Absence of influence of the Korean MELD score-based liver allocation system on pretransplant MELD score in patients undergoing living donor liver transplantation

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Background: Model for end-stage liver disease (MELD) score-based allocation system was started in 2016 in Korea. This study aimed to analyze the profiles of adult patients who underwent living donor liver transplantation (LDLT) in the pre- and post-MELD eras.

Methods: This study was a retrospective double-arm analysis using a single-institution LDLT cohort. We compared the LDLT recipient profiles by focusing on pretransplant MELD score for 4 years before and after the introduction of the MELD score-based allocation system. Patients without and with hepatocellular carcinoma (HCC) were categorized as Group A and B in the pre-MELD era and Group C and D in the post-MELD era, respectively.

Results: The number of patients in Groups A, B, C and D was 615, 599, 704 and 713, respectively; and their MELD scores were 19.0 ± 9.4 , 11.2 ± 5.6 , 17.9 ± 8.5 and 11.6 ± 5.7 , respectively. Clinical parameters of liver cirrhosis indicate that Group A had worse general conditions than Group C; and Groups B and D had similar general conditions. The comparative analysis between Groups A and C revealed the mean and median MELD scores as 19.0 ± 9.4 and 17.9 ± 8.5 ($p=0.009$), and 16 and 15 ($p=0.077$), respectively. The comparative analysis between Groups B and D revealed the mean and median MELD scores as 11.2 ± 5.6 and 11.6 ± 5.7 ($p=0.14$), and 9 and 9 ($p=0.14$), respectively.

Conclusion: Median pretransplant MELD score was in the range of 15-16 in LDLT recipients without HCC and 9 in those with HCC. Introduction of MELD score in deceased donor organ allocation system resulted in a marginal decrease in the pretransplant MELD score in patients undergoing LDLT without HCC, but no change in those with HCC.

Keywords: MELD score; Hepatocellular carcinoma; Living donor; Deceased donor; Organ allocation

INTRODUCTION

Living donor liver transplantation (LDLT) has been the most common type of liver transplantation (LT) in many Asian countries where there is scarceness or marked shortage in the incidence of deceased donors. In Korea, only one-third of the annual LT cases have been performed in the form of deceased donor liver transplantation (DDLT) [1], and LDLT has been reported to occupy the remaining two-thirds of the annual LT cases. Nearly a half of adult LDLT recipients were preoperatively diagnosed with hepatocellular carcinoma (HCC) with the lower model for end-stage liver disease (MELD) scores compared to those without HCC. [2,3]. Consequently, it was presumed that the incidence of annual deceased donors and the allocation policy of deceased donor liver organs more influenced LDLT for adult patients without HCC compared to those with HCC.

In Korea, a nationwide allocation system for deceased donor liver grafts was started in February 2000 after the establishment of the Korean Network for Organ Sharing (KONOS) [4,5]. To optimize the use of deceased donor liver organs, the Korean MELD score-based allocation system has been used since June 2016 [6-8]. This allocation system has been in practice for more than four years to date. However, the number of deceased donors in Korea did not increase and even decreased over this period. As a result, the majority of deceased donor liver organs were allocated to patients with very high MELD scores [7,9].

Consequently, many patients with relatively low MELD scores had to select LDLT when liver function deteriorated progressively or HCC progressed during the waiting period. The majority of HCC patients have usually undergone LDLT due to low MELD scores and small HCC-weighted additional points to the MELD score. On the contrary, LT recipients without HCC have received either DDL or LDLT depending on the availability of living donors and the level of MELD scores. The detailed profiles of adult patients who underwent DDLT with very high MELD scores or LDLT for HCC have been frequently presented in the literature. However, the detailed profiles of adult patients who underwent LDLT without HCC have only been rarely presented in the literature. Therefore, this study aimed to compare the profiles of adult patients who underwent LDLT according to the status of HCC before and after the introduction of the Korean MELD score-based allocation system using a high-volume single-institution cohort.

PATIENTS AND METHODS

Study Design

This study was a retrospective double-arm analysis using adult LDLT data from the Asan Medical Center. The period for the selection of study group patients was set as four years from June 2016 to May 2020 since the introduction of the MELD score-based allocation system in Korea. The control group patients were selected during the four years from June 2012 to May 2016 before MELD score-based allocation.

The purpose of this study was to analyze the influence of the Korean MELD score-based liver allocation system on the pretransplant MELD scores of adult LDLT recipients. The institutional review board of our institution approved this study protocol (IRB No. 2014-0831), which waived the requirement for informed consent due to the retrospective nature of this study. This study was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki 2013.

Korean Liver Allograft Allocation System before the Introduction of MELD Score

The Korean liver allograft allocation system was based on the UNOS system and employed Child-Turcotte-Pugh (CTP) scoring, which included status 1 (acute liver failure and early graft failure), status 2A (acute-on-chronic liver failure), status 2B, status 3, and status 7. Status 1 and 2A had a priority allocation period of 2 weeks, and relisting was not permitted.

Calculation of MELD Score

The Korean MELD score-based allocation system uses the following original calculation formula: $[9.57 \times \log_e (\text{creatinine, mg/dL}) + 3.78 \times \log_e (\text{total bilirubin, mg/dL}) + 11.2 \times \log_e (\text{INR}) + 6.43]$. Thus, this original calculation formula was used for this study. There are 5 categories of the MELD score status for DDLT: status 1 (acute liver failure and early graft failure), status 2 (MELD score 38–40, equivalent to old KONOS status 2A), status 3 (MELD score 31–37), status 4 (MELD score 21–30), and status 5 (MELD score ≤ 20). Patients with HCC within the Milan criteria receive an additional 4 or 5 points if their MELD score is less than or equal to 20 [8,9].

Patient Grouping

The patients were categorized according to the time of LDLT operation and the pretransplant diagnosis of HCC.

The control group patients who underwent LDLT between June 2012 and May 2016 were classified as Group A that included patients without HCC and Group B that included

patients with HCC. The study group patients who underwent LDLT between June 2016 and May 2020 were classified as Group C that included patients without HCC and

Table 1. Profiles of patients who underwent adult living donor liver transplantation according to the timing of transplantation and the status of hepatocellular carcinoma

Groups	Pre-MELD era		Post-MELD era		p-value			
	Without HCC	With HCC	Without HCC	With HCC	A vs B	C vs D	A vs C	B vs D
Parameters	Group A (n=615)	Group B (n=599)	Group C (n=704)	Group D (n=713)				
Age (years)	51.7±9.6	54.6±6.8	53.7±9.2	56.5±7.4	<0.001	<0.001	0.80	0.064
Sex (n)					<0.001	<0.001	0.095	0.015
Male	403 (65.5%)	512 (85.5%)	430 (61.1%)	575 (80.6%)				
Female	212 (34.5%)	87 (14.5%)	274 (38.9%)	138 (19.4%)				
ABO blood group (n)					0.59	0.003	<0.001	<0.001
A	222 (36.1%)	219 (36.6%)	243 (34.5%)	260 (36.5%)				
B	160 (26.0%)	162 (27.0%)	192 (27.3%)	209 (29.3%)				
AB	73 (11.9%)	59 (9.8%)	85 (12.1%)	76 (10.6%)				
O	160 (26.0%)	159 (26.5%)	184 (26.1%)	168 (23.6%)				
ABO-incompatibility (n)	125 (20.3%)	137 (22.9%)	136 (19.3%)	158 (22.2%)	0.28	0.083	0.31	0.096
Primary diagnosis (n)					<0.001	<0.001	0.68	0.003
HBV-associated cirrhosis	230 (37.4%)	484 (80.8%)	231 (32.8%)	511 (71.7%)				
HCV-associated cirrhosis	41 (6.7%)	41 (6.8%)	20 (2.8%)	49 (6.9%)				
Alcoholic liver disease	180 (29.3%)	48 (8.0%)	261 (37.1%)	98 (13.7%)				
Cryptogenic cirrhosis	55 (8.9%)	19 (3.2%)	72 (10.2%)	47 (6.6%)				
Acute liver failure	45 (7.3%)	2 (0.3%)	37 (5.3%)	0 (0%)				
Others	60 (9.8%)	4 (0.7%)	71 (10.1%)	8 (1.1%)				
Retransplantation	5 (0.8%)	1 (0.2%)	13 (1.8%)	1 (0.1%)				
Pretransplant condition (n)								
Varix bleeding	229 (37.2%)	134 (22.4%)	258 (36.6%)	172 (24.1%)	<0.001	<0.001	0.038	0.006
Secondary bacterial peritonitis	52 (8.5%)	16 (2.7%)	11 (1.6%)	5 (0.7%)	<0.001	0.15	<0.001	0.018
Intractable ascites	261 (42.4%)	125 (20.9%)	341 (48.4%)	178 (25.0%)	<0.001	<0.001	0.024	<0.001
Hydrothorax	117 (19.0%)	43 (7.2%)	77 (10.9%)	35 (4.9%)	<0.001	<0.001	0.003	0.41
Hepatic encephalopathy	132 (21.5%)	33 (5.5%)	57 (8.1%)	15 (2.1%)	<0.001	<0.001	<0.001	0.011
Renal replacement therapy	36 (5.9%)	36 (6.0%)	9 (1.3%)	9 (1.3%)	0.91	0.96	<0.001	<0.001
Ventilator support	43 (7.0%)	5 (0.8%)	20 (2.8%)	6 (0.8%)	<0.001	0.007	0.004	0.71
CTP score	9.1±2.2	7.0±1.8	8.9±2.4	7.0±1.0	<0.001	<0.001	0.67	0.60
Laboratory findings								
MELD score	19.0±9.4	11.2±5.6	17.9±8.5	11.6±5.7	<0.001	<0.001	0.009	0.14
Creatinine (md/dL)	1.0±1.0	0.8±0.6	1.3±5.2	1.3±7.3	<0.001	0.84	0.043	0.010
Total bilirubin (md/dL)	9.4±11.6	2.5±5.6	6.6±9.3	2.5±7.0	<0.001	<0.001	<0.001	0.63
Prothrombin time (INR)	1.9±2.0	1.3±0.3	2.0±4.0	2.1±8.3	<0.001	0.042	0.12	<0.001
Albumin (g/dL)	3.1±0.6	3.3±0.6	3.0±1.1	3.3±1.7	0.31	0.39	0.75	0.34
Emergency operation (n)	41 (6.7%)	6 (1.0%)	17 (2.4%)	5 (0.7%)	<0.001	0.012	0.002	0.80
Pretransplant hospital stay (days)	12.1±13.6	7.4±10.2	10.1±20.7	6.4±15.9	<0.001	<0.001	0.46	0.21
Posttransplant hospital stay (days)	36.4±47.5	26.9±30.4	29.4±30.1	23.6±18.9	<0.001	<0.001	0.037	0.97

MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; CTP score, Child-Turcotte-Pugh score.

Group D that included patients with HCC.

Statistical Analysis

The incidence variables were compared using the chi-square test. The continuous variables were compared using the Student t-test and Mann-Whitney U-test. A p-values<0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 22 (IBM, NY, USA).

RESULTS

Comparison of the Recipient Profiles

The number of patients in Group A, B, C and D was 615, 599, 704 and 713, respectively. The profiles of recipients

and living donors in each group are summarized Table 1 and Table 2, respectively.

A comparison between Groups A and C revealed that the recipient age and sex were comparable (p=0.80 and p=0.095, respectively); the blood groups AB and O were more common in Group A (p<0.001); the incidence of ABO-incompatible LDLT was comparable (p=0.31); the proportion of hepatitis B virus association was comparable (p=0.68); the incidences of varix bleeding, secondary bacterial peritonitis, intractable ascites, hydrothorax, hepatic encephalopathy, renal replacement therapy and ventilator support were significantly higher in Group A (p≤0.038); and the incidence of emergency LDLT operation was higher in Group A (p=0.002). These clinical parameters indicate that patients in Group A had worse general conditions than

Table 2. Profiles of living donors according to the timing of transplantation and the recipient status of hepatocellular carcinoma

Groups	Pre-MELD era		Post-MELD era	
	Without HCC	With HCC	Without HCC	With HCC
Parameters	Group A (n=672)	Group B (n=637)	Group C (n=753)	Group D (n=762) 713+49
Age (years)	28.6±8.9	27.5±8.1	29.8±8.4	29.8±8.7
Sex (n)				
Male	450 (67.0%)	458 (71.9%)	460 (61.1%)	510 (66.9%)
Female	222 (33.0%)	179 9(28.1%)	293 (38.9%)	252 (33.1%)
Graft type				
Right liver	543 (88.3%)	552 (92.2%)	646 (91.8%)	657 (92.2%)
Left liver	15 (2.4%)	9 (1.5%)	9 (1.3%)	5 (0.7%)
Dual-grafts	57 (9.3%)	38 (6.0%)	49 (7.0%)	51 (7.2%)
Graft weight (g)	705.2±185.5	722±157	682.9±146.6	692.1±145.9
GRWR (%)	1.15±0.34	1.11±0.27	1.19±0.12	1.07±0.12

MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma; GRWR, graft-to-recipient weight ratio.

Fig. 1. Comparison of the model for end-stage liver disease (MELD) score level in adult living donor liver transplantation recipients. Groups A and B indicate patients without and with hepatocellular carcinoma (HCC) respectively in the pre-MELD era. Groups C and D indicate patients without and with HCC respectively in the post-MELD era.

those in Group C. However, the CTP score and duration of pretransplant hospital stay were comparable ($p=0.67$ and $p=0.46$, respectively) between Groups A and C.

A comparison between Groups B and D revealed that the recipient age was comparable ($p=0.064$); male patients were more frequent in Group B; the blood groups AB and O were more common in Group C ($p<0.001$); the incidence of ABO-incompatible LDLT was comparable ($p=0.096$); the proportion of hepatitis B virus association was higher in Group B ($p=0.003$); the incidence of secondary bacterial peritonitis, hepatic encephalopathy, renal replacement ther-

apy was higher in Group B; the incidence of varix bleeding and intractable ascites was higher in Group D; the incidence of hydrothorax and ventilator support was comparable; and the incidence of emergency LDLT operation was comparable ($p=0.80$). These clinical parameters indicate that patients in Groups B and D had similar general conditions. The CTP score and duration of pretransplant hospital stay were comparable ($p=0.60$ and 0.21 , respectively) between Groups B and D.

Fig. 2. Comparison of the model for end-stage liver disease (MELD) score level in adult living donor liver transplantation recipients. (A) Comparison of the patients without hepatocellular carcinoma (HCC) in the pre-MELD (Group A) and post-MELD (Group C) eras. (B) Comparison of the patients with HCC in the pre-MELD (Group B) and post-MELD (Group D) eras.

Fig. 3. Comparison of the model for end-stage liver disease score (MELD) level according to the Korean Network for Organ Sharing (KONOS) and grouping with the timing of liver transplantation and the status of hepatocellular carcinoma (HCC). (A) Comparison of the incidence of the KONOS status according to the groups. (B) Comparison of the proportion of the KONOS status according to the groups. Groups A and B indicate patients without and with HCC respectively in the pre-MELD era. Groups C and D indicate patients without and with HCC respectively in the post-MELD era.

Comparison of Pretransplant MELD Scores

The mean of pretransplant MELD scores was 19.0 ± 9.4 , 11.2 ± 5.6 , 17.9 ± 8.5 and 11.6 ± 5.7 in Group A, B, C and D, respectively. The distribution of MELD scores in all 4 groups is presented in Fig. 1.

A comparison between Groups A and C revealed the mean and median MELD scores as 19.0 ± 9.4 and 17.9 ± 8.5 ($p=0.009$), and 16 and 15 ($p=0.077$), respectively (Fig. 2A). These results suggest that the level of MELD score in LDLT recipients without HCC was marginally decreased after the introduction of the Korean MELD score-based allocation system.

A comparing between Groups B and D revealed the mean and median MELD scores as 11.2 ± 5.6 and 11.6 ± 5.7 ($p=0.14$), and 9 and 9 ($p=0.14$), respectively (Fig. 2B). These results suggest that the level of MELD score in LDLT recipients with HCC was not altered after the introduction of the Korean MELD score-based DDLT allocation system.

The incidence and proportions of patients belonging to the current KONOS status category are presented in Fig. 3.

DISCUSSION

There has been an increase in the demand for LT in Korea for a long period due to the high prevalence of hepatitis B virus-associated liver cirrhosis and high incidence of HCC. In 2016, the annual number of deceased organ donors temporarily exceeded 10 per million [6]; however, a decrease has been reported since then due to certain medical and social issues, including the Life Insurance Decision Act with regulations regarding the termination of life-sustaining treatment. Annual numbers for deceased organ donors and DDLT in Korea were 573 and 508 in 2016; 515 and 450 in 2017; 449 and 369 in 2018; 450 and 391 in 2019; and 478 and 395 in 2020, respectively.

In recent years, the annual total number of LT in Korea has remained largely unchanged, thereby suggesting a reciprocal relationship between the annual case numbers of DDLT and LDLT [10,11]. Currently, critically ill patients, defined as those with very high MELD scores, are more likely to receive DDLT than before, thus they have usually waited for a significant period after enrollment in the KONOS waiting list. This allocation is associated with a waiting period of unpredictable duration. Since the number of deceased organ donors cannot meet the DDLT demand for critically ill patients, priority allocation is given only to the patients with the highest KONOS status. Considering that the daily cutoff of MELD scores for DDLT allocation was usually as high

as 38 or 39, the majority of patients regardless of the presence of HCC had a low possibility to undergo DDLT [8,9,12]. Consequently, they had to select LDLT to save their lives [10,13].

We previously presented a cross-sectional analysis of the fates of the patients on the waiting list for DDLT over a 2-month observation period [12]. There were three discrete clinical pathways for graft allocation for DDLT. The first pathway was sustained KONOS status 2 or high status 3, after which the patients underwent DDLT or died within one or two weeks. The second pathway involved a gradual increase in MELD score from low status 3 to high status 3 or status 2 over one to three weeks. The third pathway involved a fluctuation in MELD scores around low status 3 for several weeks, in which the probability of DDLT was low unless the MELD score increased gradually. Some of these patients on the waiting list decided to undergo LDLT if they had living donors because of relatively low possibility of DDLT. This is the real-world background reason why patients with KONOS status 2 and 3 had to select LDLT even after the introduction of the MELD score-based allocation system in Korea.

In the case of patients categorized as KONOS status 4 or 5, enrollment in the waiting list has nearly no clinical significance because they have a very low possibility of receiving DDLT. As a result, if they have living donors, they have to choose LDLT.

As shown in the present study, the majority of LDLT recipients had low MELD scores. After the introduction of the Korean MELD score-based allocation system, the MELD score in patients who had undergone LDLT without HCC was marginally lowered primarily due to the reduction in the number of patients belonging to KONOS status 2 and 3. On the contrary, the MELD score in patients who had undergone LDLT with HCC demonstrated no changes primarily due to a very low incidence of patients belonging to KONOS status 2 and 3.

To the best of our knowledge, the present study is the first study to present the details of MELD scores in LDLT recipients with and without HCC. The median or mean values of MELD score in the reported LDLT series were 15 (range: 3–43) in 223 patients (Kyoto University, Japan) [14]; 12.4 ± 4.0 in 165 patients (Memorial Atasehir Hospital, Turkey) [15]; 13.0 (range: 11.9–14.0) in 90 patients (Kyushu University, Japan) [16]; 11 (range: 8–14) in 348 patients (Kaohsiung Chang Gung Memorial Hospital, Taiwan) [17]; and 13 (range: -1–46) in 134 patients (Samsung Medical Center, Korea) [18].

This study has a limitation. It is a single-center study, which could potentially introduce selection bias. We therefore recommend multicenter or nationwide studies to validate our results.

In conclusion, the median pretransplant MELD score was in the range of 15–16 in LDLT recipients without HCC and 9 in those with HCC. The introduction of the MELD score in the Korean DDLT allocation system resulted in a marginal decrease of pretransplant MELD score in patients undergoing LDLT without HCC, but no change was observed in the case of patients with HCC.

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CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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AUTHORS' CONTRIBUTIONS

Conceptualization: SH. Data curation: CSA, DBM, TYH, GWS, DHJ, GCP, KHK, YIY. Methodology: WHK, HDC, MK, BGN, SMK GY, SGL. Visualization: SH. Writing - original

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