Editorial Commentary

Safely expanding surgical resection for patients with hepatocellular carcinoma and cirrhosis

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Hepatocellular carcinoma (HCC) is a world-wide clinical problem with >800,000 new cases and >800,000 deaths per year. This cancer is in the top five worldwide and when looking at the last couple of decades there is a continual rise in the number of new cases (1). The treatment options for patients with HCC has expanded over the years with therapeutic plans based on staging of the tumor and the underlying state of the patient's liver disease since the majority of patients developing HCC also have chronic liver disease. As a result of the improved clinical outcomes multiple investigators and societies have developed guidelines regarding management of patients with HCC. Both the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of Liver Disease (EASL) have practice guidelines which state that resection for patients with cirrhosis who are a Child-Pugh class A can be performed with high degrees of success and low morbidity to the patient. There is also general consensus that those patients with advanced underlying liver disease, Child-Pugh C (i.e., large volume ascites, etc.) are not candidates for surgical resection (1-3). The Barcelona Clinic Liver Cancer (BCLC) algorithm provides guidance in patient management based on tumor stage and the underlying liver disease. In this algorithm only patients with well-preserved liver function and small tumors would be a candidate for resection. It essentially limits resection to those patients with Child-Pugh A cirrhosis while recommending liver transplantation for those patients with more advanced liver disease (e.g., patient with decompensated liver disease secondary to their cirrhosis).

The Child-Pugh scoring system was initially developed to determine the risk of death amongst patients with cirrhosis who were undergoing surgery for portal hypertension. Use of the Child-Pugh grading has subsequently been adopted to risk stratify patients for multiple surgical procedures. While the Child-Pugh scale has been a standard within the domain of hepatic surgery alternative models have also been developed. One example is the albumin-bilirubin (ALBI) score which assesses the liver function in patients with HCC. In a retrospective study analyzing the ALBI score in 1,242 patients, the area under the receiver operating characteristic (ROC) curve performed better at predicting post-hepatectomy liver failure (PHLF) when compared with the Child-Pugh score (4). The ALBI grade of patients graded the patients into distinct survival cohorts (P<0.001). The Child-Pugh scoring scale did not have the same discriminatory ability. In a separate study, multivariable analyses demonstrate that the ALBI score functions as an independent predictor of PHLF. Neither the Child-Pugh grade or a patient's Model of End Stage Liver Disease (MELD) score were predictors of PHLF in either hepatectomy subgroups (e.g., minor or major) (4,5). The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) is another example of a recently developed tool. It collects patient-level data for major operations across numerous disciplines as a way

to help determine risk of complications or death. Morbidity and mortality risk for patients is calculated using a series of 21 preoperative risk factors. In one study, the NSQIP scoring system was retrospectively applied to 38 patients who had a diagnosis of cirrhosis. Using NSQIP the estimated probability of morbidity is 0.24±0.11 and probability of mortality was 0.02±0.02. The presence of cirrhosis is linked to an increased likelihood of morbidity (0.27±0.10; P=0.059) (6,7). Increased probabilities of mortality are tied to the underlying diagnosis and the amount parenchyma involved in the resection (both P<0.001) (6).

When reviewing many of these guidelines and tools patients who are diagnosed with Child-Pugh B cirrhosis remain an understudied population. This is a particularly challenging clinical population as these patients have partial compromise of their hepatic function and can be successfully managed with liver resection, but they are also at significant risk for post-resection hepatic decompensation. Berardi *et al.* used the Child-Pugh classification as a model to develop a nomogram that would guide providers in determining the risks for specific patients. This group of international hepatobiliary surgeons felt that there was an opportunity to design a predictive tool to assess risks of surgical resection for patients who are not well-compensated, those patients categorized as Child-Pugh B cirrhosis (8).

The authors sent questionnaires and databases to 14 centers with extensive experience in treating patients with HCC. The centers were defined as either Eastern or Western institutions so that they could get broader representation of contemporary clinical practices. They restricted the study to adult patients who were diagnosed with Child-Pugh class B cirrhosis and underwent resection (open or minimally invasive) for HCC. The resections were categorized as anatomical or non-anatomical and the primary endpoint of the study was to measure morbidity and mortality within 90 days from surgery while evaluating overall surgical safety (8). A multivariable logistic regression model was performed to predict the probability of morbidity. The model included correlate predictive factors (P<0.1) at the univariable analysis along with variables that were deemed clinically relevant. The regression model was subsequently used to predict the overall survival (OS) at three and 5 years after resection. A multivariable Cox regression model was subsequently applied so that the authors could identify predictive factors associated with disease-free survival based on predictive factors from the univariable analysis. This model was subsequently applied as a means to predict the disease-free survival at three and 5 years. The models accounted for clustering secondary to variation in model building amongst the various institutions. The prediction models were graphically shown as nomograms and the surgical risk nomogram was developed based on 90-day morbidity of the multivariable logistic model. Survival nomograms were subsequently developed using the multivariable Cox regression models for OS and disease-free survival (8). Beginning with a total of nearly 12,000 patients the authors identified 253 patients (1.4%) who met inclusion and exclusion criteria. They subdivided these patients based on their specific Child-Pugh score with 70.3% as a Child-Pugh score of 7 (B7), 18.5% B8, and 11% B9. Interestingly the median MELD score of these patients in this study was 9 [6–12] which demonstrates some of the discrepancies when comparing scoring systems to evaluate the degree of hepatic dysfunction. More than 80% of patients underwent a minor hepatectomy and approximately one-half of the procedures were performed using minimally invasive technique. According to univariable logistic regression analysis the odds of postoperative complications increased based on the patient's Child-Pugh score, platelet count, ascites, portal hypertension and other medical comorbidities. In addition to these patient-specific factors the type of hepatectomy and surgical approach also contribute to postoperative complications. These variables were included in a multivariable logistic model and a nomogram was subsequently developed to show the probability of postoperative complications (8). The model had a c-index of 0.79 which suggests it has good prediction capability. In this study those patients who underwent major liver resections had a significantly higher 90-day mortality (10.3% *vs.* 3.3%; P=0.04) and morbidity (69.2% *vs.* 37.9%; P<0.001) rate. Those patients undergoing major hepatectomies also had a higher incidence of major complications (46.1% *vs.* 12.1%; P=0.002) and these patients were at greater risk of developing ascites (61.5% *vs.* 33.1%; P<0.001) and/or PHLF (10.2% *vs.* 2.3%; P=0.01). Patient readmission rates were elevated compared with those patients who underwent a minor liver resection (30.7% *vs.* 8.8%; P=0.001) (8). Lastly those patients undergoing an open hepatectomy had an increased overall risk of morbidity (52.7% *vs.* 31.9%; P=0.001), an elevated rate of major complications (26.7% *vs.* 7.3%; P=0.01) and they more frequently developed ascites (46.5% *vs.* 27.8%; P=0.002) compared to patients undergoing a minimally invasive resection. Looking at resource consumption the hospital stay was also higher for patients undergoing an open hepatectomy (14 *vs.* 9 days;

P=0.009). A Cox regression model of OS demonstrated that patients with higher Child-Pugh scores (B9 v. B8 or B7), >1 lesion and elevated preoperative alpha-fetoprotein (AFP) were at higher risk of mortality (8).

Patients with an underlying condition of Child-Pugh class B cirrhosis typically have limited treatment options and they are usually restricted to non-anatomical hepatectomy. Berardi's study confirms this practice as these patients typically underwent a high rate of partial resections (8). The authors acknowledge that the ongoing debate concerning anatomical *vs.* non-anatomical resections for HCC must be balanced with the underlying degree of hepatic decompensation in order to select the lowest risk and most oncological safe treatment for the individual patient. Ultimately HCC removal while preserving liver parenchyma are equally important contributory determinants regarding the patient's OS.

The authors of this study acknowledge numerous study limitations including that this is a retrospective study that introduces selection bias and that the variations in surgical practices around the world can play a major role as there are inherent regional differences regarding surgical approaches. This component of regional variation is a challenge to overcome as providers from Asian countries tend towards a resection-dominant approach while providers from Europe and the United States are more likely to refer Child-Pugh B patients for liver transplantation. There was general agreement that patients diagnosed with Child-Pugh class B cirrhosis should not be seen as having an absolute contraindication to liver resection. These patients are best served by being evaluated in a multidisciplinary approach in order to choose the best available option that reduces the potential negative impact of surgery. Hepatectomy should be pursued as a valuable resource when a patient's comorbidities, age and/or tumor characteristics hamper the opportunity for liver transplantation (8). The model developed by Berardi and colleagues is a welcome addition to address a specific sub-population. This model in combination with other tools will provide a more granular and detailed assessment of those patients who can successfully undergo hepatic surgery.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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