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Impact of the Share 35 Policy on Perioperative Management and Mortality in Liver Transplantation Recipients

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The Share 35 policy was introduced in 2013 by the Organ Procurement and Transplantation Network (OPTN) to increase opportunities of sicker patients to access liver transplantation. However, it has the disadvantage of higher MELD score associated with adverse postoperative transplant outcomes. Early data after implementation of the Share 35 policy showed significantly poorer post-transplantation survival in some UNOS regions. We aimed to analyze the impact of Share 35 on demographics of patients, perioperative management, and perioperative mortality.

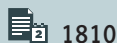
Material/Methods: A retrospective analysis of data was performed from an institutional liver transplantation cohort from 1 January 2008 to 31 December 2017. Adult patients who underwent liver transplantation before 2013 were defined as the pre-Share 35 group and the other group was defined as the post-Share 35 group. The MELD score of each patient was calculated at the time of transplantation. Perioperative mortality was defined as death within 30 days after the operation.

Results: A total of 1596 patients underwent liver transplantation. Of those, 895 recipients underwent OLT in the pre-Share 35 era and 737 in the post-Share 35 era. The median MELD score was significantly higher in the post-Share 35 group (30 vs 26, $P < 0.001$) and 45.7% of the post-Share 35 group had MELD scores ≥ 35 . In intraoperative management, patients required significantly more blood component transfusion, intraoperative vasopressor, and fluid replacement. Veno-venous bypass (VVB) usage was significantly higher in the post-Share 35 era (47.2% vs 38.1%, $P < 0.001$). In the subgroup of patients with MELD scores ≥ 35 , the median waiting time was significantly shorter (18.5 vs 14.5 days, $P = 0.045$). Overall perioperative mortality was not significantly difference between groups ($P = 0.435$).

Conclusions: After implementation of the Share 35 policy, we performed liver transplantation in significantly higher medical acuity patients, which required more medical resources to obtain a result comparable to that of the pre-Share 35 era.

Keywords: Liver Transplantation • Perioperative Care • Tissue and Organ Procurement

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Background

The Share 35 policy was introduced in 2013 by the United Network for Organ Sharing and Organ Procurement and Transplantation Network (UNOS/OPTN) to increase chances to access liver allografts and to decrease wait-list mortality. The Share 35 policy promoted broader regional sharing for patients with MELD score more than 35 (in the 11 UNOS allocation regions in the USA) by prioritizing these patients over local sharing to patients with MELD score less than 35. After implementation of the Share 35 policy, several studies showed that recipient MELD score, need for organ support, and ICU admission prior to transplantation increased with decreased waiting time and wait-list mortality [1,2]. However, it has the disadvantage that higher MELD score recipients are more likely to have with adverse postoperative transplant outcomes, especially worsening post-transplant survival, which had been shown in some organ-sharing regions [2-4]. However, later studies after implementation of the Shared 35 policy showed no significance difference in overall mortality in MELD \geq 35 recipients at the national level [5,6]. A recent study showed improved 1-year overall survival with donor-recipient matching and high MELD score recipient (MELD \geq 35) matched with low-risk liver allograft (lower donor risk index) [7]. Most previous studies of the Share 35 policy mainly focused on preoperative baseline characteristics, waiting time, cost of treatment, and donor quality, but there has been no published study on changes in perioperative management in higher medical acuity liver transplantation recipients. The present study focused on the effect of the Share 35 policy on perioperative management and 30-day mortality.

Material and Methods

Study Population

After IRB approval, we retrospectively reviewed the prospectively collected data of 1596 adult patients who underwent liver transplantation at a single center (the University of California, Los Angeles, USA) from 1 January 2008 to 31 December 2017. We included all adult patients (\geq 18 years old) who underwent liver transplantation in our institute. Patients who underwent liver transplantation before 2013 were assigned to the pre-Share 35 group and patients who underwent liver transplantation later were assigned to the post-Share 35 group.

Data collection and Outcomes Measurements

Patients' demographic data including age, comorbidities, etiology of liver disease, and baseline laboratory values were prospectively collected. MELD scores in this study were the MELD score calculated at the time of liver transplantation without

any exception point. Intraoperative variables, including duration of surgery, transfusion of red blood cell and frozen fresh plasma, requirement for vasopressors, post-reperfusion syndrome, and veno-venous bypass usage, were collected by chart review. Postoperative variables included duration of ventilator use, postoperative complications, and 30-day patient survival. The primary outcome of this study was perioperative mortality, which was defined as death on the day of surgery or death within 30 days after surgery [8]. The secondary outcomes were perioperative management, blood transfusion, preoperative organ support, intraoperative continuous renal replacement therapy, cold ischemic time, veno-venous bypass usage, use of vasopressors, and postoperative complications.

Statistical Analysis

Baseline characteristics of patients undergoing liver transplantation were compared. Categorical variables are reported as number and percentage and were compared by chi-square test. For continuous variables, the differences between 2 groups are reported as means (standard deviation) and compared by *t* test for normally distributed data. Non-normally distributed data are reported as medians with interquartile range and were compared by Mann-Whitney U test. Kaplan-Meier curves were used to demonstrate 30-day survival after liver transplantation. The log-rank test was used to compare the pre- and post-Share 35 eras. *P* values $<$ 0.05 were considered statistically significant for all analysis. IBM SPSS Statistics 23.0.0 (IBM Corporation) was used to generate all figures and analyze all data.

Results

Demographic data and comorbidities are displayed in **Table 1**. A total of 1596 patients underwent liver transplantation during 2008-2017; 895 (56.07%) of these recipients underwent OLT in the pre-Share 35 era and 737 (46.18%) underwent OLT in the post-Share 35 era. The median age and BMI of the 2 groups were not significantly different. Interestingly, although most liver transplant recipients were male, the proportion of female recipients increased significantly in the post-Share 35 era (36.1% vs 42.6%, $P=0.043$). Alcoholic cirrhosis and non-alcoholic steatohepatitis were the predominant cause of end-stage liver disease in the post-Share 35 era (42.6%). The recipients in the post-Share 35 era required more preoperative vasopressor infusion and continuous renal replacement therapy (CRRT) ($P=0.001$, 0.002 , respectively). There were more recipients with hepatic encephalopathy in the post-Share 35 era (45.6% vs 50.8%, $P=0.044$). Approximately 45% of recipients were admitted in the intensive care unit and more than a half of them required mechanical ventilator support prior to transplantation. The median MELD score of recipients was significantly

Table 1. Recipient demographics, comorbidities and medical acuity of pre- and post-Share 35 transplantation.

	Pre-Share 35 N= 859	Post-Share 35 N=737	P value
Age, yrs	57.0 (51.0-62.0)	57.0 (50.0-63.0)	0.802
BMI	26.9 (23.7-31.1)	27.0 (23.6-31.2)	0.998
Sex, Male	637 (63.9%)	471 (58.4%)	0.043
Recipient race			<0.001*
Caucasian	383 (54.8%)	174 (40.8%)	
Hispanic	162 (23.2%)	160 (37.6%)	
Asian	82 (11.7%)	48 (11.3%)	
African American and other	71 (10.2%)	41 (10.3%)	
Cause of ESLD			
Acute fulminant liver failure	32 (3.8%)	26 (6.4%)	0.039*
HBV	60 (7.1%)	23 (6.4%)	0.339
HCV	260 (30.6%)	113 (27.7%)	0.287
NASH, non-alcoholic steatohepatitis	55 (6.5%)	49 (12.0%)	0.001*
Alcohol	201 (23.7%)	125 (30.6%)	0.008*
Hepatocellular carcinoma	414 (33.8%)	190 (28.8%)	0.014*
Others	69 (4.4%)	16 (4.9%)	0.279
Diabetics	224 (27.5%)	194 (29.1%)	0.496
Hypertension	290 (35.4%)	200 (30.1%)	0.031*
Coronary artery disease	81 (10.0%)	76 (11.4%)	0.379
Preoperative factors			
Encephalopathy	371 (45.6%)	339 (50.8%)	0.044*
Vasopressors infusion	139 (17.6%)	167 (25%)	0.001*
Mechanical ventilation	191 (23.5%)	164 (24.5%)	0.637
Continuous renal replacement therapy (CRRT)	327 (38.2%)	337 (45.9%)	0.002*
Pre-transplant ICU admission	23 (42.6%)	312 (46.7%)	0.560
Pre-transplant cardiac arrhythmia	10 (18.9%)	84 (12.6%)	0.194
MELD score	26.0 (13.0-36.0)	30.0 (15.0-39.0)	<0.001*
MELD score ≥35	300 (34.9%)	337 (45.7%)	<0.001*
Waiting time in patients with MELD score ≥35	18.5 (7-198.5)	14.5 (5.0-66.3)	0.045*

* $P < 0.05$ indicating statistical significance. Continuous data reported as median (interquartile range). Categorical data reported as n (%).

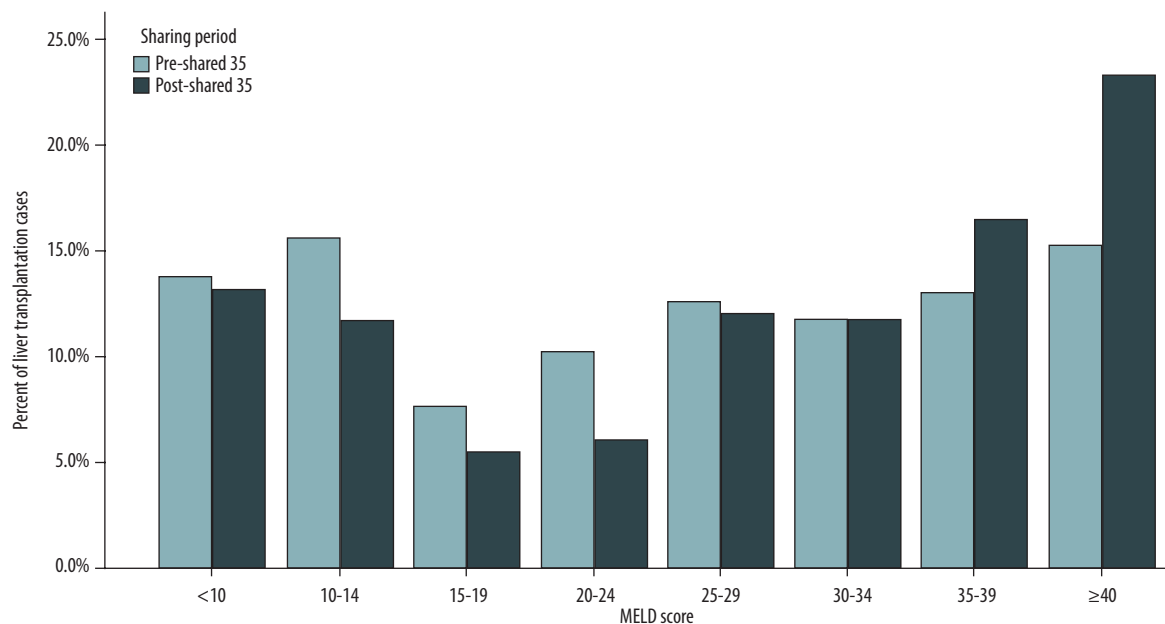


Figure 1. Percentage of patients who underwent liver transplantation in the 2 groups.

Table 2. Intraoperative data of pre- and post-Share 35 transplantation.

	Pre-Share 35 N= 859	Post-Share 35 N=737	P value
Red blood cell transfusion (units)	15.0 (9.0-26.0)	19.0 (10.0-30.0)	<0.001*
Fresh frozen plasma transfusion (units)	20.0 (11.0-31.0)	21.0 (12.0-34.0)	0.284
RBC: FFP ratio	1.2 (1.0-1.5)	1.0 (1.0-1.2)	<0.001*
Total albumin infusion (ml)	1000.0 (0.0-2000.0)	1500.0 (500.0-3000.0)	<0.001*
Total crystalloid infusion (ml)	2800.0 (2000.0-3500.0)	2700.0 (2000.0-3500.0)	0.381
Albumin: Crystalloid ratio	2.2 (1.2-4.0)	1.25 (0.7-2.5)	<0.001*
Cold ischemic time (min)	397.0 (311.0-494.0)	444.0 (369.0-529.0)	<0.001*
Warm-ischemic time (min)	41.0 (36.0-47.0)	51.0 (42.0-61.0)	<0.001*
Surgery time (min)	348.0 (280.5-424.5)	383.0 (325.0-425.0)	0.002*
Intraoperative CRRT	110 (7.3%)	170 (25.7%)	<0.001*
Veno-venous bypass usage	327 (38.1%)	346 (47.2%)	<0.001*
Post-reperfusion syndrome	125 (15.4%)	134 (21.2%)	0.004*
Intraoperative vasopressor infusion	604 (76.6%)	573 (91.1%)	<0.001*
Intraoperative vasopressor intermittent bolus	272 (32.5%)	292 (45.8%)	<0.001*

* $P < 0.05$ indicating statistical significance. Continuous data reported as median (interquartile range). Categorical data reported as n (%).

increased in the post-Share 35 group (26 vs 30, $P < 0.001$) and 45.7% of recipients in the post-Share 35 group had MELD scores ≥ 35 compared to 34.9% in the pre-Share 35 group ($P < 0.001$). The distribution and comparison of MELD scores of liver transplantation recipients in both groups are shown in **Figure 1**. Our center tended to perform liver transplantation in higher

MELD score recipients in the pre-Share 35 era, especially in MELD score 35-39 or greater than 40. In the subgroup of patients with MELD score ≥ 35 , the median MELD score at transplantation was 40 in both groups ($p = 0.057$). The waiting time in patients with MELD score ≥ 35 was significantly shorter in the post-Share 35 group (18.5 vs 14.5, $P = 0.045$).

Table 3. Postoperative data of pre- and post-Share 35 transplantation.

	Pre-Share 35 N= 859	Post-Share 35 N=737	P value
Postoperative mechanical ventilation	3.0 (1.0-5.0)	2.0 (1.0-4.0)	0.326
More than 7 days	103 (12.2%)	23 (10.6%)	0.501
More than 10 days	69 (8.2%)	12 (5.5%)	0.185
More than 14 days	46 (5.5%)	8 (3.7%)	0.280
More than 21 days	27 (3.2%)	5 (2.3%)	0.480
Pulmonary embolism	6 (1.2%)	5 (1.4%)	0.716
Myocardial infarction	23 (1.4%)	9 (2%)	0.413
Stroke	22 (2.7%)	22 (5.1%)	0.028*
Length of postoperative hospital stay	21.0 (12.5-39.0)	24.0 (14.0-52.0)	0.018*

* $P < 0.05$ indicating statistical significance. Continuous data reported as median (interquartile range). Categorical data reported as n (%).

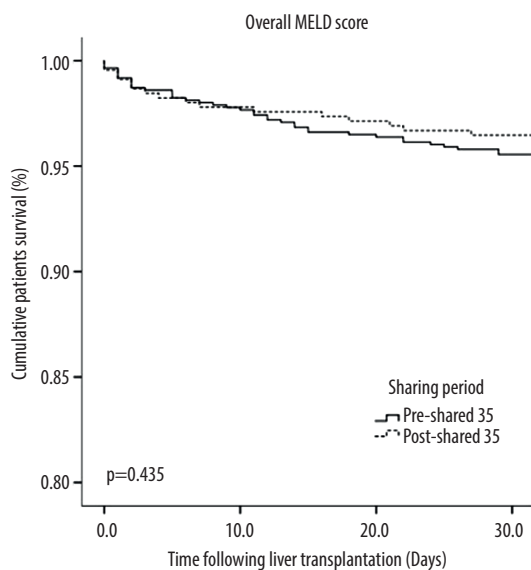


Figure 2. Cumulative patient survival for all patients who underwent liver transplantation in the 2 groups.

Intraoperative parameters are shown in **Table 2**. Recipients required more red blood cell transfusions in the post-Share 35 group (15 units vs 19 units, $P < 0.001$). In the post-Share 35 era, we used RBC and FFP at about a 1: 1 ratio ($P < 0.001$). Venovenous bypass (VVB) and intraoperative CRRT were used significantly more in the post-Share 35 era (38.1% vs 47.2%, $P < 0.001$ and 7.3% vs 25.7%, $P < 0.001$, respectively). Use of intraoperative vasopressor infusion and intermittent bolus was significantly higher in the post-Share 35 group ($P < 0.001$). Cold ischemia time, warm-ischemia time, and surgery duration were significantly longer in the post-Share 35 group ($P < 0.001$, < 0.001 , and 0.002, respectively). The incidence of post-reperfusion

syndrome was significantly higher in the post-Share 35 group (15.4% vs 21.2%, $P = 0.004$).

Postoperative data and complication are reported in **Table 3**. Postoperative ventilator stay was not significantly different between groups (3 days vs 2 days, $P = 0.326$). Postoperative pulmonary embolism and myocardial infarction were not difference between both groups ($p = 0.716$ and 0.413, respectively). However, significantly more patients had postoperative stroke in the post-Share 35 group. The postoperative hospital stay was significant longer in the post-Share 35 group (21 days vs 24 days, $P = 0.018$). **Figure 2** shows Kaplan-Meier curve analysis of 30-day survival after liver transplantation, with no significant difference in survival between the 2 groups ($P = 0.435$).

Discussion

This is one of the largest single-center studies to compare outcomes after liver transplantation between the pre-Share 35 and post-Share 35 eras. Our study demonstrated that recipients in the post-Share 35 era had significantly higher MELD scores at transplantation and shorter waiting times. Moreover, recipients in the post-Share 35 era required significantly more blood transfusion, vasopressor requirement, and intraoperative organ support. However, perioperative mortality was not significantly different between the 2 groups.

After implementation of the Share 35 policy in 2013, several studies showed a decrease in wait time and wait-list mortality among MELD ≥ 35 recipients [1,2]. A nation-wide study using UNOS data showed a significant increase in number and proportion of liver transplantation recipients with MELD score ≥ 35 after the Share 35 policy was implemented [1]. Moreover, the Share 35 policy showed decreased 1-year mortality and

improved donor-recipient matching [7]. Interestingly, the Share 35 policy also improved graft and patient survival in recipients with either MELD score ≥ 40 or re-transplantation [9,10]. Berumen et al showed that the cost of treatment for liver transplantation increased after Share 35 policy implementation [11]. Even though many studies about the Share 35 policy have been published, there is scanty research on intraoperative management for higher medical acuity liver transplantation recipients after implementation of the policy.

Baseline characteristics of our liver transplantation recipients were similar to those in national data. After implementation of the Share 35 policy, we have encountered more patients with NASH/alcoholic cirrhosis, higher MELD score, a higher proportion of MELD ≥ 35 recipients, and more patients from the ICU. Furthermore, there were more patients requiring preoperative CRRT and vasopressor infusion [12]. In the post-Share 35 era, we performed more veno-venous bypass (VVB) in patients with MELD score ≥ 35 (56.4% vs 64.1%, $P = 0.026$). Our recent publication demonstrated VVB can lower the incidence of postoperative AKI in patients with compromised preoperative renal function [13]. Although VVB was used, there are significantly more patients who require vasopressor infusion and intermittent bolus to maintain adequate blood pressure and organ perfusion during the operation, which may be due to the significantly increased incidence of post-reperfusion syndrome (PRS). PRS appears to be associated with exposure to extracorporeal circuit such as VVB and longer cold ischemia time [14-16]. Longer warm-ischemia time and surgical time might result from greater complexity of the operation and increased incidence of VVB usage, as described in several reports [17,18]. Intraoperative CRRT was more frequently used due to the significantly higher number of patients with preoperative renal impairment and dialysis. A recent study showed intraoperative CRRT improved postoperative recovery of native renal function [19].

Our center is located in UNOS region 5, which has one of the highest median MELD allocation scores and rate of regional sharing after Share 35 [1,11]. The longer distance organs must

travel due to regional sharing may have prolonged the cold ischemia time in our center.

There were several studies demonstrating the adverse effect of red blood cell transfusion on overall survival [20,21]. Although liver transplantation recipients in the post-Share 35 era required more red blood cell transfusions, there was no significant difference in perioperative survival in our cohort, and there was also no significant difference in postoperative mechanical ventilator duration. However, the post-Share 35 group had significantly longer postoperative hospital stay, possibly due to more postoperative complications. Several studies, including the present study, showed higher pre-transplant acuity, MELD score, pre-transplant mechanical ventilator use, preoperative renal failure, and increase risks of perioperative complications, especially from bleeding, which might prolong the hospital stay [22,23].

There are several limitations of this study. First, its retrospective design may have led to selection bias. Second, this was a single-center study from 1 UNOS region, so the results may not be generalizable to other centers or UNOS regions. Finally, there was potential bias from the evolution of surgical treatment and perioperative care between the 2 eras.

Conclusions

We performed liver transplantation in patients with higher medical acuity in the post-Share 35 era. Perioperative management in higher medical acuity patients required more medical resources, which might be a significant factor that decreases perioperative mortality.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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