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The Effect of Model for End-Stage Liver Disease 3.0 on Disparities between Patients with and without Hepatocellular Carcinoma in Korea

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Purpose: The model for end-stage liver disease (MELD) 3.0 has recently been suggested for determining liver allocation. We aimed to apply MELD 3.0 to a Korean population and to discover differences between patients with and without hepatocellular carcinoma (HCC).

Materials and Methods: This study is a retrospective study of 2203 patients diagnosed with liver cirrhosis at Severance Hospital between 2016–2022. Harrell's concordance index was used to validate the ability of MELD scores to predict 90-day survival.

Results: During a mean follow-up of 12.9 months, 90-day survival was 61.9% in all patients, 50.4% in the HCC patients, and 74.8% in the non-HCC patients. Within the HCC patients, the concordance index for patients on the waitlist was 0.653 using MELD, which increased to 0.753 using MELD 3.0. Among waitlisted patients, the 90-day survival of HCC patients was worse than that of non-HCC patients with MELD scores of 31–37 only (69.7% vs. 30.0%, p=0.001). Applying MELD 3.0, the 90-day survival of HCC patients was worse than that of non-HCC patients across a wider range of MELD 3.0 scores, compared to MELD, with MELD 3.0 scores of 21–30 and 31–37 (82.0% vs. 72.5% and 72.3% vs. 24.3%, p=0.02 and p<0.001, respectively).

Conclusion: MELD 3.0 predicted 90-day survival of the HCC patients more accurately than original MELD score; however, the disparity between HCC and non-HCC patients increased, particularly in patients with MELD scores of 21–30. Therefore, a novel exception score is needed or the current exception score system should be modified.

Key Words: MELD score, MELD 3.0, liver cirrhosis, hepatocellular carcinoma

INTRODUCTION

Liver transplantation (LT) is a life-saving treatment for patients with advanced liver disease, including liver cirrhosis, hepatocellular carcinoma (HCC), and acute liver failure. The mortality of patients who received LT is decreasing, attributable principally to changes in organ allocation policies using the model for end-stage liver disease (MELD) score.[1] MELD score predicts 90-day survival in patients with end-stage liver disease.[2-4] Using the "sickest first" principle,[5,6] MELD score was used to prioritize LT in the United States up to 2016, at which time MELD-NA score replaced MELD score.[7] Similarly, Korea replaced Child-Turcotte-Pugh score with MELD score for liver allocation in 2016.[8,9]

The MELD-NA score assesses the short-term survival rate of patients with end-stage liver disease, although several concerns remain, including gender disparities, in liver allocation. Several researchers have observed that MELD-NA scores are underestimated in females because baseline creatinine levels are generally lower in females than in males.[10,11] Furthermore,

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concerns have been raised about the decreasing accuracy of MELD-NA for predicting 90-day survival.[12] Hence, MELD 3.0, an updated version of MELD for the modern era, has been suggested as a new standard for determining the priority of liver allocation.[13] The major updates include additional points for females, incorporation of albumin levels and interaction terms, and adjustment of maximum creatinine values.

Patients on the waitlist for LT due to HCC are less likely to receive liver from deceased donors, and exception scores are given when determining the priority of HCC patients, which varies by country.[14] A scoring system for HCC patients with TNM-staged T2 lesions (T2: single tumor more than 2 cm in diameter that has invaded a blood vessel or several tumors all less than 5 cm in diameter) was first implemented in 2005,[15] and several revisions were later made when issues arose in terms of HCC patient over-prioritization. Currently, in the US, all HCC patients receive identical scores after 6 months of a waiting period, and the score increases over time. In Korea, additional points are added to the MELD scores of HCC patients who meet the Milan criteria.[16,17] It is, therefore, necessary to validate whether MELD 3.0 can be a new candidate for determining liver allocation in this domestic setting.

Here, we validate MELD 3.0 in a Korean population, especially in HCC patients who are eligible for Korean MELD exception policy, using data on inpatients treated at a single tertiary medical center.

MATERIALS AND METHODS

Study population

This retrospective study was performed in Severance Hospital in Seoul, Korea. A total of 2203 patients diagnosed with liver cirrhosis with a MELD score of 15 or more from 2016 to 2022 were included, regardless of waitlist enrollment. The flow of study population is shown in Fig. 1. The exclusion criteria were 1) age 18 years or less (n=9), 2) follow-up loss within 1 month (n=204), except for loss caused by death or LT, and 3) a history of LT (n=56). Finally, 1936 participants were analyzed. The population was further divided into four groups: HCC patients who were waitlisted (n=248), those without HCC who were waitlisted (n=384), those with HCC but not waitlisted (n=742), and those without HCC and not waitlisted (n=562). This study was approved by the Institutional Review Board of Severance Hospital (IRB 4-2022-0078). The need for informed consent was waived.

Clinical outcomes

All patients were followed up every 3–6 months. Laboratory tests, including routine blood chemistry parameters and serological viral markers, were evaluated. Patients underwent HCC surveillance (assessment of α-fetoprotein levels and ultrasonography) at each visit. Patients with hepatic decompensation were defined as those with at least one of ascites, variceal bleeding, hepatic encephalopathy, or liver failure.[18] HCC was diagnosed histologically or radiologically via dynamic computed tomography and/or magnetic resonance imaging (a nodule >1 cm in diameter with arterial hyper-vascularity and portal/delayed-phase washout).[19]

Definitions of MELD, MELD 3.0, and MELD exceptions

When calculating MELD and MELD 3.0 scores, we used the following formulae:

$$MELD = 9.57 * \log_e(\text{creatinine}) + 3.78 * \log_e(\text{bilirubin}) + 11.20 * \log_e(\text{INR}) + 6.43$$[2]

$$\text{MELD 3.0} = 1.33\ (\text{if female}) + [4.56 * \log_e(\text{bilirubin})] + [0.82 * (137 - \text{Na})] - [0.24 * \log_e(\text{bilirubin}) * (137 - \text{Na})] + [9.09 * \log_e(\text{PT INR})] + [11.14 * \log_e(\text{creatinine})] + [1.85 * (3.5 - \text{albumin})] - [1.83 * (3.5 - \text{albumin}) * \log_e(\text{creatinine})] + 6$$[13]

All scores were rounded to the nearest integers.

In terms of the MELD exceptions for HCC patients, we allotted an additional 4 points to patients with MELD scores of 0–13 and 5 points to those with scores between 14–20. Patients with scores between 21–25 were adjusted to a total of 25 points. This reflected the current policy of the Korean Network for Organ Sharing (KONOS).[17]

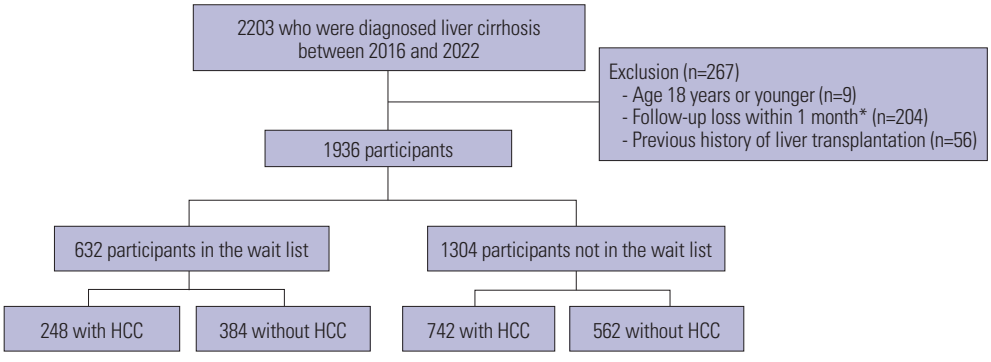

Fig. 1. Flow diagram of the study. *Follow-up loss due to death or liver transplantation was not excluded. HCC, hepatocellular carcinoma.

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Statistical analysis

Continuous variables are shown as means±SDs and categorical variables as frequencies with percentages. The baseline characteristics of patients with and without HCC were compared using Student's t-test and the Pearson chi-square test. To assess the accuracy of 90-day survival prediction, we used the concordance index of Harrell, et al.[20]: For each pair of patients, if the score and survival show similar tendencies, the pair is considered concordant. If not, the pair is discordant. The concordance index is calculated by dividing the number of concordant pairs by the sum of the number of concordant and discordant pairs. Survival and LT events were explored via Kaplan-Meier analysis. When evaluating survival outcomes, patients who underwent LT were considered as censored. The log-rank test was used to compare the survival of two groups. Two-sided *p*-values less than 0.05 were considered statistically significant. All statistical analyses were conducted using R ver. 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

The mean patient age was 60.5 years and 73.6% were male (Table 1). Of the 1936 patients, 990 (51.1%) had HCC at enrollment and 946 (48.9%) did not. Patients with HCC were older (63.2 years vs. 57.8 years, $p<0.001$); more often male (81.2% vs. 65.4%, $p<0.001$); showed a lower prothrombin time international normalized ratio (PT INR, 1.5 vs. 1.8, $p<0.001$), lower total bilirubin level (6.6 mg/dL vs. 9.2 mg/dL, $p<0.001$), lower MELD score (20.0 vs. 22.4, $p<0.001$), and lower MELD 3.0 score (22.5 vs. 24.5, $p<0.001$); and underwent less LT (8.0% vs. 20.5%, $p<0.001$) than those without HCC.

Of the 632 patients who were waitlisted, 248 (39.2%) had HCC at enrollment and 384 (60.8%) did not (Table 2). Patients with HCC were older (60.6 years vs. 53.2 years, $p<0.001$), more often male (81.5% vs. 66.2%, $p<0.001$), showed lower PT INR (1.5 vs. 1.9, $p<0.001$), lower total bilirubin level (6.2 mg/dL vs. 12.1 mg/dL, $p<0.001$), lower MELD score (19.9 vs. 23.9, $p<0.001$), and lower MELD 3.0 score (22.1 vs. 26.2, $p<0.001$); and underwent less LT (16.9% vs. 30.5%, $p<0.001$) than those without HCC. Of 1304 patients not waitlisted, 742 (56.9%) had HCC at enrollment and 562 (43.1%) did not (Supplementary Table 1, only online). Patients with HCC were older; more often male; and had lower creatinine and sodium levels, lower PT INR, and lower MELD and MELD 3.0 scores; and underwent less LT than patients without HCC.

90-day survival

During a mean follow-up of 12.9 months, the 90-day survival rate was 61.9% overall, 50.4% in the HCC patients, and 74.8% in the non-HCC patients (Fig. 2). Waitlisted patients without and with HCC and non-waitlisted patients without and with HCC showed 90-day survival rates of 84.3%, 69.8%, 69.1%, and 44.1%, respectively (Supplementary Fig. 1, only online).

Concordance index values for MELD and MELD 3.0 according to HCC and LT waitlist status

The concordance index values for waitlisted patients were 0.662 [95% confidence interval (CI) 0.604–0.716] for MELD and 0.696 (95% CI 0.644–0.743) for MELD 3.0 (Table 3 and Supplementary Fig. 2, only online). After application of the Korean exceptions, the concordance index values were 0.716 (95% CI 0.666–0.761) for MELD and 0.741 (95% CI 0.695–0.741) for MELD 3.0. The concordance index values for waitlisted patients with HCC at enrollment were 0.637 (95% CI 0.554–0.712) for MELD and 0.697 (95% CI 0.626–0.759) for MELD 3.0. After applying the MELD exceptions, the concordance index values

Table 1. Baseline Characteristics of the Study Population

	Total (n=1936)	HCC at enrollment (n=990)	Non-HCC at enrollment (n=946)	*p* value
Age (yr)	60.5±12.5	63.2±11.0	57.8±13.4	<0.001
Diabetes mellitus	830 (42.6)	431 (43.5)	399 (41.2)	0.577
Male sex	1425 (73.6)	804 (81.2)	619 (65.4)	<0.001
Creatinine (mg/dL)	1.6±0.8	1.5±0.7	1.6±0.8	0.259
PT INR	1.6±1.1	1.5±0.5	1.8±1.4	<0.001
Total bilirubin (mg/dL)	7.9±8.1	6.6±6.7	9.2±9.2	<0.001
Sodium (mmol/L)	133.6±3.9	133.3±4.0	134.0±3.4	<0.001
Albumin (g/dL)	2.8±0.5	2.8±0.5	2.8±0.5	0.654
MELD	21.2±5.8	20.0±4.9	22.4±6.4	<0.001
MELD 3.0	23.5±6.2	22.5±5.5	24.5±6.7	<0.001
Liver transplantation	273 (14.1)	79 (8.0)	194 (20.5)	<0.001

HCC, hepatocellular carcinoma; PT INR, prothrombin time international normalized ratio; MELD, model for end-stage liver disease.
The values are n (%) or means±SDs.

Table 2. Baseline Characteristics of the Patients on the Waitlist

	Total (n=632)	HCC at enrollment (n=248)	Non-HCC at enrollment (n=384)	*p* value
Age (yr)	56.1±10.7	60.6±8.0	53.2±11.2	<0.001
Diabetes mellitus	300 (47.5)	125 (50.4)	175 (45.6)	0.269
Male sex	456 (72.2)	202 (81.5)	254 (66.2)	<0.001
Creatinine (mg/dL)	1.5±0.7	1.4±0.7	1.5±0.7	0.744
PT INR	1.8±1.2	1.5±0.4	1.9±1.5	<0.001
Total bilirubin (mg/dL)	9.8±9.4	6.2±6.8	12.1±10.4	<0.001
Sodium (mmol/L)	133.6±4.0	133.8±3.9	133.4±4.0	0.207
Albumin (g/dL)	2.8±0.5	2.8±0.5	2.8±0.5	0.978
MELD	22.3±6.6	19.9±4.9	23.9±7.0	<0.001
MELD 3.0	24.6±6.8	22.1±5.4	26.2±7.1	<0.001
Liver transplantation	159 (25.2)	42 (16.9)	117 (30.5)	<0.001

HCC, hepatocellular carcinoma; PT INR, prothrombin time international normalized ratio; MELD, model for end-stage liver disease.
The values are n (%) or means±SDs.

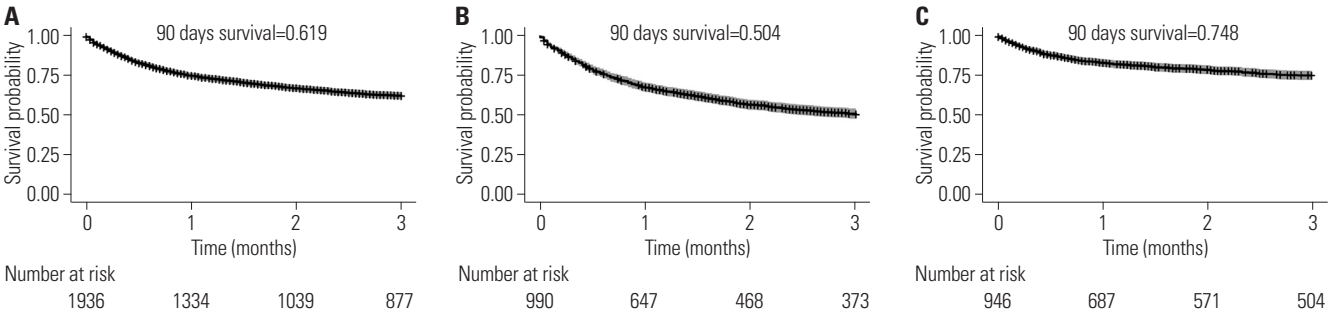

Fig. 2. 90-day survival of (A) all patients, (B) HCC patients, and (C) non-HCC patients. HCC, hepatocellular carcinoma.

Table 3. Concordance Index Values for the MELD and MELD 3.0 Criteria According to HCC Status and Waitlist Enrollment Status

	MELD	MELD 3.0	MELD (HCC exception)	MELD 3.0 (HCC exception)
On waitlist				
All	0.662 (0.604–0.716)	0.696 (0.644–0.743)	0.716 (0.666–0.761)	0.741 (0.695–0.741)
HCC	0.637 (0.554–0.712)	0.697 (0.626–0.759)	0.635 (0.548–0.715)	0.753 (0.683–0.812)
Non-HCC	0.772 (0.705–0.827)	0.777 (0.717–0.827)	-	-
Not on waitlist				
All	0.620 (0.593–0.645)	0.689 (0.665–0.712)	0.670 (0.644–0.695)	0.721 (0.695–0.746)
HCC	0.634 (0.603–0.664)	0.707 (0.679–0.734)	0.630 (0.595–0.663)	0.734 (0.702–0.764)
Non-HCC	0.662 (0.614–0.706)	0.701 (0.657–0.761)	-	-

HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.
The values are concordance index values with 95% confidence intervals.

were 0.635 (95% CI 0.548–0.715) for MELD and 0.753 (95% CI 0.683–0.812) for MELD 3.0. The concordance index values for waitlisted patients who did not have HCC at enrollment were 0.772 (95% CI 0.705–0.827) for MELD and 0.777 (95% CI 0.717–0.827) for MELD 3.0.

Reclassification of patients using MELD 3.0

Of the non-HCC patients who were waitlisted (n=384), 106 (27.6%) were up-categorized from MELD to MELD 3.0, whereas 11 (2.9%) were down-categorized (Table 4). In patients of the same MELD category, up-categorized patients exhibited poorer survival than down-categorized patients or those whose categories did not change. Of the HCC patients who were waitlisted (n=248), 31 (12.5%) were up-categorized and 15 (6.1%) were down-categorized. Again, up-categorized patients exhibited poorer survival than down-categorized patients or those whose categories did not change.

In terms of all patients and those not waitlisted, the reclassifications were similar to those of waitlisted patients. More patients were up- than down-categorized, and in general, up-categorized patients exhibited poorer survival than down-categorized patients or those whose categories did not change, except for non-waitlisted HCC patients with MELD scores of 31–37 who were up-categorized to 38 or higher by MELD 3.0 (66.7%), compared to those whose categories did not change (78.3%). The numbers of all of reclassified patients and their survival rates are shown in Supplementary Table 2 (only online), and the numbers of reclassified non-waitlisted patients and their survival rates are listed in Supplementary Table 3 (only online).

LT events in HCC and non-HCC patients

Among waitlisted patients, the LT rate of HCC patients was worse than that of non-HCC patients with MELD scores of 21–30 and 38–40 (22.5% vs. 37.5%, p=0.001 and 100% vs. 92.7%, p=0.04 respectively) (Fig. 3). When MELD 3.0 was used to classify patients, the LT rate of HCC patients was worse than that of non-HCC patients with MELD 3.0 scores of 21–30 and 31–37 (20.6% vs. 22.2%, p=0.03 and 22.1% vs. 61.4%, p=0.03, respectively) (Fig. 3), but better in HCC patients than in non-HCC patients with MELD 3.0 scores of 38 or higher (100% vs. 80.1%, p=0.02) (Fig. 3).

Survival of HCC and non-HCC patients

The survival of waitlisted patients is shown in Fig. 4. When classified by MELD, the 90-day survival of HCC patients was worse than that of only non-HCC patients with MELD scores of 31–37 (69.7% vs. 30.0%, p=0.001) (Fig. 4C). When MELD 3.0 was used to classify patients, the 90-day survival of HCC patients was worse than that of non-HCC patients across a wider range of MELD 3.0 than MELD scores, with MELD 3.0 scores of 21–30 and 31–37 (82.0% vs. 72.5%, p=0.02 and 72.3 vs. 24.3%, p<0.001, respectively) (Fig. 4F and G).

When non-waitlisted patients were classified by MELD, the 90-day survival of those with MELD scores of 0–20 and 21–30 differed between HCC and non-HCC patients (p<0.001 and <0.001 respectively) (Supplementary Fig. 3, only online). When MELD 3.0 was applied, the 90-day survival of those with MELD 3.0 scores of 0–20, 21–30, and 31–37 differed between HCC and non-HCC patients (p<0.001, p<0.001, and p<0.001, respec-

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Table 4. Re-Classification of Participants on the Waitlist According to MELD and MELD 3.0 Scores

	A. Non-HCC patients					B. HCC patients					C. All patients				
	MELD 3 0				Total	MELD 3.0				Total	MELD 3.0				Total
	0–20	21–30	31–37	38+		0–20	21–30	31–37	38+		0–20	21–30	31–37	38+	
1. Total patients (n)															
MELD															
0–20	92	68	0	0	160	3	18	0	0	21	95	86	0	0	181
21–30	4	116	31	0	151	13	191	11	0	215	17	307	4	0	328
31–37	0	2	39	7	48	0	2	6	2	10	0	42	45	9	96
38–40	0	0	5	20	25	0	0	0	2	2	0	0	5	22	27
Total	96	186	75	27	384	16	211	17	4	248	112	435	54	31	632
2. Number of deaths (n)															
MELD															
0–20	1	5	0	0	6	1	2	0	0	3	2	7	0	0	9
21–30	0	21	6	0	27	0	48	9	0	57	0	69	2	0	71
31–37	0	0	7	3	10	0	2	3	2	7	0	15	10	5	30
38–40	0	0	2	2	4	0	0	0	0	0	0	0	2	2	4
Total	1	26	15	5	47	1	52	12	2	67	2	91	14	7	114
3. Deaths (%)															
MELD															
0–20	1.1	7.4	0	0.0	3.8	33.3	11.1	0.0	0.0	14.3	2.1	8.1	0.0	0.0	5.0
21–30	0	18.1	19.4	0.0	17.9	0.0	25.1	81.8	0.0	26.5	0.0	22.5	50.0	0.0	21.6
31–37	0	0	17.9	42.9	20.8	0.0	100.0	50.0	100.0	70.0	0.0	35.7	22.2	55.6	31.3
38–40	0	0	40.0	10.0	16.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	40.0	9.1	14.8
Total	1.0	14.0	20.0	18.5	12.2	6.3	24.6	70.6	50.0	27.0	1.8	20.9	25.9	22.6	18.0

HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.
A: Total numbers of patients, numbers of deaths, and proportions of deaths (numbers of deaths divided by the total number) for non-HCC patients. B: Total numbers of patients, numbers of deaths, and proportions of deaths of HCC patients. C: Total numbers of patients, numbers of deaths, and proportions of deaths among all patients.

tively) (Supplementary Fig. 3, only online).

To assess the magnitude of the discrepancy of survival between HCC and non-HCC patients with identical MELD 3.0 scores, we gave the HCC patients additional points until the survival rates between the two groups were similar. The survival of patients who received additional exception scores in MELD 3.0 is shown in Fig. 5. When HCC patients with MELD 3.0 scores of 21–30 received an additional 5 points, the 90-day survival of those with MELD 3.0 scores of more than 38 differed between HCC and non-HCC patients (42.6% vs. 58.6%, p=0.002) (Fig. 5D). When HCC patients with MELD 3.0 scores of 21–30 acquired an additional 10 or 15 points, all groups showed identical survival (Fig. 5E-L).

DISCUSSION

We applied the MELD 3.0 scoring system to a Korean population with a focus on disparities between HCC and non-HCC patients. Patients with HCC had lower PT INRs and total bilirubin levels than those without HCC and had lower MELD and MELD 3.0 scores. When patients were stratified by their MELD and MELD 3.0 scores, HCC patients with MELD scores of 21–30 and 38–40 and MELD 3.0 scores of 21–30, 31–37, and 38 or higher underwent LT less often than non-HCC patients with the same MELD and MELD 3.0 scores.

Among the HCC patients, those who did not meet the Milan criteria or too futile to get transplanted were not waitlisted. Patients who had contraindications to LT, such as extrahepatic malignancy or metastasis, were also not waitlisted. Of the non-HCC patients, those whose liver diseases were not sufficiently terminal for us to discuss LT with the patient were not enrolled in the waitlist. Fewer patients with HCC than without HCC underwent LT, although it should be noted that transplantation events encompass both deceased donor liver transplantation (DDLT) and living donor liver transplantation (LDLT). Of the 277 patients who underwent LT, 32.1% underwent LDLT and 67.9% underwent DDLT. Of the 79 patients with HCC who underwent LT, 22.8% underwent DDLT and 77.2% underwent LDLT.

When we analyzed the concordance index values of MELD 3.0, the concordance index values of participants on the waitlist with HCC increased from MELD to MELD 3.0. Other groups had no statistically significant difference between concordance index values using MELD and MELD 3.0. The absolute value of the concordance index value (0.777) in non-HCC waitlisted pa-

tients using MELD 3.0 was smaller than that calculated in a previous study,[13] which was 0.8693 using Harrell's method.[20] This is explained by differences in the patient populations and survival rates, especially of those who underwent LT. In the previous MELD 3.0 study, over half (55.3%, calculated from the table) of the validation set had MELD-NA scores less than 20;

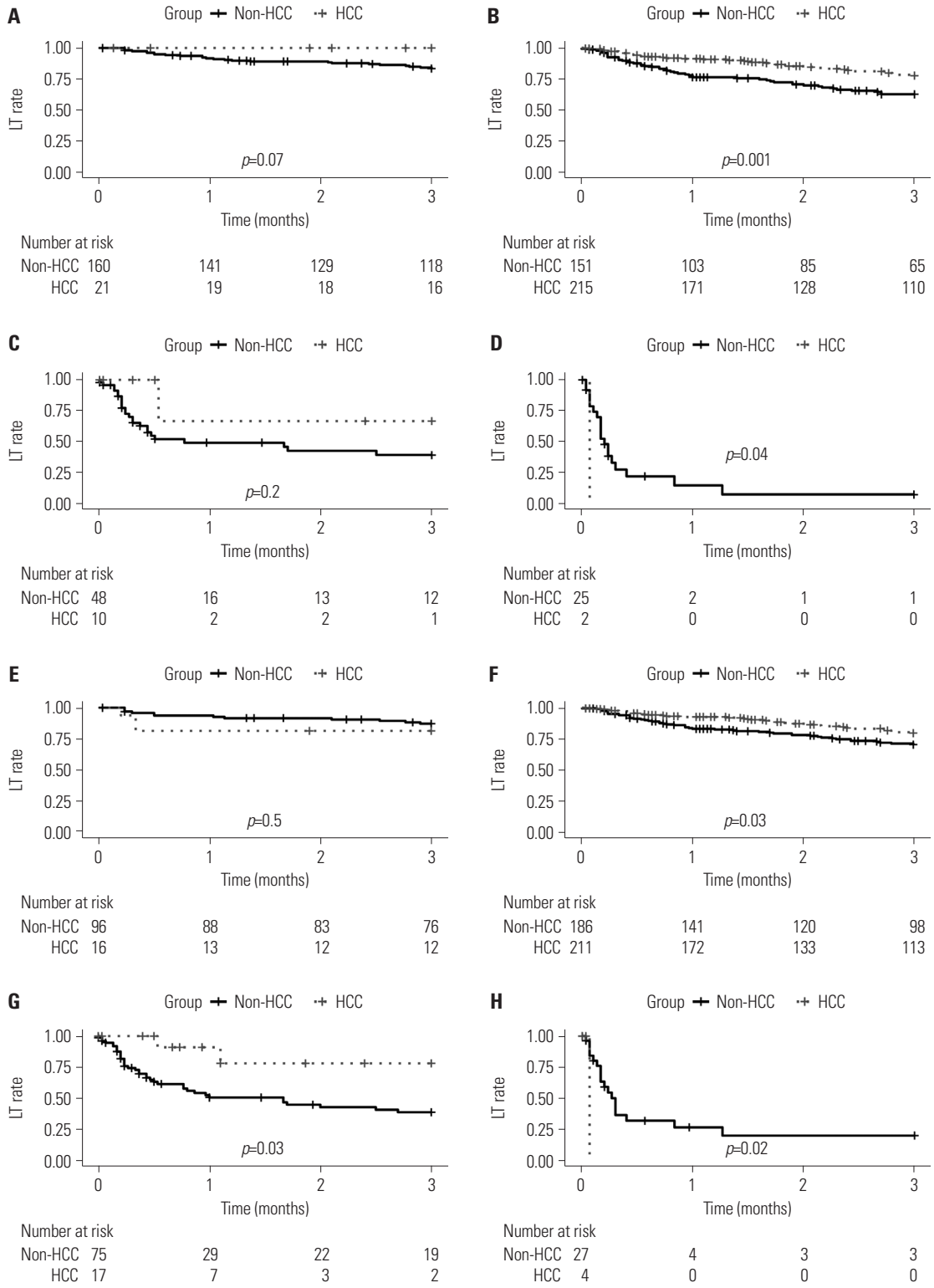

Fig. 3. The liver transplantation rates of HCC and non-HCC patients on the waitlist. Transplantation rates of patients with (A) MELD scores of 20 or lower, (B) MELD scores 21–30, (C) MELD scores of 31–37, (D) MELD scores of 38–40, (E) MELD 3.0 scores 20 or lower, (F) MELD 3.0 scores of 21–30, (G) MELD 3.0 scores of 31–37, and (H) MELD 3.0 scores of 38 or higher. HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

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in our present study, only 41.7% of waitlisted patients without HCC had MELD scores of 20 or less. Also, in the previous study, the mortality rate of patients with MELD-NA scores 21–29 was 7.9% in the validation set, whereas in our study, the mortality rate of patients with MELD scores of 21–30 was 17.9%. Moreover, the median MELD score at the time of LT in the US was

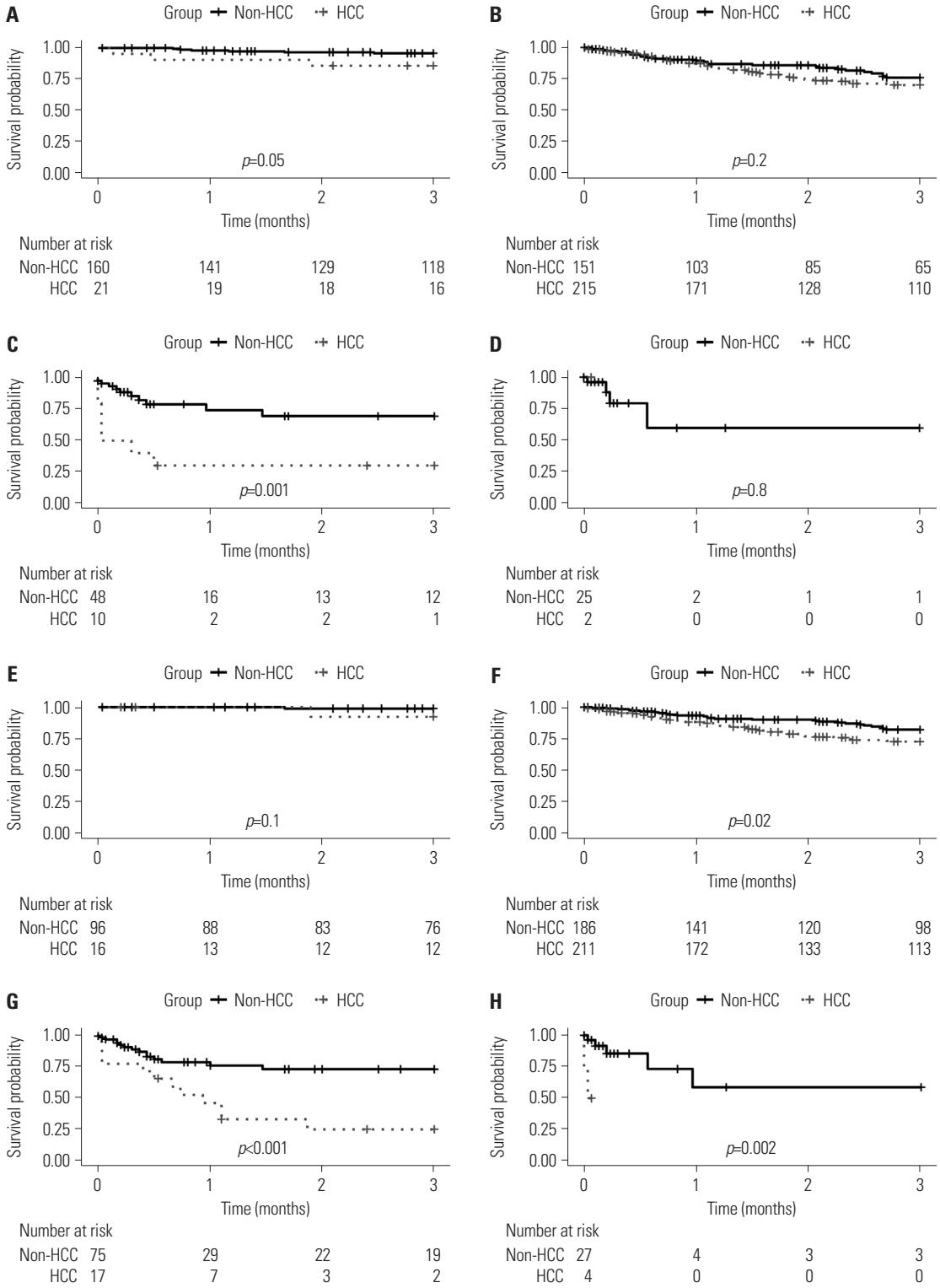

Fig. 4. Differences in 90-day survival between HCC and non-HCC patients on the waitlist. The survival rates of patients with (A) MELD scores of 20 or lower, (B) MELD scores of 21–30, (C) MELD scores of 31–37, (D) MELD scores of 38–40, (E) MELD 3.0 scores of 20 or lower, (F) MELD 3.0 scores of 21–30, (G) MELD 3.0 scores of 31–37, and (H) MELD 3.0 scores of 38 or higher. HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

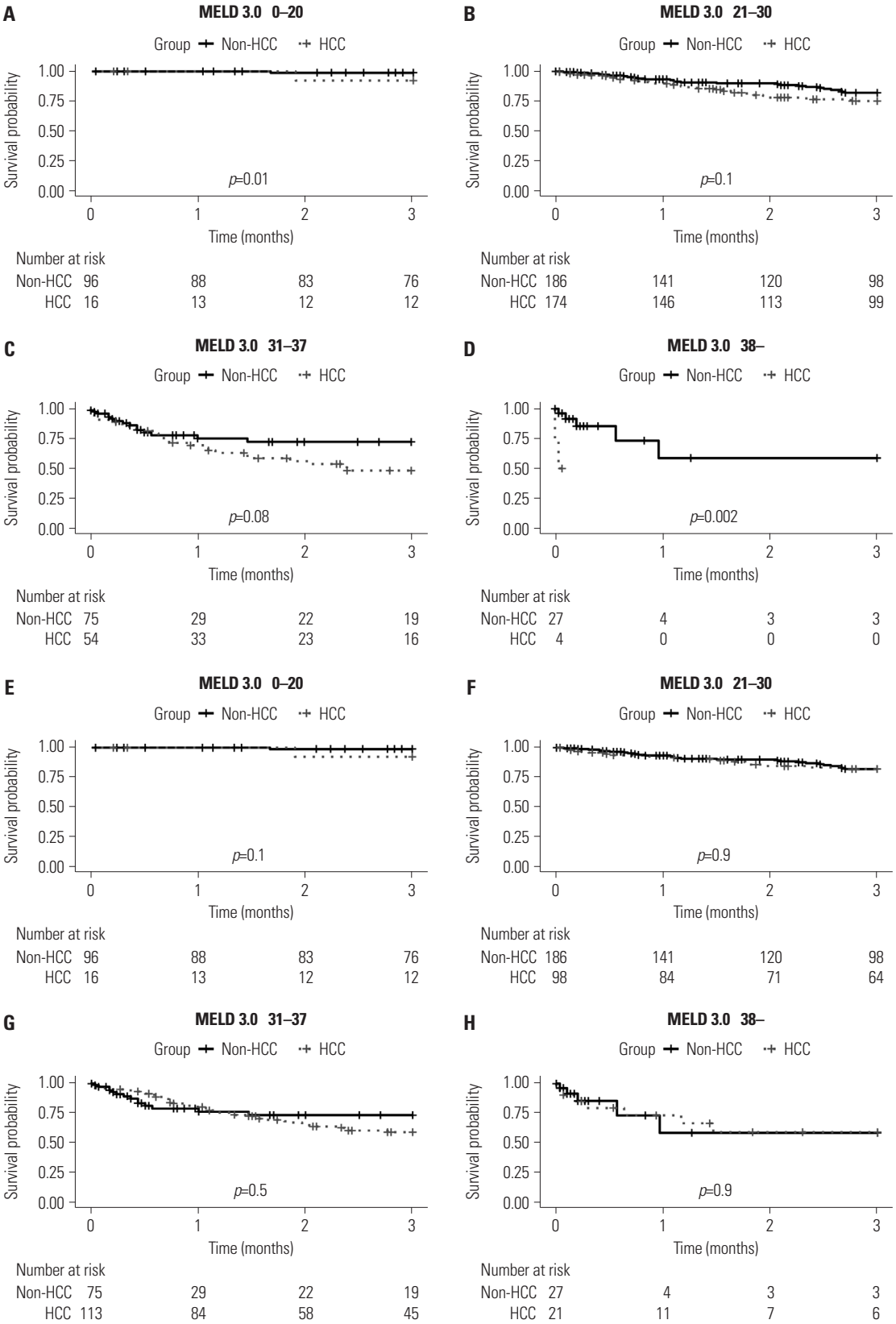

Fig. 5. 90-day survival of HCC and non-HCC patients on the waitlist when additional points were given to HCC patients. MELD 3.0 scores in participants with MELD scores of 21–30 received an additional 5 points for those of (A-D), 10 points for those of (E-H), and 15 points for those of (I-L). (A, E, I) The survival of patients with MELD 3.0 scores of 20 or lower. (B, F, J) The survival of patients with MELD 3.0 scores of 21–30. (C, G, K) The survival of patients with MELD 3.0 scores of 31–37. (D, H, L) The survival of patients with MELD 3.0 scores of 38 or higher. HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

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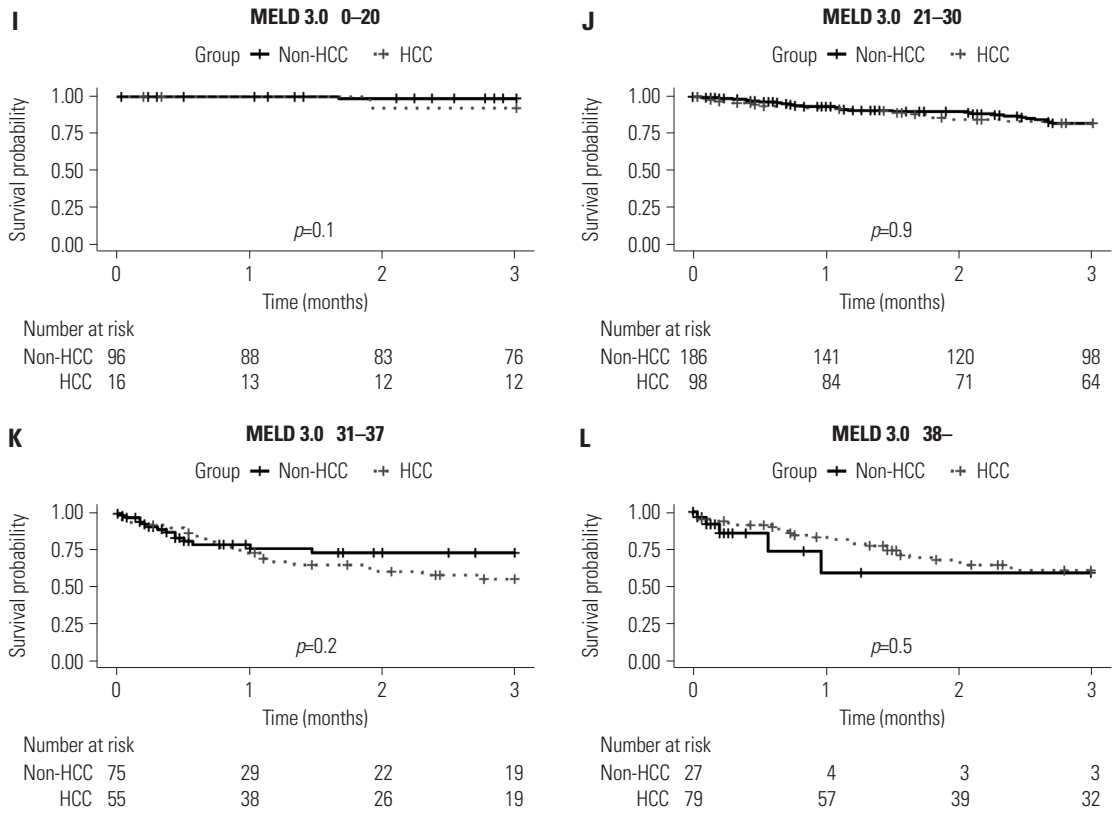

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23–30 depending on the region;[1] in Korea, the average MELD score at LT was 36.8.[21] Therefore, we suspect that these differences in the patient populations may have contributed to the discrepancy in the concordance index values.

Generally, patients up-categorized from MELD to MELD 3.0 had more death proportion than those not up-categorized, except for up-categorized HCC patients not on the waitlist, with MELD scores of 31–37 and MELD 3.0 scores of 38 or higher, compared to those whose categories did not change. This result is in agreement with that of a previous study on MELD 3.0, and the trend was maintained in all groups, including those on the waitlist and those not and those with and without HCC. Thus, MELD 3.0 predicted 90-day survival more accurately than MELD, consistent with our analysis using the concordance index.

On survival analysis of patients stratified by MELD, those with HCC and MELD scores of 31–37 showed lower survival rates than those without HCC. When patients were stratified by MELD 3.0, those with HCC and MELD 3.0 scores of 21–30 and 31–37 showed lower survival rates than those without HCC. MELD 3.0 increased the 90-day survival difference between patients with and without HCC, especially for individuals with MELD 3.0 scores of 21–30. To assess the magnitude of this difference, we added 5, 10, and 15 points to the scores of HCC patients with MELD 3.0 scores of 21–30. All additions lessened the disparity between those with and without HCC; the addition of 10 rendered the survival curves and 90-day survival nearly identical. In summary, MELD 3.0 performs better than MELD in terms of predicting 90-day survival of both HCC and non-HCC patients. However, currently, patients with HCC undergo less LT than those without HCC, and MELD 3.0 increases the difference in 90-day survival between HCC and non-HCC patients, exacerbating underestimation of disease severity in HCC, compared to non-HCC patients. Therefore, MELD 3.0 may require a new exception to ensure equity.

The MELD HCC exception system varies by country and has undergone many revisions to allocate liver transplants to HCC and non-HCC patients equally. For example, in the US, exception scores for HCC patients with lesions of grade T2 were implemented in 2005,[15] followed by several revisions when issues arose in terms of over-prioritization of HCC patients. Currently, the Organ Procurement and Transplantation Network/United Network for Organ Sharing uses a median MELD at transplant within the donor service area minus 3 points (MMaT-3) policy for liver allocation to HCC patients. HCC patients receive MMaT-3 points after 6 months of wait period, and the score increases by 3 points for each additional 3 months. In contrast, in Korea, additional points are given to HCC patients who

meet the Milan criteria. Currently, we give 4 additional points to patients with MELD scores between 0–13, 5 to patients with scores between 14–20, and patients with scores between 21–25 are adjusted to a total of 25 points.[17]

We could consider exception scores that are independent of disease severity given to all HCC patients at certain times, as in the US, or we could revise the current exception scores to correct the disparity between HCC and non-HCC patients. One important thing to consider is the high average MELD score at LT in Korea. After implementation of the MELD system in 2016, the average MELD score at LT was 36.8±4.5.[21] Another point to consider in Korea is a high LDLT rate. In 2017, the proportion of DDLTs of the total LT cases was 25% in Korea.[22] The LDLT rate was especially high in HCC patients, which accounted for 85.9% (1056 of 1229) of transplantations between 2014 and 2017 in Korea.[23] Hence, any meaningful revision of MELD exception scores must consider patients with high scores, particularly over 30. Further studies should focus on developing an effective exception score system for HCC patients considering 90-day waitlist survival, the likelihood of LT, dropout risk, and post-transplant mortality.

Our work has several limitations. First, all patients were from a single tertiary medical center, and thus, our conclusions may not be generalizable. However, our method can be used to analyze data from other organizations. Moreover, we used only 90-day waitlist survival when evaluating MELD exception scores; we did not consider the likelihood of LT, dropout risk, or post-transplant mortality, which have been examined in other studies.[24] Further studies should consider these factors. Additionally, our study population comprised HCC cases of heterogenous stages. Among the patients with available Barcelona Clinic Liver Cancer (BCLC) stage information in the HCC patients (n=868), 25.5% (n=221) were BCLC-A, 46.9% (n=407) were BCLC-B, and 27.6% (n=240) were BCLC-C. Future studies should concentrate on stratifying patients and predicting risk according to BCLC stage. Finally, although we provided an example of additional scores to MELD 3.0 scores of 21–30 and the resultant survival of HCC and non-HCC patients, we merely aimed to explore disparities between HCC and non-HCC patients, not to propose a new exception score. Thus, we have not derived a model for adjustment of disparities between HCC and non-HCC patients. Any future MELD exception score should be carefully determined, and further studies from other organizations are needed. The significance of our study is that we found that MELD 3.0 exacerbated disparities, creating the need for a new exception score.

In conclusion, MELD 3.0 predicted 90-day survival in the HCC patients more accurately than the original MELD, but the differences between HCC and non-HCC patients increased, particularly in patients with MELD scores of 21–30. Therefore, a novel exception score is needed or the current exception scoring system should be changed.

AUTHOR CONTRIBUTIONS

Conceptualization: Kunhee Kim and Hye Won Lee. Data curation: Kunhee Kim. Formal analysis: Kunhee Kim. Investigation: all authors. Methodology: Kunhee Kim. Project administration: Hye Won Lee. Resources: Deok-Gie Kim, Dong Jin Joo, and Hye Won Lee. Software: Hye Won Lee. Supervision: Hye Won Lee. Validation: Kunhee Kim and Hye Won Lee. Visualization: Kunhee Kim and Hye Won Lee. Writing—original draft: Kunhee Kim and Hye Won Lee. Writing—review & editing: Deok-Gie Kim, Jae Geun Lee, Dong Jin Joo, and Hye Won Lee. Approval of final manuscript: all authors.

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