 [6]
Hypertension, n [%]	237 [50]	1072 [57]	1018 [61]	295 [61]	2622 [58]
Insulin dependent diabetes, n [%]	22 [5]	139 [7]	188 [11]	48 [10]	397 [9]
Bleeding disorder history, n [%]	13 [3]	77 [4]	86 [5]	28 [6]	204 [5]
Operation type, n [%]					
Minor hepatectomy/lobectomy	476 [100]#	1,646 [88]	778 [46]	0 [0]	2,900 [64]
Major hepatectomy	0 [0]	231 [12]	898 [51]	481 [100]&	1610 [36]
MELD-Na, median [Q1–Q3]	6*	8 [7–9]	10 [8–13]	13 [12–16]	9 [7–11]
Mortality, n [%]	4 [1]	50 [3]	88 [5]	50 [10]	192 [4]

*, by definition, MELD-Na must be 6 for HRRS to equal 1; #, by definition, all HRRS 1 had to have a minor hepatectomy; &, by definition, all HRRS 4 had to have a major hepatectomy. BMI, basic metabolic index; COPD, chronic obstructive pulmonary disease; HeRS, hepatectomy risk score; MELD-NA, Model for End-stage Liver Disease- sodium; ASA, American society of Anesthesiologists.
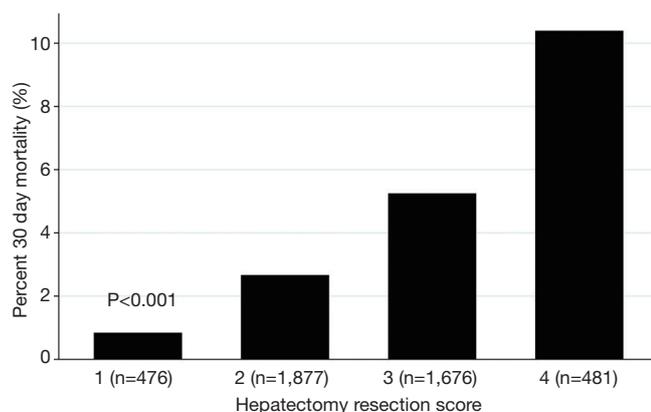
Figure 2 The 30-day mortality by HeRS. The 30-day mortality for each HeRS is plotted as bars. The distribution of mortality was significantly varied by Chi^2 test (P<0.001). The absolute number of patients in each group is shown below each bar. HeRS, hepatectomy risk score.

Table 2 HeRS only logistic regression model

Variable	OR estimate (95% CI)	P value
Intercept	0.008 (0.003–0.023)	<0.001
HeRS =1	1.0 (reference)	N/A
HeRS =2	3.23 (1.16–8.99)	0.025
HeRS =3	6.54 (2.39–17.9)	<0.001
HeRS =4	13.69 (4.90–382)	<0.001

OR estimates for the HeRS only model. HeRS, hepatectomy risk score; CI, confidence interval; N/A, not applicable; OR, odds ratio.

database between 2005 and 2015 who met inclusion criteria. After exclusions, our total study cohort was 4,510 (*Figure 1*). Patient demographics and characteristics are summarized in *Table 1*. Overall, the cohort was elderly, with a median age of 64 (Q1–Q3: 56–71), mostly male (72%), and mostly white (67%). The median MELD-Na was 9 (Q1–Q3: 7–11) and most patients underwent a minor hepatectomy (64%). The postoperative 30-day mortality varied significantly by HeRS as demonstrated in *Figure 2*.

Mortality prediction using HeRS alone

To determine how well the HeRS score predicts postoperative mortality, we performed a logistic regression on mortality using the HeRS as the predictor. Given that the HeRS yields 4 categories, we obtained 3 odds ratios (with HeRS score of 1 as the reference category) for HeRS =2 [OR =3.23 (1.16–8.99), P=0.025], HeRS =3 [OR =6.54 (2.39–17.9), P<0.001], and HeRS =4 [OR =13.69 (4.90–38.22), P<0.001] (*Table 2*). ROC analysis yielded an AUC of 0.66 (*Figure 3A*). To ensure the analysis was not biased due to the relatively low incidence of mortality, we performed Firth Logistic Regression, which yielded a similar OR for each HeRS level (Table S2).

Multivariable model for mortality prediction

In order to investigate the performance of a model utilizing the HeRS alone to a more comprehensive model, multivariable logistic regression analysis was performed
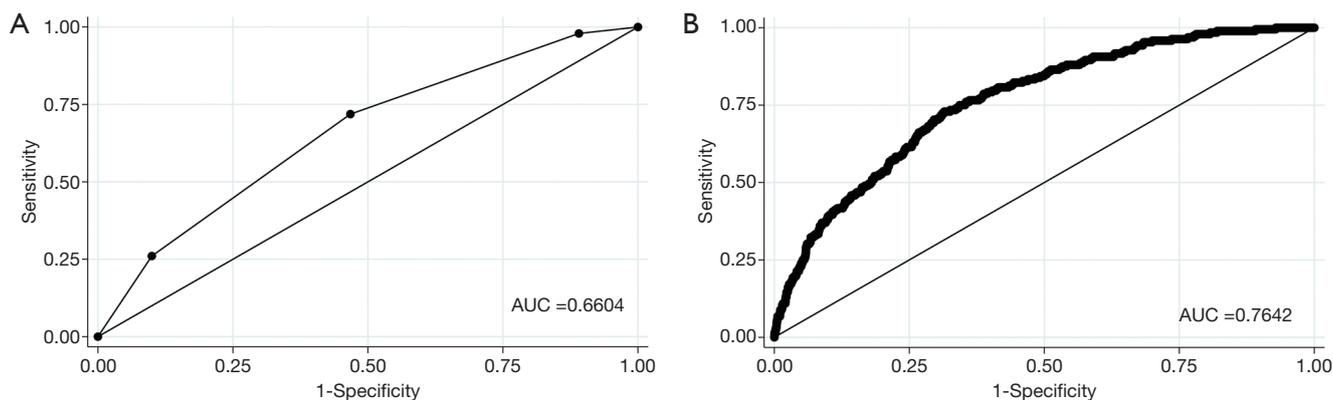

Figure 3 (A) HeRS only ROC curve; (B) ROC curve for optimal multivariable model. HeRS, hepatectomy risk score; ROC, receiver operating characteristics; AUC, area under the curve.

including the following variables: age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) class, functional status, smoking status, dyspnea (on exertion or at rest), presence of ascites, weight loss >10% in last 6 months, platelet count <100, albumin at time of surgery, steroid use at time of surgery, history of chronic obstructive pulmonary

Table 3 Optimal multivariable model

Variable	OR estimate (95% CI)	P value
Intercept	0.006 (0.001–0.036)	<0.001
HeRS =1	1.0 (reference)	N/A
HeRS =2	2.30 (0.82–6.46)	0.113
HeRS =3	3.87 (1.40–10.73)	<0.009
HeRS =4	7.25 (2.55–20.65)	<0.001
Age (years)	1.03 (1.02–1.05)	<0.001
Sex (1= male, 0= female)	1.50 (1.07–2.10)	0.018
ASA class (1= greater than 2; 0= less than 2)	2.38 (1.33–4.24)	0.003
Functional status (1= dependent, 0= independent)	2.91 (1.33–6.38)	0.008
Platelet count <100 (1= yes, 0= no)	3.32 (2.14–5.16)	<0.001
Albumin at time of surgery (g/dL)	0.53 (0.41–0.68)	<0.001

OR estimates for the optimal multivariable model. HeRS, hepatectomy risk score; CI, confidence interval; ASA, American Society of Anesthesiologists; N/A, not applicable; OR, odds ratio.

disease (COPD), history of hypertension, history of insulin dependent diabetes, and history of a bleeding disorder. Description of the full multivariable model and ROC curve can be found in Table S3 and Figure S1. Sequential backwards selection eventually yielded an optimal formula with the variables of age, sex, ASA class, functional status, platelets <100, and pre-operative albumin as well as the HeRS. Of note, though one level of the HeRS was not statistically significantly different than the reference value (2 points *vs.* 1 point) it was included in the final model for completeness (*Table 3*). A ROC curve was generated with an AUC of 0.76 (*Figure 3B*).

K-fold cross validation

In order to ensure that the model was not overfit, we re-performed the analysis using k-fold cross validation with 5 groups. Under the HeRS only condition, the AUC was 0.64. Under the optimal multivariable logistic regression, the AUC was 0.75. The PPV for the HeRS only model was 6.4% and the NPV was 97.7%. For the optimal multivariable model, the PPV was 8.4% and NPV was 98.2% (*Table 4*).

Sensitivity analysis with HCC only

Given concerns that intrahepatic cholangiocarcinoma is biologically differently than HCC, we compared mortality at a given HeRS between the two groups. There were no significant differences in mortality between patients with HCC versus those with intrahepatic cholangiocarcinoma

Table 4 K-Fold Cross Validation for HeRS-only model, full multivariable model, and optimal multivariable model

Formula	AUC	PPV (%)	NPV (%)
Full dataset			
HeRS only	0.64	6.4	97.7
Full multivariable	0.74	8.3	97.9
Optimal multivariable	0.75	8.4	98.2
Liver parenchymal primary neoplasm only dataset			
HeRS only	0.62	5.5	97.7
Full multivariable	0.71	6.4	97.8
Optimal multivariable	0.74	7.7	98.1

AUC, PPV and NPV for test sets after n=5 K-fold cross validation. PPV and NPV were optimized by the Youden Index for the test set. All values are reported for the test set. AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; HeRS, hepatectomy risk score.

(Figure S2). However, we still performed a sensitivity analysis where we repeated our analysis on only those patients with HCC. This is summarized in Tables S4-S6 and Figure S3. Finally, we performed K-fold cross validation on this subset of patients and obtained the results presented in *Table 4*. Ultimately, the estimates were similar with an AUC of 0.62 for the HeRS only and 0.74 for the optimal multivariable model.

Discussion

Preoperative assessment of liver function and prediction of postoperative functional reserve are of paramount importance to minimize surgical risk of liver resection (34). In the present study, we propose a simple model, the HeRS that is significantly correlated with 30-day mortality and has fair test characteristics in spite of its simplicity. Though a more complex multivariable model performs better in our analysis, the relative infrequency of mortality within 30 days leads to similar PPV and NPV for the HeRS and more complex multivariate model. Therefore, we argue that the simplicity of the HeRS is a benefit, not a detriment, and can serve as a useful heuristic for determining the risk for early postoperative mortality. In practice, clinicians continue to use the Child-Turcotte-Pugh (CTP) score to determine eligibility for hepatic resection in spite of a lack of validation (35). This suggests that simpler scoring systems have intrinsic properties that are useful to practicing clinicians, such as the HeRS introduced here.

It was recently shown that for patients with HCC and a MELD score >10, liver transplantation offered superior survival. This benefit was eliminated in cases of major vascular involvement or in patients with MELD scores <10 (36). Specifically, patients with a MELD score of ≥10 had a 47% 5-year survival after resection, compared to patients with a MELD score less than 10 having a 5-year survival of 67% (P<0.0001). Mean 5-year LT benefit was –4.50 months (95% CI: –4.73 to –4.27) for patients with a MELD score of <10, and 0.81 months (95% CI 0.58 to 1.04) for those with a MELD score of ≥10 (36). Similarly, a recent study demonstrated that a MELD score >7.24 can be an important predictor of post-hepatectomy mortality or metastasis and may prompt a detailed assessment with the provided risk calculator (37).

To date, there are multiple models predicting 30-day mortality after HCC resection (38-41). Also, there are several studies comparing MELD score alone to novel scoring systems as predictors of outcomes after liver resection in patients with HCC. A large Korean study evaluated platelet-albumin-bilirubin (PALBI) and albumin-bilirubin (ALBI) versus CTP class and MELD score to predict overall survival. The PALBI grade had a higher AUC than the CTP class, MELD score, or ALBI grade (overall AUC: 0.675 *vs.* 0.633, 0.645, and 0.642, respectively; P<0.001) (42). In the same setting, Mai *et al.* showed that preoperative aspartate aminotransferase-to-platelet-ratio index (APRI) score predicted post-hepatectomy liver failure significantly more accurate than Child-Pugh, MELD, or ALBI scores. The optimal sensitivity and specificity of the APRI score for predicting post-hepatectomy liver failure were 72.2% and 68.0%, respectively (43). In the setting of iCCA there are no previous studies using MELD score as predictor of early postoperative mortality after resection. Tsilimigras *et al.* recently showed that higher ALBI grade was related with prolonged length-of-stay, increased perioperative transfusion needs and higher early mortality after liver resection for iCCA (44). Also Zhang *et al.* demonstrated that major complications and early postoperative death were more common after a major versus minor hepatic resection (both P<0.01) (14).

There are some strengths and limitations of this study that deserve mention. The primary strength of the analysis is the large sample size derived from a large cohort of centers in the United States, which likely makes these results generalizable in different practice settings. A significant limitation of the NSQIP database, however, is the lack of more detailed clinical information, such as degree of cirrhosis, extent of operative resection, and postoperative pathologic analysis. We have only analyzed the performance of the HeRS in one dataset and therefore it would benefit from external validation in a separate dataset. Additionally, the primary outcome of postoperative mortality within 30 days is relatively rare, which makes logistic regression subject to bias; however, we addressed this by including analysis with Firth Logistic regression, which accounts for small event counts (45).

In conclusion, we present a simple and reliable score to assist with risk assessment in patients being considered for liver resection for primary liver cancer. Though the HeRS does not achieve the same sensitivity and specificity as some contemporary multivariable models, it is intuitive, simple to calculate, and performs favorably when compared to multiple previously published models. Ease of integration into clinical practice should be considered when developing predictive models.

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Table S1 Distribution of cases by post-operative diagnosis

Post-op diagnosis	HeRS =1	HeRS =2	HeRS =3	HeRS =4	Total cohort
Total, n [%]	476 [11]	1,877 [42]	1,676 [37]	481 [10]	4,510
155.0, n [%]	313 [66]	1,360 [72]	1,134 [67]	274 [57]	3,081 [68]
155.1, n [%]	96 [20]	312 [17]	382 [23]	166 [34]	956 [21]
155.2, n [%]	40 [8]	132 [7]	97 [6]	26 [5]	295 [7]
155 (unspecified), n [%]	27 [6]	73 [4]	63 [4]	15 [3]	178 [4]

Diagnosis codes are specified as follows: 155.0, malignant neoplasm of liver, primary; 155.1, malignant neoplasm of intrahepatic bile ducts; 155.2, malignant neoplasm of liver, not specified as primary or secondary. HeRS, hepatectomy risk score.

Table S2 Firth logistic regression for HeRS only model

Variable	OR estimate (95% CI)	P value
Intercept	0.009 (0.004–0.024)	<0.001
HeRS =1	1.0 (reference)	N/A
HeRS =2	2.90 (1.10–7.65)	0.031
HeRS =3	5.85 (2.25–15.16)	<0.001
HeRS =4	12.29 (4.64–32.51)	<0.001

HeRS, hepatectomy risk score; OR, odds ratio; CI, confidence interval; N/A, not applicable.
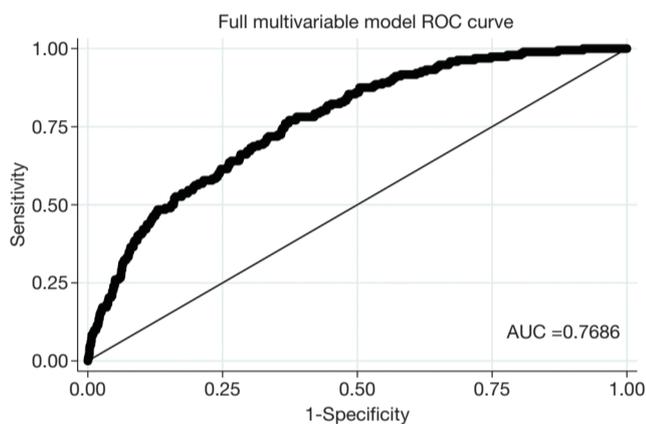

Figure S1 Full multivariable model ROC curve.
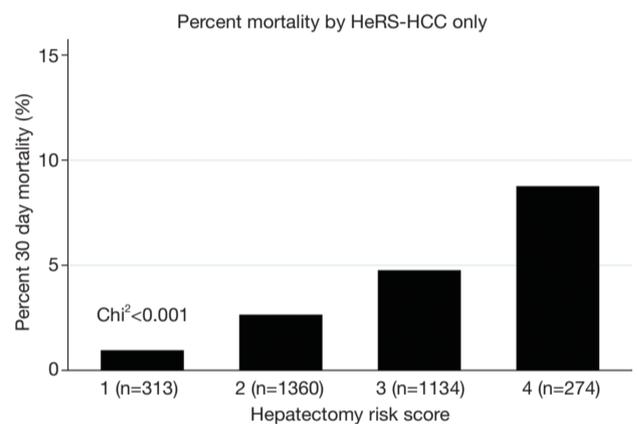

Figure S2 Mortality by HeRS for primary liver parenchymal and biliary ductal intrahepatic neoplasms.

Table S3 Full multivariable logistic regression

Variable	OR estimate (95% CI)	P value
Intercept	0.003 (0.0004–0.021)	<0.001
HeRS =1	1.0 (reference)	N/A
HeRS =2	2.35 (0.84–6.60)	0.104
HeRS =3	3.93 (1.42–10.90)	<0.009
HeRS =4	7.51 (2.63–21.44)	<0.001
Age (in years)	1.03 (1.02–1.05)	<0.001
Sex (1= male, 0= female)	1.55 (1.10–2.18)	0.012
BMI	1.02 (0.99–1.05)	0.150
ASA class (1= greater than 2; 0= less than 2)	2.27 (1.26–4.07)	0.006
Functional status (1= dependent, 0= independent)	2.88 (1.30–6.37)	0.009
Smoker within 1 year of surgery (1= yes, 0= no)	1.18 (0.80–1.72)	0.407
Dyspnea at rest or on exertion (1= yes, 0= no)	1.08 (0.66–1.78)	0.747
Ascites at time of surgery (1= yes, 0= no)	0.613 (0.25–1.51)	0.284
Weight Loss >10% in past 6 months (1= yes, 0= no)	1.43 (0.85–2.40)	0.177
Platelet count <100 (1= yes, 0= no)	3.58 (2.26–5.66)	<0.001
Albumin at time of surgery (g/dL)	0.53 (0.41–0.69)	<0.001
Steroid use at time of surgery (1= yes, 0= no)	2.02 (1.02–4.02)	0.045
History of COPD (1= yes, 0= no)	0.93 (0.50–1.74)	0.823
History of hypertension (1= yes, 0= no)	0.91 (0.64–1.28)	0.575
History of insulin dependent diabetes (1= yes, 0= no)	1.14 (0.73–1.80)	0.560
History of bleeding disorder	0.93 (0.51–1.70)	0.811

Odds ratio (OR) estimates for the Full Multivariable Model. HeRS, hepatectomy risk score; CI, confidence interval; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; BMI, basic metabolic index; N/A, not applicable.

Table S4 HeRS only logistic regression-neoplasm of primary liver parenchyma only analysis (n=3,081)

Variable	OR estimate (95% CI)	P value
Intercept	0.01 (0.003–0.03)	<0.001
HeRS =1	1.0 (reference)	N/A
HeRS =2	2.8 (0.86–9.18)	0.087
HeRS =3	5.17 (1.60–16.63)	0.006
HeRS =4	9.92 (2.95–33.32)	<0.001

OR, odds ratio; HeRS, hepatectomy risk score; CI, confidence interval; N/A, not applicable.

**Table S5** Full multivariable model for neoplasm of primary liver parenchyma only analysis

Variable	OR estimate (95% CI)	P value
Intercept	0.008 (0.006–0.10)	<0.001
HeRS =1	1.0 (reference)	N/A
HeRS =2	1.90(0.57–6.30)	0.293
HeRS =3	2.66 (0.81–8.75)	0.11
HeRS =4	4.5 (1.31–15.8)	0.02
Age (in years)	1.03 (1.01–1.06)	0.002
Sex (1=male, 0=female)	1.72 (1.08–2.76)	0.023
BMI	1.01 (0.98–1.05)	0.400
ASA class (1= greater than 2; 0= less than 2)	2.12 (1.00–4.47)	0.049
Functional status (1= dependent, 0= independent)	2.75 (0.98–7.70)	0.054
Smoker within 1 year of surgery (1= yes, 0= no)	1.20 (0.75–1.92)	0.447
Dyspnea at rest or on exertion (1= yes, 0= no)	0.96 (0.50–1.83)	0.905
Ascites at time of surgery (1= yes, 0= no)	0.40 (0.11–1.41)	0.153
Weight loss >10% in past 6 months (1= yes, 0= no)	1.32 (0.65–2.69)	0.445
Platelet count <100 (1= yes, 0= no)	3.53 (2.06–6.03)	<0.001
Albumin at time of surgery (g/dL)	0.43 (0.31–0.61)	<0.001
Steroid use at time of surgery (1= yes, 0= no)	1.65 (0.63–4.32)	0.304
History of COPD (1= yes, 0= no)	1.01 (0.46–2.23)	0.982
History of hypertension (1= yes, 0= no)	0.92 (0.59–1.43)	0.710
History of insulin dependent diabetes (1= yes, 0= no)	1.29 (0.75–2.21)	0.353
History of bleeding disorder	0.96 (0.47–1.98)	0.922

OR, odds ratio; HeRS, hepatectomy risk score; CI, confidence interval; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; BMI, basic metabolic index; N/A, not applicable.

Table S6 Optimal multivariable model for neoplasm of primary liver parenchyma only analysis

Variable	OR estimate (95% CI)	P value
Intercept	0.013 (0.001–0.12)	<0.001
HeRS =1	1.0 (reference)	N/A
HeRS =2	1.90 (0.58–6.29)	0.291
HeRS =3	2.66 (0.81–8.745)	0.106
HeRS =4	4.59 (1.33–15.84)	0.016
Age (in years)	1.03 (1.01–1.05)	0.001
Sex (1= male, 0= female)	1.65 (1.04–2.63)	0.033
ASA class (1= greater than 2; 0= less than 2)	2.26 (1.08–4.71)	0.030
Platelet count <100 (1= yes, 0= no)	3.25 (1.94–5.42)	<0.001
Albumin at time of surgery (g/dL)	0.43 (0.31–0.60)	<0.001

OR, odds ratio; HeRS, hepatectomy risk score; CI, confidence interval; ASA, American Society of Anesthesiologists; N/A, not applicable.
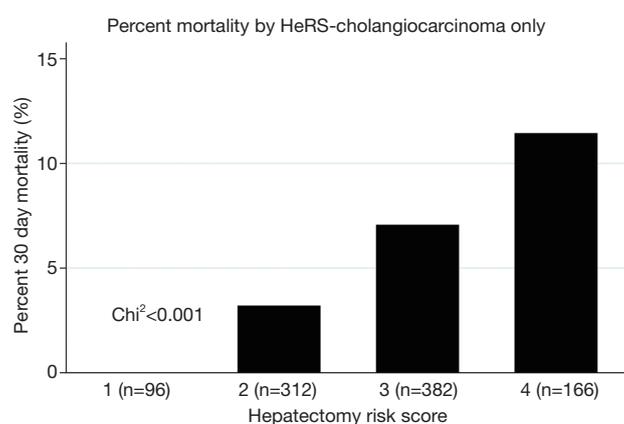
Figure S3 ROC curves for neoplasm of primary liver parenchyma only analysis.