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Outcomes Among Older Adult Liver Transplantation Recipients in the Model of End Stage Liver Disease (MELD) Era

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Abstract

Background—Since 2002, the Model of End Stage Liver Disease (MELD) score has been the basis of the liver transplant (LT) allocation system. Among older adult LT recipients, short-term outcomes in the MELD era were comparable to the pre-MELD era, but long-term outcomes remain unclear.

Material/Methods—This is a retrospective cohort study using the UNOS data on patients age 50 years who underwent primary LT from February 27, 2002 until October 31, 2011.

Results—A total of 35,686 recipients met inclusion criteria. The cohort was divided into 5-year interval age groups. Five-year over-all survival rates for ages 50–54, 55–59, 60–64, 65–69, and 70+ were 72.2%, 71.6%, 69.5%, 65.0%, and 57.5%, respectively. Five-year graft survival rates after adjusting for death as competing risk for ages 50–54, 55–59, 60–64, 65–69 and 70+ were 85.8%, 87.3%, 89.6%, 89.1% and 88.9%, respectively. By Cox proportional hazard modeling, age 60, increasing MELD, donor age 60, hepatitis C, hepatocellular carcinoma (HCC), dialysis and impaired pre-transplant functional status (FS) were associated with increased 5-year mortality. Using Fine and Gray sub-proportional hazard modeling adjusted for death as competing risk, 5-year graft failure was associated with donor age 60, increasing MELD, hepatitis C, HCC, and impaired pre-transplant FS.

Conclusions—Among older LT recipients in the MELD era, long-term graft survival after adjusting for death as competing risk was improved with increasing age, while over-all survival was worse. Donor age, hepatitis C, and pre-transplant FS represent potentially modifiable risk factors that could influence long-term graft and patient survival.

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Authors' Contribution:

Study Design A

Data Collection B

Statistical Analysis C

Data Interpretation D

Manuscript Preparation E

Literature Search F

Funds Collection G

Keywords

Age Groups; Liver Transplantation; Patient Outcome Assessment

Background

Advances in surgery and immunosuppressive therapy have improved clinical outcomes and opportunities for liver transplantation among those previously excluded (e.g., older adults) [1]. During the liver allocation system prior to 2002, liver transplant recipients ≥ 60 years old were reported to have promising graft and patient survival rates similar to younger cohorts [1–8]. Other published reports have cited significant mortality and complications among older recipients [9–12], though important clinical outcomes like functional status have been infrequently studied [4,9].

In 2002, the Model for End Stage Liver Disease (MELD) system for liver allocation was implemented and it resulted in lower waiting list death rates among recipients without changing 1-year graft and patient survival [13,14], including those ≥ 65 years [15], in comparison to the pre-MELD era. However, functional status and long-term clinical outcomes among older liver transplant recipients in the MELD era are unclear.

Based on the Scientific Registry of Transplant Recipients (SRTR), the proportion of older adults (≥ 65 years) waitlisted for liver transplantation has significantly increased in the past decade from 9.9% (1,637) in 2001 to 16% (2,460) in 2011 [16]. The demand for liver transplantation is expected to increase with high rates of hepatitis C infection among individuals born between 1945–1965 who are at risk for cirrhosis and hepatocellular carcinoma (HCC) [17]. Given the increasing numbers of older adults that will potentially require liver transplantation, it is important to evaluate outcomes in the current era using the UNOS database, which is the single largest transplant database in the United States. Thus, the aim of this study was to describe outcomes of older adults after liver transplantation in the MELD era, including post-transplant functional status, 5-year patient survival and 5-year death-censored graft survival.

Material and Methods

This study represents a retrospective cohort evaluation using the United Network for Organ Sharing (UNOS)/Organ Procurement Transplantation Network (OPTN) data on individuals who underwent primary liver transplantation (excluding combined organ transplantation) at age ≥ 50 years old during the period of February 27, 2002 through October 31, 2011. The study was deemed exempt from Institution Review Board (IRB) approval.

Pre-transplant recipient characteristics included: age at time of transplant, gender, race, body mass index, liver disease etiology, MELD score at time of transplant, co-existing illness (i.e., history of angina, diabetes mellitus, dialysis status of recipient at time of registration, cerebrovascular disease, hypertension requiring drug treatment, peripheral vascular disease, previous malignancy), CMV serostatus, care location prior to transplant, and patient functional status at time of transplantation.

Characteristics of transplantation included donor characteristics (i.e., living or deceased status, age, race, and CMV serostatus), cold ischemia time and immunosuppression (i.e., induction and maintenance). In case of a deceased donor, the donor risk index (DRI) [18] was calculated using the following variables: age, height, cause of death, race, donation after cardiac death, partial/split liver, height, sharing type (regional/national), and cold time ischemia. Post-transplantation characteristics available were length of hospital stay, graft failure, patient status (alive or dead), causes of graft failure and death, functional status and total follow-up days.

Performance of activities of daily living (ADL) was used as an assessment tool of the patient functional status. Some patients' functional status was measured using the Karnofsky performance score (KPS) scale, which ranges from 100 (i.e., indicating normal functional status with no complaints and no evidence of disease), to 0 (i.e., indicating death). The KPS approximates the ADL performance as defined in prior literature [19,20]. Patient functional status was further categorized into: good (KPS 80–100% or performs ADL with no assistance), impaired (KPS <80% or performs ADL with some or total assistance) and unknown functional status.

The study subjects were divided into the following age groups: 50–54 (i.e., the reference group), 55–59, 60–64, 65–69 and 70 years to examine the effect of age on 5-year graft failure and 5-year mortality. Data were summarized by mean and standard deviation (SD) for continuous variables except MELD scores for which medians were reported. Chi-square tests compared proportions for categorical variables. Kaplan-Meier estimator and survival curves were compared among different age groups for 5-year all-cause mortality. Cumulative incidence competing risk was compared among different age groups to describe the 5-year graft failure adjusted for death without graft failure as a competing risk. To further examine the relationship of age with 5-year mortality, Cox proportional hazards models were used. Model 1 is adjusted for age group only; model 2 further adjusted for MELD score (continuous variable), dialysis status at time of transplant, etiology of liver disease as hepatitis C or hepatocellular carcinoma, and donor age ≥ 60 ; model 3 further adjusted for functional status at time of transplantation. To examine the relationship of age with 5-year graft failure, Fine and Gray proportional hazards model adjusted for death without graft failure as a competing risk with the same models used for Cox proportional hazard model.

To determine the characteristics associated with 6-month post-transplant functional status only, patients with functional status reported at time of transplant and 6-months post transplantation were included. The 6-month functional status is clinically meaningful and thus selected as a primary outcome; missing data on functional status increased after 6 months. The patient functional status was classified as improved if there was change from pre-transplantation to an improved category in 6 months post-transplantation. The 6-month patient functional status improvement was evaluated using logistic regression adjusted for the same covariates. All statistical tests were 2-tailed and considered statistically significant when $p < 0.05$. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Cohort characteristic prior to transplantation

Based on UNOS/OPTN data as of October 31, 2011, a total of 35,686 liver transplant recipients met our inclusion criteria. Demographics and other recipient characteristics by five-year age group are summarized in Table 1. With increasing age, there were fewer recipients who were male ($p<0.001$), black ($p<0.001$), or had alcohol related liver disease ($p<0.001$); conversely, there were more recipients with hypertension ($p<0.001$), history of malignancy ($p<0.001$) and good functional status ($p<0.001$).

Transplantation characteristics

Transplant and donor characteristics are summarized in Table 1. As shown, there was an increased use of older donors (i.e., age ≥ 60 years) with increasing age of recipients ($p<0.001$). All age groups had a mean calculated donor risk index >2.0 . All other transplant characteristics did not significantly differ with age.

Post-transplant outcomes

Post-transplant data are summarized in Table 2. Post-transplant hospital length of stay was similar across all age groups, with a mean duration of 21 days (SD 39 days). Graft failure occurred in 11.6% of patients overall. The causes of graft failure, which were not mutually exclusive, included primary graft failure (28.3%), recurrent hepatitis (25.2%), recurrent primary disease (14.4%), vascular thrombosis (13.5%), infection (12.1%), biliary disease (9.6%) and acute rejection (5.2%).

The cohort's primary and contributory causes of death were most commonly related to infection, 15.4% and 22.2%, respectively. The rates of infection-related primary and contributory cause of death were not statistically different among age groups. Bacterial disease and sepsis (91%) were the most common infection-related primary cause of death; the remainder was attributed to opportunistic infections (i.e., viral or fungal disease). Malignancy was the primary cause of death for 15%, and its incidence increased with age ($p<0.001$).

Median follow up time for the cohort was 761 days. Highest all-cause mortality (32.8%) was in the ≥ 70 age group compared to other age groups. Survival analyses for patient and graft are shown in Figure 1A, 1B, respectively. The 5-year overall patient survival rates for age groups 50–54, 55–59, 60–64, 65–69, 70+ were 72.2%, 71.6%, 69.5%, 65.0%, and 57.5%, respectively. The 5-year graft survival rates after adjusting for death as competing risk for age groups 50–54, 55–59, 60–64, 65–69 and 70+ were 85.8%, 87.3%, 89.6%, 89.1% and 88.9%, respectively.

Time to event models for 5-year patient mortality and death-censored graft failure are shown in Table 3. Univariate analysis (Model 1) with age showed that all age groups ≥ 60 years had monotonically significant increased risk of 5-year mortality ($p<0.001$). Multivariable analyses (Models 2 and 3) revealed that ages ≥ 55 had significant increased risk of 5-year mortality. With multivariable analyses (Models 2 and 3), donor age ≥ 60 years, dialysis

status, increasing MELD score, hepatitis C and HCC have increased risk for 5-year mortality ($p<0.001$). Impaired functional status ($p<0.001$) and unknown functional status ($p<0.001$) at time of transplant also showed significant increased risk of mortality compared to those with good functional status (Model 3).

With univariate analysis (Model 1) of 5-year death-censored graft failure with age, increasing age had reduced risk of graft failure; however, only age groups 60–64 ($p<0.001$) and 65–69 ($p<0.001$) reached statistical significance. With multivariable analysis (Models 2 and 3), the same age groups ($p<0.001$) were also found to be associated with less risk of 5-year death-censored graft failure. Multivariable analyses also found the association of donor age ≥ 60 years, increasing MELD score, hepatitis C and HCC with increased risk for 5-year death-censored graft failure. Impaired functional status ($p=0.036$) and unknown functional status ($p<0.001$) at time of transplant were at risk for 5-year death-censored graft failure after adjusting for all other variables (Model 3).

Six-month post-transplant patient functional status

Patient functional status at time of transplant data was available among 22,188 recipients (Table 1). However, patient functional status 6 months after transplant was available only in 22,131 recipients of which 70.5% had good functional status, 18.9% had impaired functional status and 10.6% had unknown functional status. A total of 7,723 (34.9%) patients had functional status improvement (i.e., impaired to good) at 6 months post transplantation. Among those patients with impaired functional status at baseline, patients with pre-transplant dialysis (odds ratio 1.85; $p=0.009$) and patients with a high MELD score (odds ratio 1.02 for each unit increase of MELD score; $p<0.001$) were more likely to have significant improvement of functional status 6 months after transplant.

Discussion

This study evaluated long-term outcomes among older adults exclusively in the MELD era using UNOS database, in contrast to prior published studies that included recipients of both eras [7,21]. Changed prioritization and allocation policies in the MELD era can influence candidate selection and post-transplant outcomes. The current study demonstrates higher 5-year mortality but lower 5-year death-censored graft failure rates with increasing age in the current MELD era. Also, the current study highlights the impact of pre-transplant functional status, hepatitis C, and donor age on 5-year patient and graft survival outcomes among older adults.

The cohort was divided into 5-year age groups to test whether there was a monotonic (increasing or decreasing) trend of the effect by age on 5-year graft failure and 5-year mortality. Additionally, this approach could determine the threshold in the age where the effects flatten. Furthermore, since there is no *a priori* knowledge of a dichotomy in age where one would clinically expect the effect to change, this allows future researchers to have large sample estimates of the effect of age. In the current study, long-term overall survival was shown to be poor among those of advanced age. The results were not surprising due to expected risk for long-term complications and adverse outcomes as a result of chronic comorbidities, immunosuppression and immunosenescence. The latter can induce chronic

inflammation resulting in increased risk for atherosclerosis, diabetes mellitus, Alzheimer's disease and malignancy and can impair response to infection [22–24]. Due to inevitable changes from aging and its associated complications, other recipient and donor-related factors need evaluation to optimize post-transplant outcomes.

Hepatitis C, the leading indication of liver transplantation among older adults, was associated with poor outcomes in this cohort possibly due to disease recurrence, reduced patient and graft survival, accelerated cirrhosis development, and impaired quality of life (including functional status) [25,26]. Pretransplant hepatitis C viral load predicts disease progression after transplant [27]; therefore, treatment among waitlisted recipients is recommended to optimize outcomes [28]. However, hepatitis C treatment in older adults with conventional pegylated interferon and ribavirin has poor sustained virological response and higher discontinuation rates when compared with younger cohorts [29,30]. With new hepatitis C anti-viral treatments that include interferon-free regimens, treatment prior to liver transplant could improve sustained virological response and treatment completion rates [31]. The use of younger donors among those with hepatitis C has improved graft and patient survival compared to older donors (age >50); this may be an additional strategy to improve outcomes [32].

Donor quality is an essential predictor of graft outcomes in liver transplantation. A calculated scoring system, such as the donor risk index (DRI), incorporates donor characteristics (including donor age), and quantifies the increased risk for graft failure within three years. In the current study, the mean DRI for the cohort exceeded 2.0, which was unexpectedly higher than a previously reported value for all adult liver recipients (mean DRI=1.46) [33]. The 3-year graft survival rate for DRI >2.0 is estimated to be 60%. The observed graft survival in the current study was better than predicted by DRI. This is suggestive of limitation in the current models, such as the DRI, in predicting graft survival in certain recipient populations [34,35]. Other models that incorporate both donor and recipient risk prior to transplantation have shown better approximation of graft survival outcomes [36,37]. Consensus on a universal predictive model with acceptable sensitivity and specificity is needed.

Similar to prior observations, use of older donors has been independently associated with poor 5-year graft survival outcomes attributed to age-related graft qualities including fibrosis, steatosis, atherosclerosis, and increased susceptibility to ischemia-reperfusion injury, inflammation, thrombosis and T-cell mediated rejection [38–40]. In the current study, the donor age ≥ 60 years was also independently associated with increased 5-year mortality after adjusting for other variables. Similarly, other studies have observed the impact of donor age on over-all outcomes. Specifically, reports reveal an increased 1-year mortality by 10% among recipients with donor age >45 years [41] and increased 5-year mortality by 70% among those with very old donors (age >75 years) [42]. The findings of the aforementioned studies attribute the higher mortality rates to the allocation issue of older donors to older recipients and other high-risk patients who were already at risk for poor post-transplant outcomes regardless of donor quality. Despite known risk with older donors, the options are limited for alternative donors in the current setting of limited donor pool and high demand for liver transplant.

MELD score as a predictor of long-term post-transplant survival has been debated [43–46]. Previous studies show that a high MELD score (i.e., >25) loses its impact 1-year post-transplant among adults [43]. However, the current study demonstrates that high MELD scores had a significant adverse impact on long-term outcomes of older adults beyond the early post-transplant period. The MELD score accounts for both hepatic and renal function, and dysfunction of either organ could result in weight gain, muscle weakness, reduced exercise tolerance and impaired aerobic capacity that can all negatively impact post-transplant recovery and increase risk for cardiovascular disease [43,47,48]. Physiologic capability in older adults is better estimated by functional status [49,50], which also can predict prognosis [51,52]. In the current cohort, impaired pre-transplant functional status was independently associated with poor 5-year survival. Those with poor pre-transplant functional status are more likely to suffer from immobility and reduced physical activity that impairs post-transplant recovery [53]. The association of impaired functional status with worse 5-year graft survival has not been previously reported to date. One can hypothesize that those with pre-transplant impaired functional status have reduced post-transplant physical activity and mobility that limits the immunomodulatory benefit of exercise (e.g., enhanced NK cell and T cell activity, improved antibody responses, and release of neuroendocrine factors) [54,55]. These immunomodulatory benefits from exercise could provide additional protection against infection, which was a common cause of graft failure in this cohort. The association between functional status, immunoregulation and graft failure is an interesting area for future investigation.

The current study had limitations. First missing data and site-related variability of data reporting are unavoidable, especially regarding functional status measures. Future studies on functional status among transplant recipients ideally should be conducted in a single or multi-center prospective cohort using a detailed validated functional status measurement tool. Second, since the screening protocol of older liver transplant candidates varies among transplant centers, selection bias favoring healthier older adults could have accounted for better outcomes than expected. Nonetheless, unique strengths of this study are the use of the large UNOS cohort and the multivariable analyses including the survival analyses adjusting for the competing risk of death. The UNOS database is the largest database of liver recipients in the United States compared to any single or multicenter study in the MELD era. Use of death as competing risk for time-to-event analysis (such as time to graft failure) is important in geriatric clinical outcome studies [56], and not commonly applied in transplant outcome studies of older adults. With traditional time to graft failure, graft survival rates could be overestimated among older adults, since death prior to occurrence of graft failure could likely occur. To minimize the bias, the cumulative incidence competing risk estimates the probability of graft failure conditional on graft failure-free and death-free survival. Similarly, the multivariable regression modeling for graft failure with death as competing risk minimizes the chance of a bias estimate of age on graft failure that could have occurred in traditional Cox proportional hazard modeling.

Conclusions

Age was associated with worse 5-year overall survival among older liver transplant patients in the MELD era, primarily due to infections and malignancy, but better 5-year graft

survival. Results of this study suggest possible association of pre-trans-plant patient functional status with patient and graft outcomes, as well as improvement in patient functional status within 6 months post-transplantation among older liver transplant recipients. Donor age, hepatitis C and pre-transplant functional status could represent modifiable risk factors for poor outcomes and opportunities for improved graft and patient survival among older liver transplant recipients. Future efforts on improving prediction models that incorporate donor and recipient variables may assist in selection of appropriate donor-recipient matching to improve outcomes among older adults.

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Abbreviations

ADL	activity of daily living
CMV	cytomegalovirus
DRI	donor risk index
FS	functional status
HCC	hepatocellular carcinoma
KPS	Karnofsky performance score
LT	liver transplant
MELD	Model for End Stage Liver Disease
OPTN	Organ Procurement Transplantation Network
UNOS	United Network for Organ Sharing

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Figure 1. Cumulative survival curves over 5 years for all-cause post liver transplantation death (A) and Cumulative incidence Competing Risk (CICR) estimate for 5-year graft survival adjusted for death without graft failure as competing risk (B) stratified by age 5-year groups.

Table 1

Recipient and donor characteristics by five-year age intervals.

	All	50–54	55–59	60–64	65–69	70+
Recipient characteristics						
Number of recipients (%)	35686	11226 (31.5%)	11327 (31.7%)	7614 (21.3%)	4254 (11.9%)	1265 (3.5%)
Age at time of transplant, mean (SD)	58 (5.7)	52 (1.4)	57 (1.4)	62 (1.4)	67 (1.3)	72 (1.9)
Male	24510 (68.7%)	8195 (73.0%)	7942 (70.1%)	4980 (65.4%)	2627 (61.8%)	766 (60.6%)
Race						
White	26587 (74.5%)	8316 (74.1%)	8434 (74.5%)	5730 (75.3%)	3131 (73.6%)	976 (77.2%)
Black	2833 (7.9%)	1026 (9.1%)	1020 (9.0%)	513 (6.7%)	223 (5.2%)	51 (4.0%)
Hispanic	4259 (11.9%)	1378 (12.3%)	1319 (11.6%)	900 (11.8%)	544 (12.8%)	118 (9.3%)
Others	2007 (5.6%)	506 (4.5%)	554 (4.9%)	471 (6.2%)	356 (8.4%)	120 (9.5%)
Liver disease						
Hepatitis C	9571 (26.8%)	4018 (35.8%)	3280 (29.0%)	1435 (18.9%)	642 (15.1%)	196 (15.5%)
Hepatocellular carcinoma	7470 (20.9%)	1883 (16.8%)	2485 (21.9%)	1712 (22.5%)	1033 (24.3%)	357 (28.2%)
Alcohol related	5825 (16.3%)	2121 (18.9%)	1842 (16.3%)	1170 (15.4%)	572 (13.4%)	120 (9.5%)
Idiopathic/cryptogenic	2661 (7.5%)	534 (4.8%)	715 (6.3%)	716 (9.4%)	526 (12.4%)	170 (13.4%)
Others	10159 (28.5%)	2670 (23.8%)	3005 (26.5%)	2581 (33.9%)	1481 (34.8%)	422 (33.4%)
Total bilirubin at time of transplant, mean (SD)	7.0 (9.8)	7.9 (10.4)	7.2 (10)	6.6 (9.4)	5.9 (8.6)	5.2 (8.3)
INR at time of transplant, mean (SD)	1.8 (1.2)	1.8 (1.2)	1.8 (1.2)	1.7 (0.9)	1.7 (1.4)	1.6 (0.8)
Creatinine at time of transplant, mean (SD)	1.4 (1.0)	1.4 (1.1)	1.4 (1.0)	1.4 (1.0)	1.4 (1.0)	1.4 (0.8)
Calculated MELD, mean (SD)	20 (9.6)	20.7 (9.7)	20.1 (9.7)	19.7 (9.5)	19.0 (9.5)	17.8 (9.0)
Calculated MELD, median	18	19	18	18	17	15
Co-morbidities						
Diabetes mellitus	9207 (26.4%)	2261 (20.6%)	2897 (26.1%)	2302 (30.9%)	1358 (32.7%)	389 (31.4%)
History of angina [*]	677 (3.9%)	151 (2.5%)	186 (3.7%)	172 (5.2%)	143 (7.3%)	25 (4.1%)
Dialysis [§]	606 (1.9%)	192 (1.9%)	189 (1.9%)	144 (2.2%)	68 (1.8%)	13 (1.2%)

	All	50–54	55–59	60–64	65–69	70+
Hypertension ^{†,¶}	3456 (21.1%)	1010 (16.9%)	989 (20.5%)	751 (24.0%)	520 (27.7%)	186 (32.1%)
Cerebrovascular disease [†]	102 (0.6%)	18 (0.3%)	36 (0.8%)	26 (0.8%)	16 (0.9%)	6 (1.0%)
Peripheral vascular disease [†]	153 (0.9%)	46 (0.8%)	49 (1.0%)	26 (0.8%)	28 (1.5%)	4 (0.7%)
Any previous malignancy (including Hepatocellular carcinoma)	3917 (11.0%)	949 (8.5%)	1217 (10.8%)	913 (12.0%)	630 (14.8%)	208 (16.5%)
Location prior to transplant						
ICU	3433 (9.7%)	1116 (10%)	1074 (9.5%)	721 (9.5%)	414 (9.8%)	108 (8.6%)
Hospitalized but not ICU	5637 (15.9%)	1838 (16.4%)	1784 (15.8%)	1221 (16.1%)	634 (15%)	160 (12.7%)
Not hospitalized	26470 (74.5%)	8228 (73.6%)	8432 (74.7%)	5625 (74.3%)	3194 (75.3%)	991 (78.7%)
Mechanical ventilation	863 (2.4%)	280 (2.5%)	272 (2.4%)	183 (2.4%)	105 (2.5%)	23 (1.8%)
Functional status of recipient at time of transplant[‡]						
Good	8126 (36.6%)	2584 (35.8%)	2555 (36.1%)	1671 (36.8%)	1013 (39.1%)	303 (39.7%)
Impaired	11853 (53.4%)	3830 (53.0%)	3886 (55%)	2395 (52.8%)	1350 (52.1%)	392 (51.3%)
Unknown	2209 (10.0%)	811 (11.2%)	629 (8.9%)	472 (10.4%)	228 (8.8%)	69 (9.0%)
Donor characteristics						
Liver size						
Whole	33942 (95.1%)	10670 (95.1%)	10830 (95.6%)	7217 (94.8%)	4030 (94.7%)	1195 (94.5%)
Partial	1295 (3.6%)	427 (3.8%)	375 (3.3%)	289 (3.8%)	160 (3.8%)	44 (3.5%)
Split	449 (1.3%)	129 (1.2%)	122 (1.1%)	108 (1.4%)	64 (1.5%)	26 (2.1%)
Deceased donor	34326 (96.2%)	10793 (96.1%)	10937 (96.6%)	7299 (95.9%)	4082 (96.0%)	1215 (96.1%)
Age 60	6156 (17.3%)	1628 (14.5%)	1772 (15.6%)	1433 (18.8%)	976 (22.9%)	374 (27.4%)
Race						
White	24522 (68.7%)	7809 (69.6%)	7696 (68.0%)	5238 (68.8%)	2903 (68.3%)	876 (69.3%)
Black	5533 (15.5%)	1697 (15.1%)	1846 (16.3%)	1140 (15.0%)	651 (15.3%)	199 (15.7%)
Hispanic	4370 (12.2%)	1363 (12.1%)	1376 (12.2%)	939 (12.3%)	545 (12.8%)	147 (11.6%)
Others	1250 (3.5%)	355 (3.2%)	406 (3.6%)	295 (3.9%)	152 (3.6%)	42 (3.3%)
Donation after cardiac death	1613 (4.7%)	485 (4.5%)	490 (4.5%)	365 (5.0%)	195 (4.8%)	78 (6.4%)
Cold Ischemia time in hours, mean (SD)	7.1 (3.6)	7.1 (3.6)	7.1 (3.7)	7.1 (3.6)	7.0 (3.7)	7.2 (3.7)

	All	50–54	55–59	60–64	65–69	70+
DRI ^{*,**} for deceased donors, mean (SD)	2.3 (0.4)	2.3 (0.3)	2.3 (0.3)	2.4 (0.4)	2.4 (0.4)	2.4 (0.4)

* Available data on 17,508 patients. Angina was reported as with, without or unknown history of documented coronary artery disease.

[†] Available data on 16,402 patients;

[‡] available data on 22,188;

[§] history of dialysis at time of registration;

[¶] hypertension requiring treatment;

^{**} donor risk index.

Table 2

Post-transplantation outcomes among recipients by five-year age intervals.

	All	50–54	55–59	60–64	65–69	70+
Length of hospitalization, mean (SD)	21 (39)	20 (32)	21 (48)	21 (34)	21 (37)	21 (32)
Graft failure	3984 (11.6%)	1465 (13.6%)	1265 (11.6%)	709 (9.6%)	422 (10.2%)	123 (10.1%)
Re-transplantation	1630 (4.6%)	625 (5.6%)	538 (4.8%)	293 (3.9%)	137 (3.2%)	37 (2.9%)
All-cause mortality	8524 (24.0%)	2465 (23.3%)	2502 (22.2%)	1807 (23.9%)	1197 (28.2%)	413 (32.8%)
Primary causes of death						
Infection *	1306 (15.4%)	381 (14.6%)	382 (15.3%)	290 (16.1%)	191 (16.1%)	62 (15.0%)
Malignancy	1276 (15.0%)	371 (14.3%)	354 (14.2%)	275 (15.2%)	190 (16.0%)	86 (20.9%)
Graft failure	1142 (13.4%)	462 (17.8%)	351 (14.1%)	182 (10.1%)	120 (10.1%)	27 (6.6%)
Cardiac	991 (11.7%)	249 (9.6%)	297 (11.9%)	251 (13.9%)	149 (12.5%)	45 (11.0%)
Cerebrovascular	217 (2.6%)	66 (2.5%)	54 (2.2%)	52 (2.9%)	30 (2.5%)	15 (3.6%)
Others †	3566 (42.0%)	1071 (41.2%)	1055 (42.3%)	754 (41.8%)	509 (42.8%)	177 (43.0%)
Contributory causes of death						
Infection *	485 (22.2%)	147 (21.5%)	140 (21.7%)	105 (23.5%)	72 (24.0%)	21 (18.6%)
Graft failure	284 (13.0%)	109 (16.0%)	89 (13.8%)	50 (11.2%)	28 (9.3%)	8 (7.1%)
Cardiac	215 (9.8%)	53 (7.8%)	72 (11.2%)	46 (10.3%)	32 (10.7%)	12 (10.6%)
Malignancy	138 (6.3%)	51 (7.5%)	27 (4.2%)	30 (6.7%)	16 (5.3%)	14 (12.4%)
Cerebrovascular	50 (2.3%)	15 (2.2%)	14 (2.2%)	11 (2.5%)	6 (2%)	4 (3.5%)
Others †	1016 (46.4%)	308 (45.1%)	303 (47.0%)	205 (45.9%)	146 (48.7%)	44 (47.8%)

* Infections including both bacterial and opportunistic infections;

† others included unknown causes of death.

Time to death within 5 years of liver transplantation using Cox proportional hazard models and time to graft failure within 5 years of liver transplantation using Fine and Gray proportional hazard models adjusted for death without graft failure as competing risk.

Table 3

	Model 1 [‡]		Model 2 [§]		Model 3 [¶]	
	HR* (95% CI) [†]	p value	HR (95% CI)	p value	HR (95% CI)	p value
5 year patient mortality						
55–59 vs. 50–54	1.046 (0.985–1.111)	0.1407	1.066 (1.004–1.133)	0.037	1.065 (1.003–1.132)	0.0401
60–64 vs. 50–54	1.159 (1.085–1.238)	<0.001	1.216 (1.138–1.300)	<0.001	1.215 (1.137–1.299)	<0.001
65–69 vs. 50–54	1.345 (1.248–1.449)	<0.001	1.425 (1.320–1.539)	<0.001	1.428 (1.324–1.541)	<0.001
70 vs. 50–54	1.616 (1.444–1.809)	<0.001	1.724 (1.538–1.932)	<0.001	1.718 (1.532–1.926)	<0.001
Donor age 60 vs. <60			1.335 (1.260–1.414)	<0.001	1.340 (1.264–1.420)	<0.001
Dialysis vs. no dialysis at time of transplant			1.568 (1.363–1.803)	<0.001	1.553 (1.350–1.787)	<0.001
MELD score			1.021 (1.019–1.024)	<0.001	1.017 (1.014–1.020)	<0.001
Hepatitis C			1.326 (1.245–1.413)	<0.001	1.334 (1.253–1.422)	<0.001
Hepatocellular carcinoma			1.425 (1.328–1.529)	<0.001	1.435 (1.337–1.541)	<0.001
Impaired vs. good FS					1.298 (1.229–1.371)	<0.001
Unknown vs. good FS					1.466 (1.358–1.583)	<0.001
5-year graft failure						
55–59 vs. 50–54	0.922 (0.838–1.005)	0.056	0.940 (0.856–1.024)	0.148	0.942 (0.858–1.026)	0.164
60–64 vs. 50–54	0.751 (0.650–0.852)	<0.001	0.784 (0.682–0.887)	<0.001	0.785 (0.677–0.893)	<0.001
65–69 vs. 50–54	0.782 (0.661–0.903)	<0.001	0.809 (0.685–0.932)	0.001	0.811 (0.687–0.935)	<0.001
70 vs. 50–54	0.824 (0.624–1.025)	0.059	0.836 (0.634–1.039)	0.084	0.836 (0.634–1.039)	0.084
Donor age 60 vs. <60			1.665 (1.583–1.746)	<0.001	1.668 (1.586–1.749)	<0.001
Dialysis vs. no dialysis at time of transplant			1.125 (0.878–1.371)	0.350	1.116 (0.870–1.363)	0.380

	Model 1 [‡]			Model 2 [§]			Model 3 [¶]		
	HR [*]	(95% CI) [†]	p value	HR	(95% CI)	p value	HR	(95% CI)	p value
MELD score				1.008 (1.004–1.011)		<0.001	1.005 (1.001–1.009)		0.013
Hepatitis C				1.431 (1.338–1.524)		<0.001	1.439 (1.346–1.532)		<0.001
Hepatocellular carcinoma				1.151 (1.041–1.262)		0.012	1.165 (1.055–1.276)		0.007
Impaired vs. good FS							1.090 (1.009–1.170)		0.036
Unknown vs. good FS							1.350 (1.236–1.464)		<0.001

^{*} HR – hazard ratio;

[†] CI – confidence interval;

[‡] Model 1 is the age effect relative to liver transplant recipients 50 to 54 years old;

[§] Model 2 includes recipient age, MELD score (continuous), dialysis status at time of transplant, hepatitis C, and hepatocellular carcinoma, and donor age 60 years old;

[¶] Model 3 includes variables of Model 2 and functional status (FS) at the time of transplantation.