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Impact of Integrating IGF-1 Levels Into MELD Score for Survival Prediction in Hepatocellular Carcinoma Patients

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Abstract

Background: Liver reserve affects survival in hepatocellular carcinoma (HCC). Model for End-Stage Liver Disease (MELD) score is used to predict overall survival (OS) and to prioritize HCC patients on the transplantation waitlist, but more accurate models are needed. We hypothesized that integrating insulin-like growth factor 1 (IGF-1) levels into MELD score (MELD-IGF-1) improves OS prediction as compared to MELD.

Methods: We measured plasma IGF-1 levels in training (n=310) and validation (n=155) HCC cohorts and created MELD-IGF-1 score. Cox models were used to determine the association of MELD and MELD-IGF-1 with OS. Harrell's c-index were used to compare the predictive capacity.

Results: IGF-1 was significantly associated with OS in both cohorts. Patients with an IGF-1 level of ≥ 26 ng/ml in the training cohort and in the validation cohorts had significantly higher hazard ratios than patients with the same MELD but IGF-1 < 26 ng/ml. In both cohorts, MELD-IGF-1 scores had higher c-indices (0.60 and 0.66) than MELD scores (0.58 and 0.60) ($P < .001$ in both cohorts). Overall, 26% of training and 52.9% of validation cohort patients were reclassified into different risk groups by MELD-IGF-1 ($P < .001$).

Conclusions: After independent validation, the MELD-IGF-1 could be used to riskstratify patients in clinical trials, and for priority assignment for patients on liver transplantation waitlist.

Keywords

HCC; IGF-1; MELD; MELD-IGF-1; liver transplantation

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths in the world(1), and has one of the most rapidly rising mortality rates of any cancer in the United States.(2) Most HCC arises in the setting of hepatic cirrhosis from various causes, including viral hepatitis, hemochromatosis, excessive alcohol consumption, and metabolic syndrome. In current clinical practice, multiple HCC prognostic systems are used for risk-stratification to predict overall survival (OS). Model for End-Stage Liver Disease (MELD) score is used to allocate priority amongst HCC patients on the liver transplant waitlist.

Notably, the MELD score was initially developed to predict the 90-day mortality rate among cirrhotic patients who undergo elective transjugular intrahepatic portosystemic shunt (TIPS) procedure.(3) Subsequently, MELD score has been validated as a tool to assess hepatic disease severity and patients' OS in order to improve the allocation of livers to patients on the orthotopic liver transplantation (OLT) waiting list, to predict the mortality rate among patients who did not undergo liver transplantation, and to predict post-transplantation survival rates.(4, 5) MELD score is calculated based on the patient's serum bilirubin and creatinine levels, and international normalized ratio (INR).(6, 7) Higher MELD scores indicate more advanced liver disease and a higher probability of morbidity and mortality, thus higher priority on the OLT waiting. Thus, patients with higher MELD scores receive higher priority on the OLT waiting list.(8-11)

Despite the widespread use of the MELD score, there is still a debate regarding its utility in determining which patients to prioritize on the OLT waiting list.(12) Some patients who have specific conditions, such as portal hypertension, bacterial peritonitis, malnutrition, viral cirrhosis, bacterial cholangitis, and primary sclerosing cholangitis are actually sicker than their MELD score indicates and might die while waiting for an OLT. Furthermore, such patients often need frequent hospitalization, which places a burden on the healthcare system. They, therefore, warrant earlier allocation on the liver transplantation waiting list than their MELD score would indicate to minimize their risk of death.(13) Clinicians try to address this deficiency in the MELD scoring system by adding extra points — called exception MELD points — to the MELD scores of not only patients who have specific conditions but also patients who have certain diseases such as HCC, hepatopulmonary syndrome, and cystic fibrosis. This practice helps some patients get an earlier allocation on the waiting list, but it also causes others who have high MELD scores but no exception points to be moved later on the list.(14) In fact, the use of exception MELD points has conferred advantage to HCC patients in the liver transplant waiting list, with studies showing decreased waitlist mortality/dropout when compared to non-HCC candidates.(15-17) Therefore, refining OS prediction by MELD score is a priority, especially in the HCC population. An important recent study showed that adding serum sodium (Na^+) level to MELD score improved the MELD score's predictive ability of OS, and previous data suggest the MELD- Na^+ score

improves prognostic ability of the MELD system in patients with HCC.(25, 26) However, patient's Na⁺ can be variable based on his current volume status and the use of diuretics to control ascites.

Since blood insulin-like growth factor-1 (IGF-1) is mainly produced by the liver, our previous studies(27-29) in line with reports from other groups(30-34), have demonstrated that IGF-1 is a surrogate biomarker for the synthetic function of the liver, the status of underlying chronic liver diseases, and a significant predictor of OS in patients with chronic liver disease and HCC. Moreover, the expression of IGF-1 is upregulated in HCC, and *in vitro* studies have demonstrated reduction in tumor growth by inhibition of IGF-1.(35-38) In accordance with these findings, lower baseline IGF-1 correlates with worse OS in HCC patients, irrespective of liver dysfunction, and data suggest that IGF-1 levels are useful in identifying HCC patients at greater risk of relapse following TACE or liver resection.(39, 40)

We hypothesized that integrating plasma IGF-1 into the MELD score equation would help overcome the MELD score's current limitations and enables clinicians to better assess underlying chronic liver diseases in HCC patients and more accurately predict their OS.

Materials and Methods

Study Design and Study Population

The study protocol was approved by the MD Anderson Institutional Review Board. A written informed consent was obtained from patients. The procedures followed were in accordance with the ethical standards.

The current study used the same patient cohorts used in our previously published study.(27) Between January 2000 and May 2008, we enrolled 310 HCC patients whom we used as a training cohort. Then, from June 2008 to January 2011, we recruited 155 HCC patients whom we used as an independent validation cohort. We enrolled all patients who had been radiologically and/or pathologically diagnosed with HCC and had available plasma samples. All epidemiological and clinical data were prospectively collected, and we retrospectively analyzed the IGF-1 levels from plasma samples for the training cohort and prospectively for the validation cohort. A detailed description of our methods of blood sample collection and IGF-1 analysis was previously published.(27) In brief, we measured IGF-1 levels using a standard approach and an ELISA-based method. Peripheral blood samples (3-5 mL) were collected, anticoagulated by ethylenediaminetetraacetic acid (EDTA), and centrifuged at 4°C for 15 min at 3000 *rpm*. Plasma samples were aspirated, aliquoted, and frozen at -80°C until analyzed. Samples were analyzed in triplicate according to the manufacturer's instructions using the human IGF-1 Quantikine ELISA kit (Catalogue No. SG100, R&D Systems).

Statistical Analysis

To evaluate whether IGF-1 can provide additional prognostic value for OS after adjusting for the effects of the MELD score, we used a training data set to construct a formula for MELD score and IGF-1 (MELD-IGF-1) using Cox model. Specifically, we fitted this model to estimate the hazard ratio (HR) for MELD and IGF-1 for IGF-1 ≤ 26 ng/ml and IGF-1 > 26

ng/ml groups, respectively. We set an IGF-1 value of 26 ng/ml as the cutoff point because an IGF-1 value $\leq$ 26 ng/ml was previously found to be associated with significantly shorter OS by our group and in the work of others in chronic liver diseases and HCC as well.(27) The MELD-IGF-1 score was then calculated by summing the products of MELD and its normalized HR and of IGF-1 and its normalized HR. The resulting formulas for calculating the MELD-IGF-1 scores are as follows:

For IGF-1 values $\leq$ 26 ng/ml, the MELD-IGF-1 score = $0.269 + 2.068 * \text{MELD}$, and for IGF-1 values $>$ 26 ng/ml, the MELD-IGF-1 score = $0.96 * \text{MELD}$.

We computed the concordance index for each of the MELD and MELD-IGF-1 scoring systems to compare their prognostic capacities(41-43), and both log-rank test and Cox proportional hazards models were used to compare OS among patients with various score levels by using the different scoring systems. Results were thereafter validated in a validation data set.

A univariate analysis using a chi-square or Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables to compare characteristics of the patients in the training and validation data sets. Additionally, we used the Kaplan-Meier method to estimate the median OS, which was defined as the time interval between the date of the blood draw for IGF-1 measurement and the date of death or last follow-up and log-rank test used to detect the statistically significant differences in OS between the MELD and MELD-IGF-1 subgroups. Then, we used the Cox proportional hazard model to calculate HRs and 95% confidence intervals (95% CIs) in order to identify the independent prognostic factors for OS.

Finally, Harrell's c-index was calculated to compare the predictive capacity MELD and MELD-IGF-1 to OS in the training and validation cohorts. S-Plus software, Version 8.2 (TIBCO, Palo Alto, CA); R software, Version 3.0.2 (The R Project for Statistical Computing); SAS software, Version 9.3 (SAS Institute Inc., Cary, NC), and IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY) were used to analyze our data. Two-sided *P* values of less than 0.05 were considered to be statistically significant.

Results

Patient Characteristics

In the training cohort, 218 (70.3%) of the patients were males, and the male-to-female ratio was 2.4:1. In the validation cohort, 113 (72.9%) of the patients were males, and the male-to-female ratio was 2.7:1. Overall, the two cohorts were well matched. The only significant differences in the demographic, clinical, and epidemiological features of the two cohorts were in tumor differentiation ($P = .05$); presence of lymph node, extrahepatic metastasis, and aspartate transaminase levels ($P < .001$), IGF-1 ($P < .0001$); Barcelona Clinic Liver Cancer stage ($P = .009$), MELD-IGF-1 score ($P = .0001$) and the use of local therapy ($P < .001$) (Table 1).

MELD-IGF-1 score in association with overall survival

In a univariate Cox regression analysis (Table 2), we confirmed that MELD score was significantly associated with OS in HCC patients in our cohorts. The MELD score in the training cohort had a HR of 1.08 and 95% CI (1.05 – 1.12) ($P < .001$); in the validation cohort, it had an HR of 1.07 and 95% CI (1.01 – 1.14) ($P = .03$).

When we evaluated the association between OS and plasma IGF-1 after adjusting for the MELD score, our data showed that patients with an IGF-1 ≤ 26 ng/ml had significantly shorter OS than patients with an IGF-1 > 26 ng/ml. This finding was consistent for both the training cohort (HR = 2.003, 95% CI = 1.48 – 2.72, $P < .001$) and the validation cohort (HR = 2.29, 95% CI = 1.4 – 3.76, $P = .001$). Finally, our results supported that the MELD-IGF-1 score was a significant predictor of patients' OS in both cohorts ($P < .001$).

Superior Prognostication for MELD-IGF-1 Score over MELD

Our data showed a statistically significant variation in OS between different categories of the MELD and MELD-IGF-1 scoring systems. In addition, most patients with a risk score of 10 or higher had significantly higher HRs than patients with a risk score of ≤ 9 . The only exceptions were patients in the training cohort with MELD scores of 30-39 and patients in the validation cohort with MELD scores of 20-29 and a MELD-IGF-1 score of ≤ 40 . These patients had higher HRs, but the differences were not statistically significant, which may have been a result of the very small sample sizes within these classes. (Table 3)

Incorporating plasma IGF-1 levels into the MELD score improved this score's prognostic capacity. The MELD-IGF-1 score's c-index (0.60), was higher than the MELD score (0.58), and the P value was $< .001$ for the training cohort. The same result was obtained in the validation cohort, where the MELD-IGF-1 score's c-index was 0.66, compared to 0.60 for MELD's c-index ($P < .001$).

Impact of Reassignment of Patients from MELD to Different MELD-IGF-1 Categories

Based on the availability of these scores' parameters, we obtained MELD data for 299 patients in the training cohort and 155 patients in the validation cohort. When we assessed the redistribution of patients from MELD to MELD-IGF-1, we found that 26% of patients in the training cohort and 52.9% of patients in the validation cohort were reclassified into different risk groups when using MELD-IGF-1 scoring (Figure 1). For a MELD scores of 10-19, a significant number of patients (42.8% in training and 77.2% in validation sets) changed to new categories of MELD-IGF-1 with different survival estimates.

In the training cohort, 150 out of 174 patients (86.2%) classified with a score ≤ 9 in both the MELD and MELD-IGF-1 scoring systems had a median OS of 21.78 months (95% CI: 15.04 – 28.53 months) (Table 5). Their counterparts in the validation cohort, 60 of 95 patients (63.2%) hadn't reached their median OS yet. In contrast, in the validation cohort 35 out of 95 patients (36.8%) who were classified with a MELD score ≤ 9 and reclassified by MELD-IGF-1 into class 10-19 had a significantly worse median OS (18.89 months; 95% CI: 12.11– 25.67 months) than patients who had a score ≤ 9 in both the MELD and MELD-IGF-1 scoring systems (HR = 1.996; $P = 0.04$). This result was not statistically significant in

the training cohort ($HR = 1.24$; $P = 0.4$), but the ability to find statistical significance in this effect may have been affected by the small sample size for this comparison that is due to the fact that only 22 of 174 patients who classified as MELD score 9 and reclassified by MELD-IGF-1 into class 10-19 in that cohort.

Moreover, of the 112 patients in the training cohort classified with a MELD score of 10-19, 24 (21.4%) were reclassified with a MELD-IGF-1 score of 20-29 (median OS = 6.34 months; $HR = 2.37$; 95% CI: 1.43 – 3.93; $P = .001$) and 12 (10.7%) were reclassified with a MELD-IGF-1 score of 30-39 (median OS = 1.48 months; $HR = 8.1$; 95% CI = 4.02 – 16.32; $P < .001$). Of the 57 patients in the validation cohort classified with a MELD score of 10-19, 13 patients remained under same category (median OS = 22.64 months), 5 patients were reclassified as 9 (median OS not reached, $HR = .86$; 95% CI = 0.17 – 4.25; $P = 0.8$), 32 (56.1 %) were reclassified with a MELD score of 20-29 (median OS = 9.04 months; $HR = 2.12$; 95% CI: 0.84 – 5.36; $P = 0.1$) and 7 (12.3%) were reclassified with a score of 30-39 (median OS = 3.71 months; $HR = 3.1$; 95% CI: 0.94 – 10.2; $P = 0.06$). We see a trend in these data with similar median OS and HR across these comparisons, but not statistically significant results.

Discussion

In our study, we found that higher MELD and MELD-IGF-1 scores are significantly associated with shorter OS in HCC patients. However, the MELD-IGF-1 concordance index demonstrated that MELD-IGF-1 was a significantly better predictor of OS than the original MELD score. Importantly, a substantial number of patients were reclassified to different risk categories per MELD-IGF-1 score, which suggests that MELD-IGF-1 may more accurately predict expected survival than originally presumed by the original MELD score which could subsequently change their priority score on the waitlist and change how we allocate organs for liver transplantation. Additionally, for non-surgical candidates, the new MELD-IGF-1 score could complement current prognostic HCC staging systems and aid in risk stratifying patients' before clinical trials entry.

Notably, although the MELD score is widely used as standard tool used to prioritize patients for liver transplantation based on their probability of death, it has several limitations. For instance, there is a debate regarding the correlation between a higher MELD score and a shorter OS.(10, 18-22) Moreover, the majority of HCC patients have underlying cirrhosis and develop serious conditions related to portal hypertension such as refractory ascites, hepatic encephalopathy, hepatorenal syndrome, and variceal bleeding, which are important prognostic factors not inherently taken in consideration by the MELD score despite the fact that they are all critically important in evaluating the severity of liver disease, OS, and determining the need for and timing of OLT.(13, 44) Additionally, two previous studies (45, 46) showed that the differences in the INR, as well as in bilirubin and creatinine levels result in significant differences in MELD scores between different centers. Therefore, refining MELD score ability to predict OS is a priority. A recent example of this strategy is the incorporation of serum Na^+ levels into MELD score calculations (MELD-Na), which has led to improving the ability to predict patient's survival.(47) However, hyponatremia can be induced in HCC patients by several transient factors affecting patient's volume status other

than cirrhosis, e.g., poor nutrition, the administration of intravenous hypotonic fluids and diuretics, as well as excessive vomiting and diarrhea.

We believe that IGF-1 incorporation into MELD is very valuable from the biologic standpoint given that more than 75% of blood circulating IGF-1 is synthesized by the liver (30-32). In fact, a mounting evidence accumulating from studies published by our group and others (27-34), confirmed the role of plasma IGF-1 concentration in determining the liver reserve capacity in HCC patients as well as its correlation with OS. Notably, previous study reported that the MELD score has a C-index of 0.83 as compared with 0.76 for the Child-Turcotte-Pugh (CTP) score(4). Although the difference between C-indices was < 0.07 , it was statistically significant ($P < .001$). (4) Similarly, in our study, differences in C-indices between MELD and MELD-IGF-1 was .06, however, they were statistically significant. Therefore, we conclude that the MELD-IGF-1 score was more accurate than the MELD score in predicting OS in both our training and validation cohorts. Of note, 26% of the training cohort and 52.9% of the validation cohort (for MELD score 10-19, 42.8% and 77.2%, respectively) were reclassified into different risk groups by MELD-IGF-1 ($P < .001$).

Importantly, reclassification of patients from the MELD to the MELD-IGF-1 score showed that 32.1% of the patients who were classified as MELD score 10-19 and reclassified into higher scores based on MELD-IGF-1 had significantly higher HR for death compared to patients who were classified into the same risk group by both scoring systems. A better OS prediction of patients within this MELD category (10-19) is a key to their prioritization on the liver transplantation waitlist since they obtain extra 13 additional MELD points as long as their tumors remain within transplant criteria.

A major strength of our study is the large number of the patients included which enabled testing the MELD and MELD-IGF-1 scoring systems using two independent cohorts with available comprehensive clinicopathological and demographic data, and the inclusion of retrospective training and prospective validation cohorts. Furthermore, OS prediction was validated in an independent heterogeneous group of 155 patients with significant differences in some clinicopathological parameters and therapies received. Additionally, IGF-1 is a laboratory variable that is routinely assessed in daily practice; therefore, the new score can be easily implemented in routine clinical practice. Finally, our study is clinically meaningful given the significant number of patients whose prognostic classification changes based on IGF-1 integration into MELD.

Our study had a few potential limitations. The single-institution design could lend itself to selection bias, especially since many of our patients are not transplant candidates when we first evaluated them. However, we tested and validated MELD score in 2 different cohorts and showed the significant OS prediction by MELD-IGF-1 over MELD. However, further validation studies in HCC transplant candidates is therefore warranted. Moreover, because the two cohorts were chosen based on their temporal presentation [before or after June 2008], there were recent changes/advances in local and systemic treatment options over the course of the two eras, which could have influenced the OS model. Both cohorts had significant differences in several factors including tumor stage and IGF-1 levels. Nevertheless, despite these differences, the prognostic value of IGF-1 and its integration into

MELD have been validated. Finally, because the majority of our patients were treated with different local and systemic therapies at different time points than initial blood draw dates, we could not establish a correlation between the pre-treatment MELD-IGF-1 score and response to specific therapies. Therefore, future randomized studies are warranted to evaluate the ability of pre-treatment MELD-IGF-1 score to predict therapy outcomes and also to compare MELD-Na to MELD-IGF1.

In conclusion, integrating the circulating plasma levels of IGF-1 into the MELD score significantly improved the score's ability to predict OS in 2 independent cohorts of HCC patients. After validation in HCC patients on liver transplant waitlist, priority assignment according to the MELD-IGF-1 may result in improved OS prediction and earlier transplantation. However, further international validation in larger studies is warranted to assess the prognostic and predictive significance of the MELD-IGF-1 score in patient populations who have different demographics, disease risk factors, and clinicopathological parameters.

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Abbreviations:

HCC	Hepatocellular Carcinoma
IGF-1	Type 1 Insulin-Like Growth Factor
MELD	Model for End-Stage Liver Disease
CI	Confidence Interval
HR	Hazard Ratio
IGF-1, MELD-IGF-1	Model for End-Stage Liver Disease Incorporating Type 1 Insulin-Like growth Factor
OLT	Orthotopic Liver Transplantation
OS	Overall Survival
SD	Standard Deviation

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Figure 1: Redistribution of HCC patients between the different MELD scoring systems. A) From the MELD score to the MELD-IGF-1 score in the training cohort. B) From the MELD score to the MELD-IGF-1 score in the validation cohort.

Table 1:

Baseline characteristics of patients in the training and validation cohorts

Patient characteristic	Parameter	Training cohort N=310 (%) [*]	Validation cohort N=155 (%) [†]	P value
Age (years)	60	136 (43.9%)	67 (43.2%)	.92
	>60	174 (56.1%)	88 (56.8%)	
Sex	Male:female ratio	2.4:1	2.7:1	.59
	Male	218 (70.3%)	113 (72.9%)	
	Female	92 (29.7%)	42 (27.1%)	
Viral hepatitis	HCV, HBV, or both	139 (44.8%)	78 (50.3%)	.28
	None	171 (55.2%)	77 (49.7%)	
Serum α -FP (ng/mL)	<400	207 (66.8%)	99 (63.9%)	.15
	400	97 (31.3%)	56 (36.1%)	
Tumor differentiation	Well	122 (39.4%)	49 (31.6%)	.05
	Moderate	100 (32.3%)	42 (27.1%)	
	Poor	52 (16.7%)	38 (24.5%)	
Tumor nodularity	Uninodular	108 (34.8%)	47 (30.3%)	.2
	Multinodular	192 (61.9%)	108 (69.7%)	
% of liver involvement	50%	203 (65.5%)	113 (72.9%)	.14
	>50%	103 (33.2%)	41 (26.5%)	
Vascular invasion	Yes	88 (28.4%)	54 (34.8%)	.3
	No	221 (71.3%)	100 (64.5%)	
Lymph node metastasis	Yes	126 (40.6%)	90 (58.1%)	<.001
	No	181 (58.4%)	65 (41.9%)	
Extrahepatic metastasis	No	242 (78.1%)	70 (45.2%)	<.001
	Yes	66 (21.3%)	85 (54.8%)	
ALT (U/L)	40	137 (44.2%)	67 (43.2%)	.84
	>40	171 (54.8%)	88 (56.8%)	
AST (U/L)	45	93 (30%)	26 (16.8%)	<.001
	>45	192 (61.9%)	129 (83.2%)	
IGF-1 (ng/ml)	>50	133 (42.9%)	61 (39.4%)	<.0001
	26-50	109 (35.2%)	17 (10.9%)	
	<26	68 (21.9%)	77 (49.8%)	
Cirrhosis	No	116 (37.4%)	52 (36.4%)	.83
	Yes	194 (62.6%)	93 (63.6%)	
CTP score	A	221 (71.2%)	126 (81.3%)	.06
	B	79 (25.5%)	25 (16.1%)	
	C	8 (2.6%)	4 (2.6%)	
BCLC stage	0	20 (6.5%)	2 (1.3%)	.009

Patient characteristic	Parameter	Training cohort N=310 (%) [*]	Validation cohort N=155 (%) [†]	P value
	A	27 (8.7%)	13 (8.4%)	
	B	30 (9.7%)	17 (11%)	
	C	196 (63.2%)	119 (76.8%)	
	D	23 (7.4%)	4 (2.5%)	
MELD	MELD score (Mean ± SD)	9.75 ± 3.43	9.76 ± 3.36	.98
	9	176 (56.8%)	95 (61.3%)	.9
	10-19	116 (37.4%)	57 (36.8%)	
	20-29	6 (1.9%)	3 (1.9%)	
	30-90	1 (0.3%)	0	
	40	0	0	
MELD-IGF	MELD-IGF score (Mean ± SD)	12.11 ± 7.55	15.42 ± 9.14	<.001
	9	164 (52.9%)	65 (41.9%)	.008
	10-19	91 (29.4%)	48 (31%)	
	20-29	28 (9%)	32 (20.6%)	
	30-90	13 (4.2%)	7 (4.5%)	
	40	3 (1%)	3 (1.9)	
Treatment history	Systemic ± Local therapy	143 (46.1%)	89 (57.4%)	<.001
	Local therapy only	29 (9.4%)	40 (25.8%)	
	Surgery ± Local therapy	94 (30.3%)	15 (9.7%)	
	Best supportive care	44 (14.2%)	11 (7.1%)	

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; α-FP, α-fetoprotein; ALT, alanine transaminase; AST, aspartate transaminase; IGF, insulin like growth factor; CTP, Child-Turcotte-Pugh; BCLC, Barcelona Clinic Liver Cancer; MELD, Model for End-Stage Liver Disease; MELD-IGF, Model for End-Stage Liver Disease incorporating insulin-like growth factor 1; SD, standard deviation;

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^{*} Some baseline (at time of blood draw) clinical information were missing from patients' medical records in the training cohort including (AFP, N=6; tumor differentiation, N=36; tumor nodularity, N=10; tumor involvement, N=4; vascular invasion, N=1; lymph node metastasis, N=3; extrahepatic metastasis, N=2; ALT, N=2; AST, N=25; CTP score, N=2; IGF-CTP score, N=11; BCLC stage, N=14)

[†] Some baseline (at time of blood draw) clinical information were missing from patients' medical records in the validation cohort including (tumor differentiation, N=26; tumor involvement, N=1; vascular invasion, N=1)

Table 2:

Cox models used to evaluate the association between overall survival (OS) and both MELD and MELD-IGF in two independent cohorts

Scores	Training cohort			Validation cohort		
	HR	95%CI	P value	HR	95%CI	P value
MELD	1.08	1.05 – 1.12	<.001	1.07	1.01 – 1.14	.03
IGF (26 vs >26)*	2.003	1.48 – 2.72	<.001	2.29	1.4 – 3.76	.001
MELD-IGF	1.07	1.05 – 1.1	<.001	1.04	1.02 – 1.07	<.001

Abbreviations: HR, hazard ratio; MELD, Model for End-Stage Liver Disease; MELD-IGF, Model for End-Stage Liver Disease incorporating insulin-like growth factor 1;

* IGF adjusted for MELD

Table 3:

Cox model results for overall survival in two cohorts by MELD and MELD-IGF classes

Scoring system	Class	Training cohort (N = 310)				Validation cohort (N = 155)			
		N	E	Median OS, months (95% CI)	P value	No	E	Median OS, months (95% CI)	P value
MELD	9	174	124	19.78 (13.85 – 25.71)	<.001	95	37	NA (NA – NA)	.01
	10-19	112	94	10.38 (6.30 – 14.46)		57	32	16.23 (3.4 – 29.06)	
	20-29	6	6	2.3 (0.05 – 4.55)		3	2	21.78 (NA – NA)	
	30-90	1	1	8.35 (NA – NA)		0	0	-----	
	40	0	0	-----		0	0	-----	
MELD-IGF	9	162	116	21.78 (15.18 – 28.38)	<.001	65	23	NA (NA – NA)	<.001
	10-19	87	66	13.67 (9.61 – 17.72)		48	22	19.91 (11.34 – 28.48)	
	20-29	28	27	6.34 (4.94 – 7.75)		32	19	9.04 (5.74 – 12.33)	
	30-90	13	13	2.23 (0.77 – 3.7)		7	5	3.71 (NA – 10.12)	
	40	3	3	1.25 (0.36 – 2.14)		3	2	21.78 (NA – NA)	
MELD					P value			HR (95% CI)	P value
	9							1 (Reference)	
	10-19			1.6 (1.22 – 2.1)	.001			1.99 (1.24 – 3.2)	.004
	20-29			7.47 (3.22 – 17.35)	<.001			2.37 (0.57 – 9.89)	.2
	30-90			2.73 (0.38 – 19.67)	.3			-----	-----
MELD-IGF	40			-----	-----			-----	-----
	9			1 (Reference)				1 (Reference)	
	10-19			1.27 (0.94 – 1.71)	.1			1.72 (0.95 – 3.08)	.07
	20-29			2.51 (1.64 – 3.83)	<.001			3.31 (1.79 – 6.11)	<.001
	30-90			9.01 (4.93 – 16.45)	<.001			4.28 (1.62 – 11.29)	.003
	40			20.72 (6.28 – 68.32)	<.001			2.99 (0.7 – 12.77)	.1

Abbreviations: OS, overall survival; CI, confidence interval; MELD, Model for End-Stage Liver Disease; MELD-IGF, Model for End-Stage Liver Disease incorporating insulin-like growth factor 1

Table 4:

Concordance index for MELD and MELD-IGF in two independent cohorts

Scores	Training cohort			Validation cohort		
	C-index	95% CI	P value	C-index	95% CI	P value
MELD	0.58	0.53 - 0.62	<.001	0.60	0.53 - 0.68	<.001
MELD-IGF	0.60	0.56 - 0.64		0.66	0.59 - 0.68	

Abbreviations: c-index, concordance index; CI, confidence interval; MELD, Model for End-Stage Liver Disease; MELD-IGF, Model for End-Stage Liver Disease incorporating insulin-like growth factor 1

Table 5: Log-rank and Cox model results for overall survival and redistribution between MELD and MELD-IGF scores in two cohorts

Cohort	Original MELD Score	Level	N	Event	Median OS, months (95%CI)	HR (95%CI)	P value
Training cohort	9		174	124	19.78 (13.85 – 25.71)		
		MELD-IGF					
		9	150	107	21.78 (15.04 – 28.53)	1 (Reference)	
		10-19	22	16	10.94 (NA – 22.08)	1.24 (0.74 – 2.11)	.4
		20-29	2	1	13.54 (NA – NA)	0.55 (0.08 – 3.91)	.5
	10-19	30-39	0	0	-----	-----	
		40	0	0	-----	-----	
		10-19	112	94	10.38 (6.30 – 14.46)		
		MELD-IGF					
Validation Cohort	9		95	37	NA (NA – NA)		
		MELD-IGF					
		9	60	21	NA (NA – NA)	1 (Reference)	
		10-19	35	16	18.89 (12.11 – 25.67)	1.996 (1.04 – 3.85)	.04
	10-19	10-19	57	32	16.23 (3.4 – 29.06)		
		MELD-IGF					
		10-19	13	6	22.64 (NA – NA)	1 (Reference)	
		9	5	2	NA (NA – NA)	0.86 (0.17 – 4.25)	.8
		20-29	32	19	9.04 (5.74 – 12.33)	2.12 (0.84 – 5.36)	.1
		30-39	7	5	3.71 (NA – 10.12)	3.1 (0.94 – 10.2)	.06

Abbreviations: OS, overall survival; CI, confidence interval; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; MELD-IGF, Model for End-Stage Liver Disease incorporating insulin-like growth factor I; NA, not available