Delta MELD as a predictor of early outcome in adult-to-adult living donor liver transplantation

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ABSTRACT

Background/Aims: An increased post-operative mortality risk has been reported among patients who undergo living donor liver transplantation (LDLT) with higher model for end-stage liver disease (MELD) scores. In this study, we investigated the effect of MELD score reduction on post-operative outcomes in patients with a high MELD (≥20) score by pre-transplant management.

Materials and Methods: We retrospectively analyzed 386 LDLT cases, and patients were divided into low-MELD (<20, n=293) vs. high-MELD (≥20, n=93) groups according to their MELD score at the time of index hospitalization. Patients in the high-MELD group were managed specifically according to a treatment algorithm in an effort to decrease the MELD score. Patients in the high-MELD group were further divided into 2 subgroups: (1) responders (n=34) to pre-transplant treatment with subsequent reduction of the MELD score by a minimum of 1 point vs. (2) non-responders (n=59), whose MELD score remained unchanged or further increased on the day of LDLT. Responders vs. non-responders were compared according to etiology, demographics, and survival.

Keywords: Living donor liver transplant, MELD change, survival

INTRODUCTION

Liver transplantation (LT) is an effective treatment for a wide spectrum of liver diseases, where similar outcomes have been reported either with deceased donor or living donor grafts (1). In deceased donor LT (DDLT), the allocation of organs is based on the model for end-stage liver disease (MELD) scoring system since 2002, which is established as an important predictor of waiting list mortality as well as post-LT mortality risk (2). Although the MELD score does not play a role in organ allocation in living donor LT (LDLT), pre-LT disease severity has also been shown as one of the predictive factors for post-transplant patient survival. An increased post-operative mortality risk has been reported among patients who undergo LDLT with higher MELD scores (3). It was reported that a MELD score >20 was independently associated with reduced graft survival (4), and a MELD score of 25 or higher was evaluated as an independent adverse prognostic factor for in-hospital mortality after LDLT (5). Therefore, despite the suggestion that the sickest patients are those who derive the highest benefit from LT, the use of LDLT in patients with a high MELD score has been controversial (6).

In DDLT, post-LT survival of the patients maintained on the waiting list has a relationship with MELD changes, which has led to some further investigation related to MELD score changes. Multiple studies have accepted the description of "delta MELD" as the maximum change in MELD score calculated at 2 time points between listing and transplantation (7-11). In a single-center, retrospective analysis of 1,125 patients listed for DDLT, delta MELD as a continuous variable was found to be the only significant risk factor for overall survival after LT (8).

In LDLT, patients are often admitted to the hospital before the anticipated surgery to be able to maximize the management of their liver disease. This provides a unique opportunity to manage the patients pre-operatively for optimal clinical conditions and reduce the MELD score. Since 2010, our group has developed a pre-transplant management policy that patients with a planned LDLT surgery are hospitalized before the transplantation for a treatment algorithm applied in an effort to decrease the MELD score. According to the response to the therapy, the time for the surgery is scheduled. In this study, we aimed to explore if 1-point reduction in the MELD score,

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on the day of the LT surgery, will demonstrate a survival benefit.

MATERIALS AND METHODS

We retrospectively reviewed all elective primary adult-to-adult right-lobe LDLT cases that were performed between January 2010 and December 2014 at the Liver Transplantation Unit, Istanbul Bilim University, Florence Nightingale Hospital, Istanbul, Turkey. This study has been approved by Istanbul Bilim University Clinical Research Ethics Committee, February 16, 2016/45-322.

After making the decision regarding the need for LT in the Outpatient Clinic or in the Emergency Unit, the patients were hospitalized. The recipients with a high MELD score were evaluated and treated according to our pre-transplant management policy. During this period, the live donor selection and work-up was completed, preparing the appropriate donor for the surgery. According to the response to the therapy, the time for LDLT was determined. Patients in the high-MELD group were managed specifically according to a treatment algorithm in an effort to decrease the MELD score. We used various treatment options during pre-transplant hospitalization for different kinds of chronic liver disease complications. Patients with gastrointestinal bleeding were treated with both pharmacologic and endoscopic interventions. Hepatorenal syndrome therapy consisted of terlipressin, human 20%, and antibiotics. Spontaneous bacterial peritonitis was treated with culture-antibiogram and antibiotics. For refractory ascites, diuretics such as furosemide 40-160 mg/day and spironolactone 100-400 mg/day and human 20% albumin were used. Cholangitis episodes due to sclerosing cholangitis were treated with biliary drainage and antibiotics. Other than these, as a general approach, combination of intravenous amino acid and L-ornithine L-aspartate (LOLA) and plasmapheresis were administered.

In this retrospective analysis, patients were divided into 2 groups: those with a MELD score ≥20 (high-MELD group) vs. <20 (low-MELD group) at the time of index hospitalization. The term index hospitalization refers to the hospitalization during which the recipient eventually received the right-lobe LDLT. In all patients, the MELD score was recalculated on the day of surgery again. Then, patients in the high-MELD group were further divided into 2 subgroups: (1) responders to pre-transplant treatment with subsequent reduction of the MELD score by a minimum of 1 point vs. (2) non-responders, whose MELD score remained unchanged or further increased on the day of LDLT as compared with the initial MELD score at the time of index hospitalization.

Patients with acute fulminant hepatic failure and acute-on-chronic liver failure were excluded. The listing MELD score was defined as the MELD score at the time when the patient was initially referred to our center for LDLT. Delta MELD was defined as the difference between the MELD scores calculated at the time of index hospitalization and on the day of LDLT. No Na-MELD (MELD sodium) score was used as well as no hepatocellular carcinoma (HCC) MELD exception points were included.

All the recipients were admitted to the hospital after the donor work-up was completed as outpatient.

Statistical Analysis

Comparisons between the groups, high-MELD vs. low-MELD and responders vs. non-responders, were performed with 2 sample t-tests for continuous measures and with chi-square analyses for categorical variables. The analyses were performed using STATA v 13.1 (StataCorp., College Station TX, 2015).

RESULTS

Of the 386 patients included, 93 (24.1%) were in the high-MELD group and 293 (75.9%) were in the low-MELD group at the time of index hospitalization. The distribution of MELD scores is shown in Figure 1. Patient demographics of patients in low-MELD vs. high-MELD groups are listed in Table 1. There were 278 (72.0%) male

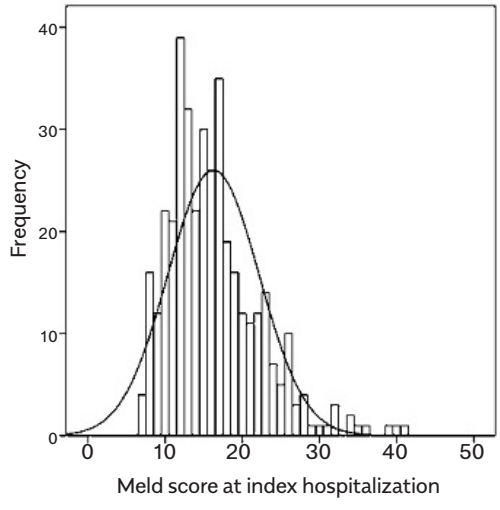

Figure 1. Distribution of MELD score.

Table 1. Demographic characteristics in low- and high- MELD groups.

	MELD groups		
	Low-MELD (<20) (n=293)	High-MELD (≥20) (n=93)	p
Recipient age	51.9±10.4	49.0±11.3	0.02
CTP score	7.9±1.8	10.5±1.6	<0.001
Listing MELD score	13.4±3.6	23.1±6.4	<0.001
Waiting-time (days)	65.8±122.0	60.2±102.8	0.6
MELD score at index hospitalization	13.6±3.1	24.6±4.6	<0.001
MELD score at liver transplantation	13.7±3.3	24.4±5.8	<0.001
Pre-transplant hospital stay (days)	5.2±5.2	10.2±9.8	<0.001
Delta MELD	0.8±1.4	-0.2±3.6	0.1
Donor age	31.5±8.4	32.8±9.6	0.2
GRWR (%)	1.2±0.8	1.1±0.2	0.2
Anterior sector drainage (%)	130 (44.4)	38 (40.9)	0.3
Red blood cell transfusion (units)	3.7±4.7	6.5±7.0	<0.001
Post-transplant hospital stay (days)	20.1±20.1	24.9±26.2	0.07
Postoperative day-7 bilirubin level (mg/dL)	5.0±4.9	8.9±8.2	<0.001
Postoperative day-7 INR level	1.3±0.2	1.5±0.6	<0.001

MELD: model for end-stage liver disease; CTP: Child Tutgot Pugh; GRWR: graft recipient weight ratio; INR: International normalized ration.

and 108 (28.0%) female patients with a mean age of 51.2±10.4 years (range 19-74). The most common etiology of the underlying liver disease was hepatitis B virus (HBV) (n=143, 36.6%), followed by cryptogenic (n=65, 16.6%), hepatitis C virus (HCV, n=56, 14.3%), alcohol induced (n=43, 11%), cholestatic (n=31, 7.9%), and others (n=52, 13.3%). HCC was present in 92 (23.8%) patients, which was significantly higher in the low-MELD group (28.0% vs. 11.8%, p=0.001). Patient follow-up was complete as of May 2016, with a mean follow-up time of 38.0±20.0 months.

The median time from listing to LDLT was 33 (17-70) days, and the median MELD score at the time of LDLT was 15.0 (12.0-19.0). Patients with a MELD score ≥20 at the time of LDLT had a significantly higher rate of 90-day mortality (17.6% vs. 3.4%, p<0.001; odds ratio [OR] 6.0, 95% confidence interval [CI] 2.6-13.9).

Overall, mean pre-transplant hospital stay was 6.0±6.9 days. In the low-MELD group, where the mean pre-transplant hospital stay was 5.2±5.2 days, the mean MELD score did not show a significant difference between the index hospitalization and LT (13.6±3.1 and 13.7±3.3, respectively), and all MELD scores remained below the MELD 20 level. In the high-MELD group, a total of 34 (36.5%) patients responded to pre-transplant treatment (Table 2). Although, mean MELD scores were similar at index hospitalization (24.9±5.0 in responders vs. 24.5±4.4 in non-responders, p=0.6), responders ended up with a significantly lower mean MELD score on the day of LT (21.5±4.7 vs. 26.1±5.7, p<0.001). Mean delta MELD was −3.3±2.7 among responders, whereas it was 1.6±2.4 among non-responders (p<0.001). In comparison with non-responders, responders were found to have a significantly longer pre-transplant hospital stay (12.5±10.1 vs. 8.9±9.4, p=0.04). The length of pre-transplant hospital stay showed a significant correlation with treatment response in high-MELD patients (Pearson coefficient=0.253, p<0.001).

Among responders, Child Tutgot Pugh (CTP) score at index hospitalization was significantly lower than that of non-responders (10.0±1.8 vs. 10.8±1.4, p=0.03). Among

Table 2. Patient demographics of responders vs. non-responders in the high-MELD group.

	High-MELD group		p
	Responders (n=34)	Non-responders (n=59)	
Recipient age	48.0±13.2	49.6±10.2	0.4
Listing MELD score	22.5±6.1	23.5±6.6	0.4
CTP score at index hospitalization	10.0±1.8	10.8±1.4	0.03
MELD score at index hospitalization	24.9±5.0	24.5±4.4	0.6
MELD score at liver transplantation	21.5±4.7	26.1±5.7	<0.001
Delta MELD	-3.3±2.7	1.6 ±2.4	<0.001
Pre-transplant hospital stay (days)	12.5±10.1	8.9±9.4	0.09
Red blood cell transfusion (units)	5.6±7.4	7.1±6.7	<0.001
Post-transplant hospital stay (days)	20.0±20.1	24.8±25.4	0.06
Postoperative day-7 bilirubin level (mg/dL)	7.5±6.6	9.7±8.8	0.2
Postoperative day-7 INR level	1.4±0.3	1.6±0.7	0.3

MELD: model for end-stage liver disease; CTP: Child Tutgot Pugh; INR: International normalized ration.

Table 3. Demographic data among low-MELD, high-MELD responders and high-MELD non-responders.

	Low-MELD group (n=293)	High-MELD Responders (n=34)	High-MELD Non-responders (n=59)	p
MELD score at index hospitalization	13.6±3.1	24.9±5.0	24.5±4.4	<0.001
MELD score at the time of LDLT	13.7±3.3	21.5±4.7	26.1±5.7	<0.001
Pre-transplant hospital stay (days)	52±5.2	12.5±10.1	8.9±9.4	<0.001
Postoperative 90-day mortality (%)	3.4	5.9	23.7	<0.001
1-year patient survival (%)	91.6	88.1	67.9	<0.001

MELD: model for end-stage liver disease; LDLT: living donor liver transplantation.

pre-transplant factors, only CTP score at index hospitalization showed a significant correlation with delta MELD (Spearman's coefficient=0.295, p=0.004) and response to treatment (Pearson's coefficient=0.215, p=0.03).

A total of 26 (6.7%) patients died post-operatively within 3 months after surgery. There was a statistically significant difference between the high-MELD and low-MELD groups in terms of post-operative mortality favoring low-MELD group (3.4% vs. 17.4%, p<0.001; OR 5.9, 95% CI 2.6-13.7). However, when high-MELD patients were further analyzed as responders vs. non-responders, responders had similar post-transplant outcomes to those of low-MELD patients (Table 3, Figure 2; Kaplan-Meier: the patients were stratified according to the MELD score on the day of LT).

Although etiology was not found to be a significant factor in treatment response, the etiology of the patients demonstrating an increased MELD change was 22.3% in HBV (n=32), 21.5% in cryptogenic (n=14), 22.8% in HCV (n=13), 16.2% in alcoholic (n=7), 12.9% in cholestatic (n=4), and 34% in the others group (n=17).

We used various treatment options during LDLT hospitalization, which consisted of terlipressin, diuretics with furosemide 40–160 mg/day and spironolactone 100–400 mg/day, combination of intravenous amino acid and

Table 4. The relationship among the MELD score, their components and delta MELD with perioperative and overall mortality.

	Perioperative mortality		All mortality	
	%95 C.I	p	%95 C.I	p
Delta MELD	1.16	0.100	1.14	0.037
Preoperative MELD	1.11	0.0005	1.08	0.000
MELD≥20 at the time of transplantation	6.08	0.0005	3.32	0.000
MELD≥at hospitalization	5.88	0.0005	3.19	0.000
Preoperative Creatinin	2.01	0.009	1.66	0.033
Preoperative Bilirubin	1.04	0.067	1.06	0.001
Preoperative INR	1.95	0.006	1.94	0.002

MELD: model for end-stage liver disease; INR: International normalized ration.

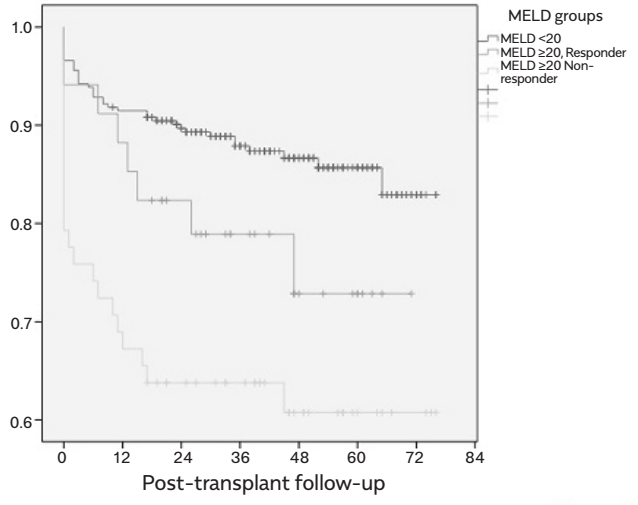

Figure 2. Kaplan-Meier survival curves of the low-MELD, high-MELD responder, and high-MELD non-responder group.

LOLA, human 20% albumin, plasmapheresis, and antibiotics. We investigated the treatment effectivity of the responder and non-responder patients with MELD score ≥20. We used terlipressin in 5 (7.81%) patients among non-responders and 8 (22.86%) patients among responders (p=0.034). We used antibiotics, combination of intravenous amino acid plus LOLA treatment and human albumin, respectively, in 15 (23.44%), 1 (1.56%), and 2 (3.13%) patients among non-responders and 16 (45.71%), 5 (14.29%), and 5 (14.29%) patients among responders, so the p values found were 0.022, 0.011, and 0.038, respectively. In summary, we can say that terlipressin, antibiotic, intravenous amino acid plus LOLA treatment, and human albumin treatment are associated with a good response in MELD change (Figure 3).

We also investigated post-LT complications of the responder and non-responder patients within MELD ≥20 group. In this group, non-responders had a significantly higher percentage of peri-operative mortality when compared with the responders (21.88% vs. 5.71%, p=0.037). There was no significant difference in peri-operative mortality, when comparing non-responders and responders in MELD score <20 (3.24% in non-responders, 4.65% in responders, p=0.639). There was no relationship between (1) delta MELD and peri-operative mortality and (2) pre-operative bilirubin level and peri-operative mortality (Table 4).

When we compared donor age and graft recipient weight ratio (GRWR), there was no statistical difference between low-MELD, high-MELD responder, and high-MELD non-responder groups, as outlined below.

DISCUSSION

In this retrospective analysis of 386 primary right-lobe LDLT patients, we investigated the delta-MELD parameter as a prognostic indicator for post-LT survival. We found that among patients with a high MELD score who were undergoing LDLT, an extended pre-transplant hospitalization with intent to reduce the MELD score is an effective strategy to improve early post-transplant outcomes.

Recently, liver allocation based on the MELD score has been implemented worldwide to determine which patients should be prioritized for receiving an organ from

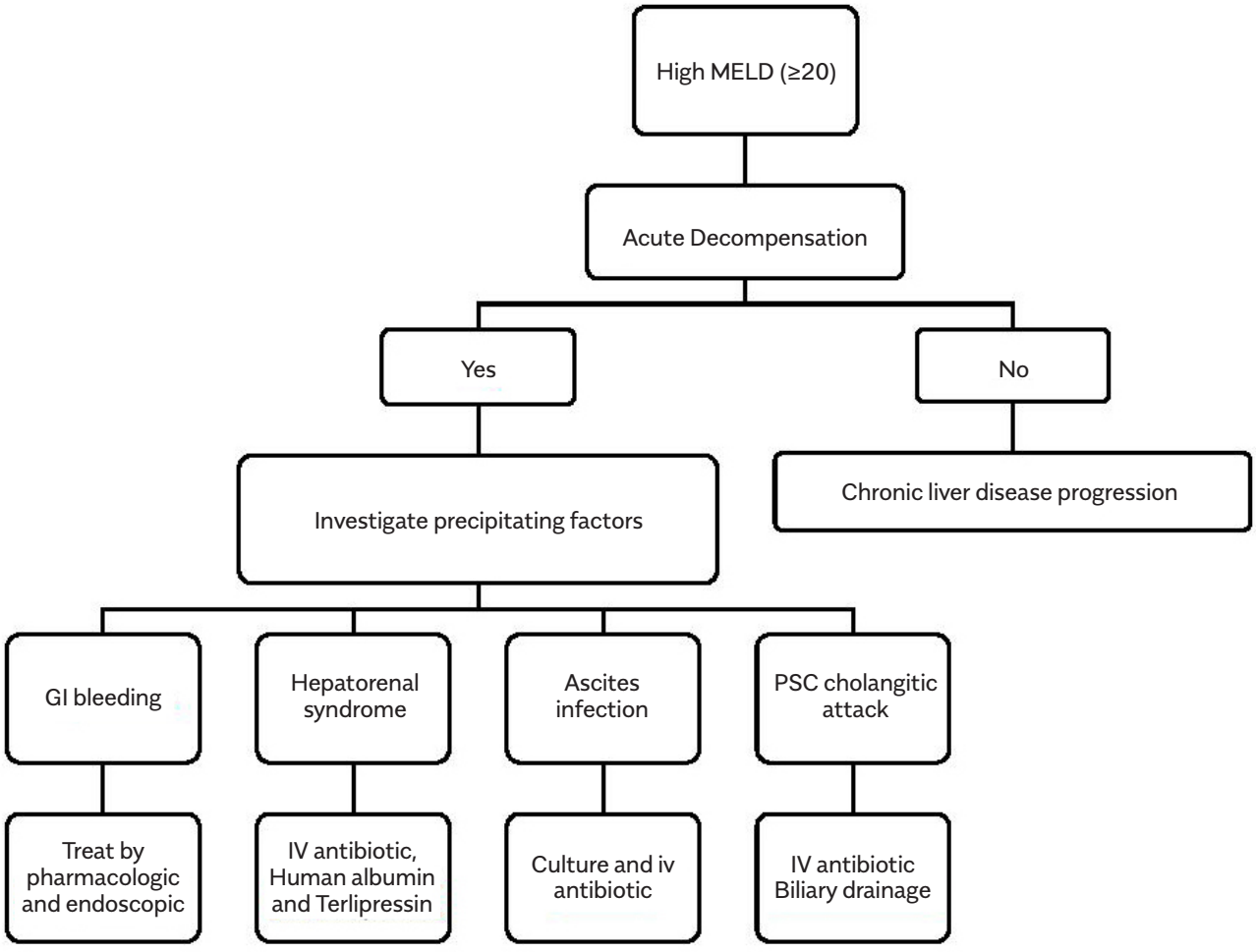

Figure 3. Clinical approach to the patient with high MELD score..

a deceased donor. However, allocation of organs to the sickest patients first has changed the characteristics of liver transplant recipients toward more severe end-stage liver disease. Therefore, the MELD score has been challenged to function as an indicator for post-transplant mortality. Recent publications that investigated the MELD score as a predictive factor for post-transplant survival have reported controversial results in the setting of both DDLT (12-14) and LDLT (15, 16).

The MELD score has been defined as an ideal prognostic model to predict the probability of survival, which incorporates objective variables that are weighted according to their influence on prognosis. Because the MELD score is not a time-dependent model, several studies have proposed that the change in the MELD score over time might have additional prognostic value (17).

A high MELD score is a predictive risk factor leading to graft failure after LDLT (18-21), although according to some authors, it is not useful to determine the post-transplant survival (12, 22). We are particularly interested in short-term survival after LDLT because predictors for short- and long-term outcomes are different. Petrowsky et al. (23) have shown that in high-risk recipients, the risk of death was the highest within the first year after LT, whereas long-term prognosis was excellent for patients who survived beyond the first year.

Györi et al. (24) identified the delta MELD as the difference between the listing MELD score and the MELD score on the day of LT. There was a statistically significant difference when comparing the delta MELD and 1-year survival; reduction in MELD score at least by 3 points had 91.7% survival vs. increase over 4 points that had 69.7% survival ($p<0.01$).

In a study by Kaltenborn et al. (25), among 454 patients, the post-transplant 90-day mortality was 15.4% and long-term mortality was 25%. In addition, Györi et al. (8), retrospectively evaluated 1,125 patients on the waiting list, and 539 (69%) of them had undergone LT with 1-, 3-, and 5-year survival determined, respectively, as 83%, 78%, and 75%. They illustrated that delta MELD score is effective on 1 year as well as predicting the overall survival. It was reported that delta MELD score was higher among those with alcoholic cirrhosis. However, in our study, etiology was not a factor in MELD change.

Northup et al. (9) analyzed 1,510 patients who underwent LT and studied the MELD score changes in pre-LT 30 days. They calculated the delta MELD as the difference between transplant day MELD score and prior 25- to 30-day MELD score. The MELD score was increased among 52% of patients and reduced among 13%. The overall median preoperative delta MELD was 3.1. They concluded that delta MELD score is not a predictive factor in short-term survival post-LT . This is different from our overall change in mean MELD score of 0.01 after 6.4 days of pre-LT hospitalization, but our MELD ≥20 group has demonstrated −3.4 change in MELD among the responder subgroup and 1.4 among the non-responder subgroup. LDLT can give us the best option to be able to schedule the transplant surgery at a time when it is considered to be the most effective period, as predicted by the change in MELD, rather than the unscheduled urgency of the deceased donation.

We have also not noticed statistical difference when the donor age is taken into consideration among the groups (26), as revealed in the Results section.

One of the limitation of the study was its retrospective nature. In addition, MELD-Na was not in routine clinical usage at the time of the study. Compared with DDLT, in LDLT, kidney insufficiency is less likely to be encountered. Only 18 (6%) patients presented with creatinine levels of >1.5 mg/dL, signifying the underrepresentation of renal insufficiency in our study population.

When we examined the pre-transplant MELD score components of the high-MELD responder and non-responder groups, there was statistical difference only with International normalized ration (INR) (creatinine: 0.9±0.4 mg/dL vs. 0.9±0.8 mg/dL, $p=0.8$; total bilirubin: 9.0±9.3 mg/dL vs. 12.5±9.1 mg/dL, $p=0.08$; INR: 1.8±0.4 vs. 2.3, $p=0.01$). Since fresh frozen plasma was not routinely administered during the pre-operative period, one can consider INR to be the most important factor.

Our experience is unique, since we studied the impact of MELD change before transplantation only among adult right-lobe LDLT recipients, whereas the current literature concentrates more on the DDLT. Not surprisingly, patients with higher MELD scores may feel a sense of urgency. This study could potentially improve upon the theoretical advantage of LDLT, which can be performed on an elective basis, by including the use of the delta-MELD parameter as a potential criteria for optimization of pre-LT treatment and by better controlling the timing of operation.

The research was limited to adult LDLT patients. In Turkey, despite notable efforts to increase rates of deceased organ donation, the supply of livers has not kept pace with the growing demand for LT. Currently, utilization of livers from living donors is the only effective strategy to overcome the severe organ shortage.

In LDLT, transplant hepatologists and surgeons have the opportunity to decide on the exact timing of the operation and also to discuss the optimal timing with both the patient and the donor. Of note, with LDLT, there's a lack of an ideal decision tool to determine the optimal timing of transplantation, which will quantify a patient's chance of survival in the short- to medium term. Predicting post-LT outcome is important, as this would enable a more rational utilization of a precious resource, that is, the living donor, to achieve the maximum benefit.

In conclusion, according to our study, a MELD score of ≥20 is a significant risk factor for peri-operative mortality following LDLT. Even a 1-point MELD reduction just before the anticipated LDLT, by the way of inpatient hospitalization to be able to deliver the intense liver disease management, will positively affect the long-term post-transplant survival among this group of patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Istanbul Bilim University Clinical Research Ethics Committee, February 16, 2016/45-322.

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

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