Original Article

Preoperative survival calculator for resectable hepatocellular carcinoma

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Background: Estimation of preoperative overall survival (OS) of hepatocellular carcinoma (HCC) may guide surgical decision-making.

Methods: OS was analyzed using the National Cancer Data Base from 1998–2012. Patients with HCC who underwent wedge resection, lobectomy or extended lobectomy were selected. Patients who had metastatic disease or previous treatment prior to surgery were excluded. Data was randomly allocated to model building (n_b =4,364) and validation cohorts (n_v =1,091). Multivariable regression analyses of the n_b were used to construct prediction models and optimized using n_v.

Results: HCC patients (n=5,455) who underwent curative resection had a median OS of 36 months (95% CI, 34–38 months) with 1- and 3-year OS of 73% (95% CI, 72–74%) and 50% (95% CI, 49–51%), respectively. The patient median age was 65, 66% of patients were male, median tumor size was 60 mm; clinical stage 1 =25%, stage 2 =30% and stage 3 =45%. Alpha fetoprotein (AFP) was elevated in 63% of patients. Factors significant in the prediction model included degree of resection, age, race, tumor size, grade, and histologic subtype.

Conclusions: A preoperative OS calculator was developed to assist in the treatment evaluation and OS prediction of HCC patients.

Keywords: Hepatocellular carcinoma (HCC); survival calculator

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer related death worldwide (1,2). For patients with early stage disease, liver resection provides a potential for a cure but the overall prognosis is poor. Overall survival (OS) of HCC is affected not only by the aggressiveness of the type of tumor, but also the patient's underlying liver disease, as up to 90% of HCC patients have been reported to have cirrhosis (3). Several clinical models of liver disease such as the Child-Pugh classification and Model for End-Stage Liver Disease (MELD) attempt to estimate the patients' overall liver health and are used as part of the multidisciplinary and surgical evaluation of HCC patients (4,5). Due to the role of underlying liver dysfunction and the varying tumor biology, clinical staging systems such as tumor, node, and metastasis (TNM) and Cancer of the Liver Italian Program (CLIP) are less reliable as

preoperative assessments for surgical resection.

Methods to predict morbidity and OS during the preoperative assessments can facilitate the decision making process. However, the development of propensity scores for estimating survival has been primarily from single or cooperative Asian and European institutions that combine both postsurgical factors and preoperative factors (6,7). There exists a paucity of literature for predicting oncologic outcomes for HCC patients based on preoperative factors from a US population or from a large nationwide database. Prediction of preoperative OS could potentially impact multidisciplinary decisions regarding further treatment recommendations for these complex patients. To this end, the purpose of this study was to develop a novel preoperative calculator that accurately predicted OS.

Methods

Patients

The American College of Surgeons National Cancer Data Base (NCDB), 1998–2012, was utilized to identify patients with HCC who had undergone surgical resection. As this study utilized a de-identified national database, it was deemed exempt from IRB review. The NCDB captures 70% of cancer related surgery in the United States. Although data existed for patients from 1998–2013 at the time of the study, survival data was only validated until 2012. Patients with HCC were identified using International Statistical Classification of Diseases (ICD O-3) codes 8170, 8171, 8173, 8174, 8175 and 8180.

Inclusion criteria consisted of patients who had TNM clinical stages 1–3, invasive behavior on pathology, and known vital status. Surgery of the primary site included wedge resection or segmental resection (NCDB site codes 20–25), right or left lobectomy (NCDB site codes 30, 36–37) and right or left extended lobectomy (NCDB site codes 50, 51–52). Patients who underwent segmental resection and local tumor ablation (NCDB site code 26), lobectomy and local tumor destruction (NCDB site code 38) and extended lobectomy and local tumor destruction (NCDB site codes 59) were excluded from analysis as the primary purpose was to develop a calculator for surgical resection only. It is difficult to compare patients who underwent ablation as this carries a higher risk for local recurrence and the indication for surgical ablation vs resection may also be due to underlying liver disease that is not available in dataset.

Local recurrence data is also not available from NCDB for HCC. To ensure exclusion of metastatic patients from analysis, patients with clinical or pathologic stage M1 disease were also excluded. Additionally, patients who had undergone previous treatment were excluded from the analysis.

Statistical analysis

In developing the OS calculator, the patients were randomly divided into building (n_b) and validation (n_v) cohorts using a 80/20 allocation using previously described methods (8,9). Descriptive statistics were reported using the mean, median and standard deviation for continuous variables; and using frequencies and relative frequencies for categorical variables. Cohorts were compared using Mann-Whitney U and Pearson's chi-square tests for continuous and categorical variables respectively. Kaplan-Meier (KM) methods were used to summarize OS, from which estimates of median survival rates were obtained with 95% confidence intervals (CI).

The following analyses were conducted using the n_b cohort. Univariate associations between OS and patient variables were examined using a Cox regression model. The models were fit using Firth's penalized function and hazard ratios (HRs), with 95% CI, were obtained from model estimates. A prediction model was then developed using a multivariable Cox regression model, where the model form was developed in two steps. First, the main effects were chosen using a bootstrap backwards selection (BBS) method (alpha exit =0.1) with selected candidate variables as listed in the model. Second, all two-way interactions between the selected main effects were considered, and significant interactions were selected using the BBS method.

The final model included the selected main effects and two-way interactions; and model estimates were obtained using a multivariable Cox regression model fit using Firth's method. The estimated baseline 1- and 3-year OS rates were obtained from the model using the BASELINE function available in SAS v9.4 software's PHREG procedure, and corresponds to the estimated 1- and 3-year OS rate for individuals with reference-level covariate values. The final model's parameter estimates and the corresponding baseline 1- and 3-year OS estimates were then used to generate 1- and 3-year OS prediction models. The models were recalibrated using standard bootstrap cross-validation methods. Model performance was assessed using time-dependent receiver operating characteristic (ROC) curves, the corresponding area under the ROC curve (AUC), and

calibration plots (10).

The 1- and 3-year OS prediction models were then applied to the n_v cohort, with model performance assessed using ROC curves with corresponding AUC and calibration plots. The calibration plots for 1- and 3-year OS showed the predicted survival rates (grouped by deciles) on the horizontal axis versus the observed survival rates (with corresponding 95% CI) on the vertical axis. These calibration plots identify when the prediction models over, under or accurately predicted the OS rates. All analyses were conducted using SAS v9.4 (Cary, NC, USA), at a significance level of 0.05.

Results

Of 6,297 patients with invasive HCC, 5,455 patients met inclusion criteria and 4,364 (80%) patients were used in the n_b cohort and 1,091 (20%) patients were used in the n_v cohort. The majority of the patients had HCC "not otherwise specified" on histology, and the median size of the resected tumors was 6.0 cm (range, 0.5–9.9 cm). Comparison of and n_b and n_v cohorts based on these variables showed no statistical differences (*Table 1*). In the study population, 32.8% underwent wedge resection, 10.0% underwent partial hepatectomy, 49.9% underwent formal lobectomy, and 7.3% underwent extended lobectomy.

The median OS for the overall cohort was 36 months (95% CI, 34–38 months), and the median follow up was 90 months (95% CI, 0–173 months). There was no difference between the n_b and n_v cohorts with respect to median follow-up or median OS (*Figure 1*).

Several factors associated with OS were analyzed to build the calculator. Factors that were found to be significant on univariate analysis included age, gender, race, Charlson-Deyo score, tumor histology, tumor grade, tumor size, clinical T and N stage, AFP (alpha fetoprotein), presence of cirrhosis, and the degree of surgical resection (*Table 2*). Chemotherapy and radiation therapy were not found to be significant on univariate analysis, which is not unexpected since adjuvant therapy has not been shown to improve survival and thus not recommended by National Comprehensive Cancer Network (NCCN) guidelines.

Although several preoperative factors including AFP, Charlson-Deyo score and presence of biopsy proven cirrhosis were found to be significant on univariate analysis, they were not included in the model. This is because more than 30% of the values were missing and thus would risk being misrepresented in the calculator. Therefore, using the BBS method, only the variables of age, gender, race, tumor histology, tumor grade, tumor size, clinical stage and type of surgery were included in the model.

The equation derived from the OS prediction model is depicted in *Figure 2*. In assessing the accuracy of our model, the area under the ROC curve (AUC) for 1- and 3-year OS were 0.658 and 0.672 respectively, which suggests moderate performance of the model. There was minimal difference between the ROC and the AUC of the n_b cohort compared to the n_v cohort, with the latter AUC values for 1- and 3-year OS being 0.679 and 0.671, respectively (*Figure 3*). This suggested that the model performed reasonably well.

Discussion

Unlike other resectable tumors, the decision to proceed with resection for HCC is more complex. This is partly due to the variety of treatments available including radioembolization, transarterial chemoembolization (TACE), ablation, chemotherapy, surgical resection, or a combination of the therapies. Additionally, the preoperative and postoperative liver function complicates the assessment. The decision on the type of treatment is usually made by multidisciplinary groups. However, there is limited prospective data to compare these treatments to make strong evidence-based decisions at this time. Although both retrospective and prospective studies have shown that for early stage HCC (tumors <5 cm), surgical resection results in improved OS and lower recurrence rate than ablation, there are no prediction calculators that compare these treatments (11-15). For large Barcelona Clinic Liver Cancer (BCLC) stage A tumors, surgical resection has been reported to show improved OS compared to TACE in specific patients. However, the participants in the study were not prospectively matched (16). Some retrospective studies on highly selected patients suggest that for larger tumors (>7 cm), survival is equivalent for resection versus embolization-ablation. However, it is difficult to compare these methods based on known preoperative factors (17,18).

A calculator that estimates OS with known preoperative factors may allow for comparisons of different treatments and assist in the clinical decision making process. It also provides the patients an estimate of their outcome when considering surgical intervention. As an example, if the calculator predicts a low likelihood of 1- and 3-year OS after surgery, then less invasive treatments may be more strongly considered. This may help guide therapy for complex patients. As most retrospective studies show that patients with more advanced tumors are being considered

Table 1 Model building (n_b) and validation (n_v) cohort demographics. Patients diagnosed between 1998 and 2012 were identified from the NCDB. From the entire cohort, 80% were randomly assigned to model development derived from the n_b and 20% to the n_v

Variables	Model building (n_b)	Model validation (n_v)	P value
Overall (n, %)	4,364 (80.0)	1,091 (20.0)	
Age (median, range in years)	65.0 (18.0–90.0)	65.0 (18.0–90.0)	0.57
Gender (n, %)			0.29
Male	2,874 (65.9)	737 (67.6)	
Female	1,490 (34.1)	354 (32.4)	
Race			0.12
White	3,172 (72.7)	766 (70.2)	
Black	478 (11.0)	114 (10.4)	
Other	136 (3.1)	44 (4.0)	
Asian	578 (13.2)	167 (15.3)	
Charlson-Deyo comorbidity score			0.87
0	1,292 (29.6)	318 (29.1)	
1	625 (14.3)	160 (14.7)	
2	297 (6.8)	70 (6.4)	
Missing	2,150 (49.3)	543 (49.8)	
Histology			0.53
HCC NOS	4,089 (93.7)	1,031 (94.5)	
Fibrolamellar	92 (2.1)	17 (1.6)	
Sarcomatoid	10 (0.2)	1 (0.1)	
Clear cell	70 (1.6)	14 (1.3)	
Pleomorphic	4 (0.1)	0 (0.0)	
Combined HCC/ICC	99 (2.3)	28 (2.6)	
Grade			0.54
Well	985 (22.6)	227 (20.8)	
Moderate	1,674 (38.4)	418 (38.3)	
Poor	675 (15.5)	182 (16.7)	
Unknown/undifferentiated	1,030 (23.6)	264 (24.2)	
Tumor size			0.08
(cm, median, range)	6.0 (0.5–9.9)	6.0 (0.5–6.5)	
Clinical T stage			0.33
1	881 (20.2)	241 (22.1)	
2	1,034 (23.7)	236 (21.6)	
3	1,439 (33.0)	382 (35.0)	
4	87 (2.0)	20 (1.8)	
Missing	923 (21.2)	212 (19.4)	

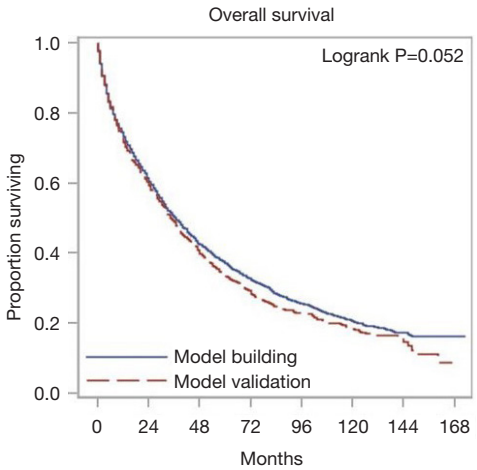
Table 1 (*continued*)

Table 1 (*continued*)

Variables	Model building (n_b)	Model validation (n_v)	P value
Clinical N stage			0.27
0	2,611 (59.8)	679 (62.2)	
1	86 (2.0)	12 (1.1)	
Missing	1,667 (38.2)	400 (36.7)	
Alpha fetoprotein (AFP)			0.35
Non-elevated	413 (9.5)	85 (7.8)	
Elevated	703 (16.1)	166 (15.2)	
Missing	3,248 (74.4)	840 (77.0)	
Cirrhosis			0.81
Yes	138 (3.2)	34 (3.1)	
No	222 (5.1)	58 (5.3)	
Missing	4,004 (91.8)	999 (91.6)	
Surgery			0.94
Wedge resection	1,431 (32.8)	358 (32.8)	
Partial hepatectomy	437 (10.0)	116 (10.6)	
Lobectomy	2,178 (49.9)	538 (49.3)	
Extended lobectomy	318 (7.3)	79 (7.2)	
Margin status			0.40
Negative	3,378 (77.4)	845 (77.5)	
Positive	410 (9.4)	113 (10.4)	
Missing	576 (13.2)	133 (12.2)	
Radiation therapy			0.10
Yes	4,272 (97.9)	1,082 (99.2)	
No	48 (1.1)	6 (0.5)	
Missing	44 (1.0)	2 (0.2)	
30-day mortality			0.42
No	3,961 (90.8)	996 (91.3)	
Yes	374 (8.6)	85 (7.8)	
Missing	29 (0.7)	10 (0.9)	

ICC, intrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; NOS, not otherwise specified.

for or undergoing surgical resection, surgery is often only recommended for those with smaller tumors and good liver performance (19,20). For patients with multifocal disease or extensive disease that requires a more complex operation, the benefit of surgery on OS is less well-established. Nonetheless, these resections are still performed and published especially within Asian centers (21). Therefore, preoperative survival estimates may have a substantial impact on decision making especially in these complex patients. Additionally, preoperative survival estimates can also be used as a gauge for transplantation (if the patient is a potential candidate) or interventional treatment.



Variables	1-year surv. rate (95% CI)	3-year surv. rate (95% CI)	5-year surv. rate (95% CI)	Median surv. (95% CI)	Median follow-up (range)	Sample
Total	0.73 (0.72, 0.74)	0.50 (0.49, 0.51)	0.36 (0.35, 0.38)	36.0 (34.0, 38.0)	90.0 (0.0, 173.0)	E =3,826; C =1,629; T =5,455
Model building	0.73 (0.72, 0.75)	0.50 (0.49, 0.52)	0.37 (0.36, 0.39)	37.0 (34.0, 39.0)	90.0 (0.0, 173.0)	E =3,030; C =1,334; T =4,364
Model validation	0.72 (0.69, 0.74)	0.49 (0.46, 0.52)	0.33 (0.30, 0.36)	35.0 (32.0, 39.0)	91.0 (0.0, 167.0)	E =796; C =295; T =1,091

Figure 1 Kaplan Meier curves for overall survival (OS) comparing model building (nb) and validation (nv) cohorts. Minimal difference between the model building and validation cohorts was observed, with similar median OS of model building cohort (37 months) compared to validation cohort (35 months). CI, confidence interval.

Based on the current literature, the NCDB has not been used to create a preoperative OS calculator for HCC patients. The NCDB allows for a large database of surgically resected patients that captures 70% of cases in the United States. HCC calculators that have been developed were not based on US population databases. The NCDB has been effectively used to power a post-operative calculator for stage 2 and 3 colon cancer (9). Similar to this colon calculator, our HCC calculator takes into account several variables related to survival, like the degree of surgical resection, patient age, race, size of lesion, and the subtype of HCC if known. Input of this data into the calculator can provide an estimate of survival during the preoperative evaluation (22-24). Tumor size and tumor volume has also been suggested as factors that contribute to OS (25). It has been suggested that for patients with early tumors and unfavorable histologic features, anatomic resection can lead to lower rates of early recurrence and improved OS. Interestingly, for patients with well/moderately differentiated tumors, non-anatomic resection can have a similar benefit, decreasing local recurrence and improving OS (15,26-28). Our novel calculator allows the caregiver to compare the estimated OS depending on the extent of resection as part of preoperative planning.

There are several calculators that aim to estimate post-operative survival in HCC patients but are often used to compare other treatment modalities such as ablation or chemoembolization. It has been suggested that some perioperative factors may impact OS and are therefore maybe pertinent to survival calculators. Length of stay and postoperative complications are known to affect long term survival (29-31). However, neither of these items is known preoperatively so they were not pertinent to the formulation of our calculator. Additionally, prognostic biomarkers like those in the 5 gene signature were found to be predictive of recurrence and survival in French patients following resection (32). Gene signature data on HCC patients was not available for our model.

One Asian retrospective series identified a scoring system that incorporated preoperative values of prealbumin, alkaline phosphatase, AFP, tumor size >8 cm, platelet count and gamma-glutamyl transferase (GGT) revealing a 1-year morality rate of 62% in patients with scores ≥5 *vs.* a rate of 5% in patients with scores <5 (33). The patients in

Table 2 Univariate analysis of variables associated with overall survival (OS)

Variable	HR (95% CI)	P value
Age (increase per year)	1.02 (1.02–1.02)	<0.001
Gender		<0.001
Male	1.00	
Female	0.78 (0.72–0.84)	
Race		<0.001
White	1.00	
Black	1.14 (1.02–1.27)	
Other	0.76 (0.61–0.95)	
Asian	0.72 (0.64–0.81)	
Charlson-Deyo score		<0.001
0	1.00	
1	1.22 (1.09–1.37)	
2	1.39 (1.20–1.62)	
Histology		<0.001
HCC NOS	1.00	
Fibrolamellar	0.49 (0.37–0.66)	
Sarcomatoid	2.70 (1.40–5.19)	
Clear cell	1.10 (0.84–1.45)	
Pleomorphic	2.83 (1.06–7.55)	
Combined HCC/ICC	1.30 (1.04–1.63)	
Grade		<0.001
Well	1.00	
Moderate	1.23 (1.11–1.36)	
Poor	1.72 (1.53–1.93)	
Unknown/undifferentiated	1.30 (1.17–1.45)	
Tumor size (mm)	1.00 (1.00–1.00)	0.003
Clinical T stage		<0.001
1	1.00	
2	1.31 (1.13–1.51)	
3	1.73 (1.51–1.98)	
4	3.01 (2.22–4.07)	
Clinical N stage		<0.001
0	1.00	
1	1.75 (1.27–2.42)	
AFP		<0.001
Non- elevated	1.00	
Elevated	1.40 (1.20–1.64)	
Cirrhosis		<0.001
No	1.00	
Yes	1.86 (1.44–2.42)	
Surgery		0.004
Wedge resection	1.00	
Partial hepatectomy	0.80 (0.70–0.92)	
Formal lobectomy	0.93 (0.86–1.01)	
Extended lobectomy	1.04 (0.90–1.20)	

HR, hazard ratio; IC, confidence interval; HCC, hepatocellular carcinoma; NOS, not otherwise specified; ICC, intrahepatic cholangiocarcinoma; AFP, alpha fetoprotein .

the former group also had a higher risk of microvascular invasion, poor tumor differentiation and cirrhosis. This scoring system, however, did not take into account the degree of resection. There are several studies that report an association of inflammatory markers with OS in resection patients including the Glasgow Prognostic Score and inflammation-based score (6,7). These features, however, were also not available for consideration in our model.

There are several limitations to our study. Although several preoperative factors including AFP, Charlson-Deyo score and presence of biopsy proven cirrhosis were found to be significant on univariate analysis, they were not included in the mode as the values were missing for most of the patients. Preoperative AFP is known to be associated with both disease free survival and OS (34). Although it is useful to know preoperative liver function status, the practice of liver biopsy to document cirrhosis is not uniform unless the patient is being considered for transplantation. These variables have been added with more recent data collections of the NCDB and may play a significant role in a future calculator.

With HCC, the causes of recurrence and death are multifactorial. They are related to both the tumor biology

$$P\ (1\text{-year OS}) = 0.96^{\exp(\text{risk score})}$$

$$P\ (3\text{-year OS}) = 0.90^{\exp(\text{risk score})}$$

Risk Score =0.99×[0.022× (Age) −0.24× (Female)
−0.35× (Race=Asian) −0.39× (Race = Other) +0.24× (Race = Black)
−0.0011× (Tumor size in mm)
+0.12× (Undifferentiated) +0.48× (Poorly differentiation) +0.20× (Moderate differentiation)
−0.14× (Fibrolamellar) +1.26× (Sarcomatoid) +0.16× (Clear Cell) +0.97× (Pleomorphic) +0.18× (Combined HCC/ICC)
+ 0.37× (Clinical Stage 2) +0.66× (Clinical Stage 3)
+ (Partial Hepatectomy)× (0.022−0.0029× Age +0.0029× Tumor Size)
+ (Formal Hepatectomy)× (−0.032−0.0020× Age +0.0019× Tumor Size)
+ (Extended Hepatectomy)× (0.88−0.015× Age +0.0021× Tumor Size)]

Figure 2 Model equation estimating overall survival (OS). Likelihood of OS expressed as P (year OS) is a function of risk score calculated by the above factors. Parentheses indicate the type of variable incorporated into the model. For continuous variables including age or tumor size, the numeric value specific to the patient is entered. All other variables are treated as indicator variables whereby the parentheses take on a value of 1 (if the patient has that characteristic value) or a value of 0 if the patient does not. The coefficients were obtained from a Cox regression model based on the model building cohort with the necessary data available. HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

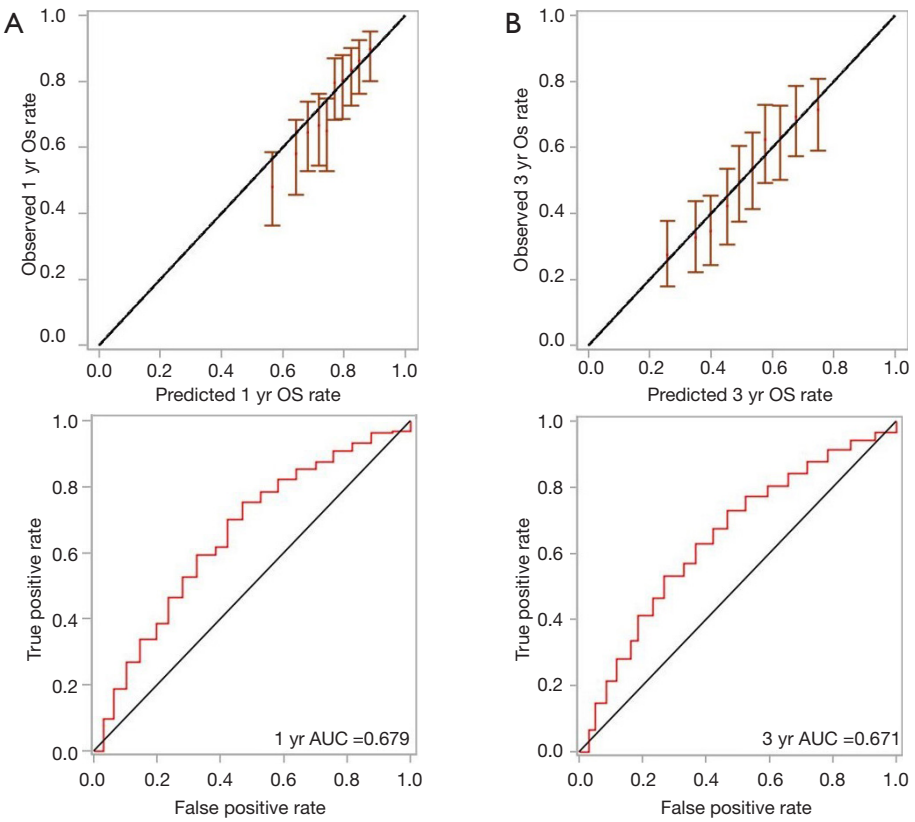


Figure 3 Calibration plots and Receiver Operative Characteristic curves for validation model of overall survival (OS) for (A) 1 year and (B) 3 years. The calibration plots and receiver operating characteristic (ROC) curves for the 1- and 3-year OS prediction models applied to the model validation cohort were based on the patients who had available data as described in the Methods. For the calibration plot, the predicted OS rates (grouped by decile) are plotted against the observed OS rates (as estimated by Kaplan-Meier methods, with error-bars corresponding to 95% CI). The plot of a well performing model will follow the diagonal line, indicating concordance between the observed and predicted rates. For the ROC curve, the closer the value of the area under the curve (AUC) is to 1.0, the higher the performance of the model.

and intrinsic liver function. The power of our calculator is limited by the availability of information related to these factors. The NCDB only provides select elements of liver function as mentioned above and does not contribute related information such as platelet count, INR, Child-Pugh score, and others. The NCDB is also limited on data elements to accurately assess recurrence for HCC, a factor that would further benefit our calculator if known. To obtain an estimate of the OS during the preoperative setting, we purposefully excluded postoperative variables including the length of stay, postoperative complications, or recurrence. Exclusion of these variables may diminish the calculator's accuracy of estimating the OS in the post-operative setting. However, this was not the intended purpose of our calculator.

Despite these limitations, using this calculator we aim to prospectively validate the results with patients from our institutional dataset. Furthermore, as NCDB collects more site specific factors, incorporating additional variables associated with tumor biology and liver function, our calculator's ability to predict OS may be further enhanced. In conclusion, the decision to proceed with surgical resection as opposed to interventional treatment, chemotherapy, or transplantation involves consideration of the likelihood of cure, benefit of survival, technical feasibility, as well as the ability of the patient's liver to tolerate resection. Our preoperative calculator incorporates known factors to assess OS and performs reasonably well in order to contribute to clinical decision-making.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: As this study utilized a de-identified national database, it was deemed exempt from IRB review.

Disclaimer: The American College of Surgeons Committee on Cancer provided the Participant User File from the National Cancer Data Base, but has not reviewed or validated the results or conclusions of our study.

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