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Magnetic Resonance Imaging Predictors of Hepatocellular Carcinoma Progression and Dropout in Patients in Liver Transplantation Waiting List

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Background. With the rising incidence of hepatocellular carcinoma (HCC), more patients are now eligible for liver transplantation. Consequently, HCC progression and dropout from the waiting list are also anticipated to rise. We developed a predictive model based on radiographic features and alpha-fetoprotein to identify high-risk patients. **Methods.** This is a case-cohort retrospective study of 76 patients with HCC who were listed for liver transplantation with subsequent liver transplantation or delisting due to HCC progression. We analyzed imaging-based predictive variables including tumor margin (well- versus ill-defined), capsule bulging lesions, volumetric analysis and distance to portal vein, tumor numbers, and tumor diameter. Volumetric analysis of the index lesions was used to quantify index tumor total volume and volumetric enhancement, whereas logistic regression and receiver operating characteristic curve (ROC) analyses were used to predict the main outcome of disease progression. **Results.** In univariate analyses, the following baseline variables were significantly associated with disease progression: size and number of lesions, sum of lesion diameters, lesions bulging the capsule, and total and venous-enhancing (viable) tumor volumes. Based on multivariable analyses, a risk model including lesion numbers and diameter, capsule bulging, tumor margin (infiltrative versus well-defined), and alpha-fetoprotein was developed to predict HCC progression and dropout. The model has an area under the ROC of 82%, which was significantly higher than Milan criteria that has an area under the ROC of 67%. **Conclusions.** Our model has a high predictive test for patient dropout due to HCC progression. This model can identify high-risk patients who may benefit from more aggressive HCC treatment early after diagnosis to prevent dropout due to such disease progression.

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Hepatocellular carcinoma (HCC) has become the second fastest-growing cancer in the United States,[1] with 600 000 new patients diagnosed worldwide (20 000 in the United States).[2] With the rising incidence of HCC, more patients with HCC are being listed for liver transplantation, cementing it as one of the most common listing diagnoses.[3] However, not all patients with HCC listed for liver transplants can withstand the waitlist duration, which can vary up to 2 y depending on region and blood type. Considering the current waiting period with exception criteria, 20%–35% of US patients eventually drop from the list because of disease progression.[4]

Dropout from the waiting list due to HCC progression occurs despite ongoing bridging therapy with liver-directed treatments such as transarterial chemo-embolization (TACE) and radio-embolization.[5] This suggests there is a substantial heterogeneity of the HCC population on the transplant list, despite strict criteria such as the Milan criteria that limit the tumor burden to a specific size and number.[6] Eligibility is also complicated by a downstaging process that includes baseline tumors beyond Milan criteria but with reduction in tumor burden due to good treatment response.[7]

Understanding that HCC is a heterogeneous disease with various risk factors of disease progression,[8] there is an urgent need to identify those with more aggressive features at risk of progression and dropout earlier in the evaluation process. This is imperative as more than 90% of HCC emerges in cirrhosis and that progressive decline in liver function in these patients often restricts HCC treatment options.[9] Given that systemic therapies in HCC have advanced significantly, including immunotherapy and other tyrosine kinase inhibitors,[10-13] early identification of high-risk patients with HCC using an accurate risk score may now allow for concurrent systemic therapy with standard locoregional treatments before the further decline of their liver function.

Previous studies have associated certain risk factors with a higher dropout rate, including liver decompensation, tumor size, and the number of lesions.[14,15] However, large national database studies are limited to reported 2D tumor dimensions based on standard clinical practice.[16] Recent advances in high-resolution imaging now allow 3D reconstruction of CT and MRI for volumetric analysis and functional imaging measures such as diffusion-weighted imaging and viable tumor volume.[17-19] These clinical tools are yet to be incorporated routinely into prognostic models. Our group has previously shown the predictive use of volumetric imaging analysis in HCC in predicting overall survival.[20] Therefore, this advanced postprocessing of radiographic data from baseline imaging may help identify patients with a high dropout risk due to HCC progression.

We set out to test whether more detailed radiographic parameters, in addition to standard HCC measurements, could better predict which patients with HCC progression while on the liver transplant list would result in dropout from the list. We hypothesized that such a predictive model would include tumor border, volumetric analysis, proximity to a vessel, and touching the capsule. A predictive model will identify high-risk patients for broader or earlier aggressive treatments. To our knowledge, this is the first predictive model for HCC progression while on the liver transplant waitlist.

MATERIALS AND METHODS

This single-center case-control study was HIPAA-compliant and approved by our local institutional review board. We identified 389 patients from the UNOS database listed in our center for liver transplantation between 2010 and 2017, with the primary diagnosis of hepatobiliary malignancy. Of those, we reviewed 69 patients with a confirmed diagnosis of HCC and transplant listing, with subsequent removal from listing due to HCC progression. Patients who were removed from the waitlist due to non–cancer-related medical conditions, psychosocial reasons, or lost follow-up were excluded. Among the included patients were 34 cases with baseline MRI available in our system. We randomly selected for comparison an additional 42 HCC patients who received liver transplantation during the same period with available baseline MRI results. A total of 76 patients met the selection criteria (Figure 1). In this study cohort, 69 out of 76 (91%) patients received TACE. Among those 7 patients who did not receive locoregional treatment, 6 were from liver transplantation group and 1 from progression group. Four patients received radiofrequency ablation, 2 from each group. Two patients from the progression group had sorafenib toward the end of their delisting date. No patients received immunotherapy.

HCC treatment history, transplant listing date, waitlist dropout, and transplantation dates were retrieved from electronic medical records. We obtained clinical data including etiology of liver disease, alpha-fetoprotein (AFP) level, and baseline labs at the time of referral to assess the severity of liver disease using model for end-stage liver disease (MELD) with sodium (MELD-Na). Detailed imaging analysis was performed as described below. Dropout from the waiting list due to HCC progression was the primary outcome for patients in our study.

Imaging Analysis

MRI was independently reviewed and analyzed by 1 senior radiologist and 3 radiology research fellows, blinded to the patient's information. The largest tumor on baseline imaging was selected as the index lesion for all patients; the index lesions were segmented on baseline imaging. Image analysis included the total number of lesions, the diameter of the largest lesion, the sum of diameters of all lesions, lesion bulging outside the liver capsule, lesion touching the liver capsule, lesion touching the portal vein, tumor margin (ill-defined versus well-defined), tumor volume, and volumetric venous enhancement.

Standalone prototype software (Parametric Toolbox, version 1; Siemens Healthcare, Malvern, PA) was used to obtain portal venous enhancement maps from precontrast (P) and portal venous phase (V) images. To calculate venous enhancement maps, $\frac{V-P}{P} \times 100$, precontrast images were coregistered to portal venous phase images by nonrigid 3D registration. They were exported in Digital Imaging and Communications in Medicine format. Subsequently, portal venous phase enhancement maps were uploaded to MR OncoTreat prototype software (MR OncoTreat, Siemens Healthcare, Princeton, NJ) for volumetric analysis. The volume of the tumor and voxel-wise histograms of enhancement values were calculated using the software mentioned above.

Viable tumor volume was derived from venous enhancement maps based on a threshold of viability for venous enhancement. This method was described in a previous study.[21] Voxels with enhancement values equal to or lower than this threshold were considered necrotic, and those above the threshold were deemed viable. The
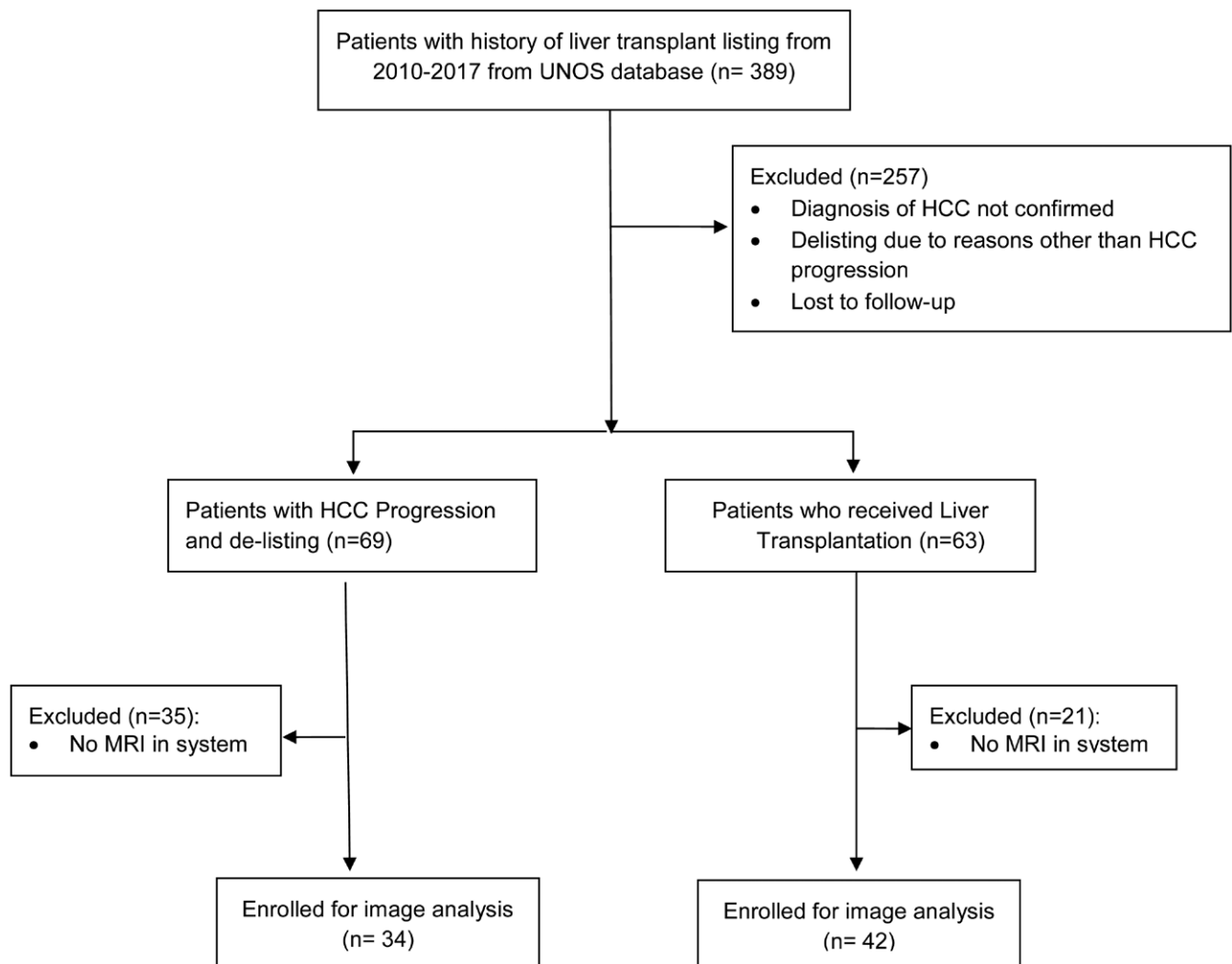
FIGURE 1. Patient selection criteria. Patients were first identified from UNOS database with the diagnosis of "hepatobiliary malignancy" and then subsequently included based on MRI availability and if their delisting was due to HCC progression outside Milan criteria. HCC, hepatocellular carcinoma.

following equation was used to calculate viable volume: $\frac{Number\ of\ voxels\ showing\ enhancement\ above\ threshold}{Total\ number\ of\ voxels} \times$ Tumor volume.

Statistical Analysis

Patients were grouped into those who underwent transplantation and those who progressed. Categorical parameters are presented as the number and percentage, and continuous data as the median and interquartile range. The relationship between variables of interest and group (transplant or progression) was evaluated using the Student's t-test and Wilcoxon rank sum test when appropriate for continuous variables and using the chi-squared test or Fisher's exact test for categorical variables. Logistic regression was used to identify candidates for predictors of disease progression. Multivariable logistic regression predicting disease progression was performed using the selected variables and AFP. Collinearity and dependency among variables were examined, and variables showing a high level of correlation and dependency were removed from the final model. For risk-scoring analysis, continuous variables were dichotomized before performing multivariable logistic regression. Cut-off values were determined based on univariate analyses. From the multivariable model, the predicted risk was calculated using the following formula $\bar{p} = \frac{e^{(b0\ +\ b1X1+b2X2+\ldots+bnXn)}}{1\ +\ e^{(b0\ +\ b1X1+b2X2+\ldots+bnXn)}}$, in which b_0 is the constant and b_1 through b_n are the regression coefficients

(log of odds ratios), X_1 through X_n are dichotomized predictors of disease progression (Yes = 1 and No = 0), and the numerator is the risk score. The model's predictive performance was evaluated by the Hosmer-Lemeshow goodness-of-fit test and the receiver operating characteristic (ROC) analysis. ROC curves for all models were constructed[22] and compared statistically.[15] Prediction model validation was performed using 10-fold cross-validation, in which our data were randomly divided into 10 subgroups. The model was then fitted with the data in the 9 subgroups, and the remaining subgroup was used for validation. The analysis was repeated 10 times, with each subgroup being used once as the validation set. After each analysis, the AUC and the root mean square error were calculated, and from these 10 statistics, the mean, SD, and 95% confidence interval were determined.[23] All analyses were performed using StataCorp 2017 (College Station, TX: Statacorp LLC). $P < 0.1$ was considered suggestive significance for inclusion in model building. For all other analysis, the threshold for statistical significance was at $P < 0.05$.

RESULTS

Meeting the eligibility criteria were 76 patients, of whom 42 received liver transplants (transplant group), whereas 34

TABLE 1.

Baseline clinical characteristics of patients who received liver transplantation vs those with disease progression

		Transplanted (n = 42)	Progressed (n = 34)	P
Age, y, median (range)		63 (44–69)	63 (42–71)	0.757
Sex, n (%)	Female	7 (43.8)	9 (56.2)	0.447
	Male	35 (58.8)	25 (42.2)	
Etiology, n (%)	HCV	23 (51.1)	22 (48.9)	0.803
	HBV	5 (100.0)	0 (0.0)	
	EtOH	4 (66.7)	2 (33.3)	
	HCV, EtOH	1 (20.0)	4 (80.0)	
	NAFLD	7 (58.3)	5 (41.7)	
	EtOH, NAFLD	1 (100.0)	0 (0.0)	
	Other	1 (50.0)	1 (50.0)	
Milan criteria, n (%)	Yes	39 (66.1)	20 (33.9)	<0.001
	No	3 (17.6)	14 (82.4)	
MELD-Na, median (IQR)		8 (7–9)	9 (8–11)	0.075
AFP, ng/mL, median (IQR)		7.4 (4.7–16.3)	23.1 (9.8–122.2)	<0.001
Waitlist duration, d, median (IQR)		316 (250–386)	253 (193–405)	0.212
Listing to end point, d, median (IQR)		269 (205–364)	196 (107–417)	0.210
Number of lesions, median (IQR)		1 (1–1)	2 (1–3)	<0.001
Lesion diameter, cm, median (IQR)		2.5 (1.8–3.3)	3.7 (2.6–4.6)	<0.001
Number of TACE, median (IQR)		1.5 (1–2)	2.5 (1–4)	0.004

AFP, alpha-fetoprotein; EtOH, alcoholic hepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; MELD-Na, model for end-stage liver disease with sodium; NAFLD, nonalcoholic fatty liver disease; TACE, transarterial chemoembolization treatments.

experienced disease progression and were dropped from the waitlist (progression group). Age, sex, MELD, and etiology of liver disease were similar between the 2 groups. As expected, more patients in the transplant group met the Milan criteria at baseline imaging than those in the progression group (66% versus 34%, $P = 0.0004$) (Table 1). In the transplant group, AFP trended to be lower than in the progression group, and the difference was statistically significant ($P = 0.0008$). For those who received a liver transplant (transplant group), time on the waitlist calculated from the day of listing to the day of transplant was longer (269 d) than the duration from listing to dropout (196 d) for those who dropped off the list before a transplantable organ became available (progression group). Duration from first baseline imaging to transplant was 316 d, whereas duration from baseline imaging to waitlist dropout was 253 d. Patients who remained in the transplant group were less likely (mean number 1.5 versus 2.5) to get locoregional treatment with TACE, despite remaining on the waitlist longer than patients in the progression group who dropped out sooner.

To identify the key radiographic differences between the 2 groups, we used logistic regression analysis for each variable. At the significance level of $P < 0.10$, the following baseline radiographic variables were associated with HCC progression and waitlist dropout (Table 2): number of lesions, diameter of dominant lesion, sum of diameters of all lesions, lesion bulging outside of liver capsule, tumor margin, tumor volume and venous enhancement volume of the dominant lesion, and Milan criteria. A tumor touching the portal vein and MELD-Na were not associated with progression. Based on this univariable analysis and the exclusion of collinear and dependent variables, we selected the number of lesions, the diameter of the dominant lesion, capsule bulging lesion, tumor border, and AFP to create a predictor model of HCC progression in the transplant waitlist period.

TABLE 2.

Univariate analysis of clinical and radiographic variables as predictors of disease progression and liver transplantation waitlist dropout

	Odds ratio	95% CI	P
Milan criteria, yes vs no	0.11	0.028-0.427	0.001
MELD-Na, per point	1.07	0.960-1.202	0.210
AFP, per 1 ng/mL	1.01	0.999-1.020	0.078
Number of lesions, multiple vs solitary	5.63	1.960-16.147	0.001
Diameter of dominant lesion, (per 1 cm)	2.42	1.491-3.943	<0.001
Sum of diameters of all lesions, (per 1 cm)	2.20	1.487-3.243	<0.001
Capsule bulging, yes vs no	4.09	1.565-10.687	0.004
Touched portal vein, yes vs no	1.53	0.518-4.520	0.442
Tumor margin, ill-defined vs well-defined	2.57	0.940-7.010	0.066
Tumor volume, (per 1 mL)	1.04	1.008-1.074	0.014
Venous enhancement volume, (per 1 mL)	1.04	1.006-1.075	0.019

AFP, alpha-fetoprotein; CI, confidence interval; MELD-Na, model for end-stage liver disease with sodium.

Multivariable Analysis and Risk Prediction

To build a clinically useful predictor model and risk scoring analysis, we first created cut-off values for the continuous variables. Cut-off values were determined based on our univariate analysis: number of lesions >1, diameter of dominant lesion >3.0 cm, and AFP >60 ng/dL. We performed a multivariable logistic regression analysis (Table 3). At the significance level of $P < 0.05$, the association between disease progression and the number of lesions and dominant lesion diameter was still observed. The associations of tumor bulging, tumor margin, and AFP were attenuated. The direction of all associations remained similar to the univariate analysis, and the Hosmer-Lemeshow goodness-of-fit test ($P = 0.37$) showed that the prediction model was a good fit. As Milan criteria are the standard criteria for transplant eligibility at the time of listing, we compared our prediction model with

TABLE 3.

Multivariable logistic regression analysis predicting disease progression and liver transplantation waitlist dropout (n = 76)

	Odds ratio	95% CI	*P*
Number of lesions, multiple vs solitary	5.88	1.715-20.180	0.005
Lesion diameter of dominant lesion, >3 cm vs ≤3 cm	3.48	1.095-11.086	0.035
Ill-defined margin, yes vs no	1.36	0.385-4.810	0.632
Capsule bulging, yes vs no	2.29	0.731-7.152	0.155
AFP, >60 ng/mL vs ≤60 ng/mL	3.86	0.860-17.346	0.078

AFP, alpha-fetoprotein; CI, confidence interval.

Milan criteria for predicting HCC progression and dropout. This current model improved the prediction of HCC progression by 15% compared with Milan criteria, which has area under the ROC (AUROC) 0.67 (95% confidence interval [CI]: 0.577-0.763). At 83% specificity, the sensitivity of the model is 68% (Figure 2). The model has a high discriminating power for predicting disease progression (AUROC = 0.82, 95% CI: 0.728-0.919). Using a 10-fold cross-validation technique, the model had a mean AUROC of 0.82 (95% CI: 0.633-0.866) and a root mean squared error of 0.43, confirming a strong predictive performance and relatively high accuracy (Figure S1, SDC, http://links.lww.com/TXD/A448).

For clinical application, we then formulated an equation for risk scoring based on the multivariable analysis and, finally, the predicted risk analysis. The predicted risk for HCC progression and waitlist dropout ranged from 83% to 95%, if a patient had any of the 4 predictors (Table 4). Based on this risk score, a patient with 2 lesions, with the largest lesion having a diameter of 2.8 cm, infiltrative tumor margin, bulging the capsule, and AFP of 90 µg/dL would have a risk score of 2.1 and predicted risk of progression of 89%.

DISCUSSION

Despite strict eligibility criteria and bridging therapy for liver transplantation, patients with HCC remain at risk of HCC progression and dropout from the waiting list. This study demonstrated the use of additional radiographic data combined with AFP to develop a predictive risk model for HCC progression and dropout. We also show that 3D volumetric image data can be analyzed from standard high-resolution MR imaging.

Liver transplant eligibility criteria have remained stringent to improve patient outcomes, mainly focused on survival and HCC recurrence after transplantation; limited studies have assessed risk factors for patients dropping off the list due to disease progression. We performed a comprehensive image analysis to consider new radiographic markers associated with HCC progression, including information about tumor characteristics, which is more detailed than that reported in national databases such as UNOS. We also evaluated baseline imaging from all patients referred to liver transplantation, including those outside Milan criteria, to reduce any bias of previous treatment response. Before adopting Milan criteria, Yao et al initially suggested a similar cut-off of tumor lesion size and numbers as predictors for dropout.[24] Since then, studies have associated AFP,[25] multifocal HCC lesions, and MELD as risk factors for overall dropout.[26] Our findings show similar MELDs between transplant and progression groups. This may be due to our selection of dropout cases from HCC progression only, rather than other causes of liver decompensation or transplant-limiting medical conditions.

More accurate prediction of HCC progression and early identification of these high-risk patients on the waitlist have several important implications. First, the treatment landscape of HCC has evolved with more effective systemic treatment options, including new tyrosine-kinase inhibitors and immunotherapy options.[27] Clinical trials are underway to investigate
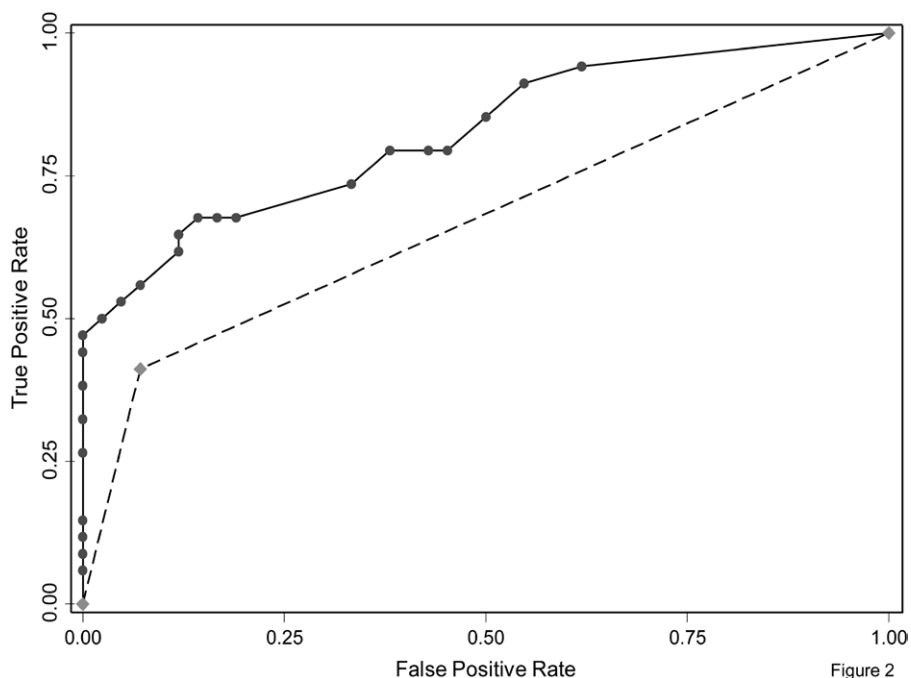

FIGURE 2. Model performance in distinguishing patients who drop out from the waitlist due to HCC progression. Model (solid line) is compared with Milan criteria (dotted line). HCC, hepatocellular carcinoma.

TABLE 4.

Risk score and predicted risk of disease progression and liver transplantation waitlist drop out using selected predictors

Number of lesions >1	Dominant lesion diameter >3 cm	Ill-defined margin	Capsule bulging	AFP >60 ng/mL	Predicted risk
5 out of 5 risk factors					
Yes	Yes	Yes	Yes	Yes	97%
4 out of 5 risk factors					
Yes	Yes	No	Yes	Yes	95%
Yes	Yes	Yes	No	Yes	93%
Yes	No	Yes	Yes	Yes	89%
Yes	Yes	Yes	Yes	No	88%
No	Yes	Yes	Yes	Yes	83%
3 out of 5 risk factors					
Yes	Yes	No	No	Yes	90%
Yes	No	No	Yes	Yes	86%
Yes	Yes	No	Yes	No	84%
Yes	No	Yes	No	Yes	78%
No	Yes	No	Yes	Yes	78%
Yes	Yes	Yes	No	No	76%
No	Yes	Yes	No	Yes	68%
Yes	No	Yes	Yes	No	68%
No	No	Yes	Yes	Yes	58%
No	Yes	Yes	Yes	No	56%
2 out of 5 risk factors					
Yes	No	No	No	Yes	72%
Yes	Yes	No	No	No	70%
No	Yes	No	No	Yes	61%
Yes	No	No	Yes	No	61%
No	No	No	Yes	Yes	51%
Yes	No	Yes	No	No	48%
No	Yes	No	Yes	No	48%
No	No	Yes	No	Yes	38%
No	Yes	Yes	No	No	35%
No	No	Yes	Yes	No	27%
1 out of 5 risk factors					
Yes	No	No	No	No	41%
No	No	No	No	Yes	31%
No	Yes	No	No	No	29%
No	No	No	Yes	No	21%
No	No	Yes	No	No	14%

AFP, alpha-fetoprotein.

combination treatments that include locoregional therapies with systemic treatments for intermediate stage HCC and are expected to impact our transplant patient population.[28] At this critical junction, an accurate risk score for prognosis can identify patients with HCC who may not benefit from locoregional treatment alone. These patients can potentially start concurrent therapy with closer surveillance before the further decline of their liver function.

Some key findings merit further discussion. First, there were no significant differences in MELDs between the groups, as noted in another study, suggesting that patients in these 2 groups had a comparable liver function at baseline. Second, capsule bulging and tumor margin were associated with list dropout. It has been well-known that exophytic lesions and liver capsules are supplied by extrahepatic collateral vessels,[29,30] which may mitigate the embolization effect of TACE. Capsular interruption and irregular tumor margins could indicate microvascular invasion, a prognostic factor for post-transplant recurrence and metastases.[31]

In contrast, volumetric analysis, including tumor volume and venous enhancement volume, was associated with progression in univariate analysis but not in multivariable analysis. This finding contradicts our previous studies that associated volumetric venous enhancement with HCC histology and patients' overall survival in both HCC and intrahepatic cholangiocarcinoma.[21,32] This may be due to the strong effects of the number of lesions and lesion diameter and the dichotomization of continuous variables in the current study cohort. The discrepant finding in this study may include a contribution by the overall smaller tumor volume in general for patients awaiting liver transplantation compared with more advanced stage HCC, or due to smaller sample size, and importantly, limited follow-up duration (ie, transplant or progression exceeding Milan) compared with earlier studies.

Our study has some limitations. This is a single-center retrospective study specific to the demographics in our region. Sample size is relatively small, as patients in the progression group were selected after confirmation that they had dropped off the list because of HCC rather than other causes of dropout including social issues, lack of follow-up, or other medical comorbidities. Furthermore, baseline tumor characteristics at the time of referral may be variable per geographic region,

especially in Asia. Our transplant center also uses the UCSF downstaging protocol, which includes initial tumor burden outside Milan criteria; this may not apply to all other transplant centers. Lastly, regional variability should be considered, as the average waitlist period can impact the incidence of HCC progression when longer waitlist time is associated with higher dropout. Future prospective studies with a larger sample size are needed to validate our results.

In conclusion, HCC progression and dropout from the transplant list are associated with tumor size, the number of lesions, capsule bulging, tumor margin, and AFP levels at baseline. A risk model built from these variables can be used as a predictive test for HCC progression within the transplant waitlist. Overall, our findings imply that HCC patients can be risk-stratified from their baseline MR imaging; those identified as high risk for progression and delisting may benefit from more aggressive treatment, which is now available for HCC.

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