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Hierarchic Interaction of Factors Associated With Liver Decompensation After Resection for Hepatocellular Carcinoma

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IMPORTANCE Liver resection is the treatment of choice for hepatocellular carcinoma (HCC) in well-compensated liver cirrhosis. Postoperative liver decompensation (LD) is the most representative and least predictable cause of morbidity and mortality.

OBJECTIVES To determine the hierarchy and interaction of factors associated with the risk for LD and to define applicable risk classes among surgical candidates.

DESIGN, SETTING, AND PARTICIPANTS This retrospective review collected data from 543 patients with chronic liver disease who underwent hepatic resection for HCC from January 1, 2000, through December 31, 2013, in a tertiary comprehensive cancer center. Final follow-up was completed on January 31, 2015, and data were assessed from February 1 to 28, 2015.

MAJOR OUTCOMES AND MEASURES Preoperative prognostic factors and risk stratification for postoperative LD. Multivariate logistic regression was performed, and the independent risk factors for LD were included in a recursive partitioning analysis model. Results were validated by means of 10-fold cross-validation.

RESULTS The analysis included 543 patients, of whom 411 (75.7%) were male, 132 (24.3%) were female, and the median age was 68 (interquartile range, 62-73) years. An independent association with LD was found for major hepatectomy (odds ratio [OR], 2.41; 95% CI, 1.17-4.30; *P* = .01), portal hypertension (OR, 2.20; 95% CI, 1.13-4.30; *P* = .01), and Model for End-Stage Liver Disease (MELD) score greater than 9 (OR, 2.26; 95% CI, 1.10-4.58; *P* = .02). Recursive partitioning analysis confirmed portal hypertension as the most important factor (OR, 2.99; 95% CI, 1.93-4.62; *P* < .001), followed by extension of hepatectomy with (OR, 2.76; 95% CI, 1.85-4.77; *P* = .03) and without (OR, 2.98; 95% CI, 1.97-4.52; *P* < .001) portal hypertension, and MELD score (OR, 1.79; 95% CI, 1.23-2.13; *P* < .001). Low-risk patients (LD rate, 4.9% [11 of 226]) without portal hypertension underwent minor resection with a MELD score of 9 or less; intermediate-risk patients (LD rate, 28.6% [85 of 297]) had no portal hypertension and underwent major resections or, in case of minor resections, had portal hypertension or a MELD score greater than 9; and high-risk patients (LD rate, 60.0% [12 of 20]) underwent major resection with portal hypertension. Risk-class progression paralleled median length of stay (7, 8, and 11 days, respectively; *P* < .001) and liver-related mortality (4.4% [10 of 226], 9.0% [27 of 297], and 25.0% [5 of 20], respectively; *P* = .001). A 10-fold cross-validation of the model resulted in a C index of 0.78 (95% CI, 0.74-0.82) and an overall error rate of 0.06.

CONCLUSIONS AND RELEVANCE The risk for postoperative LD after resection for HCC in chronic liver disease is associated with preoperative hierarchic interaction of portal hypertension, planned extension of hepatectomy, and the MELD score.

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Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality and is currently the main cause of death in patients with cirrhosis.[1] Liver resection is the first therapeutic option in patients with early tumors and well-preserved liver function.[2-4] In the past 2 decades, a significant improvement in the perioperative management of HCC has occurred, with a parallel reduction of resection-related mortality from 10% and 20% to a near-zero rate in referral centers.[3,5,6] Despite this reduction, liver resection for HCC is still burdened by potentially life-threatening complications, among which liver decompensation (LD) remains the most fearsome and least effectively treated.

Liver decompensation is in fact the leading cause of prolonged hospitalization, increased costs, and poor long-term outcomes in patients undergoing surgical procedures.[7] Surgery should be offered only after an objective quantification of risks for LD,[8,9] accurately balanced with the expected outcomes of nonsurgical therapeutic options.

All the reported scores used to describe the functional hepatic reserve and therefore the risk for LD have proved to be suboptimal in the surgical setting. Major guidelines do not recommend liver resection in patients with impaired liver function (Child-Pugh classification other than A) and portal hypertension.[2,3] However, recent studies[10-13] demonstrated that liver resection can be safely performed in patients with 1 or more variables adversely associated with postoperative LD. The composite Model for End-Stage Liver Disease (MELD) score (range, 6 to 40, with higher scores indicating worse liver function and increased risk for mortality) is associated with liver failure and mortality after liver resection for HCC.[14-16] In Japan, the indocyanine green (ICG) clearance test is recommended for stratification of postoperative LD risk and decision making about the extent of resection,[17,18] whereas in western countries few data confirm its value in selecting candidates for liver resection.

Despite recognition of these and other crucial factors, whether a hierarchic interaction exists among recognized perioperative variables associated with LD is poorly understood. The aims of this study are to evaluate the importance of preoperative determinants of LD and their hierarchic interaction and to define applicable risk classes in a large series of liver resections for HCC.

Key Points

Question Is resection of hepatocellular carcinoma (HCC) associated with an appreciable risk for liver decompensation (LD)?

Findings In this study of 543 patients undergoing liver resection for HCC, the hierarchy of preoperative variables associated with the risk for postoperative LD was determined using logistic regression and recursive partitioning analysis. Portal hypertension, extent of hepatectomy, and Model for End-Stage Liver Disease score—in this order—informed a prognostication tree that identified 3 risk classes significantly associated with postoperative hepatic failure, length of hospital stay, and liver-related mortality.

Meaning A model built on easy-to-access preoperative variables may contribute to balanced decisions concerning liver resection for HCC.

Methods

Patients and Data Collection

Patients who underwent curative liver resection for HCC from January 1, 2000, through December 31, 2013, at the Liver Transplantation and Hepato-Biliopancreatic Surgery Unit of the National Cancer Institute of Milan were identified from a prospectively collected database. The institutional review board of the National Cancer Institute of Milan approved the study and waived the need for informed consent after anonymization of the data.

Preoperative Assessment and Surgical Indication

Preoperative investigations included performance status evaluation, physical examination, upper endoscopy, biochemical liver function tests, ICG retention test at 15 minutes (ICG-R15), Child-Pugh classification, serum level of α-fetoprotein, abdominal ultrasonography, and contrast-enhanced computed tomography and/or magnetic resonance imaging. Clinically relevant portal hypertension was defined by the presence of at least F1 esophageal varices (ie, small and straight) at endoscopy or by the coexistence of a low platelet count ($<100 \times 10^3/\mu L$ [to convert to 10^9 per liter, multiply by 1.0]) and splenomegaly (>120 mm diameter).[19] Major resections were defined as the removal of 3 or more adjacent segments.[20]

Liver resections were performed within conventional guidelines (ie, resection of a single nodule of HCC) but also beyond recommendations when surgical tumor removal was judged to give a higher benefit compared with other available options such as liver transplantation, locoregional therapies, or systemic therapies (eg, sorafenib tosylate). All indications for surgery were discussed within a multidisciplinary HCC board (including D.C., C.S., S.B., and V.M.).

Perioperative Management

Low-molecular-weight heparin was given as antithrombotic prophylaxis and cefazolin sodium as antibiotic prophylaxis. After abdominal exploration, intraoperative ultrasonography was used to rule out the presence of additional lesions, assess resectability, and guide resection. In all cases, parenchymal transection was conducted with the use of an ultrasonic dissector (CUSA [cavitron ultrasonic surgical aspirator]; Valleylab Inc) and irrigated monopolar or bipolar forceps or an irrigated bipolar coagulator (Aquamantys; Medtronic Inc). The Pringle maneuver was not used routinely but only on demand during the parenchymal transection. Intraoperatively the central venous pressure was targeted below 5 mm Hg.

Complications and LD Assessment

Postoperative complications were graded using the Dindo-Clavien classification (DCC) (range, 1 to 5, with higher scores indicating a greater affect on the clinical course and 5 indicating a fatal complication).[21] Postsurgical LD was defined as previously reported[22] by the occurrence of any of the following liver-related complications graded as DCC greater than 1 during hospitalization: (1) refractory ascites causing a delay in the removal of surgical drains and/or requiring paracentesis (grade 2 or grade 3a complication); (2) increase of bilirubin levels to more than 3 mg/dL (to convert to micromoles per liter, multiply by 17.104); (3) alteration of coagulation factors requiring fresh-frozen plasma infusion with an international normalized ratio of more than 1.50 (in the absence of serum bilirubin levels >12 mg/dL); and (4) renal impairment, defined as a serum urea nitrogen level of more than 2.00 g/L (to convert to millimoles per liter, multiply by 0.357) and/or increase of serum creatinine level to more than 2 mg/dL (to convert to micromoles per liter, multiply by 88.4) requiring dopamine hydrochloride or terlipressin therapy or dialysis. Grade 1 liver-related complications did not qualify for LD because of their irrelevant effect on the postoperative course.

Follow-up

Patients were followed up on an outpatient basis every 4 months for the first 2 years and every 6 months thereafter. Tumor recurrences and liver status were monitored and patients were treated according to disease presentation. All events with a major impact (eg, cancer recurrence, LD, death) were recorded. Follow-up for this study was completed on January 1, 2015.

Statistical Analysis

Data were analyzed from February 1 to 28, 2015. Conventional statistics were used for patient characteristics with median and interquartile range (IQR) for continuous variables and absolute frequencies and percentages for categorical data. Liver decompensation, as defined above, was the main outcome measure. Preoperative factors with a potential prognostic effect on LD were analyzed first by means of logistic regression test. We performed multivariate analysis, including those variables with $P < .05$. To rank the relevance of each predictor variable and obviate overfitting, we estimated random-forest (RF) variable importance measures through permutation of variable values.[23] Random-forest variable importance was defined as the mean decrease in accuracy consequent to the random permutation of each variable value. The resulting variables associated with LD were then tested by recursive partitioning analysis, which aimed at identification of risk groups for the clinical point of interest based on maximization of logistic regression or log-rank test.[24] This identification is made through classification trees built by means of the ctree function (http://cran.r-project.org/web/packages/party/index.html). A minimum of 20 observations in a node was required to enable further splitting with a mincriterion requiring $P < .05$ to avoid pruning at each node.[25] Once we identified risk groups, the model compared differences in LD rate, liver-related mortality, and length of stay (LOS) by means of χ^2 and log-rank tests. A 10-fold cross-validated Harrell C index (with 95% CIs) and classification error rate were calculated to validate the model (eMethods in the Supplement). We performed the analysis using R software (Foundation for Statistical Computing).

Results

Patient Characteristics and Intraoperative Variables

The study population included 543 patients, of whom 411 (75.7%) were male, 132 (24.3%) were female, and the median age was 68 (IQR 62-73) years (**Table 1**). Most patients presented with cirrhosis related to hepatitis C virus (287 [52.8%]) and a well-preserved liver function indicated by Child-Pugh classification of A (508 [93.6%]) and a median MELD score of 8 (IQR 7-10). Portal hypertension was present in 163 cases (30.0%) and median ICG-R15 was 16% (IQR, 7%-23%). Tumor staging included Barcelona Clinic Liver Cancer stage 0 in 76 patients (14.0%), A in 381 (70.2%), B in 64 (11.8%), and C in 22 (4.1%). Four hundred eight patients (75.1%) met the Milan criteria (single tumor ≤5 cm; maximum of 3 tumors <3 cm).[26] Tumors presented as single nodule in 420 cases (77.3%) and the median size of the largest nodule was 37 (IQR 24-57) mm.

Major resections were performed for 105 patients (19.3%) and minor resections for 438 (80.7%); 485 resections (89.3%) were anatomical whereas 58 (10.7%) were nonanatomical. Median operative time was 210 (IQR, 180-270) minutes; blood loss was no greater than 100 mL in 376 cases (69.2%), 100 to 500 mL in 83 cases (15.3%), 500 to 1000 mL in 42 cases (7.7%), and greater than 1000 mL in 42 cases (7.7%). Red blood cell transfusions were administered in 64 cases (11.8%).

Postoperative Course and Patient Outcome

Table 2 summarizes the main variables related to the postoperative course. The overall postoperative complications in the entire series occurred in 265 patients (48.8%), with 11 (2.0%) undergoing a second operation. Liver-related complications were observed in 181 patients (33.3%), of whom 73 did not require any specific treatment (DCC grade 1), and 108 (19.9%) had potentially life-threatening complications and were considered within the LD category. Most cases of LD were DCC grade 2 (101 patients [93.5%] with LD), whereas only one grade 3 complication occurred in a patient requiring surgery for wound dehiscence caused by ascites and one grade 4 complication required intensive care unit management and transjugular intrahepatic portosystemic shunt positioning. Of the 101 patients with grade 2 LD, 16 (15.8%) presented with an isolated deviation of laboratory findings (coagulation and bilirubin levels), whereas 85 (84.2%) presented with ascites as an isolated or associated condition. In this subgroup of patients, postoperative ascites was mild in 33 cases (output, <500 mL/d), moderate in 45 cases (output 500-1000 mL/d), and severe in 7 cases (>1000 mL/d).

Five patients (0.9%) died, all of whom had LD. One of these patients underwent urgent liver transplant on postoperative day 29 to correct LD but died of sepsis 180 days after the first operation. The other 4 patients were not listed for transplantation because of advanced age and comorbidities and died 32, 36, 69, and 183 days after surgery.

Risk Stratification for LD

Univariate and multivariate analysis of preoperative factors potentially associated with LD are reported in **Table 3**.

Table 1. General Characteristics of 543 Patients With Chronic Liver Disease Who Underwent Elective Liver Resection for Hepatocellular Carcinoma

Characteristic	No. (%) of Patients (N = 543)[a]
Age, median (IQR), y	68 (62-73)
Sex	
Male	411 (75.7)
Female	132 (24.3)
Child-Pugh classification	
A	508 (93.6)
B	35 (6.4)
MELD score, median (IQR)[b]	8 (7-10)
Cause of cirrhosis	
HCV	287 (52.8)
HBV	115 (21.2)
Other	141 (26.0)
Portal hypertension[c]	163 (30.0)
AST level, median (IQR), UI/L	42 (27-77)
ALT level, median (IQR), UI/L	44 (27-78)
Total bilirubin level, median (IQR), mg/dL	0.91 (0.69-1.28)
Sodium level, median (IQR), mEq/L	139 (137-140)
Creatinine level, median (IQR), mg/dL	0.9 (0.79-1)
Albumin level, median (IQR), g/dL	4.16 (3.8-4.46)
ICG-R15, median (IQR), %	16 (7-23)
BCLC stage	
0	76 (14.0)
A	381 (70.2)
B	64 (11.8)
C	22 (4.1)
Milan criteria	
Met	408 (75.1)
Did not meet	135 (24.9)
Bilobar disease	52 (9.6)
Single nodule	420 (77.3)
Multiple tumors	123 (22.7)
Diameter of the largest nodule, median (IQR), mm	37 (24-57)
AFP level, median (IQR), ng/mL	12 (4-87)
Presurgical treatments	120 (22.1)
TACE	74 (13.6)
Radiofrequency ablation	34 (6.3)
Liver resection	12 (2.2)
Operative time, median (IQR), min	210 (180-270)
Extension of hepatectomy	
Major	105 (19.3)
Minor	438 (80.7)
Type of resection	
Anatomical	485 (89.3)
Nonanatomical	58 (10.7)
Intermittent hilar clamping	34 (6.3)

(continued)

Table 1. General Characteristics of 543 Patients With Chronic Liver Disease Who Underwent Elective Liver Resection for Hepatocellular Carcinoma (continued)

Characteristic	No. (%) of Patients (N = 543)[a]
Blood loss, mL	
<100	376 (69.2)
>100 and <500	83 (15.3)
>500 and <1000	42 (7.7)
>1000	42 (7.7)
Intraoperative RBC transfusions	64 (11.8)

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; ICG-R15, indocyanine green retention test at 15 minutes; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; RBC, red blood cell; TACE, transarterial chemoembolization.

SI conversion factors: To convert albumin to grams per liter, multiply by 10; ALT and AST to microkatals per liter, multiply by 0.0167; bilirubin to micromoles per liter, multiply by 17.104; creatinine to micromoles per liter, multiply by 88.4; sodium to millimoles per liter, multiply by 1.0.

[a] Percentages have been rounded and may not total 100.

[b] Scores range from 6 to 40, with higher scores indicating worse liver function and increased risk for mortality.

[c] Defined by the presence of esophageal varices or the coexistence of low platelet count (<100 × 10^3/mm^3 [to convert to 10^9 per liter, multiply by 1.0]) and splenomegaly (>120 mm diameter).[19]

Univariate analysis showed that Child-Pugh classification greater than B7 (odds ratio [OR], 3.34; 95% CI, 1.62-6.75; *P* < .001), serum aspartate aminotransferase (OR, 2.47; 95% CI, 1.56-3.93; *P* < .001) and alanine aminotransferase (OR, 1.87; 95% CI, 1.18-2.95; *P* = .007) levels greater than 60 UI/L (to convert to microkatals per liter, multiply by 0.0167), ICG-R15 greater than 20% (OR, 2.03; 95% CI, 1.18-3.46; *P* = .009), MELD score greater than 9 (OR, 2.51; 95% CI, 1.52-4.11; *P* < .001), portal hypertension (OR, 2.99; 95% CI, 1.93-4.62; *P* < .001), and major hepatectomy (OR, 2.98; 95% CI, 1.85-4.77; *P* < .001) were associated with the likelihood of developing postresection LD. At the multivariate analysis, major hepatectomy (OR, 2.41; 95% CI, 1.17-4.30; *P* = .01), portal hypertension (OR, 2.20; 95% CI, 1.13-4.30; *P* = .01), and MELD score greater than 9 (OR, 2.26; 95% CI, 1.10-4.58; *P* = .02) remained the sole factors independently associated with LD. This finding was confirmed in the RF model (**Figure 1**) in which the decrease in accuracy identified the same 3 variables as significantly weighing more than any others in determining the association with LD.

The recursive partitioning analysis demonstrated that the risk for LD is stratified on the basis of the presence of portal hypertension (OR, 2.99; 95% CI, 1.93-4.62; *P* < .001), extension of hepatectomy in the absence (OR, 2.98; 95% CI, 1.97-4.52; *P* < .001) and the presence (OR, 2.76; 95% CI, 1.85-4.77; *P* = .03) of portal hypertension, and the MELD score (OR, 1.79; 95% CI, 1.23-2.13; *P* < .001), namely, the same factors hierarchically superior to the others in association with LD in the RF model. Accordingly, the whole series of liver resection could be split in the following 3 risk classes: low

Table 2. Postoperative Complications

Variable	No./Total No. of Patients (%)[a]
Overall complications	265/543 (48.8)
Complication grade[b]	
1	77/265 (29.1)
2	161/265 (60.8)
3a	7/265 (2.6)
3b	11/265 (4.2)
4	4/265 (1.5)
5	5/265 (1.9)
30-d mortality	0
In-hospital mortality	5/543 (0.9)
Second laparotomy	11/543 (2.0)
Type of complication	
Liver-related	181/543 (33.3)
Pulmonary	67/543 (12.3)
Cardiologic	11/543 (2.0)
Biliary fistula	8/543 (1.5)
Intrabdominal abscess	7/543 (1.3)
Renal	5/543 (0.9)
Neurologic	2/543 (0.4)
Other	43/543 (7.9)
LD	108/543 (19.9)
LD grade[c]	
2	101/108 (93.5)
3	1/108 (0.9)
4	1/108 (0.9)
5	5/108 (4.6)

Abbreviation: LD, liver decompensation.

[a] Percentages have been rounded and may not total 100.

[b] Complications are graded according to Dindo-Clavien classification.[21]

[c] Defined by the occurrence of any of the following liver-related complications with a grade higher than 1: (1) refractory ascites causing a delay in the removal of surgical drains and/or requiring paracentesis; (2) increase of bilirubin levels to more than 3 mg/dL (to convert to micromoles per liter, multiply by 17.104); (3) alteration of coagulation factors requiring fresh-frozen plasma infusion with an international normalized ratio of more than 1.50; and (4) renal impairment.

risk, with 11 of 226 (4.9%); intermediate risk, with 85 of 297 (28.6%); and high risk, with 12 of 20 (60.0%) (P < .001).

The hierarchic interaction of prognostic variables for LD as determined by recursive partitioning analysis is summarized in **Figure 2**. In the presence of portal hypertension, the risk for LD depends only on the extension of the hepatectomy, and the minor vs major extent of hepatectomy separated the likelihood of LD into an intermediate- vs high-risk class. In the intermediate-risk class, 2 other subgroups converged, including patients without portal hypertension undergoing a major hepatectomy and patients who underwent minor resections with a MELD score greater than 9. The low-risk class consisted of patients without portal hypertension who underwent a minor hepatectomy with a MELD score of 9 or less.

Median LOS in the entire population was 8 days (95% CI, 6-10 days); when stratified according to the low-, intermediate-, and high-risk groups, median LOS was 7 (95% CI, 7-7) days, 8 (95% CI, 8-9) days, and 11 (95% CI, 9-16) days, respectively (P < .001). At a median follow-up of 66 (95% CI, 56-73) months, the effect of liver-related complications on mortality at any time after surgery (ie, after exclusion of cancer-related death) was 10 of 226 (4.4%) in the low-risk patients, 27 of 297 (9.0%) in the intermediate-risk patients, and 5 of 20 (25.0%) in the high-risk patients (P = .001).

The model performance was distinguished by a classification error rate of 0.06 (eTable in the Supplement) and a C index of 0.76 (95% CI, 0.74-0.79). The model was validated by means of 10-fold cross-validation (eFigure in the Supplement) that resulted in a C index of 0.78 (95% CI, 0.74-0.82) and in an overall error rate of 0.06.

Discussion

The decision to refer a patient with HCC for liver resection derives from a balance between benefits and risks of the procedure with respect to other therapeutic options such as liver transplant or locoregional or systemic treatments. In the decision-making process, the expected long-term oncologic outcomes of tumor removal should be balanced with the expected short-term risks for mortality and morbidity. For short-term outcomes, locoregional treatments in properly selected patients bear a very low risk for postprocedural liver-related complications, whereas in liver surgery most of the efforts have sought to identify—and therefore to exclude—the least favorable candidates for liver resection.[22,27-29] Nevertheless, a precise quantification of the risk for postoperative LD is still suboptimal,[10-12,14-16] and none of the proposed algorithms has entered routine surgical practice.

The present study demonstrates that the most important factor associated with LD after liver resection for HCC is portal hypertension, followed by extension of hepatectomy and the MELD score. By assessing these simple factors, which are all available preoperatively, an accurate map of the risk for LD occurrence can be depicted, thus providing a useful tool for clinical decision making (Figure 2). The recursive partitioning analysis made on a sample of 543 resections for HCC demonstrates that in the presence of portal hypertension, the risk for LD depends mostly on the extension of the liver resection being a major hepatectomy at a 60.0% risk for postoperative LD. In the hierarchic stratification of risk factors, the extension of liver resection is followed by the MELD score with a cutoff of 9, and in patients lacking all risk factors the risk for LD is 4.9%.

Such a relatively simple scheme built on a partition-tree model may simplify decision making and offer an objective tool for preoperative short- and long-term prognosis for physicians and patients. The 3 preoperatively defined classes have a significant effect on outcome, because patients at low, intermediate, and high risk for LD have a corresponding significant lengthening of LOS (7, 8, and 11 days, respectively; P < .001) and an increase in liver-related mortality (4.4%, 9.0%, and 25.0%, respectively; P = .001). We found a slight difference between the classification tree and the RF analysis in terms of hierarchy of the analyzed factors, owing to different

Table 3. Factors Associated With Postoperative Liver Decompensation at Univariate and Multivariate Analysis[a]

	Univariate Analysis		Multivariate Analysis	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age >65 y	0.83 (0.54-1.28)	.41	NA	NA
Male sex	0.89 (0.72-0.95)	.75	NA	NA
HBV (vs HCV)	1.05 (0.61-1.76)	.50	NA	NA
Child-Pugh classification>B7	3.34 (1.62-6.75)	<.001	1.38 (0.40-4.69)	.59
Laboratory findings				
Sodium level >140 mEq/L	0.57 (0.24-1.18)	.16	NA	NA
AST level >60 UI/L	2.47 (1.56-3.93)	<.001	2.16 (0.89-5.40)	.09
ALT level >60 UI/L	1.87 (1.18-2.95)	.007	1.20 (0.47-2.90)	.97
ICG-R15				
>14%	1.58 (0.94-2.69)	.08	NA	NA
>20%	2.03 (1.18-3.46)	.009	NA	NA
MELD score >9[b]	2.51 (1.52-4.11)	<.001	2.26 (1.10-4.58)	.02
Portal hypertension	2.99 (1.93-4.62)	<.001	2.20 (1.13-4.30)	.01
Major hepatectomy	2.98 (1.85-4.77)	<.001	2.41 (1.17-4.30)	.01
Presurgical treatments	1.75 (1.12-2.88)	.06	NA	NA

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; ICG-R15, indocyanine green retention test at 15 minutes; MELD, Model for End-Stage Liver Disease; OR, odds ratio.

SI conversion factors: To convert ALT and AST to microkatals per liter, multiply by 0.0167; sodium to millimoles per liter, multiply by 1.0.

[a] Oncological variables were not considered because they did not influence postoperative liver decompensation.

[b] Scores range from 6 to 40, with higher scores indicating worse liver function and increased risk for mortality.

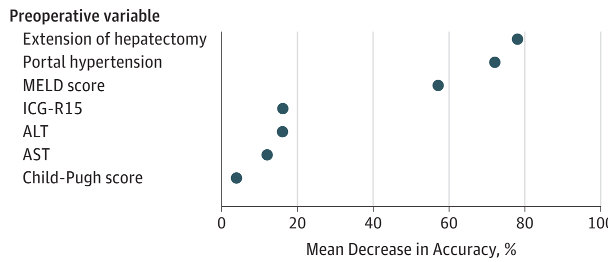
computational characteristics between the 2 methods (eMethods in the Supplement). In fact, owing to random sampling in the selection of the variables, the RF analysis is unable to provide univocal classification trees and is therefore used for validation purposes only after tree generation by means of the recursive partitioning method.

The in-hospital mortality of the whole series was 0.9% (5 patients), which is consistent with the expected outcomes in a tertiary care setting. Despite all efforts, LD remained a frequent complication, with an incidence of 19.9%, and the only complication leading to death.

Reliable tools for the assessment of LD in patients with chronic liver disease undergoing liver resection for HCC could reduce or even eliminate postsurgical mortality. A significant help in reducing the incidence of postsurgical LD is conceivable with the current introduction of new direct antivirals against hepatitis C virus, which represents about half of the observed population undergoing surgery for HCC (Table 1). A low hepatitis C virus load at surgery is associated with better long-term survival in patients undergoing resection of HCC,[30] and in the postoperative setting future use of direct antivirals will help to convert decompensated into compensated cirrhosis,[31] therefore reducing LD incidence within each of the identified risk classes.

Several different definitions of LD have been proposed, which explain the wide range of LD rates reported in various studies.[32] Liver decompensation can be defined on the basis of postoperative variables, such as the 50-50 criteria[27] (prothrombin time <50% with total bilirubin level >50 µmol/L on postoperative day 5) or according to the International Study Group of Liver Surgery recommendations[32] (ie, increased international normalized ratio and concomitant hyperbilirubinemia on or after postoperative day 5). These and other criteria[33] are based on abnormal laboratory findings, but definitions of LD exclusively based on serologic markers of liver function may have a relatively low clinical relevance.[34] That relevance raises questions on the utility of such scores in daily practice in consideration of the inherently multifactorial nature of postoperative LD.

Figure 1. Different Weight of Preoperative Variables Associated With Postoperative Liver Decompensation (LD) According to the Random-Forest Model

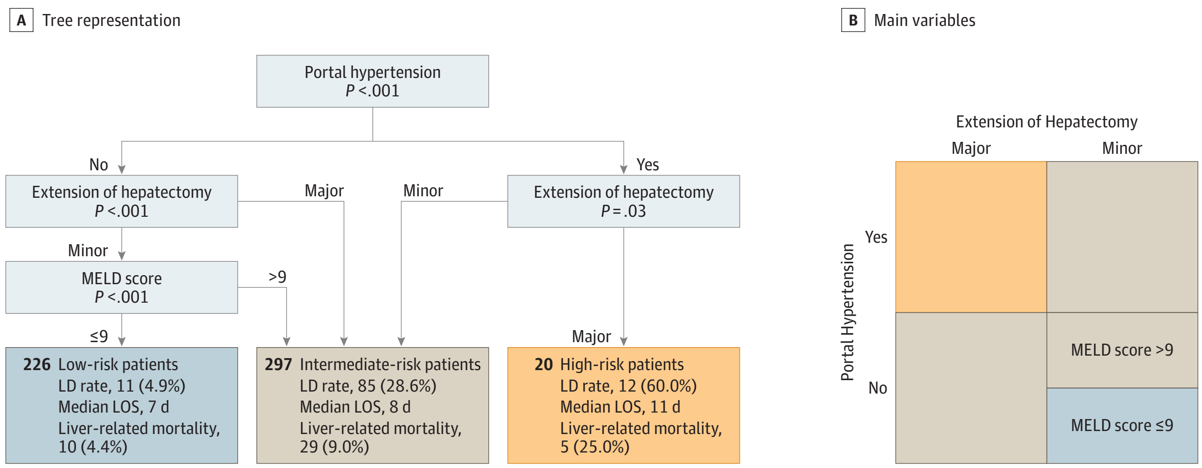


Permutation-based decreased accuracy associated with postresection LD is depicted among 543 patients undergoing liver resections for hepatocellular carcinoma. Higher values indicate variables that weight more in association with LD. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; ICG-R15, indocyanine green retention test at 15 minutes; and MELD, Model for End-Stage Liver Disease.

In this study, we adopted a broader definition of LD, including the occurrence of postoperative ascites, because this complication is frequently a postoperative manifestation of liver insufficiency with potentially life-threatening consequences such as the hepatorenal syndrome. The inclusive approach given to LD in this study proved to be effective because a direct correlation with outcome was observed. The assessment of postsurgical complications according to the DCC grade helped in considering the real clinical effect of general and liver-related complications on the patient's outcome.

The main limitation of the present study is the retrospective nature of the analysis, even if data were consecutively collected; in addition, the proposed risk stratification was not externally validated, although an internal 10-fold

Figure 2. Recursive Partitioning Classification Tree of Hierarchic Interaction of Prognostic Factors for Postoperative Liver Decompensation (LD)



The tree representation (A) corresponds to a rectangular recursive partition of the feature space among the 3 main variables associated with postsurgical LD (B) in the 543 patients undergoing liver resection for hepatocellular carcinoma. The terminal nodes categorized the study sample into 3 prognostic groups according to LD rate ($P < .001$). The 3 groups differed also in terms of liver-related mortality during the study period and median length of stay. Major hepatectomy indicates removal of at least 3 liver segments; minor hepatectomy, less than 3 segments. LOS indicates length of stay; MELD, Model for End-Stage Liver Disease. The MELD score ranges from 6 to 40, with higher scores indicating worse liver function and increased risk for mortality.

cross-validation test was conducted. The predictive accuracy of the model resulted in a misclassification rate of only 6% in estimating the risk for postoperative LD; this rate is in line with the well-sustainable, real-life association of the postoperative risk in patients undergoing resection for HCC. Although indications for surgery and extensions of tumor burden slightly expanded over time (35 patients [6.4%] had Child-Pugh classification B and 163 patients [30.0%] had portal hypertension), all preoperative variables that may have influenced the treatment algorithm were included in the multivariate analysis.

Conclusions

Our study demonstrates that the risk for LD after liver resection can be stratified accurately before surgery according to a hierarchic order of factors represented by the presence of portal hypertension, extension of the hepatectomy, and the MELD score. The potential influence of the proposed model on the decision-making process regarding surgery in HCC could turn out to be significant not just for physicians but for patients too.

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Invited Commentary

Decision Tree for Liver Resection for Hepatocellular Carcinoma

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The incidence of hepatocellular carcinoma in the United States has grown steadily during the past 2 decades and the associated mortality has increased proportionally.[1] In 2012, there were an estimated 30 000 new cases of liver cancer and 24 000 liver cancer-associated deaths.[2] Underlying liver disease associated with hepatitis, autoimmune disorders, alcoholic cirrhosis, or nonalcoholic fatty liver disease has become the major risk factor for hepatocellular carcinoma in the United States.[3] In fact, liver dysfunction in some form is found in upwards of 90% of patients who present with hepatocellular carcinoma.[4] In these patients, curative resection is often challenging because underlying liver disease may render the functional liver remnant inadequate. An inadequate functional liver remnant can lead to the most dreaded complication following liver resection, posthepatectomy liver decompensation (LD). Given the morbidity and mortality associated with LD, appropriate preoperative risk prediction and stratification are paramount.[5,6]

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Despite decades of research, our current risk prediction tools for identifying those at risk for LD have major shortcomings. This has been further hindered by inconsistent definitions of LD and varying complexity of the preoperative diagnostic workup of these patients. In this issue of *JAMA Surgery*, Citterio et al[7] use recursive partitioning to design a novel and simple algorithm that not only assists in prediction of patients at risk for LD but also provides a hierarchical assessment of the associated risk factors. While statistically sophisticated, the end result is a simple decision tree that sorts patients into 3 distinct risk groups. In an era when medical decision making has become increasingly complex, not only is their decision tree intuitive and easy to use, it is also quite refreshing.

What is lacking is guidance for decision making past risk determination. For those at low risk, the decision is relatively straightforward. To use the decision tree analogy, the liver resection branch is sturdy and sound, and it is not likely to break if you venture out onto it. For those at intermediate risk, additional clinical and diagnostic information is neces-