WAITLIST TIME PREDICTS SURVIVAL AFTER LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA: A COHORT STUDY IN THE UNITED NETWORK FOR ORGAN SHARING REGISTRY

By

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LIST OF ABBREVIATIONS

AFP	Alpha-fetoprotein
BMI	Body mass index
CI	Confidence interval
DDLT	Deceased-donor liver transplantation
DMF	Death Master File
DRI	Donor risk index
ECD	Expanded criteria donor
HCC	Hepatocellular carcinoma
HCC+MP	Hepatocellular carcinoma with Model for End-Stage Liver Disease prioritization group
HCC-MP	Hepatocellular carcinoma without Model for End-Stage Liver Disease prioritization group
HCV	Hepatitis C
HR	Hazard ratio
IQR	Interquartile range
ITT	Intention-to-treat
LDLT	Living-donor liver transplantation
LT	Liver transplantation
MELD	Model for End-Stage Liver Disease
NASH	Non-alcoholic steatohepatitis
NHCC	Non-hepatocellular carcinoma group
OPTN	Organ Procurement and Transplantation Network
PBC	Primary biliary cirrhosis
PSC	Primary sclerosing cholangitis
SSA	Social Security Administration
STAR	Standard Transplant Analysis and Research registry
UCSF	University of California San Francisco
UNOS	United Network for Organ Sharing

BACKGROUND & LITERATURE REVIEW

HCC is the third most common malignancy worldwide, and its incidence is rising in both developing and Western nations.[1,2] HCC is an aggressive cancer, with an incidence approximating the annual death rate.[3] Surgical resection, locoregional tumor ablation, and LT are the primary therapies for HCC, however LT is the optimal therapy when HCC is deemed unresectable.[4]

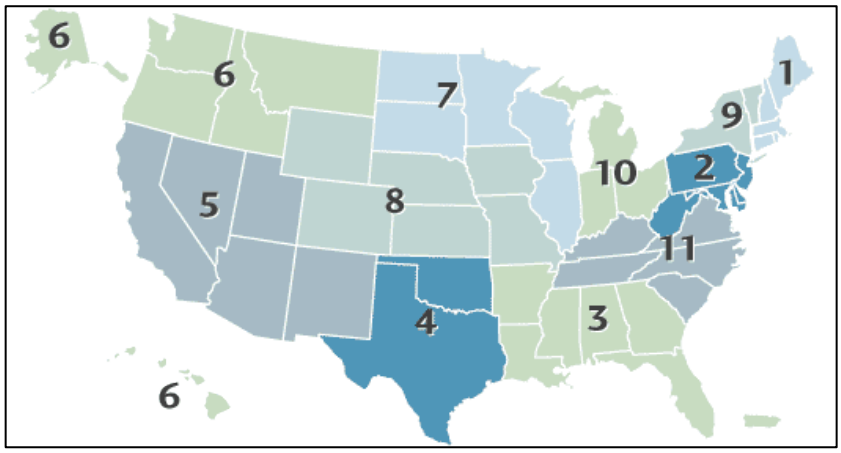
In the United States, HCC usually occurs in the setting of underlying cirrhosis. LT affords an opportunity, unique among HCC therapies, to simultaneously cure the HCC and the underlying 'field defect' of chronic liver disease, preventing both the morbidity and mortality associated with advanced cirrhosis as well as future *de novo* HCC. In 1996, a prospective trial of LT in cirrhotic patients with unresectable HCC conducted at the National Cancer Institute of Milan demonstrated 4-year overall and recurrence-free survival of 75% and 83%, respectively, using restrictive criteria (a single tumor < 5 cm or up to 3 tumors < 3 cm in total diameter), survival rates similar to LT for non-HCC indications.[5] In multivariate analysis, smaller tumor size and lower tumor counts were associated with improved post-LT survival. After additional studies validated 5-year survival exceeding 70%, the United Network for Organ Sharing (UNOS) adopted these 'Conventional Milan Criteria' as the standard criteria for selection of HCC patients for LT in the United States.[6,7,8] Studies using the Milan listing criteria have demonstrated an 8 to 20% risk of post-LT HCC recurrence, at a median 23 to 25 months after LT.[9,10,11] The median survival after post-LT HCC recurrence is less than 1 year.

LT is prioritized by patients' anticipated mortality – 'the sickest first.' In cirrhosis, the MELD scoring system incorporates three biochemical variables (total bilirubin, creatinine, and the international normalized ratio of prothrombin time) into a predictive model,

generating a score ranging from 6 to 40, prospectively validated to correlate with 3-month survival.[12] However, HCC and certain other liver diseases (e.g. severe hepatopulmonary syndrome and primary sclerosing cholangitis) confer mortality independent of the presence or severity of underlying cirrhosis; these diseases may exhibit poor prognoses despite low calculated MELD scores.[13,14] Further, HCC progression beyond the Milan criteria occurs with increasing duration on the wait list for LT, leading to loss of candidacy for LT while the MELD score remains low (wait list 'dropout' of 7.3% at 6 months, 25.3% at 12 months, and 43.6% at 24 months in one analysis).[15] To account for under-represented mortality using the calculated MELD score and wait list 'dropout' due to tumor progression, UNOS adopted a prioritization system for liver allocation on February 27th, 2002; HCC patients were awarded a priority status in the MELD system. Based on reported tumor doubling times[16,17], patients with 1 nodule < 2 cm were awarded a MELD of 24, correlating with a 15% probability of progressing beyond Milan criteria within 3 months, and patients with 1 nodule between 2 to 5 cm, or up to 3 lesions < 3 cm, were awarded a MELD of 29, correlating with a 30% probability.

Several modifications of the HCC-adjusted liver transplant allocation policy were subsequently enacted by UNOS to optimize equitable organ allocation for HCC and non-malignant LT indications. After the initial MELD prioritization system was enacted, the fraction of liver transplants performed for HCC increased from 7% to 22%, wait list duration decreased from 2.28 years to 0.69 years, and the 5-month wait list 'dropout' rate decreased from 25.9% to 6.7%.[18] The wait list 'dropout' rate at 1-year was 10% for the group with 1 nodule < 2 cm, and 50% for the group with large or multiple tumors, supporting the notion that patients with more advanced cancer within the Milan criteria be given allocation priority for LT.[18,19] However, deaths on the wait list and development of illness preventing LT in the HCC groups was significantly lower than for MELD-matched

patients without HCC.[19] The MELD prioritization for HCC was subsequently devalued three times; in April 2003, single < 2 cm tumors were awarded a MELD of 20 and larger or multiple tumors within Milan criteria were awarded a MELD 24; in January 2004, single < 2 cm tumors were not awarded any MELD prioritization and more advanced HCC within Milan criteria remained with a MELD of 24; and in March 2005, single < 2 cm tumors remained without MELD prioritization and the MELD prioritization awarded to advanced tumors within Milan criteria was reduced to 22.[20] Additional MELD points are added per 3-month period on the waiting list (equivalent to a 10% mortality decrement). The MELD prioritization system adopted in March 2005 remains in use today; however, evidence continues to support over-valued MELD prioritization for HCC in the present system, with wait list 'dropout' rates consistently higher for non-HCC indications across all Organ Procurement and Transplantation Network (OPTN) geographic regions of the United States (shown in **Background Figure 1).**[21]



Background Figure 1. Organ Procurement and Transplantation Network (OPTN) regions in the United States.[22]

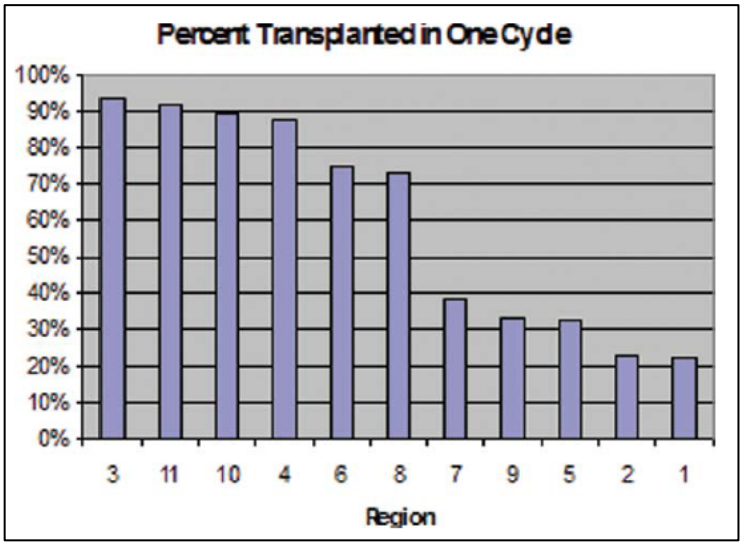
The association of increasing HCC size and count with poor post-LT survival identified in the original Milan study was considered a surrogate for adverse tumor biology, however this assumption was questioned due to the absence of microvascular tumor invasion or poorly differentiated tumor histology in all study patients. Later studies demonstrated that

tumor de-differentiation, microvascular invasion, and response to locoregional therapy predict post-LT recurrence independent of tumor size and count.[23,24,25] Further, tumor recurrence after LT was anecdotally observed in a subset of patients with early HCC, and recurrence-free survival was observed in a subset of patients with advanced HCC beyond the Milan criteria. In an attempt to identify and offer LT to highly selected patients beyond the Milan criteria with favorable post-LT prognoses, both 'expanded' criteria and 'down-staging' for HCC were conceived. In the former, exemplified by the University of California San Francisco (UCSF) criteria, patients were allowed a single lesion up to 6.5 cm or up to 3 lesions not exceeding 8 cm in total diameter, with post-LT 5-year survival rates of 75 to 80%.[26,27] In the down-staging approach, patients were allowed a single tumor up to 8 cm or up to 5 tumors with total diameter of 8 cm; if Milan criteria were achieved after locoregional therapies were performed, LT was permitted after an additional 3-month waiting period.[28] In prospective trials, down-staging yielded 4- and 5-year survival rates of 69% and 66%, respectively.[29,30]

An observed 10% tumor recurrence rate after LT for patients within the Milan criteria, and the inverse, that excellent post-LT outcomes were achieved in down-staged patients initially beyond the Milan criteria, prompted speculation that a waiting period for all potential LT candidates, irrespective of Milan criteria, might allow discrimination of patients with favorable tumor biology and a consequent reduced risk for post-LT tumor recurrence.[31] Patients with aggressive tumors or unrecognized extrahepatic disease would theoretically progress during the LT waiting period and 'dropout' from the LT list, allowing transplantation of the residual HCC patients with favorable tumor biology and lower risks for post-LT tumor recurrence. However, a risk of progression beyond the Milan criteria for patients initially without extrahepatic disease was also recognized. This strategy, termed 'ablate and wait,' was proposed with a waiting period of 6 months based on an observation

that tumor progression precluding LT occurs at a median duration of 7 months after locoregional ablative procedures. The author proposed that HCC progression within 6 months of treatment suggested initially undetected disease rather than adverse tumor biology in the treated primary HCC. The HCC recurrence rate in living donor liver transplantation (LDLT) recipients with HCC, who benefit from short waiting times relative to deceased donor liver transplant (DDLT) recipients, has been mixed, with an initial cohort analysis finding a higher tumor recurrence rate in the LDLT group, and a more recent study finding no difference in tumor recurrence rates.[32,33] The strategies of 'ablate and wait' versus the usual allocation of LT for HCC without an imposed waiting period have not been prospectively compared.

The supply of donor organs exhibits both geographic and blood type variation. Because of geographic variation in the supply of donor organs and persons needing LT, wait list duration varies widely across the 11 OPTN regions of the United States; accordingly, the MELD at the time of LT also exhibits marked geographic heterogeneity. In certain OPTN regions, persons listed for OLT with MELD prioritization for HCC are rapidly transplanted, whereas in other OPTNs, persons with HCC and MELD prioritization wait extended durations for their MELD score to increase sufficiently for LT; the fraction of persons listed for HCC receiving LT within 3-months of initial listing ranges from <25% to >90% (**Figure 2).**[31] Similarly, median wait list duration varies from 76 days for blood type AB to 459 days for blood type O LT recipients, based on 2003 to 2004 data[34], and blood type O is an established predictor of 'dropout' from the OLT wait list.[35] Variation in wait list duration across OPTN regions and blood types may predict tumor recurrence and survival after LT for HCC.



Background Figure 2. Percentage of patients with model for end-stage liver disease (MELD) exceptions for hepatocellular carcinoma undergoing liver transplantation during the first 3-month cycle in 2007.[31]

Since aggressive carcinomas within the Milan criteria are more likely to progress beyond the Milan criteria with increasing duration on the wait list, variability in the wait list duration for LT may be a surrogate model of the proposed 'ablate and wait' strategy, in effect a length-time bias in which prolonged wait list duration prior to LT for HCC selects for biologically less aggressive cancers that have improved post-LT outcomes, at the expense of a higher proportion of wait list 'dropouts' due to tumor progression. The primary goal of this study is to determine the risk of cancer recurrence and survival after LT for HCC with varying durations on the transplant wait list. The secondary goal of this study is to evaluate the intention-to-treat survival of persons listed for LT for HCC with MELD prioritization, including persons who 'dropout' from the wait list or die on the wait list, persons who survive without LT, and persons who undergo LT.

ABSTRACT

Background. Recipients of liver transplantation (LT) for hepatocellular carcinoma (HCC) harbor an 8-20% risk of post-LT HCC recurrence. Studies of 'downstaging' HCC outside the Milan criteria suggest that a monitoring period after liver-directed HCC therapy results in comparable post-LT survival to LT of early HCC. I sought to evaluate whether wait list time after MELD prioritization for HCC predicts post-LT survival. ***Methods.*** In the UNOS registry, I selected 3 groups registered on the LT wait list from March 2005-March 2008: (1) patients receiving MELD prioritization for HCC, HCC+MP; (2) patients without HCC, NHCC, and (3) patients with HCC who did not receive MELD prioritization, HCC-MP. The primary exposure was the MELD status at LT, a marker of wait list time from initial HCC MELD prioritization to LT. Recipients of LT were followed until death or censoring through October 2012. I compared the association of MELD status at LT with post-LT survival between groups using multiple Cox proportional-hazards regression. In an intention-to-treat (ITT) analysis using time-dependent models, I evaluated ITT survival from wait list registration and the mortality risk of wait list 'dropout' or LT. ***Results.*** The median MELD at LT was 22 in the HCC+MP group and 24 in the non-prioritized groups. One, 3- and 5-year post-LT survival was highest for the NHCC group (91%, 84%, 77%), intermediate for the HCC+MP group (92%, 81%, 73%), and lowest for the HCC-MP group (89%, 77%, 70%. Increasing MELD status at LT was independently associated with longer survival in the HCC+MP group (HR 0.84; 95% CI: 0.73-0.98); in contrast, increasing MELD status at LT was associated with shorter survival in the NHCC (HR: 1.20; 95% CI: 1.15-1.25) and HCC-MP (HR 1.17, 95% CI: 1.02-1.33) groups. In the ITT cohort, 75% of the HCC+MP group received LT and 23% experienced wait list 'dropout' or death, compared to 42% and 48% of the NHCC and 57% and 40% of the HCC-MP groups. Five-year ITT survival was 62%, 57%, and 48%, respectively. ***Conclusion.*** Increasing MELD at LT in MELD-prioritized HCC patients

independently predicted greater post-LT survival, due to the selection of candidates with favorable cancers for LT. In contrast, increasing MELD at LT independently predicted lower post-LT survival in non-prioritized patients, due to poor liver function. MELD-prioritized HCC patients have enhanced access to LT, greater ITT survival, and lower post-LT survival relative to non-prioritized patients. Delaying LT in this group may optimize ITT survival and equitable organ allocation across the overall pool of LT candidates.

Keywords: hepatocellular carcinoma, liver transplantation, cirrhosis.

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) is rising in both developing and Western nations.[1,2] Unique among HCC therapies, liver transplantation (LT) affords an opportunity both to cure HCC that remains confined to the liver and to prevent future *de novo* HCC by removing the background 'field defect' of cirrhosis, the main risk factor for hepatocarcinogenesis.[4] Although LT of early HCC results in acceptable survival,[5,6,7,8] recipients nevertheless harbor an 8 to 20% risk of HCC recurrence at a median 23 to 25 months after LT.[9,10,11] Retransplantation of recurrent HCC is generally not performed due to poor survival and organ scarcity;[36] the median survival is less than 1 year.[37]

Although increasing size and number of HCC tumors are associated with lower survival after LT,[4,38] patients with HCC exceeding the Milan criteria have demonstrated low rates of post-LT HCC recurrence and mortality in 'downstaging' protocols when a tumor response was achieved with liver-directed HCC therapy.[25,28,29] A shared feature of these studies was a period of monitoring during and after HCC therapy in which candidates either had cancer progression, resulting in wait list 'dropout' or death, or cancer stability, resulting in LT. These findings prompted speculation that a 3 to 6 month observation period before LT for all patients with HCC might facilitate the selection of LT candidates at low risk for post-LT HCC recurrence.[31,39] This theory is analogous to length bias observed in cancer screening; indolent tumors spend more time in the pre-clinical disease phase and are therefore more likely to be screen-detected than aggressive tumors that spend less time in the pre-clinical disease phase and present with symptoms. Similarly, an observation period before LT may allow the exclusion of patients with biologically aggressive cancers who derive minimal survival benefit from LT due to a high risk of post-LT cancer recurrence.

Despite modifications of Organ Procurement and Transplantation Network (OPTN) policy intended to deemphasize MELD prioritization for HCC, patients with HCC continue to have greater opportunities to receive LT than other LT indications.[21] Although increasing wait list time in candidates with HCC predicts wait list death or 'dropout' due to cancer progression,[14,15,35] wait list 'dropout' and death are nevertheless more frequent in non-HCC candidates.[21] Strategies to equalize rates of wait list death and 'dropout' between LT indications have been proposed.[40] However, allocation policies exclusively focusing on pre-LT outcomes ignore differences in post-LT survival that contribute to the indication-specific utility of LT.[39] Consideration of the intention-to-treat (ITT) survival from wait list registration may inform an allocation policy that equitably balances ethical considerations of the individual right to access a scarce resource with system utility.[41]

In the present study, I hypothesized that increasing time on the LT wait list after MELD prioritization for HCC would be associated with better post-LT survival in a national transplant registry. I also hypothesized that this association would not be observed in patients without HCC or with HCC and advanced cirrhosis. In an ITT cohort followed from wait list registration, I sought to correlate the hypothesized associations evaluated in the post-LT cohort with ITT survival, rates of wait list death or 'dropout', and receipt of LT.

METHODS

The aims of this study were to (1) determine whether duration on the LT wait list after MELD prioritization for HCC, expressed as the MELD status at LT, was associated with post-LT survival, (2) compare the association of MELD status at LT and post-LT survival between patients with HCC with MELD prioritization, no HCC, and HCC without MELD prioritization, and (3) compare ITT survival, wait list death and 'dropout,' and receipt of LT

between patients with HCC with MELD prioritization, no HCC, and HCC without MELD prioritization.

To achieve the first two aims, I performed a survival analysis of persons registered for LT in the current MELD prioritization era (in which stage T2 HCC is granted 22 MELD points, per OPTN policy 3.6.4.4),[42] from the time of LT. Wait list duration varies considerably by center and region, thus it is a poor indicator of patient status at the time of LT. Consequently, I elected to use the MELD status at LT, which is useful as both a marker of increasing time from MELD prioritization to LT for MELD prioritized patients with HCC (a 10% increase in the MELD status is awarded for every 3 months on the wait list) and a marker of increasing liver disease severity for patients without MELD prioritization, thus allowing patients with and without MELD prioritization to be compared. High MELD status centers transplanted patients who either waited longer durations with MELD exceptions for HCC or who had more severe liver dysfunction, compared to low MELD status centers. The primary outcome was post-LT survival.

To achieve the third aim, I performed an ITT analysis of persons registered for LT in the current HCC MELD prioritization era, from the time of wait list registration. The primary outcome was ITT survival.

Data source. I performed a retrospective cohort study using the Standard Transplant Analysis and Research (STAR) registry of the United Network for Organ Sharing (UNOS), which includes prospectively collected data on all United States solid organ donation and transplant events reported to the Organ Procurement and Transplantation Network (OPTN) since October 1st, 1987.[43] The STAR version used in this analysis was current through October 18th, 2012. I linked the STAR registry to the Death Master File (DMF) of the Social Security Administration (SSA), supplementing deaths included in the STAR

registry reported by individual centers. The DMF is maintained by the National Technical Information Service of the United States Department of Commerce, and contains over 86 million records of persons with social security numbers whose deaths were reported to the SSA.[44] The DMF version used in this analysis was current through November 1st, 2011.

Study population. I selected three groups with differing exposures who were registered on the LT wait list from March 1st, 2005 to March 1st, 2009. The primary group was comprised of patients receiving MELD prioritization for HCC with 22 MELD points **('HCC+MP' group).** The second group was comprised of persons without HCC who did not receive MELD prioritization for non-HCC indications **('NHCC' group).** The third group was comprised of persons with HCC who either did not apply for MELD prioritization for HCC or were declined MELD prioritization for HCC **('HCC-MP' group).** To be included in the HCC+MP group in the post-LT cohort, subjects were required to have an active MELD exception for HCC at the time of LT, whereas to be included in the HCC+MP group in the ITT cohort, subjects were required to have had active MELD prioritization for HCC at any time while on the LT wait list (since subjects receiving MELD prioritization for HCC did not necessarily receive LT). March 1st, 2005 was selected as the initial date of wait list registration for my sample because this is the date on which the current MELD prioritization protocol for HCC was enacted. March 1st, 2009 was selected as the end date of wait list registration for my sample to allow sufficient at-risk time for post-LT HCC recurrence and associated mortality; since most candidates with MELD prioritization for HCC will receive LT within 1 year, MELD-prioritized subjects in my study were anticipated to have a minimum 30 months of at-risk time after LT (registered for LT through March 1st, 2009, LT anticipated by March 1st 2010, and end of data collection on October 18th, 2012), which exceeds the reported median time to post-LT HCC recurrence by 5 to 7 months.

I excluded patients <18 years at LT, Pediatric End-Stage Liver Disease registrants, OPTN Status 1 indications, living donor liver transplant (LDLT) recipients, split or partial liver recipients, multiorgan recipients, prior LT recipients, and candidates receiving MELD prioritization for non-HCC indications. Subjects with incidental HCC identified in their explants were excluded because the HCC diagnosis was not recognized until the time of LT. I also excluded patients receiving MELD prioritization for HCC for alpha-fetoprotein (AFP) levels ≥ 500 ng/mL without radiographically identifiable liver tumors, because few patients with this indication have HCC in their explants.[45] Recipients of expanded criteria donors (ECD) were excluded from the post-LT analysis because ECD organs may be associated with worse post-LT outcomes in the lower MELD status recipients to whom they are preferentially offered.[46] ECD status thus acts as an effect modifier in the relationship between MELD status at LT and overall post-LT survival in the post-LT model. Since this effect modification was not directly relevant to my study's aims, I chose not to perform ECD-stratified analyses of my post-LT model, and instead restricted my post-LT analysis to recipients of high-quality organs, with adjustment for the donor risk index (DRI) to account for residual differences in donor quality.[47] Finally, subjects with HCC exceeding the Milan criteria were included in the appropriate groups, depending whether MELD prioritization was granted; these subjects presumably fulfilled downstaging or expanded listing criteria before LT.

Predictors and outcomes. For the post-LT analysis, clinical and demographic variables of donors and recipients were recorded at the time of LT. For the HCC+MP group, the peak values of certain HCC-specific variables were recorded since testing was serially performed every 3 months on the LT wait list ('peak AFP', 'peak aggregate tumor diameter', and 'peak tumor number'). Receipt of liver-directed therapy was defined as a subject having received a locoregional HCC therapy at any time while on the wait list. HCC-specific variables were

available for subjects who applied for MELD prioritization for HCC; since 70.6% of the HCC-MP group had never applied for MELD prioritization and thus had missing data, I could not adequately evaluate HCC-specific variables for this group. The primary outcome in the post-LT analysis was the time from LT to death (the first death date of those reported by UNOS or the DMF) or the time from LT to last reported living status, whichever occurred first (right censoring).

For the ITT analysis, clinical and demographic variables were recorded at the time of wait list registration. As with the post-LT analysis, HCC-specific variables were reported only for the HCC+MP group (92.2% of the HCC-MP group never applied for MELD prioritization and thus had missing data). The time from wait list registration to either wait list 'dropout' or LT were recorded, permitting evaluation of these events as time-dependent covariates. The primary outcome in the ITT analysis was the time from wait list registration to death (the first death date between those reported by UNOS or the DMF) or the time from wait list registration to last reported living status, whichever occurred first (right censoring). For subjects who dropped off the wait list but did not have a reported death, the date of wait list 'dropout' was used as the censoring date since these patients did not have additional documented follow-up.

Statistical analysis. Normally distributed variables were expressed as mean ± standard deviation and non-normally distributed variables as median ± interquartile range (IQR). Baseline variables were compared between the three groups in group-wise fashion using the chi-square test if categorical, the one-way ANOVA test if normally distributed continuous, and the Kruskal-Wallis test if non-normally distributed continuous. Median and 1-, 3-, and 5-year actuarial survival, with associated 95% confidence intervals (CIs), were calculated for the overall post-transplant and ITT cohorts and for each group within

each cohort. Mortality rates were compared between groups using relative risks with associated 95% CIs, and the estimated survival functions were compared between groups using the log-rank test.

For the post-LT analysis, I performed univariable Cox proportional-hazards regressions for all candidate predictors of post-LT survival. Variable selection for a multiple Cox regression model was performed using a combination of automated sequential procedures (with p-value thresholds of 0.05 for selection and 0.10 for elimination) and manual review, with the MELD status at LT a required covariate in the final model. Multicollinearity was assessed with variable inflation factors. I evaluated pairwise interactions comparing the HCC+MP group to the other two groups for the association of MELD status at LT with post-LT survival. Group-specific predictors of survival were then evaluated in multiple Cox regression models. Interactions were tested for all covariates and the association between MELD status at LT and post-LT survival in each group-specific model. The proportional-hazard for each covariate was tested using an approximate score statistic of linear correlation between the rank order of failure times in the cohort and Schoenfeld partial residuals.[48] Covariates that violated the proportional-hazards assumption were stratified in final multiple regression models.

For the ITT analysis, I performed univariable Cox proportional-hazards regressions of all candidate predictors of ITT survival. I evaluated the mortality risk associated with wait list 'dropout' or receipt of LT by expressing these dichotomous exposure variables as time-dependent covariates in the Cox regression analysis.

A two-sided p-value<0.05 was considered to be statistically significant. Calculations were performed using STATA/IC version 11.0 for Macintosh OS X (StataCorp, College Station, TX). The OHSU institutional review board approved the study protocol.

RESULTS

11,312 subjects were selected for the post-LT cohort: 3,256 in the HCC+MP group, 7,397 in the NHCC group, and 659 in the HCC-MP group **(Table 1).** Subjects with HCC, with or without MELD prioritization, were more frequently male and non-White, and more frequently had hepatitis B or hepatitis C (HCV) ($p<0.01$). MELD status at LT was similar between the three groups (median 22 in the HCC+MP group compared to 24 in the other two groups), however the calculated MELD score was considerably higher in the groups without MELD prioritization (median 12 in the HCC+MP group compared to 23 in the other two groups) ($p<0.01$). The median durations on the wait list were broad: 3.3 months (range 0 to 85 months) for the HCC+MP group, 1.6 months (range 0 to 81 months) for the NHCC group, and 1.5 months (range 0 to 69 months) for the HCC-MP group. Most HCC+MP patients had tumors within the Milan criteria, peak AFP levels less than 100 ng/mL, and received liver-directed HCC therapy.

32,166 patients were selected for the ITT cohort: 6,451 in the HCC+MP group, 24,541 in the NHCC group, and 1,174 in the HCC-MP group **(Table 1).** 75% of subjects in the HCC+MP group received LT and 23% died without LT or dropped off the wait list, compared to 42% and 48% in the NHCC group and 57% and 40% in the HCC-MP group, respectively. Most wait list 'dropout' was due to medical deterioration, and 47% of patients removed from the wait list died in a median 1.8 months. Detailed descriptive statistics are available in **Supplemental Tables 1-3.**

Association of MELD status at LT with post-LT survival. Dichotomizing MELD status at LT into high (>24) and low (≤24) MELD strata clearly demonstrated longer post-LT survival in HCC+MP patients with high MELD status, and the inverse relationship in the

non-prioritized groups **(Figure 1).** These relationships were further investigated in the Cox proportional-hazards regression models **(Table 2)**. Increasing MELD status at LT significantly predicted increased post-LT survival in the HCC+MP group, in a dose-dependent fashion with higher MELD status categories demonstrating higher magnitude associations with survival. In contrast, the inverse relationship was observed for the NHCC and HCC-MP groups: increasing MELD status at LT significantly predicted shorter post-LT survival, also in a dose-dependent fashion **(Figure 2).** Modeling the entire post-LT cohort, the interaction of group with the association between MELD status at LT and post-LT survival was significant ($p=0.02$ and $p<0.01$ for pairwise interactions comparing the HCC+MP group to the NHCC and HCC-MP groups, respectively). As expected, wait list time was not a significant predictor of post-LT survival, given the broad variation in wait list time arising from the variable threshold at which centers register candidates on the LT wait list.

In group-specific models, no significant interactions were identified between covariates and the association of MELD status at LT with post-LT survival. In the entire post-LT cohort, hepatitis C significantly interacted with the association between group and post-LT survival when the HCC+MP and NHCC groups were compared ($p=0.049$). Group status did not significantly interact with the association with between wait list time and post-LT survival ($p=0.84$ and $p=0.25$ comparing HCC+MP to the other groups), congruent with the observed non-significance of wait list time in the multiple regression model.

Increasing DRI significantly predicted shorter post-LT survival in all groups. The listing liver disease diagnosis was associated with post-LT survival in the NHCC group only, with hepatitis C predicting shorter post-LT survival and PBC or PSC predicting longer post-LT survival. Of the HCC-specific variables (evaluated only in the HCC+MP group), peak AFP

level and receipt of liver-directed therapy independently predicted shorter post-LT survival, and tumor status within the Milan criteria independently predicted longer post-LT survival (though the latter was non-significant).

Comparison of post-LT and ITT survival. Survival in the post-LT and ITT cohorts is shown in **Table 3.** In the post-LT cohort, the relative risk of death was highest in the HCC-MP group, lowest in the NHCC group, and intermediate in the HCC+MP group. In the first year after LT, survival was higher in the HCC+MP group compared to the NHCC group, however survival in the NHCC group then eclipsed that of the HCC+MP group **(Figure 3A).** In the ITT cohort, the relative risk of death after wait list registration was also highest in the HCC-MP group, but in contrast, the relative risks of death were lowest in the HCC+MP group and intermediate in the NHCC group. Non-prioritized groups had a greater fraction of deaths occur soon after wait list registration relative to the HCC+MP group **(Figure 3B).** Survival significantly differed among groups in both the post-LT and ITT cohorts (log-rank $p<0.01$).

ITT survival benefit of LT. Predictors of survival from the time of wait list registration are shown in **Table 4.** Receipt of LT, evaluated as a time-dependent variable, conferred a 58% reduction in the hazard of death relative to the pre-LT period. This mortality reduction was greatest in the HCC-MP group (67%), and similar in the HCC+MP and NHCC groups (both 61%). Wait list 'dropout' without LT strongly predicted death (hazard ratio 18.1). The direction and magnitude of the hazard ratios for other predictors were similar to those obtained from univariable regressions in the post-LT cohort.

Post hoc analyses. To exclude the lead time from registration to MELD prioritization, I performed a post-LT analysis using the duration from first successful application for MELD prioritization for HCC to LT as the primary exposure. I identified a cohort of 4,732 patients

receiving MELD prioritization for HCC from March 1st, 2005 to March 1st, 2009. In univariable regressions, both increasing wait list duration after MELD prioritization for HCC (HR 0.95; 95% CI: 0.88-1.02) and increasing MELD status (HR 0.90; 95% CI: 0.81-0.99) predicted longer post-LT survival. However, this method did not permit comparison to the non-prioritized groups, because use of the duration from the laboratory-based MELD score first reaching 22 to LT as the primary exposure would have introduced a selection bias from the exclusion of a large number of LT recipients transplanted with MELD scores less than 22.

I also evaluated post-LT HCC recurrence as a secondary outcome. Data on "recurrence of pre-transplant malignancy" are supplied to the OPTN by individual centers; unfortunately, records are not linked to cancer registries, and prior studies have noted an extremely low rate of HCC recurrence in the STAR registry compared to that observed in single-center studies.[31,32] Because of this unreliability, I considered an analysis of HCC recurrence using STAR data to be exploratory due to poor ascertainment and probable outcome misclassification. I identified 241 HCC recurrences in the HCC+MP group and 72 HCC recurrences in the HCC-MP group, yielding incidence rates of 1.9 per 1000 person-years (95% CI: 1.6-2.1) and 2.7 per 1000 person-years (95% CI: 2.1-3.4), respectively **(Supplemental Table 4).** One-year HCC recurrence-free survival was 97% in the HCC+MP group and 95% in the HCC-MP group. In multiple Cox regression, increasing MELD status was a non-significant predictor of post-LT HCC recurrence for both the HCC+MP (HR: 0.94, 95% CI: 0.71-1.24) and HCC-MP groups (HR: 0.86, 95% CI: 0.69-1.06) **(Supplemental Table 5)**.

DISCUSSION

In this observational cohort study of the national transplant registry, I demonstrated that increasing MELD at LT independently predicted greater post-LT survival in MELD-prioritized patients with HCC. In contrast, increasing MELD at LT predicted worse post-LT survival in non-prioritized patients. Based on these results, I infer that extending wait list duration in patients with HCC causes the selective transplantation of candidates with favorable tumor biology and a consequent lower risk of post-LT mortality, whereas post-LT mortality is driven by the severity of liver dysfunction rather than wait list time in non-prioritized patients. Further, MELD-prioritized HCC patients exhibited greater ITT and worse post-LT survival than non-HCC patients, a discrepancy that reflects an enhanced access to LT despite inferior post-LT outcomes (a 33 percentage-point advantage in the probability of receiving LT). These novel findings highlight the need for changes to an inequitable organ allocation policy.

The association between wait list duration and post-LT survival in MELD-prioritized recipients with HCC could stem from differences in the clinical behavior of their cancers or from differences in patient characteristics that predict survival independent of their cancers. The former scenario describes the tendency of increasing wait list time to select for indolent HCC that lingers within transplantable criteria for long durations and has a low risk of post-LT HCC recurrence. The latter scenario, termed survivor bias, describes the tendency of increasing wait list time to select for an overall healthier pool of candidates with greater post-transplant survival due to superior pre-LT health status. Regardless which effect dominates, there is a trade-off between the greater post-LT survival gained from selection of the favorable sample for LT and a greater proportion of wait list 'dropout' and death in patients not receiving LT.

Several features of this study argue against survivor bias as the causal pathway in the association. The association persisted after adjustment for covariates associated with favorable survival on the wait list (gender, race/ethnicity, liver disease severity, etc.). Second, the association was internally consistent in strata of these covariates (strata associated with better health status did not have stronger associations with post-LT survival). Third, the non-prioritized groups did not demonstrate associations between increasing waiting list duration and greater post-LT survival, but these two groups would be expected to be vulnerable to the same survivor bias as the HCC+MP group (since it is hypothetically independent of cancer characteristics). For these reasons, I believe that the association is a manifestation of differences in tumor biology rather than the health status of LT candidates.

The association fulfills epidemiologic criteria for validity and causality. It is independent of known confounders, statistically significant, consistent across strata of covariates, and exhibits a gradient of effect, with increasing categories of MELD status more strongly associated with post-LT survival. The *post hoc* analysis using the time from first HCC MELD prioritization to LT as the primary exposure also identified a consistent association between wait list time and post-LT survival; although the effect size was smaller than that identified in the main analysis, the inability of the STAR registry to adequately track the "time from when Milan criteria is met" to LT is a recognized deficiency in the data source (and the justification for my use of MELD status as the marker of wait list time).[49] The association is coherent with similar findings in smaller studies of liver-directed HCC therapy with or without tumor down-staging that incorporated a waiting period before LT,[25,28,29,50] and with national cohort studies comparing cadaveric and LDLT, in which higher HCC recurrence rates were observed in LDLT recipients with short waiting times.[32,51] Finally, the purported causal pathway is plausible; occult metastatic disease may

become evident with increasing wait list time, precluding LT and selecting for transplantation of the remaining cohort less likely to have extrahepatic disease.[31] The relationship is analogous to 'overdiagnosis' observed in screening studies for non-liver cancers; for example, studies of frequent mammography have demonstrated an increased detection of indolent breast cancers that would not have resulted in clinical disease, undermining the benefit of screening.[52] Accordingly, HCC followed for long periods on the LT wait list, remaining within transplantable criteria, is likely to have less aggressive behavior, and a consequent lower risk of post-LT cancer recurrence and death.

In non-prioritized recipients, increasing MELD at LT was associated with poor post-LT survival. Consistent with prior studies,[53,54,55] post-LT deaths were most frequent in the first year and then plateaued. MELD at LT inversely correlated with wait list time in non-prioritized recipients. Although patients with high MELD scores were more rapidly transplanted, increasing MELD predicted post-LT mortality whereas wait list time did not. The qualitative difference in the association between MELD at LT and post-LT survival between the HCC+MP group and the non-prioritized groups exposes a pathophysiologic distinction; the HCC+MP group, which had good liver function at LT, accumulated a post-LT survival benefit with increasing time on the wait list, while the non-prioritized groups accumulated a post-LT survival benefit from having better liver function at LT. The behavior of the HCC-MP group was similar to the NHCC group – poor liver function at LT was associated with poor post-LT survival – but fared worse after LT than either of the other two groups, presumably due to a joint mortality risk from transplantation with poor liver function (exerting early post-LT mortality risk) and HCC recurrence (exerting delayed post-LT mortality risk).

The interaction of group status on the association of HCV with post-LT survival warrants special consideration. HCV infection only predicted short post-LT survival in the NHCC group. Previous studies have reported the same lack of association between HCV infection and post-LT outcomes in recipients transplanted for HCC.[56, 57,58] I theorize that HCV reinfection after LT imparts post-LT mortality risk by increasing the risk of recurrent cirrhosis, not recurrent HCC. Since recurrent cirrhosis and recurrent HCC are competing risks in patients transplanted with both HCV and HCC (HCC recurrence is likely independent of HCV-related graft fibrosis), it follows that HCV would be a weaker predictor of post-LT survival in the dual diagnosis HCV/HCC group compared to recipients with HCV alone. Poor ascertainment of post-LT HCC recurrence in the STAR registry precluded my testing of this hypothesis.

In my ITT analysis, the hazard ratio of death was 58% lower in LT recipients relative to comparable candidates. The magnitude of this mortality reduction is lower than that reported by Merion et al in a non-HCC cohort (79%)[59] or Pelletier et al in a cohort with HCC (77%).[35] These discrepancies likely arise from methodological differences. The former study used a period of only 2 years from wait list registration to post-LT death or censoring, which may be inadequate to capture subjects who survive for long periods on the LT wait list and thus derive less of mortality risk reduction in the post-LT period compared to their lengthy waiting list period. The latter study evaluated HCC patients registered on the wait list from 1998 to 2006, thus the majority received MELD prioritization based on a historical OPTN protocol; since prior iterations granted more MELD points for HCC (up to 29 points for T2 cancers), rapid LT would be expected relative to the current OPTN prioritization protocol. I would expect transplantation of tumors with aggressive biology and low post-LT survival compared to the current MELD era, which was not observed. However, receipt of LT was not evaluated as a time-dependent covariate,

resulting in a Cox regression model that compared patients who received LT to patients who did not, rather than comparing pre- to post-LT mortality risk. It is conceivable that this historical cohort had minor or no reduction in mortality risk from LT due to a high risk of HCC recurrence.

My study bolsters proposals currently under review by UNOS to reduce or cap MELD prioritization points for HCC.[60] I found that MELD-prioritized candidates with HCC had much lower rates of wait list 'dropout' and higher rates of LT than non-prioritized candidates. Further, MELD-prioritized HCC candidates had markedly better ITT survival from registration compared to non-prioritized candidates. I posit that equalizing ITT survival across different indications for LT, rather than by the probability of wait list 'dropout' or death, would best optimize the utility of LT in the overall candidate pool. Since MELD-prioritized HCC patients had worse post-LT survival than non-HCC patients and their post-LT survival was improved by prolonging the wait list time, it follows that a strategy of delaying LT for MELD-prioritized HCC patients may equalize their ITT survival with other LT indications by increasing post-LT survival in MELD-prioritized HCC patients, while simultaneously increasing the probability of LT in non-prioritized patients who have a high risk of wait list 'dropout' and death despite their greater post-LT survival.

Although the STAR registry provided a large sample size with national representation, prospective data collection, and excellent ascertainment of LT candidates and recipients with few missing data, I recognize several limitations of this study. Mortality ascertainment was likely imperfect despite using the combination of the STAR and DMF registries; linking STAR to other death registries such as the National Death Index would improve ascertainment but was cost-prohibitive.[61] Additionally, the results of my *post hoc* analysis of HCC recurrence-free survival are of dubious value due to misclassification of the

outcome (3-5% one-year post-LT HCC recurrence is well below the expected incidence); I was unable to link the STAR registry to cancer registries to confirm that recurrent HCC was the dominant reason for post-LT mortality in the HCC groups. Assessment of post-LT HCC recurrence using formal linkage to cancer registries is fertile ground for future investigations.

In conclusion, I report an independent association between increasing MELD at LT in MELD-prioritized patients with HCC and greater post-LT survival in a national transplant database, and I present strong evidence that the association is causally mediated by the selection of biologically favorable cancers for transplantation. HCC patients receiving MELD prioritization benefit from enhanced access to LT that results in superior ITT survival relative to non-HCC indications, overwhelming their lower post-LT survival. The burden of HCC is rising while donor organs remain scarce. Delaying LT in MELD-prioritized HCC patients may maximize ITT survival, and system utility, across the overall pool of LT candidates.

DISCLAIMER

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Table 1. Demographic and clinical characteristics of patients registered on the wait list for liver transplantation in the United States from March 1st, 2005 to March 1st, 2009.

	Post-transplant cohort* N=11,312				**Intention-to-treat cohort**** N=32,166		
	HCC+MP N=3,256	**NHCC** N=7,397	**HCC-MP** N=659		**HCC+MP** N=6,451	**NHCC** N=24,541	**HCC-MP** N=1,174
Age (years), median (IQR)	57 (52-61)	53 (48-59)	56 (51-61)	Age (years), median (IQR)	56 (52-62)	54 (48-59)	56 (51-61)
Male gender, %	79	67	82	Male gender, %	78	63	82
Race/ethnicity, %				Race/ethnicity, %			
White	67	75	67	White	65	74	64
Black	8	9	10	Black	8	8	9
Hispanic	14	13	16	Hispanic	15	15	16
Asian	10	3	6	Asian	11	3	10
Other	1	1	2	Other	1	1	2
BMI (kg/m^2), median (IQR)	28 (25-31)	28 (24-32)	28 (24-31)	BMI (kg/m^2), median (IQR)	28 (25-32)	28 (25-32)	28 (25-32)
Listing diagnosis, %				Listing diagnosis, %			
Hepatitis C	60	43	55	Hepatitis C	57	41	49
Alcohol	18	31	23	Alcohol	19	30	23
Hepatitis B	8	4	7	Hepatitis B	9	3	10
NASH or cryptogenic	8	17	10	NASH or cryptogenic	8	17	8
PBC or PSC	2	10	3	PBC or PSC	2	9	2
Lab MELD at LT, median (IQR)	12 (9-15)	23 (18-30)	23 (16-31)	Lab MELD at registration, median (IQR)	11 (8-14)	16 (12-22)	15 (11-23)
MELD status at LT, median (IQR)	22 (22-25)	24 (18-31)	24 (17-32)	Received liver transplant, %	75	42	57
Donor characteristics				Dropped off wait list, %	18	29	28
Donor risk index, median (IQR)	1.44 (1.28-1.63)	1.45 (1.29-1.67)	1.50 (1.32-1.76)	Died on wait list, %	5	18	12
Male donor gender, %	64	64	64	Died or dropped off wait list, %	23	48	40
Donor BMI (kg/m^2), median (IQR)	26 (23-30)	26 (23-30)	26 (23-30)	Died or dropped off wait list due to medical deterioration, %	12	27	24
HCC-specific variables				HCC-specific variables			
Within Milan, %	95			Within Milan, %	94		
Peak aggregate tumor diameter (cm), median (IQR)	3.2 (2.4-4.2)			Peak aggregate tumor diameter (cm), median (IQR)	3.3 (2.4-4.3)		
Peak tumor number, median (IQR)	1 (1-2)			Peak tumor number, median (IQR)	1 (1-2)		
Received liver-directed therapy, %	60			Received liver-directed therapy, %	58		
Peak AFP (ng/mL), median (IQR)	15 (6-68)			Peak AFP (ng/mL), median (IQR)	16 (6-82)		

*Variables recorded at time of liver transplantation. **Variables recorded at time of wait list registration. Abbreviations: HCC+MP, hepatocellular carcinoma with MELD prioritization group; HCC-MP, hepatocellular carcinoma without MELD prioritization group; NHCC, non-hepatocellular carcinoma group; IQR, interquartile range; BMI, body mass index; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; MELD, Model for End-stage Liver Disease; LT, liver transplantation; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein.

Table 2. Cox proportional-hazards regression of post-transplant survival of patients registered on the wait list for liver transplantation in the United States from March 1st, 2005 to March 1st, 2009.

	HCC+MP		NHCC		HCC-MP	
	Crude HR (95% CI)	Adjusted HR* (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)
MELD status at LT						
Overall	0.86 (0.75-0.99)	0.84 (0.73-0.98)	1.16 (1.11-1.21)	1.20 (1.15-1.25)	1.14 (1.01-1.28)	1.17 (1.02-1.33)
<22			0.85 (0.73-0.99)	0.82 (0.70-0.95)	0.95 (0.61-1.49)	0.92 (0.58-1.44)
22-24	referent	referent	referent	referent	referent	referent
25-30	0.86 (0.74-1.01)	0.86 (0.73-1.01)	1.07 (0.90-1.28)	1.11 (0.94-1.33)	1.18 (0.71-1.97)	1.30 (0.78-2.18)
>30	0.71 (0.42-1.19)	0.64 (0.38-1.09)	1.35 (1.16-1.58)	1.40 (1.20-1.64)	1.40 (0.90-2.19)	1.59 (1.01-2.50)
Lab MELD at LT**	1.10 (0.96-1.27)	1.13 (0.97-1.30)	1.19 (1.12-1.25)		1.11 (0.97-1.27)	
Age	1.02 (1.01-1.03)		1.02 (1.01-1.021)		1.02 (1.001-1.04)	
BMI	1.01 (1.01-1.04)	1.02 (1.004-1.04)	0.99 (0.99-1.004)	0.99 (0.98-1.002)	0.99 (0.96-1.02)	
Male gender	0.98 (0.82-1.17)		0.95 (0.85-1.06)		0.89 (0.61-1.31)	
Race/ethnicity (referent=White)						
Black	1.37 (1.08-1.73)	1.25 (0.98-1.60)	1.32 (1.12-1.55)	1.28 (1.08-1.51)	1.28 (0.80-2.06)	1.10 (0.67-1.82)
Hispanic	0.87 (0.69-1.10)	0.87 (0.69-1.10)	0.91 (0.77-1.07)	0.86 (0.73-1.02)	0.68 (0.43-1.09)	0.58 (0.35-0.95)
Asian	0.59 (0.44-0.81)	0.64 (0.46-0.88)	0.76 (0.53-1.10)	0.69 (0.48-1.004)	0.92 (0.47-1.81)	1.16 (0.57-2.39)
Other	1.08 (0.58-2.01)	1.06 (0.56-2.01)	0.95 (0.51-1.76)	0.94 (0.50-1.76)	0.83 (0.27-2.62)	0.78 (0.25-2.47)
Listing diagnosis						
Hepatitis C	1.07 (0.92-1.25)		1.28 (1.15-1.42)	1.35 (1.20-1.51)	1.02 (0.76-1.37)	
Alcohol	0.97 (0.80-1.17)		0.99 (0.89-1.11)		0.79 (0.55-1.14)	
Hepatitis B	0.70 (0.51-0.94)		0.83 (0.62-1.12)		0.69 (0.35-1.35)	
NASH or cryptogenic	1.31 (1.01-1.69)		0.95 (0.83-1.10)		1.23 (0.78-1.97)	
PBC or PSC	0.91 (0.50-1.64)		0.68 (0.56-0.83)	0.77 (0.63-0.95)	0.52 (0.17-1.64)	
Donor characteristics						
Donor risk index	1.45 (1.16-1.82)	1.34 (1.07-1.68)	1.64 (1.43-1.90)	1.80 (1.55-2.09)	1.59 (1.11-2.27)	1.94 (1.31-2.89)
Male donor gender	0.98 (0.84-1.14)		1.02 (0.92-1.13)	1.12 (1.01-1.26)	0.90 (0.66-1.22)	
Donor BMI	1.01 (0.999-1.02)	1.01 (0.99-1.02)	1.007 (0.99-1.02)	1.01 (0.99-1.02)	0.97 (0.95-0.99)	0.98 (0.95-1.01)
HCC-specific characteristics						
Within Milan	0.89 (0.64-1.23)	0.94 (0.67-1.32)				
Peak aggregate tumor diameter	1.04 (0.99-1.10)					
Peak tumor number	1.003 (0.90-1.12)					
Receipt of liver-directed therapy	1.12 (0.96-1.30)	1.21 (1.03-1.42)				
Peak AFP (referent <10 ng/mL)						
Overall	1.30 (1.20-1.42)	1.31 (1.20-1.43)				
10-100 ng/mL	1.28 (1.07-1.52)	1.30 (1.09-1.56)				
100-1000 ng/mL	1.74 (1.42-2.13)	1.78 (1.44-2.19)				
>1000 ng/mL	2.10 (1.51-2.91)	2.14 (1.52-3.00)				

*Multiple regressions were age-stratified (<55 or ≥55 years) due to violation of the proportional-hazards assumption. **Lab MELD was excluded from the NHCC and HCC-MP multiple regression models due to multicollinearity with MELD status.
Abbreviations: HCC+MP, hepatocellular carcinoma with MELD prioritization group; HCC-MP, hepatocellular carcinoma without MELD prioritization group; NHCC, non-hepatocellular carcinoma group; HR, hazard ratio; CI, confidence interval; MELD, Model for End-stage Liver Disease; LT, liver transplantation; BMI, body mass index; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein.

Table 3. Post-transplant and intention-to-treat survival of patients registered on the wait list for liver transplantation in the United States from March 1st, 2005 to March 1st, 2009.

	Post-transplant cohort				**Intention-to-treat cohort**			
	Overall N=11,312	**HCC+MP** N=3,256	**NHCC** N=7,397	**HCC-MP** N=659	**Overall** N=32,166	**HCC+MP** N=6,451	**NHCC** N=24,541	**HCC-MP** N=1,174
Deaths	2,356	717	1,463	176	12,504	2,218	9,715	571
Person-years (x1000)	481	133	320	27.9	1,223	263	919	40.4
Mortality rate, per 1000 person-years (95% CI)	4.9 (4.7-5.1)	5.4 (5.9-5.8)	4.6 (4.3-4.8)	6.3 (5.4-7.3)	10.2 (10.1-10.4)	8.4 (8.1-8.8)	10.6 (10.4-10.8)	14.1 (13.0-15.3)
Relative risk (95% CI)*		referent	0.9 (0.8-0.93)	1.2 (0.99-1.4)		referent	1.3 (1.2-1.31)	1.7 (1.5-1.8)
Kaplan-Meier survival								
S_{90}, months	13.8	15.0	13.6	10.0	3.5	9.7	2.6	2.2
(95% CI)	(12.5-15.1)	(13.5-16.7)	(12.0-15.5)	(7.2-12.7)	(3.3-3.8)	(9.1-10.5)	(2.4-2.8)	(1.7-2.8)
S_{75}, months	63.4	54.6	68.9	46.1	21.2	30.1	19.5	11.0
(95% CI)	(60.5-67.6)	(51.1-61.8)	(65.4-73.2)	(30.6-57.6)	(20.3-21.9)	(28.3-32.0)	(18.6-20.4)	(9.2-13.0)
S_{50}, months	.	.	.	.	79.1	87.1	77.0	53.2
(95% CI)					(77.2-82.2)	(84.7-.)	(75.1-79.2)	(46.7-63.4)
Log-rank p-value	.		<0.01		.		<0.01	
Actuarial survival								
1-year (95% CI)	0.91 (0.90-0.914)	0.92 (0.91-0.93)	0.91 (0.90-0.913)	0.89 (0.86-0.91)	0.81 (0.807-0.82)	0.88 (0.87-0.89)	0.80 (0.79-0.802)	0.74 (0.71-0.76)
3-year (95% CI)	0.83 (0.82-0.832)	0.81 (0.80-0.83)	0.84 (0.83-0.85)	0.77 (0.73-0.80)	0.67 (0.666-0.68)	0.72 (0.71-0.73)	0.67 (0.66-0.671)	0.57 (0.54-0.60)
5-year (95% CI)	0.76 (0.75-0.77)	0.73 (0.72-0.75)	0.77 (0.76-0.79)	0.70 (0.66-0.74)	0.57 (0.567-0.58)	0.62 (0.60-0.63)	0.57 (0.56-0.573)	0.48 (0.45-0.51)

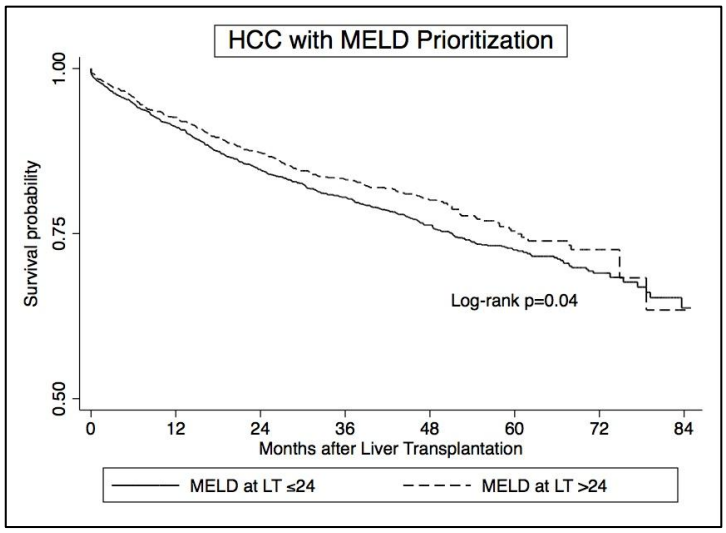
*Relative to HCC+MP group. Abbreviations: HCC+MP, hepatocellular carcinoma with MELD prioritization group; HCC-MP, hepatocellular carcinoma without MELD prioritization group; NHCC, non-hepatocellular carcinoma group; CI, confidence interval.

Table 4. Univariable Cox proportional-hazards regression of intention-to-treat survival of patients registered on the wait list for liver transplantation in the United States from March 1st, 2005 to March 1st, 2009.

	HCC+MP	**NHCC**	**HCC-MP**
	Crude HR (95% CI)	Crude HR (95% CI)	Crude HR (95% CI)
Receipt of liver transplant*	0.39 (0.36-0.43)	0.39 (0.37-0.41)	0.33 (0.28-0.40)
Dropped out from wait list*	15.7 (14.3-17.2)	19.7 (18.8-20.7)	12.5 (10.4-14.9)
Lab MELD at registration	1.22 (1.16-1.28	1.26 (1.24-1.28)	1.06 (0.98-1.13)
Age	1.02 (1.01-1.03)	1.02 (1.019-1.024)	1.02 (1.01-1.03)
BMI	1.0001 (0.99-1.001)	0.99 (0.99-1.0002)	0.99 (0.99-1.003)
Male gender	1.07 (0.97-1.19)	0.95 (0.91-0.99)	0.99 (0.81-1.24)
Race/ethnicity (referent=White)			
Black	1.26 (1.10-1.45)	1.18 (1.10-1.27)	1.21 (0.93-1.59)
Hispanic	0.99 (0.88-1.11)	1.04 (0.98-1.10)	0.87 (0.68-1.11)
Asian	0.80 (0.69-0.92)	0.82 (0.72-0.94)	1.001 (0.74-1.35)
Other	0.88 (0.58-1.34)	1.05 (0.85-1.29)	1.06 (0.57-1.99)
Listing diagnosis			
Hepatitis C	1.15 (1.05-1.25)	1.21 (1.17-1.26)	1.02 (0.87-1.20)
Alcohol	1.08 (0.98-1.20)	0.97 (0.93-1.01)	0.83 (0.68-1.02)
Hepatitis B	0.78 (0.66-0.91)	0.83 (0.74-0.94)	0.91 (0.68-1.22)
NASH or cryptogenic	0.98 (0.84-1.14)	0.97 (0.92-1.02)	0.83 (0.61-1.12)
PBC or PSC	0.82 (0.59-1.13)	0.74 (0.69-0.80)	0.43 (0.19-0.97)
HCC-specific characteristics			
Within Milan	0.85 (0.72-1.0001)		
Peak aggregate tumor diameter	1.07 (1.04-1.10)		
Peak tumor number	1.07 (1.01-1.13)		
Receipt of liver-directed therapy	0.99 (0.91-1.08)		
Peak AFP	1.38 (1.32-1.44)		

*Variables evaluated as time-dependent covariates. Abbreviations: HCC+MP, hepatocellular carcinoma with MELD prioritization group; HCC-MP, hepatocellular carcinoma without MELD prioritization group; NHCC, non-hepatocellular carcinoma group; HR, hazard ratio; CI, confidence interval; MELD, Model for End-stage Liver Disease; BMI, body mass index; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein.

FIGURES



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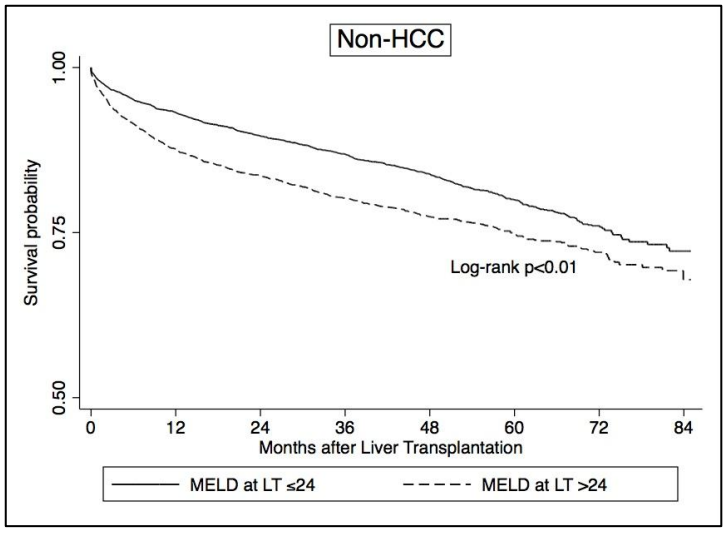

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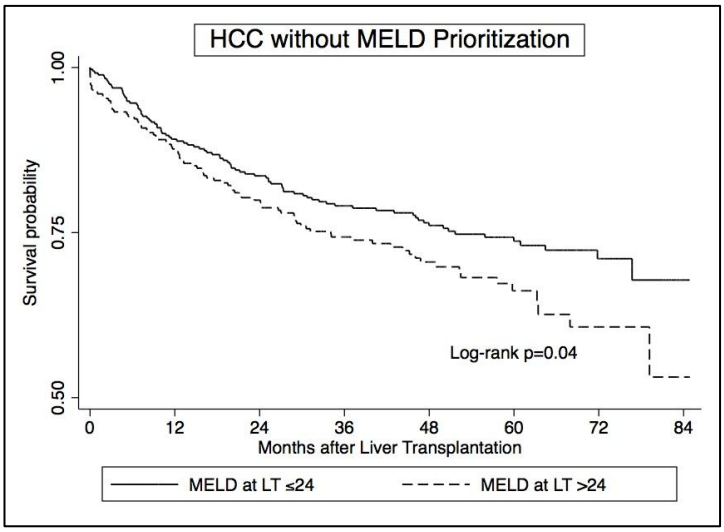


1C.

Figure 1. Post-transplant survival of MELD-prioritized HCC patients **(1A)**, non-HCC patients **(1B),** and non-MELD-prioritized HCC patients **(1C)** registered on the wait list for liver transplantation in the United States from March 1st, 2005 to March 1st, 2009. Higher MELD at liver transplantation (>24) was associated with better post-transplant survival in MELD-prioritized HCC patients**,** whereas the inverse association was observed in non-prioritized patients.

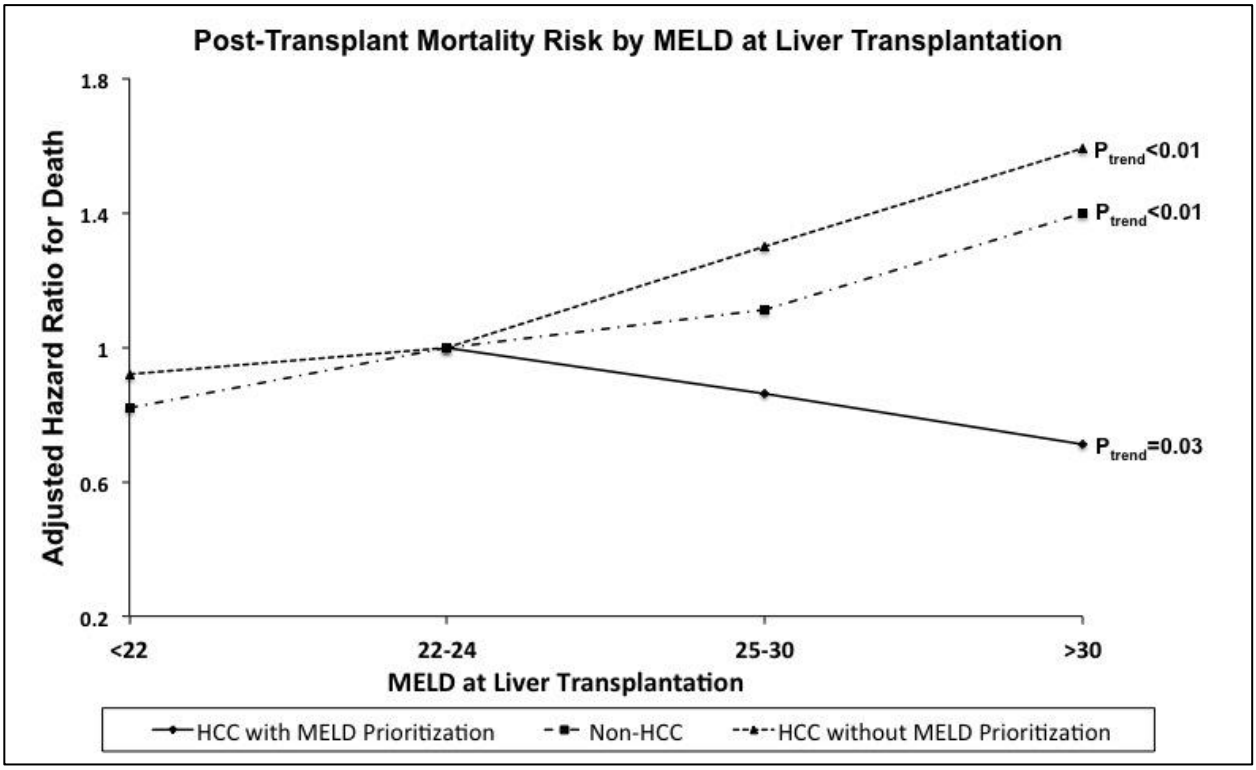
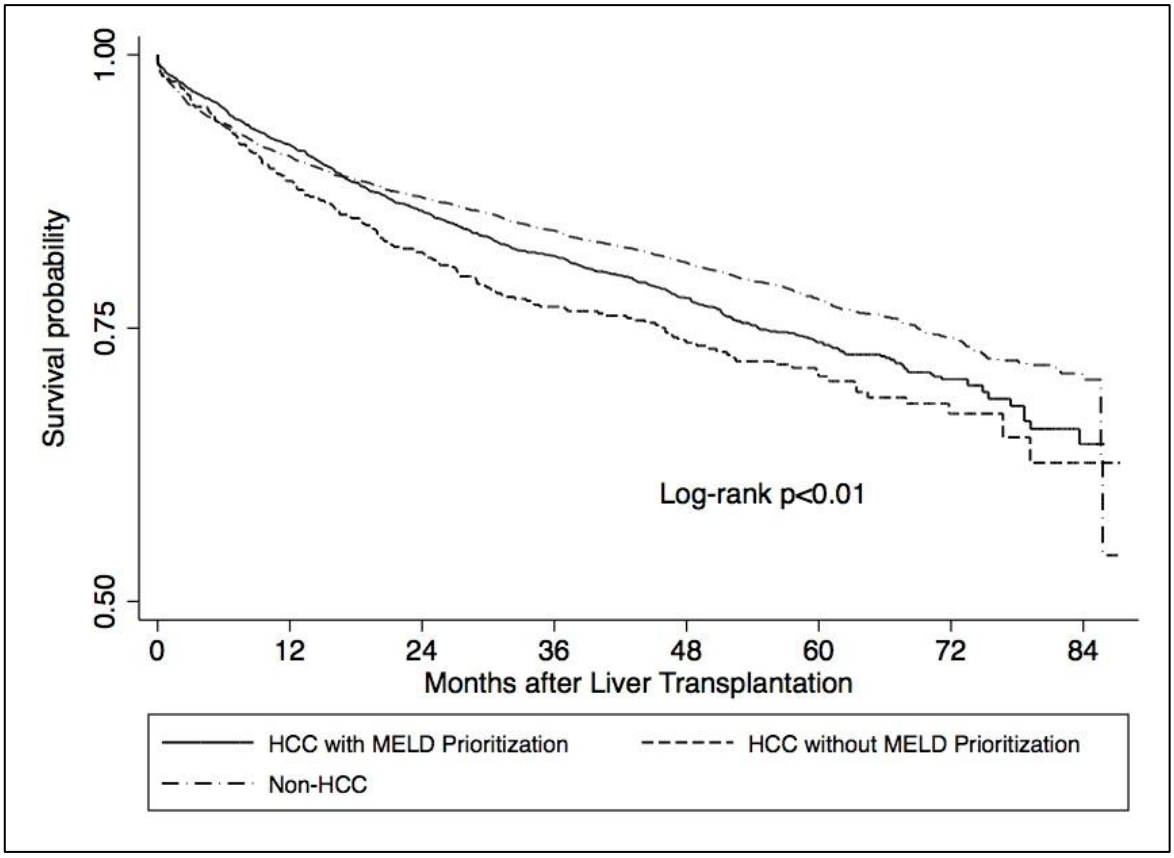


Figure 2. Increasing MELD at LT was independently associated with a lower hazard of mortality in MELD-prioritized HCC patients in a dose-dependent fashion. The inverse dose-response was observed in non-prioritized patients.



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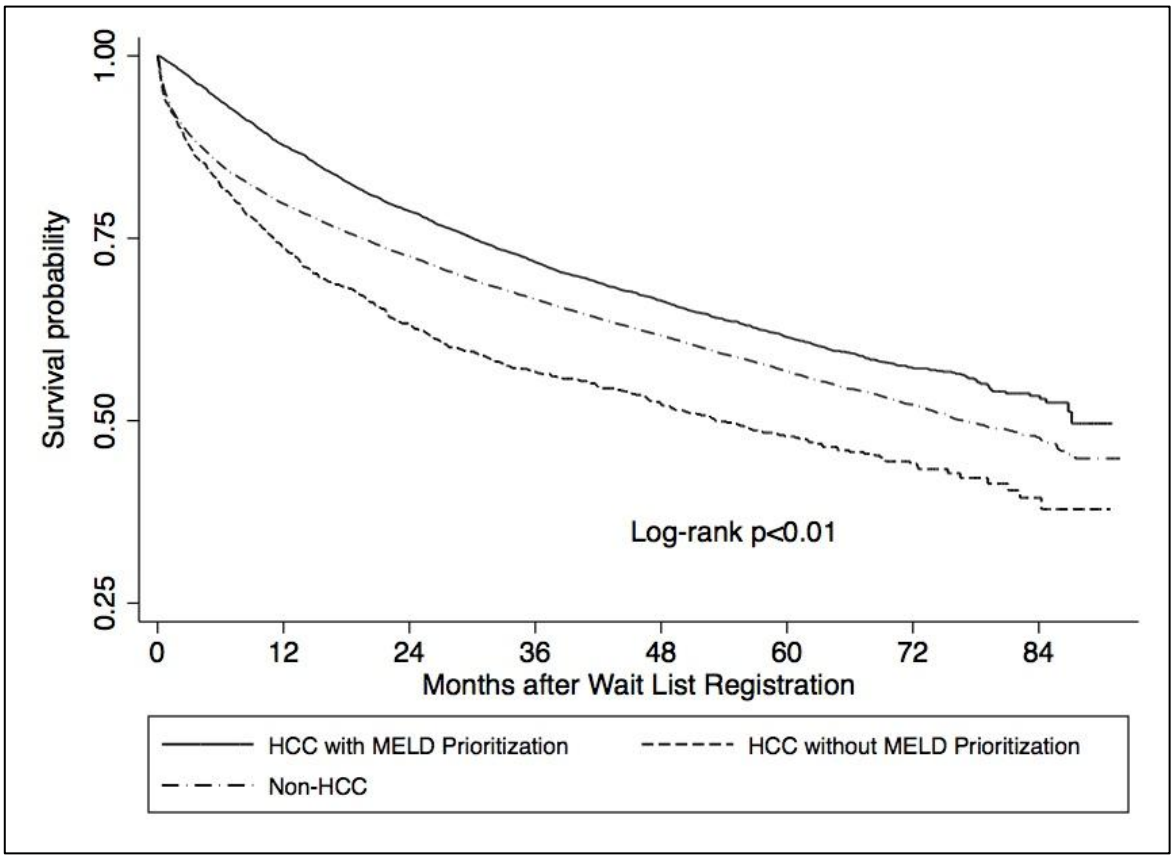

3B.

Figure 3. Post-transplant **(3A)** and intention-to-treat **(3B)** survival of patients registered on the wait list for liver transplantation in the United States from March 1st, 2005 to March 1st, 2009.

Supplemental Material

Supplemental Table 1. Demographic and clinical characteristics of persons registered on the wait list for liver transplantation in the United States from March 1st, 2005 to March 1st, 2009, at time of liver transplantation (post-transplant cohort).

Variable	Overall N=11,312	HCC+MP N=3,256	NHCC N=7,397	HCC-MP N=659	P
Age (years), median (IQR)	55 (49-60)	57 (52-61)	53 (48-59)	56 (51-61)	<0.01*
Male gender, n (%)	8,086 (72)	2,559 (79)	4,986 (67)	541 (82)	<0.01**
Race/ethnicity, n (%)					
White	8,135 (72)	2,182 (67)	5,510 (75)	443 (67)	<0.01**
Black	1,002 (9)	269 (8)	674 (9)	59 (10)	
Hispanic	1,503 (13)	443 (14)	1,503 (13)	105 (16)	
Asian	557 (5)	319 (10)	199 (3)	39 (6)	
Other	115 (1)	43 (1)	59 (1)	13 (2)	
BMI (kg/m^2), median (IQR)	28 (24-32)	28 (25-31)	28 (24-32)	28 (24-31)	0.53*
Listing diagnosis, n (%)					
Hepatitis C	5,458 (48)	1,941 (60)	3,155 (43)	362 (55)	<0.01**
Alcohol	3,048 (27)	595 (18)	2,299 (31)	154 (23)	<0.01**
NASH or cryptogenic	1,541 (14)	247 (8)	1,230 (17)	65 (10)	<0.01**
PBC or PSC	824 (7)	54 (2)	752 (10)	18 (3)	<0.01**
Hepatitis B	572 (5)	262 (8)	267 (4)	43 (7)	<0.01**
Region, n (%)					
1	325 (3)	125 (4)	179 (2)	21 (3)	<0.01**
2	1,232 (11)	373 (12)	790 (11)	69 (11)	
3	1,872 (17)	402 (12)	1,357 (18)	113 (17)	
4	1,215 (11)	425 (13)	728 (10)	62 (9)	
5	1,681 (15)	616 (19)	939 (13)	126 (19)	
6	435 (4)	143 (4)	270 (4)	22 (3)	
7	838 (7)	222 (7)	578 (8)	38 (6)	
8	813 (7)	223 (7)	555 (8)	35 (5)	
9	693 (6)	217 (7)	399 (5)	77 (12)	
10	1,055 (9)	254 (8)	745 (10)	56 (9)	
11	1,153 (10)	256 (8)	857 (12)	40 (6)	
MELD status at LT, n (%)					
<22	3,080 (27)	0 (0)	2,839 (38)	241 (37)	<0.01**
22-24	3,271 (29)	1,907 (59)	1,247 (17)	117 (18)	
25-30	2,661 (24)	1,218 (37)	1,333 (18)	110 (17)	
>30	2,300 (20)	131 (4)	1,978 (27)	191 (29)	
Median (IQR)	23 (21-29)	22 (22-25)	24 (18-31)	24 (17-32)	<0.01*
Lab MELD at LT, median (IQR)	19 (14-27)	12 (9-15)	23 (18-30)	23 (16-31)	<0.01*
Donor risk index, median (IQR)	1.45 (1.29-1.66)	1.44 (1.28-1.63)	1.45 (1.29-1.67)	1.50 (1.32-1.76)	<0.01*
Male donor gender, n (%)	7,212 (64)	2,068 (64)	4,723 (64)	421 (64)	0.94**
Donor BMI (kg/m^2), median (IQR)	26 (23-30)	26 (23-30)	26 (23-30)	26 (23-30)	0.08*
HCC-specific variables					
Within Milan criteria, n (%)	.	3,089 (95)	.	.	.
Peak aggregate tumor diameter (cm), median (IQR)	.	3.2 (2.4-4.2)	.	.	.
Peak tumor number, median (IQR)	.	1 (1-2)	.	.	.
Received liver-directed therapy, n (%)	.	1,944 (60)	.	.	.
Peak AFP (ng/mL), median (IQR)	.	15 (6-68)	.	.	.

*Kruskal-Wallis test; **Chi-square test. Abbreviations: HCC+MP, hepatocellular carcinoma with MELD prioritization group; HCC-MP, hepatocellular carcinoma without MELD prioritization group; NHCC, non-hepatocellular carcinoma group; HCC, hepatocellular carcinoma; IQR, interquartile range; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; LT, liver transplantation; MELD, Model for End-stage Liver Disease; AFP, alpha-fetoprotein.

Supplemental Table 2. Demographic and clinical characteristics of persons registered on the wait list for liver transplantation in the United States from March 1st, 2005 to March 1st, 2009, at time of wait list registration (intention-to-treat cohort).

Variable	Overall N=32,166	HCC+MP N=6,451	NHCC N=24,541	HCC-MP N=1,174	P
Age (years), median (IQR)	54 (49-60)	56 (52-62)	54 (48-59)	56 (51-61)	<0.01*
Male gender, n (%)	21,441 (67)	5,038 (78)	15,440 (63)	963 (82)	<0.01**
Race/ethnicity, n (%)					
White	22,955 (71)	4,160 (65)	18,050 (74)	745 (64)	<0.01**
Black	2,552 (8)	538 (8)	1,904 (8)	110 (9)	
Hispanic	4,817 (15)	966 (15)	3,665 (15)	186 (16)	
Asian	1,513 (5)	716 (11)	684 (3)	113 (10)	
Other	329 (1)	71 (1)	238 (1)	20 (2)	
BMI (kg/m^2), median (IQR)	28 (25-32)	28 (25-32)	28 (25-32)	28 (25-32)	0.58*
Listing diagnosis, n (%)					
Hepatitis C	14,270 (44)	3,654 (57)	10,037 (41)	579 (49)	<0.01**
Alcohol	8,931 (28)	1,252 (19)	7,410 (30)	269 (23)	<0.01**
NASH or cryptogenic	4,759 (15)	529 (8)	4,131 (17)	99 (8)	<0.01**
PBC or PSC	2,421 (8)	126 (2)	2,273 (9)	22 (2)	<0.01**
Hepatitis B	1,544 (5)	585 (9)	840 (3)	119 (10)	<0.01**
Region, n (%)					
1	1,255 (4)	315 (5)	899 (4)	41 (4)	<0.01**
2	3,996 (12)	776 (12)	3,094 (13)	126 (11)	
3	3,824 (12)	658 (10)	2,993 (12)	173 (15)	
4	4,105 (13)	860 (14)	3,148 (13)	97 (8)	
5	5,986 (19)	1,386 (22)	4,357 (18)	243 (21)	
6	968 (3)	214 (3)	722 (3)	32 (3)	
7	2,448 (8)	454 (7)	1,924 (8)	70 (6)	
8	1,805 (6)	352 (6)	1,403 (6)	50 (4)	
9	3,075 (10)	648 (10)	2,240 (9)	187 (16)	
10	2,291 (7)	414 (6)	1,787 (7)	90 (8)	
11	2,413 (8)	374 (6)	1974 (8)	65 (6)	
Lab MELD at registration, median (%)	15 (11-20)	11 (8-14)	16 (12-22)	15 (11-23)	<0.01*
Received liver transplant, n (%)	15,704 (49)	4,830 (75)	10,206 (42)	668 (57)	<0.01**
Dropped off wait list, n (%)	8,673 (27)	1,155 (18)	7,188 (29)	330 (28)	<0.01**
Died on wait list, n (%)	4,939 (15)	330 (5)	4,471 (18)	138 (12)	<0.01**
Died or dropped off wait list, n (%)	13,612 (42)	1,485 (23)	11,659 (48)	468 (40)	<0.01**
Died or dropped off wait list due to medical deterioration, n (%)	7,732 (24)	781 (12)	6,669 (27)	282 (24)	<0.01**
HCC-specific variables					
Within Milan criteria, n (%)	.	6,058 (94)	.	.	.
Peak aggregate tumor diameter (cm), median (IQR)	.	3.3 (2.4-4.3)	.	.	.
Peak tumor number, median (IQR)	.	1 (1-2)	.	.	.
Received liver-directed therapy, n (%)	.	3,770 (58)	.	.	.
Peak AFP (ng/mL), median (IQR)	.	16 (6-82)			

*Kruskal-Wallis test; **Chi-square test. Abbreviations: HCC+MP, hepatocellular carcinoma with MELD prioritization group; HCC-MP, hepatocellular carcinoma without MELD prioritization group; NHCC, non-hepatocellular carcinoma group; HCC, hepatocellular carcinoma; IQR, interquartile range; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; MELD, Model for End-stage Liver Disease; AFP, alpha-fetoprotein.

Supplemental Table 3. Wait list time by MELD status at liver transplantation in persons registered on the wait list for liver transplantation in the United States from March 1st, 2005 to March 1st, 2009.

	Wait list time (months), median (IQR)				
	Overall	**HCC+MP**	**NHCC**	**HCC-MP**	**P**
MELD status at LT					
Overall	2.1 (0.5-6.7)	3.3 (1.1-7.9)	1.6 (0.4-6.3)	1.5 (0.4-5.2)	<0.01*
<22	2.9 (0.9-7.5)	.	3.0 (0.9-7.8)	1.8 (0.6-4.7)	<0.01**
22-24	1.5 (0.6-3.8)	1.4 (0.6-2.7)	1.8 (0.6-6.5)	1.7 (0.6-5.1)	
25-30	4.3 (0.8-8.3)	6.6 (4.5-10.5)	1.0 (0.3-4.8)	1.2 (0.3-4.2)	
>30	0.7 (0.2-6.2)	17.2 (13.4-30.5)	0.5 (0.2-3.5)	1.2 (0.3-7.7)	

*Kruskal-Wallis test; *Non-parametric test of trend between ordered groups. Abbreviations: HCC+MP, hepatocellular carcinoma with MELD prioritization group; HCC-MP, hepatocellular carcinoma without MELD prioritization group; NHCC, non-hepatocellular carcinoma group; MELD, Model for End-stage Liver Disease; LT, liver transplantation.

Supplemental Table 4. HCC recurrence-free post-transplant survival of persons registered on the wait list for liver transplantation in the United States from March 1st, 2005 to March 1st, 2009.			
	Overall N=3,915	**HCC+MP** N=3,256	**HCC-MP** N=659
HCC recurrences	313	241	72
At-risk time, 1000 person-years	157	130	27.0
HCC recurrence rate, per 1000 person-years (95% CI)	2.0 (1.8-2.2)	1.9 (1.6-2.1)	2.7 (2.1-3.4)
Relative risk (95% CI)	.	referent	1.4 (1.1-1.9)
Kaplan-Meier survival			
S_{90}, months (95% CI)	57.7 (42.9-73.5)	70.2 (52.7-.)	33.4 (19.9-44.3)
S_{75}, months (95% CI)	.	.	.
S_{50}, months (95% CI)	.	.	.
Log-rank p-value	.	<0.01	
Actuarial survival			
1-year (95% CI)	0.97 (0.96-0.971)	0.97 (0.96-0.975)	0.95 (0.93-0.96)
3-year (95% CI)	0.92 (0.91-0.93)	0.92 (0.91-0.93)	0.89 (0.86-0.91)
5-year (95% CI)	0.90 (0.89-0.91)	0.90 (0.89-0.92)	0.86 (0.83-0.89)

Abbreviations: HCC+MP, hepatocellular carcinoma with MELD prioritization group; HCC-MP, hepatocellular carcinoma without MELD prioritization group; HCC, hepatocellular carcinoma, MELD, Model for End-stage Liver Disease; CI, confidence interval.

Supplemental Table 5. Cox proportional-hazards multiple regression of HCC recurrence-free survival in persons registered on the wait list for liver transplantation in the United States from March 1st, 2005 to March 1st, 2009.

Covariate	HCC+MP* HR (95% CI)	HCC-MP** HR (95% CI)
MELD status at LT		
Overall	0.94 (0.71-1.24)	0.86 (0.69-1.06)
<22	.	ref
22-24	ref	0.65 (0.31-1.35)
25-30	0.87 (0.63-1.19)	0.56 (0.25-1.25)
>30	1.13 (0.56-2.28)	0.67 (0.35-1.26)
Lab MELD***	1.03 (0.80-1.34)	
Male gender	1.42 (1.01-2.00)	
Race/ethnicity		
Black	0.95 (0.61-1.48)	
Hispanic	0.57 (0.35-0.92)	
Asian	0.95 (0.62-1.47)	
Other	1.15 (0.42-3.12)	
Region		
1	ref	
2	0.49 (0.24-0.996)	
3	0.56 (0.27-1.14)	
4	0.60 (0.30-1.19)	
5	0.56 (0.29-1.07)	
6	0.96 (0.44-2.07)	
7	0.39 (0.17-0.90)	
8	0.76 (0.37-1.57)	
9	1.09 (0.56-2.13)	
10	0.80 (0.39-1.66)	
11	0.76 (0.37-1.57)	
Donor risk index	1.71 (1.15-2.52)	1.06 (0.53-2.14)
Within Milan criteria	0.87 (0.50-1.54)	
Peak aggregate tumor diameter	1.12 (1.01-1.25)	
Receipt of liver-directed therapy	1.65 (1.24-2.20)	
Alcohol listing diagnosis		0.40 (0.19-0.83)

*Peak alpha-fetoprotein-stratified regression; **Age-stratified regression; ***Lab MELD excluded from HCC-MP model due to multicollinearity with MELD status. Abbreviations: HCC+MP, hepatocellular carcinoma with MELD prioritization group; HCC-MP, hepatocellular carcinoma without MELD prioritization group; NHCC, non-hepatocellular carcinoma group; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; MELD, Model for End-stage Liver Disease.

IMPLICATIONS FOR PUBLIC HEALTH POLICY

So long as transplant candidates outnumber donors, policymakers will need to grapple with an inherent tension between social justice and utility in organ allocation. Each year in the United States, approximately 6,000 liver transplants are performed and an additional 4,000 to 5,000 transplant candidates are removed from the wait list due to illness or death. If donor organs were immediately available for all transplant candidates, the number of annual liver transplants would markedly increase and wait list 'dropouts' would precipitously decline. Organ scarcity imposes a delay in transplantation during which very ill transplant candidates are vulnerable to events that cause wait list 'dropout.' Organ allocation may be guided by various ethical principles, three of which have been formally employed or at least considered in the setting of liver transplantation.

The principle of 'treating people equally' is exemplified by a 'first come, first served' policy of organ allocation; this policy was universally applied in liver transplantation prior to 1998 (within four strata of illness severity). Since 1998, a 'first come, first served' remains active for candidates with HCC within the Milan criteria. The 'first come, first served' policy emphasizes equal opportunity for access to scarce resources, but it practically results in favored access to transplantation for candidates with advantages in health literacy, medical insurance, and ability to travel or afford unemployment.

The principle of 'sickest first' favors prioritizing transplant candidates with the highest risk of death without transplantation. MELD-based allocation of donor livers represents a 'sickest first' policy. Since enacting this policy in 1998, marked reductions in wait list 'dropout' and median wait list time have been observed for liver transplant candidates. Allocation of organs to the 'sickest first' delivers life-saving medical care to patients with

the worst prognoses if left untreated, but it does not account for differences in post-treatment prognosis and favors acutely ill over progressive illness.

The principle of utilitarianism seeks to maximize benefits with an intervention. Benefit may be defined as the number of individual lives saved or by the aggregate number of life-years saved. Utilitarian organ allocation is represented by a policy in which organs are distributed to transplant candidates with the greatest anticipated intention-to-treat survival. Utilitarianism seeks to distribute the 'greatest good to the greatest number,' but may violate the principle of individual justice by allocating treatments to healthier patients who may have an incrementally greater benefit with treatment compared to an ill patient. The latter issue could be partially abrogated by allotting more value to life-years gained in persons with more severe illness (quality or disability adjustment).

Each ethical principle has advantages and flaws. Historically, organ allocation in the United States has used a combination of 'first come, first served' and 'sickest first' principles, as is the case for liver transplantation currently. The principle of utilitarianism is neglected; egregious examples include multivisceral transplantation (three organs given to one candidate, when three lives could have been saved), retransplantation (confers a markedly worse prognosis compared to a first transplant), and de-emphasis on donor-recipient matching by factors known to influence prognosis (viral hepatitis status, gender, and others). It will be necessary to achieve a balance between important ethical principles to preserve individual democratic rights while simultaneously seeking to maximize health for the greatest number of persons in need of scarce medical treatments such as transplantation. The first step towards this goal in liver transplant allocation will be a greater focus on utilitarianism through consideration of intention-to-treat survival.