

Indication of the Extent of Hepatectomy for Hepatocellular Carcinoma on Cirrhosis by a Simple Algorithm Based on Preoperative Variables

Matteo Cescon, MD; Alessandro Cucchetti, MD; Gian Luca Grazi, MD; Alessandro Ferrero, MD; Luca Viganò, MD; Giorgio Ercolani, MD; Matteo Zanello, MD; Matteo Ravaioli, MD; Lorenzo Capussotti, MD; Antonio Daniele Pinna, MD

Objective: To produce a model indicating the extent of hepatectomy for hepatocellular carcinoma on cirrhosis based on easily available preoperative data.

Design: Retrospective study based on multicenter prospectively updated databases.

Setting: Two tertiary referral centers specializing in hepatobiliary surgery.

Patients: A total of 466 patients undergoing hepatectomy for hepatocellular carcinoma on cirrhosis between 1995 and 2006.

Main Outcome Measures: To create a decision tree for safe liver resection based on factors affecting irreversible postoperative liver failure (IPLF).

Results: A total of 23 patients (4.9%) developed IPLF. The model for end-stage liver disease (MELD) score (categorized as <9, 9-10, and >10; $P < .05$ for all comparisons) and extent of hepatectomy were independent pre-

dictors of IPLF. In patients with a MELD score of less than 9, the IPLF rate was 0.4%. In patients with a MELD score of 9 or 10, the IPLF rate was 1.2% for resections of less than 1 segment, 5.1% for segmentectomies or bisegmentectomies, and 11.1% for major hepatectomies. In this category of MELD, serum sodium levels identified a low-risk group (sodium ≥ 140 mEq/L; to convert to millimoles per liter, multiply by 1.0) not experiencing IPLF and a high-risk group (sodium < 140 mEq/L) in which resections of less than 1 segment led to an IPLF rate of 2.5% and resections of 1 segment or more led to an IPLF rate of more than 5% ($P < .05$). In patients with a MELD score of more than 10, the IPLF rate was more than 15% in all types of hepatectomies.

Conclusion: A simple algorithm based on the MELD score and serum sodium level can indicate the maximum tolerable extent of hepatectomy for hepatocellular carcinoma on cirrhosis.

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DESPITE RECENT DEMONSTRATIONS of satisfactory results of nonsurgical procedures,¹ liver resection still represents the treatment of choice for hepatocellular carcinoma (HCC) arising in well-compensated cirrhosis. The value of hepatectomy has recently been outlined on the

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basis of decreased mortality and morbidity achieved in specialized centers.^{2,3} However, excluding an extraordinary single-institution report of zero mortality in a long observational period,² all of the largest published series show an intrinsic link between surgical treatment and risk of mortality and life-threatening complications,

the most frightening of which is postoperative liver failure.

Several methods of establishing functional hepatic reserve and the feasibility of liver resection have been reported.⁴ Probably the most detailed guides to decision-making in resectional surgery are those produced in Eastern countries,^{5,6} where the indocyanine green test plays a pivotal role. Unfortunately, this evaluation is expensive and time consuming; it is perhaps for these reasons that it has not achieved great popularity in Western countries. On the other hand, the simple use of the Child-Pugh classification^{7,8} does not permit a precise estimation of postoperative hepatic functional recovery, being often insufficient to define the extent of or even the indication for hepatectomy. A more accurate assessment of liver function based solely on routine biochemical data would be useful.

Author Affiliations: Liver and Multiorgan Transplant Unit, Department of Surgery and Transplantation, University of Bologna, Bologna (Drs Cescon, Cucchetti, Grazi, Ercolani, Zanello, Ravaioli, and Pinna); and Unit of Surgical Oncology, Institute for Cancer Research and Treatment, Candiolo, Torino, Italy (Drs Ferrero, Viganò, and Capussotti).

The model for end-stage liver disease (MELD) score, initially developed to predict mortality of patients receiving transjugular intrahepatic portosystemic shunts⁹ and subsequently applied as a disease severity index for the waiting list for liver transplantation,^{10,11} has recently been applied to predict liver failure after resection of HCC on cirrhosis^{12,13} and to define the risk of mortality after surgery in patients with cirrhosis.¹⁴ However, a MELD score-related system able to quantify the extent of the hepatectomy to reduce the occurrence of irreversible postoperative liver failure (IPLF) to a minimum has never been reported.

The aim of the present study was to retrospectively review the occurrence of IPLF and postoperative complications of a large series of hepatectomies for HCC on cirrhosis performed in 2 Italian centers to create a MELD score-based system to indicate the extent of the hepatectomy.

METHODS

The study population consisted of 341 cirrhotic patients who underwent hepatic resection for HCC at the Liver and Multiorgan Transplant Unit, Department of Surgery and Transplantation of the University of Bologna, between January 1995 and September 2006, and of 125 cirrhotic patients who underwent the same surgical procedure within the same study period at the Unit of Surgical Oncology of the Institute for Cancer Research and Treatment of Turin. This study population of 466 patients did not include 20 subjects receiving anticoagulant therapy that did not allow a reliable measurement of the MELD score or those who died early in the postoperative course for causes not related to IPLF (sepsis, 4 cases; myocardial infarction, 2 cases; pulmonary embolism, 2 cases; hemoperitoneum, 1 case).

The etiology of the liver disease and the diagnosis of cirrhosis were preoperatively based on virological markers (hepatitis B and C serology), abdominal imaging (Doppler ultrasound and computed tomography and/or magnetic resonance imaging), and assessment of biochemical liver function tests (serum bilirubin, albumin, transaminases, and international normalized ratio [INR]); the presence of cirrhosis was confirmed in the surgical specimen in all cases.

The indications for hepatic resection and the early outcomes of the 2 contributing centers were similar.¹⁵⁻¹⁷ In more recent years, the selection criteria were extended at both centers to include more advanced tumors and, at the Bologna center, higher degrees of liver dysfunction, considering liver transplantation as a feasible option for patients developing liver failure or tumor recurrence after hepatectomy.^{18,19}

The Child-Turcotte-Pugh score was obtained according to the well-known classification.^{7,8} The MELD score was calculated the day prior to surgery according to the formula $MELD = [0.957 \times \ln(\text{creatinine in milligrams per deciliter; to convert to micromoles per liter, multiply by } 88.4) + 0.378 \times \ln(\text{bilirubin in milligrams per deciliter; to convert to micromoles per liter, multiply by } 17.104) + 1.12 \times \ln(\text{INR}) + 0.643] \times 10$.¹¹ The extent of the hepatectomy referred to the International Hepato-Pancreato-Biliary Association classification.²⁰ Major hepatic resection was defined as the removal of more than 2 segments. No more than 4 segments were removed in any of the series. All resections were performed with the aim of achieving a tumor-free margin of at least 1 cm, based on intraoperative examination and ultrasonography.

The primary endpoint of the study was the investigation of the relationship between patients' preoperative characteristics

and surgical planning with the development of IPLF; this was defined as a growing impairment of liver function after resection that led to patient death or required transplantation. The relationship between the MELD score and postoperative complications (morbidity) and length of hospital stay represented secondary end points. Postoperative morbidity included occurrence of refractory ascites (requiring drainage) and jaundice (defined as a serum bilirubin level of more than 3 mg/dL), whereas alteration of coagulation factors requiring fresh frozen plasma was not included in the analysis because the 2 centers had not standardized the criteria for postoperative plasma administration. The hospital stay was computed from the day of surgery until death, transplantation, or discharge to home.

STATISTICAL ANALYSIS

Continuous variables were analyzed for normal distribution using the Kolmogorov-Smirnov test and expressed as mean and standard deviation or as median and range as appropriate. Differences between subgroups were explored by the independent-samples *t* test after a Levene test for equality or Mann-Whitney *U* test where necessary. Categorical variables were reported in number of cases and prevalence, and differences between subgroups were compared using the χ^2 analysis with Yates correction. The effect of each variable in determining the occurrence of IPLF was assessed by the means of logistic regression model and the forward and backward conditional methods were applied to determine their independent values. Pearson correlation was also applied to investigate possible relationships existing between variables.

When required, the prognostic value of preoperative variables in predicting IPLF was assessed using receiver operating characteristic (ROC) curve analysis; a ROC curve plot was obtained by calculating the sensitivity and specificity of every observed prognostic data value and plotting sensitivity against 1-specificity. The area under the curve and the best operating point in terms of sensitivity and specificity were then calculated and reported as previously described.²¹

A significance level of .05 was used in all analyses. The statistical analysis was done using SPSS version 10.0 software for a PC computer (SPSS, Chicago, Illinois) and ROC analysis was performed using MedCalc Version 7.2.1.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

The study population included 367 men (78.8%) and 99 women (21.2%). The mean (SD) age was 63.9 (9.3) years (range, 22-85 years); baseline characteristics of the study population are reported in **Table 1**. In the postoperative course, 23 patients (4.9%) developed IPLF. Of these, 4 were considered eligible for liver transplantation and successfully transplanted, whereas the remaining 19 had absolute contraindications for liver transplantation and died postoperatively; therefore, the mortality rate for IPLF was 4.1%. The mean (SD) time from surgery to liver transplantation or patient death was 51.1 (49.7) days (range, 5-166 days); in particular, patients who underwent transplantation had a mean time between liver resection and liver transplantation of 108.5 days (range, 24-166 days) and those who died had a mean time of 39.1 days (range, 5-86 days). Considering all 495 patients operated on during the study period, 3-month mortality was 4.6% (23 of 495 cases). At the end of the study period, the overall actual survival rate was 66%.

PREOPERATIVE PREDICTORS OF IRREVERSIBLE IPLF

We initially analyzed the relationship between preoperative assessable variables and the occurrence of IPLF (**Table 2**); the univariate regression model showed serum sodium levels of less than 140 mEq/L (to convert to millimoles per liter, multiply by 1.0) ($P = .03$), with Child-Turcotte-Pugh class B ($P = .002$), a higher MELD score ($P < .001$), and extent of hepatectomy ($P = .001$) as prognostic factors for IPLF.

Two intraoperative variables, use of total pedicle clamping (Pringle maneuver), and requirement of blood transfusions were also analyzed because of their possible effect on postoperative outcome. The use of the Pringle maneuver was not significant at univariate analysis (odds ratio, 0.67; 95% confidence interval, 0.28-1.60; $P = .36$), whereas the need for blood transfusions, even if significantly related to IPLF (odds ratio, 10.64; 95% confidence interval, 3.86-29.32; $P = .001$) was strictly related to the extent of the hepatectomy (Pearson correlation $P = .003$) and thus excluded from further analysis. Multivariate analysis confirmed the preoperative MELD score ($P = .001$) and the extent of the hepatectomy ($P = .01$) as the only independent predictors of IPLF; it should be noted that the serum sodium level was close to statistical significance ($P = .09$).

MELD SCORE AND EXTENT OF HEPATECTOMY

Based on the results obtained from logistic regression analysis, we investigated the prevalence of IPLF, postoperative complications, and length of hospital stay in groups of patients with different MELD scores who underwent different hepatectomies (**Table 3**). Only 1 patient with a MELD score of less than 9 experienced IPLF (0.4%); this patient, who died, had a preoperative MELD score of 7 and underwent right hepatectomy. The prevalence of IPLF in major hepatectomies was 3.3% (1 of 30 cases). Conversely, patients who underwent minor hepatectomies did not experience this event.

Patients with MELD scores of 9 or 10 showed an increasing prevalence of IPLF (3.8%) compared with patients with lower MELD scores ($P = .02$), and the occurrence of the event was strictly related to the extent of the hepatectomy. The prevalence of IPLF rose from 1.2% of patients who underwent resection of less than 1 segment (subsegmentectomy or limited resection) to 5.1% of patients in whom 1 or 2 segments were removed and reached the highest value in patients undergoing major hepatectomies, with a prevalence of 11.1%.

Patients with MELD scores higher than 10 experienced the highest prevalence of IPLF (20.3%), significantly higher than patients with lower MELD scores ($P = .001$). Again, the occurrence of the event was strictly related to the extent of the hepatectomy, rising from 15.2% of patients in whom less than 1 segment was removed to 22.2% of patients undergoing segmentectomy or bisegmentectomy and to 30.0% of patients undergoing major hepatectomies. One of 4 patients with a MELD score of 15 or more (a commonly accepted allocation cut-off for transplant) experienced IPLF after a limited resec-

Table 1. Baseline Characteristics of the Study Population

| Variables | All Patients, No. (%) (n=466) |
|---|----------------------------------|
| Mean (SD) age, y | 63.9 (9.3) |
| Age >65 y | 211 (45.3) |
| Male | 367 (78.8) |
| Hepatitis serology | |
| Hepatitis C | 258 (55.4) |
| Hepatitis B | 70 (15.0) |
| Hepatitis B and C | 34 (7.3) |
| Negative or not determined | 104 (22.3) |
| Presence of mild ascites | 23 (4.9) |
| Presence of esophageal varices | 131 (28.1) |
| Mean (SD) laboratory values | |
| Serum albumin, g/dL | 3.8 (0.4) |
| Platelet count, $\times 10^3/\text{mm}^3$ | 140.1 (72.7) |
| Serum creatinine, mg/dL | 0.92 (0.18) |
| Serum bilirubin, mg/dL | 1.02 (0.51) |
| Serum sodium, mEq/L | 139.6 (2.8) |
| Mean (SD) INR | 1.16 (0.12) |
| Mean (SD) CTP score | 5.4 (0.6) |
| CTP class A | 439 (94.2) |
| CTP class B | 27 (5.8) |
| Mean (SD) MELD score | 8.9 (1.8) |
| MELD score >10 | 79 (17.0) |
| Mean (SD) size of the largest tumor, cm | 4.4 (2.5) |
| Solitary tumor | 398 (85.0) |
| Extent of hepatectomy | |
| Subsegmentectomy or limited resection | 212 (45.5) |
| Segmentectomy | 138 (29.6) |
| Bisegmentectomy | 58 (12.4) |
| Major hepatectomy (≤ 4 segments) | 58 (12.4) |
| Intraoperative RBC transfusion | |
| No | 336 (72.1) |
| Yes | 130 (27.9) |
| Pringle maneuver | |
| Yes | 261 (56.0) |
| No | 205 (44.0) |

Abbreviations: CTP, Child-Turcotte-Pugh; INR, international normalized ratio; MELD, model for end-stage liver disease; RBC, red blood cell.

SI conversion factors: To convert albumin to grams per liter, multiply by 10; platelets to $\times 10^9/\text{L}$, multiply by 1.0; creatinine to micromoles per liter, multiply by 88.4; bilirubin to micromoles per liter, multiply by 17.104; and sodium to millimoles per liter, multiply by 1.0.

tion (25%). Postoperative complications and length of hospital stay were also related to the preoperative MELD score and extent of hepatectomy

ANALYSIS OF PROGNOSTIC VARIABLES IN PATIENTS WITH MELD SCORES OF 9 OR 10

Considering that patients with preoperative MELD scores of less than 9 showed a very low risk of IPLF and, conversely, patients with MELD scores of more than 10 experienced a very high occurrence, further analysis was performed to obtain a more accurate stratification of patients with MELD scores of 9 or 10 at different risks of IPLF in relation to the extent of the hepatectomy.

Serum sodium levels were accurate in predicting IPLF with an area under the curve of 0.77 (95% confidence interval, 0.69-0.83); a cut-off of 140 mEq/L was selected to discriminate patients with different risks of IPLF because of higher sensitivity (100%) and because it represented the median value of the study population. Pa-

Table 2. Predictive Factors of Irreversible Postoperative Liver Failure After Hepatectomy

| Variables | Analysis | | | |
|--|-------------------|---------|-------------------|---------|
| | Univariate | | Multivariate | |
| | OR (95% CI) | P Value | OR (95% CI) | P Value |
| Age >65 y | 0.51 (0.21-1.27) | .15 | | |
| Male | 0.97 (0.35-2.68) | .95 | | |
| Viral cirrhosis | 1.97 (0.57-6.76) | .28 | | |
| Presence of esophageal varices | 1.69 (0.71-4.01) | .23 | | |
| Platelet count <100 × 10 ³ /mm ³ | 1.83 (0.78-4.28) | .16 | | |
| Serum sodium level <140 mEq/L | 2.75 (1.11-6.82) | .03 | 2.18 (0.83-5.75) | .09 |
| CTP class B | 5.32 (1.81-15.65) | .002 | 1.84 (0.54-6.33) | .33 |
| MELD score <9 vs 9-10 vs >10 | 7.03 (3.36-14.74) | <.001 | 7.11 (3.38-14.94) | .001 |
| Segments resected, No. | 1.46 (1.08-1.96) | .001 | 1.51 (1.10-2.11) | .01 |

Abbreviations: CI, confidence interval; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; OR, odds ratio.
SI conversion factor: To convert sodium to millimoles per liter, multiply by 1.0.

Table 3. Relationship Between MELD Score, Extent of Hepatectomy, Serum Sodium Level, and IPLF, Morbidity, and Hospital Stay

| Variable | No. (%) | | | |
|--|-------------------|---|--|--------------------------|
| | All Cases (N=466) | Subsegmentectomy or Limited Resection (n=212) | Segmentectomy or Bisegmentectomy (n=196) | Major Hepatectomy (n=58) |
| MELD score <9 | | | | |
| IPLF | 1/227 (0.4) | 0/96 (0) | 0/101 (0) | 1/30 (3.3) |
| Postoperative complications | 31/227 (13.7) | 11/96 (11.5) | 11/101 (12.9) | 7/30 (23.3) |
| Median hospital stay, d (range) | 8 (4-45) | 8 (4-30) | 9 (5-45) | 9 (6-38) |
| MELD score of 9-10 ^a | | | | |
| IPLF | 6/160 (3.8) | 1/83 (1.2) | 3/56 (5.1) | 2/18 (11.1) |
| Serum sodium level ≥140 mEq/L | 0/80 (0) | 0/43 (0) | 0/26 (0) | 0/11 (0) |
| Serum sodium level <140 mEq/L | 6/80 (7.5) | 1/40 (2.5) | 3/33 (9.1) | 2/7 (28.6) |
| Postoperative complications | 49/160 (30.6) | 23/83 (27.7) | 19/59 (32.2) | 7/18 (38.9) |
| Serum sodium level ≥140 mEq/L | 20/80 (25.0) | 12/43 (27.9) | 5/26 (19.2) | 3/11 (27.3) |
| Serum sodium level <140 mEq/L | 29/80 (36.3) | 11/40 (27.5) | 14/33 (42.4) | 4/7 (57.1) |
| Median hospital stay, d (range) | 10 (5-166) | 9 (5-166) | 10 (6-156) | 10 (7-27) |
| Median serum sodium level ≥140 mEq/L (range) | 10 (5-67) | 10 (5-67) | 10 (6-34) | 10 (7-15) |
| Median serum sodium level <140 mEq/L (range) | 10 (5-166) | 9 (5-166) | 11 (6-156) | 24 (8-27) |
| MELD score >10 (n=79) | | | | |
| IPLF | 16/79 (20.3) | 5/33 (15.2) | 8/36 (22.2) | 3/10 (30.0) |
| Postoperative complications | 61/79 (77.2) | 24/33 (72.7) | 28/36 (77.8) | 9/10 (90.0) |
| Median hospital stay, d (range) | 14 (5-150) | 13 (5-150) | 14 (5-97) | 15 (7-35) |

Abbreviations: IPLF, irreversible postoperative liver failure; MELD, model for end-stage liver disease.

SI conversion factor: To convert sodium to millimoles per liter, multiply by 1.0.

^aIn patients with a MELD score of 9 or 10, the serum sodium level was dichotomized at 140 mEq/L based on the cut-off with the highest sensitivity obtained at the receiver operating characteristics analysis (area under the curve, 0.77; 95% confidence interval, 0.69-0.83; sensitivity, 100%; specificity, 51.9%).

tients with serum sodium levels of 140 mEq/L or more did not experience IPLF, whereas the prevalence of IPLF in patients with serum sodium levels of less than 140 mEq/L was 7.5% ($P=.01$).

Conversely, in patients with MELD scores of less than 9, the IPLF rate was 0% (0 of 92 patients) when the serum sodium level was less than 140 mEq/L and 0.7% (1 of 135 patients) when it was 140 mEq/L or higher ($P=.40$), whereas in patients with a MELD score of more than 10, the IPLF rate was 22.2% (10 of 45 patients) when the serum sodium level was less than 140 mEq/L and 17.6% (6 of 34 patients) when it was 140 mEq/L or higher ($P=.61$).

In patients with a MELD score of 9 or 10, parameters expressing portal hypertension such as presence of esoph-

ageal varices ($P=.99$) and a platelet count of less than $100 \times 10^3/\text{mm}^3$ ($P=.86$), did not affect IPLF, nor did other variables used for univariate analysis.

Table 3 illustrates the relationships observed between serum sodium level, extent of hepatectomy, and IPLF; in patients with a serum sodium level of less than 140 mEq/L, the occurrence of IPLF was strictly related to the extent of the hepatectomy, rising from 2.5% of patients who underwent resection of less than 1 segment to 9.1% of patients in whom 1 or 2 segments were removed and 28.6% of patients undergoing major hepatectomies. Postoperative complications and length of hospital stay were also related to preoperative serum sodium level and extent of hepatectomy.

This study explored the possibility of indicating the maximum extent of hepatectomy for HCC on cirrhosis with the lowest risk of IPLF on the basis of variables available preoperatively. These data came from a large population of patients who underwent liver resection in 2 tertiary Italian centers in the past 11 years. Both institutions have established experience with liver surgery and consider hepatectomy to be the first-line treatment of early HCC with preserved liver function. The indication for surgery, patient evaluation, and postoperative morbidity and mortality were similar between the centers.¹⁵⁻¹⁷

As for other surgical procedures, postoperative mortality in cirrhotic patients can be determined by many causes and defined by arbitrarily chosen time periods after surgery. This latter consideration especially has led to still-unsolved controversies on the optimal end point to quantify the risk of liver resection.^{3,22} Our main outcome variable was IPLF, whose definition is univocal and irrespective of the time elapsing after surgery.

The multivariate analysis showed that 2 variables obtainable preoperatively by routine biochemical and radiological data, ie, MELD score (categorized as <9, 9-10, and >10¹²) and extent of hepatectomy, were independently correlated with IPLF. The premise for the present study emerged from our previous study showing that preoperative MELD score, postoperative course of MELD, and extent of hepatectomy are major determinants of postresection liver function recovery.²³

In the present study, the preoperative serum sodium level did not reach statistical significance when investigated in the whole population, but it emerged as a predictor of IPLF in patients with MELD scores between 9 and 10. The serum sodium level can indicate the degree of hepatic illness. In particular, a low serum sodium level can predict the formation of ascites in cirrhotic patients^{24,25} and, in the field of liver transplantation, the incorporation of this parameter into the MELD score has been demonstrated to increase the accuracy of survival prediction for cirrhotic patients.²⁶ In the formula proposed by Biggins et al, the serum sodium cut-off value of 135 mEq/L corresponded to its lower limit for normal serum concentration, while our cut-off was well within the normal range. This discrepancy could be attributed to the 2 populations because cirrhotic patients eligible for hepatic resection generally had better liver function, and possibly higher serum sodium levels, than candidates for liver transplantation.

Two intraoperative variables, pedicle clamping and blood transfusions, were not considered for the regression model because of the lack of statistical effect at univariate analysis (pedicle clamping) and because of correlation with the extent of the hepatectomy (blood transfusions). Patients with MELD scores of less than 9 and undergoing limited resection, subsegmentectomy, segmentectomy, or bisegmentectomy had no IPLF, whereas only 1 patient undergoing right hepatectomy developed IPLF, representing 3.3% of 30 patients undergoing major hepatectomies. We consider these results sufficient evidence that resection of up to 4 segments can be per-

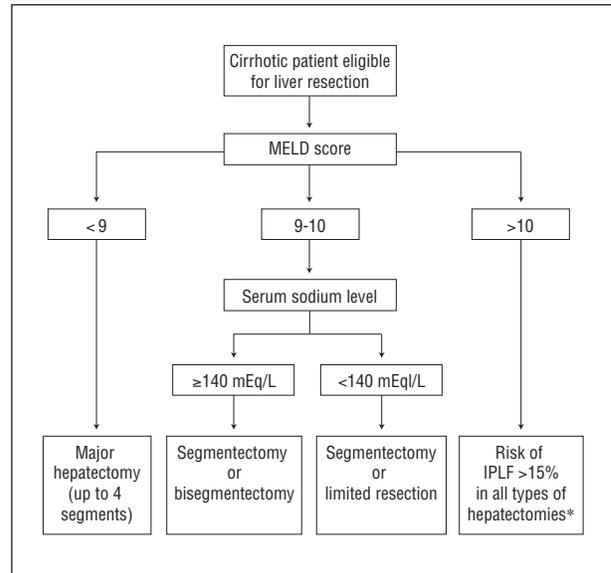


Figure. Algorithm of selection of candidates for hepatectomy for hepatocellular carcinoma on cirrhosis. MELD indicates model for end-stage liver disease; IPLF, irreversible postoperative liver failure. (To convert sodium to millimoles per liter, multiply by 1.0.) *Considering the high risk of hepatectomy, alternative treatments should be considered.

formed with reasonably low risk of IPLF (0.4%) in this MELD-score category. Patients with MELD scores between 9 and 10 showed an acceptable rate (1.2%) of liver failure only in the case of resection of less than 1 segment. By introducing the sodium level, we were able to better stratify this group into low risk (sodium ≥ 140 mEq/L), not experiencing IPLF, and high risk (sodium < 140 mEq/L), in which only patients undergoing resection of less than 1 segment had an IPLF rate less than 5%. The remaining patients of this group and those with MELD scores of more than 10 showed IPLF rates of far more than 5%. Complication rates and postoperative hospital stay reflected the results observed for liver failure according to these categorizations.

In the **Figure**, we synthesized our proposed algorithm. In patients with MELD scores of less than 9, resection of up to 4 liver segments can be performed. Patients with MELD scores between 9 and 10 and with serum sodium levels of 140 mEq/L or higher can safely undergo resection of up to 2 segments. Although we observed no IPLF in 11 patients undergoing major hepatectomy, this number is probably too low to assume that these procedures are absolutely safe in this group. Conversely, patients with sodium levels of less than 140 mEq/L can only tolerate a subsegmentectomy or a limited resection, whereas in patients with MELD scores higher than 10, all procedures had a risk of IPLF that was more than 15% and proportional to the number of segments removed.

Although it was recently reported that liver resections are generally safe when the MELD score is less than 9,^{12,13,22} the definition of the maximum tolerable extent of hepatectomy according to a specific MELD-score range was not available until now. Our analysis provides a stratification of postoperative values that is more similar to Eastern models,^{2,5} without using additional quantitative tests for liver function.

We determined the MELD score the day prior to surgery when the final decision whether to proceed with hepatectomy or indicate an alternative treatment was taken. One may question whether a single MELD calculation can be more reliable than Δ MELD (ie, the variation of MELD score of a given subject within a definite period of time), as recently reported in retrospective analyses of pretransplant and posttransplant mortality.²⁷⁻³¹ However, the actual MELD score remains the most important variable,^{28,29,31} and prospective studies demonstrating any superiority of Δ MELD over the actual MELD score in predicting posttransplant mortality are lacking. In addition, the magnitude of the Δ MELD increases with higher actual MELD score^{28,29,31} and is likely to be irrelevant in patients with MELD scores far lower than those of patients listed for transplant, such as those undergoing liver resection.

The above considerations, together with the considerable number of patients supporting a minimization of errors in predicting mortality, should confirm the validity of our proposed algorithm. One limitation of this study is the absence of validation in an independent patient sample. Unfortunately, this would have required another large group of patients receiving similar preoperative work-up, surgical procedures, and postoperative care in at least 1 specialized large-volume center. This was beyond our possibilities, given the low number of such centers and of expected IPLF events in recent years.^{2,3}

The application of this algorithm would have indicated treatments other than liver resection in 25% of our patients. This important issue should be carefully evaluated because the best therapeutic strategy needs to be defined within centers in which multidisciplinary approaches are available. In particular, the indication for liver transplantation in patients at high risk for hepatectomy should be balanced with access to local waiting lists and with the limited size of the donor pool. From this point of view, recent studies have pointed out the feasibility of a strategy of liver resection as a bridge to transplantation¹⁹ and the acceptable results of transplant in patients developing liver failure after hepatectomy.¹⁸ One of the 2 centers participating in the present study has recently espoused these concepts, considering cases with tumors exceeding commonly recognized criteria for hepatectomy (ie, multiple tumors and mildly decompensated cirrhosis) for resection. This fact, together with cases of hepatectomies performed for HCC already not indicated for other therapies, certainly contributed to the 25% of patients with a risk of IPLF of more than 5% in our series.

In conclusion, this study presents a stratification of the risk of postoperative liver failure in patients undergoing liver resection for HCC on cirrhosis according to the extent of hepatectomy, MELD score, and serum sodium level. Using these latter 2 factors, a categorization of the upper tolerable limit of resected segments can be predicted preoperatively.

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Correspondence: Matteo Cescon, MD, Unità Operativa Chirurgia Trapianti di Fegato e Multiorgano, Padiglione 25, Policlinico Sant'Orsola-Malpighi, Via Massarenti 9, 40138 Bologna, Italy (matteo.cescon@aosp.bo.it).

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INVITED CRITIQUE

Paramount to the treatment of patients with low MELD scores with HCC is the question of resection vs listing for liver transplantation with or without bridging therapy. Two previous articles (one from this group) have demonstrated that carefully selected patients with a MELD score of less than 9 can undergo limited liver resection safely.^{1,2} Cescon and colleagues present data from a 2-center retrospective review of liver resections for HCC in patients with compensated cirrhosis. Their data support using serum sodium levels and MELD scores in combination to make resection decisions for patients with MELD scores of 9 and 10. Algorithms such as this are important aids for therapeutic planning and illustrate that liver resection in patients with MELD scores greater than 9 should be undertaken cautiously. The reader should note that the authors censored all causes of death except liver failure. A similar cohort of cirrhotic patients (MELD scores, 7 to 11) would have an estimated 30-day operative mortality rate between 5% and 10% (1-year mortality rate, 19%-29%).³ The decision to resect any HCC with background cirrhosis is complicated because completely resected patients lose United Network for Organ Sharing exception points for liver transplantation, which remains the standard of care for United Network for Organ Sharing stage II HCC. Furthermore, the decision to list a patient for transplant can be complicated by the scarcity of organs and prolonged wait times with significant regional variation. When examined on an intention-to-treat basis, patients undergoing liver transplantation following HCC resection have increased operative mortality, lower disease-free survival rates, and lower 5-year survival rates.⁴ Further complicating this scenario is the debate surrounding the optimal "bridge to transplant" therapy for HCC.⁵ However, one must remember that when decid-

ing on resection in cirrhotic patients with HCC, other factors are equally important to the risk of liver failure. The optimal therapeutic strategy for an individual patient is best decided via a multidisciplinary approach of hepatobiliary and liver transplant surgeons and hepatologists. The patient's suitability for transplantation, current institutional expertise and strategies, and current regional organ allocation schemes are all important considerations. An incorrect initial decision can dramatically damage future therapeutic options and inadvertently worsen the patient's prognosis. The study by Cescon and colleagues adds further to our ability to assess risk with easily available clinical variables. This may be useful in determining the safest and most effective treatment strategies for these challenging patients.

Christopher D. Anderson, MD
David C. Linehan, MD

Correspondence: Dr Linehan, Department of Surgery, Washington University in St Louis, 660 S Euclid, St Louis, MO 63110 (linehand@wustl.edu).

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