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A novel waitlist dropout score for hepatocellular carcinoma - identifying a threshold that predicts worse post-transplant survival

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Abstract

Background & Aims: It has been suggested that patients with hepatocellular carcinoma (HCC) at high risk of waitlist dropout would have done poorly after liver transplantation (LT) due to tumor aggressiveness. To test this hypothesis, we analyzed risk of waitlist dropout among HCC patients in long wait regions (LWR) to create a dropout risk score, and applied this score in short (SWR) and mid wait regions (MWR) to evaluate post-LT outcomes. We sought to identify a threshold in dropout risk that predicts worse post-LT outcome.

Methods: Using the UNOS database including all patients with T2 HCC receiving priority listing from 2010–2014, a dropout risk score was created from a developmental cohort of 2,092 LWR patients, and tested in a validation cohort of 1,735 SWR and 2,894 MWR patients.

Results: On multivariable analysis, 1 tumor 3.1–5 cm or 2–3 tumors, AFP >20 ng/ml, and increasing Child-Pugh and MELD-Na scores significantly predicted waitlist dropout. A dropout risk score using these four variables (C-statistic 0.74) was able to stratify 1-year cumulative incidence of dropout from 7.1% with a score ≤7 to 39.5% with a score >23. Patients with a dropout risk score >30 had 5-year post-LT survival of 60.1% versus 71.8% for those with a score ≤30 (p=0.004). There were no significant differences in post-LT survival below this threshold.

Conclusions: This study provided evidence that HCC patients with the highest dropout risk have aggressive tumor biology that would also result in poor post-LT outcomes when transplanted quickly. Below this threshold risk score of ≤30, priority status for organ allocation could be

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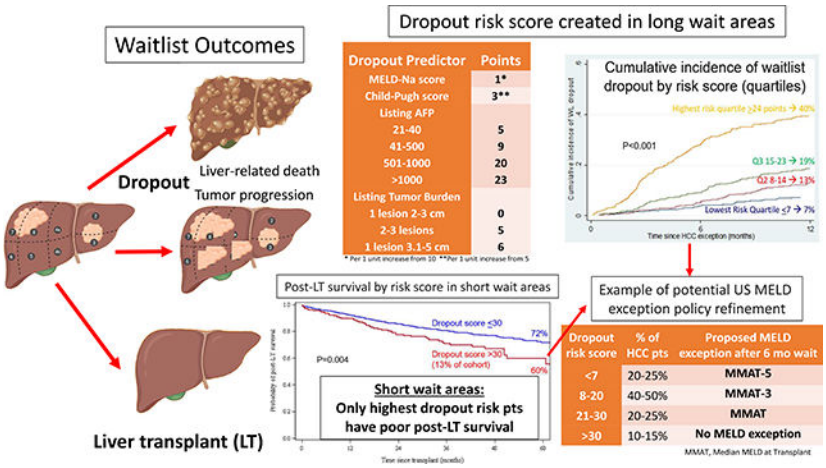
stratified based on the predicted risks of waitlist dropout without significant differences in post-LT survival.

LAY SUMMARY

Prioritizing patients with hepatocellular carcinoma (HCC) for liver transplant (LT) based on risk of waitlist dropout such as increasing tumor burden or AFP has been considered but may lead to inferior post-transplant survival. In this study of nearly 7000 patients, we created a threshold dropout risk score based on tumor and liver-related factors beyond which HCC patients will likely have poor post-LT outcomes (60% at 5 years). For patients below this risk score threshold, priority status could be stratified based on the predicted risk of waitlist dropout without compromising post-LT survival.

Graphical Abstrac



Keywords

liver transplantation; alpha-fetoprotein (AFP); HCC; United Network for Organ Sharing (UNOS); MELD exception

INTRODUCTION

Following the implementation of the Model for End Stage Liver Disease (MELD) system of organ allocation for hepatocellular carcinoma (HCC) in 2002, the proportion of liver transplants (LT) performed in the United States for HCC has dramatically increased from <5% before 2002 to nearly 30% (1–3). The rising incidence of HCC in the aging hepatitis C population and in those with non-alcoholic fatty liver disease and metabolic syndrome are major contributing factors (4–7). Additionally, HCC screening in at-risk populations, recommended by all liver societies, increases the proportion diagnosed with early stage HCC. As a result, HCC waitlist registrations in the United States rose by nearly 2,000 within the 5-year period from 2005–2009 to 2010–2014 (8).

As the transplant community is faced with the increasing demands of deceased donors for HCC, maximizing LT survival benefit by improving patient selection (utility) must be

carefully balanced against serving those with a higher risk for waitlist removal due to tumor progression (urgency) (9–12). The lack of a reliable instrument built upon optimal LT timing for HCC patients according to specific tumor characteristics represents one of the greatest challenges in organ allocation for HCC (11). Several systems have been proposed to give additional priority to HCC patients with a greater risk for dropout, which typically include those with larger tumors and higher alpha-fetoprotein (AFP) (13–16). This strategy, however, raises the concern of selecting those with less favorable tumor biology for LT, leading to a higher rate of post-LT HCC recurrence and worse survival (17, 18).

Another confounding factor is the wide regional variations in waiting time for LT across the United States (8, 19). Regions with short wait time offer the inherent advantage of rapid LT and a very low probability of waitlist dropout (8). On the other hand, studies using the United Network for Organ Sharing (UNOS) database have also suggested worse post-LT survival and a greater risk of HCC recurrence with short wait time (2, 20), possibly due to inclusion of more aggressive tumors for LT without sufficient time to observe tumor behavior.

In the present study, we analyzed the risk of waitlist dropout among HCC patients in long wait regions (LWR) to create a dropout risk score, and to apply this score in mid wait regions (MWR) and short wait regions (SWR) to evaluate post-LT outcomes. Using this novel approach, we aimed to test the hypothesis that those with the highest dropout risk (determined in long wait time regions) have aggressive tumor biology that would also result in poor post-LT outcomes when transplanted in shorter wait time regions. Based on the same assumption, we also sought to identify a threshold in this dropout risk score beyond which LT should no longer be considered an acceptable immediate treatment option.

PATIENTS AND METHODS

Study Design and Patient Population

This was a retrospective cohort study of patients aged 18 years and older listed for primary liver transplant in the UNOS database (Standard Transplant Analysis and Research files released March 2018) who received initial MELD exception for stage T2 HCC between January 2010 and December 2014. Patients were excluded from the study if they were listed for multi-organ transplant or received a live donor liver transplant. We also excluded patients who ever exceeded Milan criteria prior to listing given that there was no uniform approach to down-staging nationally during the study period.

The study population was divided into a development cohort and two validation cohorts based on UNOS region. UNOS regions were subdivided into long (LWR: 1,5,9), mid (MWR: 2,4,6,7,8), and short wait regions (SWR: 3,10,11) based on median time from initial listing with MELD exception to LT consistent with previous publications (8, 21). The development cohort was comprised of patients listed in LWR to capture a cohort with a relatively long period of waitlist observation and substantial dropout rate. The validation cohorts included patients listed in MWR or SWR.

Study variables collected from the UNOS database at listing with MELD exception included age, gender, race/ethnicity, etiology of liver disease, body mass index, blood type, MELD and Child-Pugh score, size and number of HCC, AFP, listing UNOS region, local-regional therapy (LRT), and time on the waiting list. Post-LT HCC recurrence was identified by physician review of liver malignancy follow-up data and cause of death variables (author NM). Records indicating post-transplant recurrence of pre-transplant malignancy or a cause of death indicating HCC or metastatic malignancy were classified as having HCC recurrence.

Outcomes and Dropout Risk Score Creation

The primary outcome was dropout from the LT waiting list for any of the following reasons: death without LT, tumor progression or being too sick to undergo LT. The secondary outcomes were (1) LT, specifically defined as receipt of a deceased donor LT, (2) post-LT patient survival, (3) post-LT HCC recurrence, and (4) intention-to-treat (ITT) survival.

Demographic and clinical characteristics were summarized using medians and inter-quartile ranges (IQR) for continuous variables and proportions for categorical variables and stratified by development and validation cohorts. Comparisons between cohorts were evaluated using Wilcoxon rank sum and chi-square test statistics.

The cumulative incidence of waitlist dropout and LT were each estimated while accounting for competing risks (22). When estimating cumulative incidence of dropout, patients receiving a LT were consider to have the competing event. When estimating the cumulative incidence of LT, patients with a waitlist death or removal for too sick to undergo LT were considered to have the competing event. Patients removed for other reasons or remaining alive on the waitlist were censored at their last date on the waitlist. Patient follow-up time was measured from the date of first MELD exception approval to the waitlist outcome (dropout or LT) or last date on the waiting list.

To determine predictors of waitlist dropout in the development cohort of LWR patients, univariate Fine and Gray competing risk regression (23) estimated risk of waitlist dropout within 1 year of listing with MELD exception as sub-distribution hazard ratios (HR) and 95% confidence intervals (CI) for each explanatory variable. Multiple cutoffs were tested to categorize variables and evaluated using Akaike information criterion (AIC) (24). Lower AIC values indicated better model fit. Factors with a univariate p-value less than 0.1 were evaluated in the multivariable analysis with the final model selected by backward elimination (p for removal greater than 0.05). Multicollinearity was assessed using the variance inflation factor with all values below the standard cut-off of 10 suggesting no collinearity in the final model. The dropout risk score was then created based on the final multivariable model coefficients. Model coefficients were scaled to the coefficient for MELD-Na and rounded to the nearest integer. This produced a simplified point scale reflecting the relative impact of model co-variables. The integer value for each model component was then summed to calculate the dropout risk score. The overall C-index assessed model discrimination.

The performance of the dropout risk score was tested in the two validation cohorts (MWR and SWR), separately. We utilized the overall C-index to assess the ability of the score to discriminate between events and nonevents for the outcome of waitlist dropout and calculated 95% CIs using the bootstrap method with 100 replicates.

Additionally, the dropout risk score was applied with respective post-LT survival and HCC recurrence probabilities estimated by the Kaplan-Meier method and compared using the log-rank test. Post-LT follow-up time for the survival analysis ended at death, with patients remaining alive censored at last follow-up. For the recurrence analysis, post-LT follow-up time ended at the first event of HCC recurrence or HCC death with patients censored at the time of non-HCC death or last follow-up.

Finally, ITT survival was compared between LWR, MWR, and SWR across dropout risk scores and compared using the log-rank test. The ITT event of death included deaths occurring while waiting for LT, waitlist removals for too sick to undergo LT, and deaths after LT. Patients remaining alive were censored at the last known date on the waiting list (for those not transplanted), date of re-transplant, or last follow-up date after LT. Statistical analyses were performed using SAS v9.4 (Cary, NC) and Stata/IC 11.1 (College Station, TX). This study was approved by the UCSF Committee for Human Research as minimal study risk.

RESULTS

Patient Characteristics

Baseline demographic and clinical characteristics of the 2092 HCC patients comprising the LWR development cohort are summarized in Table 1 and compared with the two validation cohorts which included 1735 patients listed in SWR and 2894 patients listed in MWR. Overall, the median age was 59 years (IQR 55–63) and 76.6% were men. A significantly higher percentage of non-Caucasians were listed in LWR. Hepatitis C was the most common etiology of liver disease. Hepatitis B and alcoholic liver disease were more common in LWR whereas non-alcoholic fatty liver disease was more common in SWR. At the time of listing with MELD exception, the median laboratory MELD-Na score was 10 (IQR 8–16). The median Child-Pugh score was 7 with LWR having the highest proportion of Child's A patients (47.7%) and SWR having the highest proportion of Child's C patients (18.8%). Median AFP and initial tumor burden were similar across cohorts. Only 4.6% of patients had an AFP >500 ng/ml at listing. Patients in LWR and MWR more commonly received at least one LRT (80.4% and 80.3%, respectively) than those in SWR (65.6%).

Predictors of Waitlist Dropout in Long Wait Regions (LWR)

Of the 2092 patients in the LWR development cohort, 522 (25.0%) experienced dropout due to tumor progression, being too sick for LT, or death while on the waiting list with a median time from MELD exception to dropout of 7.1 months (IQR 3.4–12.8) (Table 1). Cumulative probabilities of dropout were 10.8% (95% CI 9.5–12.2) within 6 months and 18.6% (95% CI 16.9–20.3) within 12 months of listing with MELD exception (Figure 1). In multivariate CR regression, the following variables all significantly predicted waitlist dropout within 1 year

of listing with MELD exception: MELD-Na score, Child-Pugh score, AFP at the following cutoffs: 21–40, 41–500, 501–1000, and >1000 ng/ml, and multiple tumors or a solitary 3.1–5cm tumor. The multivariable model coefficients for these four significant variables were then used to calculate a simplified dropout risk score. An individual patient's dropout risk score at listing is calculated by adding the individual points for each of the four variables (Table 2). Patients receive 1 point for every 1 unit increase in MELD-Na from 10 and 3 points for every 1 unit increase in Child-Pugh score starting from 5. For example, a patient with MELD-Na of 16 and Child-Pugh score of 8 would receive 15 points, 6 points for his MELD-Na and 9 points for his Child-Pugh score. MELD-Na and Child-Pugh were both included in the score because both variables were independently associated with waitlist dropout and the interaction term between them was not statistically significant (p=0.19). Additionally, the model including both variables had the lowest AIC compared to models with MELD-Na alone and Child-Pugh alone suggesting better model fit.

Predicted Waitlist Dropout Risk

Median dropout risk score in LWR was 14 (IQR 7–23). A patient with a MELD-Na of ≤10, Child's score of 5, AFP ≤20 ng/ml, and a single 2–3 cm lesion at the time of listing with MELD exception would receive a dropout risk score of 0. A dropout risk score of ≤7 predicts 6 and 12-month dropout risk of only 3.6% (95% CI 2.3–5.5) and 7.1% (95% CI 5.1–9.5), respectively. Predicted risk of dropout rose with each quartile (Figure 2a) such that a patient with a dropout risk score of >23 (highest risk quartile) has a predicted 6 and 12-month dropout risk of 28.1% (95% CI 24.1–32.3) and 39.5% (95% CI 34.9–44.1), respectively. In the subgroup in LWR at highest risk for dropout with a risk score of >30 (11.1% of the cohort), the cumulative probability of dropout was 46.6% (95% CI 40.2–52.8) at 1 year compared to 15.1% (95% CI 13.5–16.9) in those with a dropout score ≤30 (p<0.001). The cumulative probability of dropout based on a risk score >30 versus 8–30 and ≤7 are shown in Figure 2b. The continuous dropout risk score C-index was 0.74 (95% CI 0.71–0.76) in the LWR development cohort for predicting waitlist dropout. When we censor follow-up at 3 months, essentially eliminating dynamic changes in tumor burden and disease progression, the C-index was 0.78 (95% CI 0.73–0.82).

Waitlist Outcomes in SWR and MWR Validation Cohorts Compared to LWR Development Cohort

Median time to dropout was 3.0 months in SWR and 5.5 months in MWR (p<0.001 compared to LWR 7.1 months). Dropout occurred in 8.4% in SWR and 16.5% in MWR (p<0.001 compared to 25.0% in LWR). Overall, 34.4% of dropouts were due to death on the waitlist with the remaining 65.6% delisted for being too sick to transplant. Cumulative probabilities of dropout within 12 months of listing with MELD exception were 8.0% (95% CI 6.8–9.4) in SWR and 15.0% (13.6–16.4) in MWR (p<0.001 compared to LWR) (Figure 1). Median dropout risk score in SWR was 16 (IQR 9–25) and in MWR was 15 (IQR 9–23) (p<0.001 compared to LWR). A dropout risk score of ≤7 predicted 12-month dropout risk of 3.0% (95% CI 1.5–5.3) in SWR and 5.2% (95% CI 3.6–7.3) in MWR whereas a score of >23 predicted 12-month dropout risk of 15.7% (95% CI 12.7–19.1) in SWR and 29.2% (95% CI 25.7–32.8) in MWR. The C-index for the risk score in predicting dropout risk in SWR was 0.73 (95% CI 0.68–0.78) and in MWR was 0.71 (0.69–0.74).

Median waitlist time from MELD exception to LT was 11.6 months in the LWR development cohort compared to 2.2 months in SWR and 6.4 months in MWR (p<0.001). Only 54.2% of patients underwent LT in LWR by the end of study follow-up compared to 68.2% in MWR and 87.4% in SWR (p<0.001) (Table 1). The cumulative probability of LT within 1 year of MELD exception was 30.2% (95% CI 28.1–32.2) for LWR compared to 88.8% (95% CI 87.2–90.2) in SWR and 61.0% (95% CI 59.1–62.9) in SWR (p<0.001). Explant characteristics for the overall cohort stratified by dropout risk score ≤30 vs >30 in those who underwent LT since April 2012 (date when explant data became available in the UNOS database) are shown in Supplemental Table 1. Notably, complete tumor necrosis was found in 24.3% of patients with dropout score ≤30 compared to only 12.3% in those with dropout risk score >30.

Post-LT Outcomes in SWR and MWR by Dropout Risk Score and Identification of a Threshold Predicting Worse Post-LT Survival

In the validation cohorts, the median post-LT follow-up was 2.1 years (IQR 1.0–3.7) in SWR and 2.0 years (IQR 1.0–3.3) in MWR. Post-LT survival at 5 years was 70.1% (95% CI 66.0–73.8) in SWR and 73.2% (95% CI 69.3–76.7) in MWR. In SWR, 5-year post-LT survival was similar for patients with a dropout risk score of ≤10, 11–20, and 21–30 (71.0%, 71.2%, and 73.9%, respectively) but was significantly decreased to 60.1% in the 191 patients (13.2% of SWR LT recipients) with a dropout risk score of >30 (p=0.004) (Figure 3). Similar findings were found in MWR when comparing post-LT survival in those with dropout risk score ≤30 vs >30 though this finding did not reach statistical significance (p=0.07).

Post-LT recurrence at 5 years was 11.5% (95% CI 9.2–14.3) in SWR and 8.0% (95% CI 6.2–10.4) in MWR. In SWR, there was a trend towards increased 5-year post-LT recurrence in those with dropout risk score of >30 (17.3%) compared to those with score ≤30 (10.6%, p=0.07) (Figure 4a). In MWR, 5-year post-LT recurrence for those with dropout risk score of >30 was 13.3% compared to only 7.5% with score ≤30 (p=0.02) (Figure 4b).

Baseline listing characteristics based on the variables that comprised the dropout risk score are shown in Table 3 for all included patients stratified by risk score >30 (n=835) vs ≤30 (n=5886). On average, patients in the highest risk category had both decompensated liver disease with median MELD-Na 21 and Child-Pugh score 10 as well as more aggressive tumor biology with median AFP four times that of the lower risk group and only 32% with single lesion ≤3 cm compared with 52% in the lower risk group. Among the 835 patients in the highest risk category with a dropout risk score of >30, severely decompensated liver disease (based on MELD-Na and Child-Pugh score) was the only cause of dropout in only 106 patients (12.7%). The rest (87.3%) had a combination of more aggressive tumor features as well as decompensated liver disease.

Intention-to-Treat Survival by Dropout Risk Score and Wait Region

Overall ITT survival at 5 years for patients with a dropout risk score of ≤10, 11–30, and >30 were 69.5% (95% CI 66.2–72.5), 60.5% (58.2–62.8), and 43.0% (38.2–47.6), respectively with 446 subjects remaining in the ITT analysis at this 5 year mark. At each of these risk

score categories, ITT survival was lowest in LWR and highest in SWR. In LWR, ITT 5-year survival by risk score category was 67.1%, 52.3%, and 31.6% (all p<0.005). However, in SWR, 5-year ITT survival was similar for patients with risk score ≤10 and 11–30 (72.2% vs 68.0%, p=0.58) but was only 48.4% for SWR patients with risk score >30 (p<0.001 compared with all other SWR patients).

DISCUSSION

HCC is a heterogeneous disease with highly variable patterns of progression after the initial diagnosis (25). This tumor heterogeneity is not accounted for under the traditional dogma of restricting LT for HCC solely on the basis of tumor size and number. Observing tumor behavior following LRT while on the waiting list for LT has recently emerged as the main driver for improving candidate selection beyond the “one size (and number) fits all” approach (11, 26). A crucial element in patient selection under this “ablate and wait” priniciple (27) is a minimal observation period following LRT, as time is a surrogate for tumor aggressiveness and therefore an additional factor in the selection process (11). In this context, mandating a period of observation would likely lead to exclusion of the most aggressive tumors from LT (waitlist dropout) as a result of rapid tumor progression to beyond transplantable criteria. Along the same line, rapid LT of these tumors may result in significantly worse post-LT outcomes. The paucity of patient outcome data to prove these concepts provides the impetus for the present study to evaluate the post-LT outcomes of a subgroup of HCC patients who received LT in shorter wait regions but would have been excluded from LT in long wait time regions due to tumor progression to beyond acceptable criteria for LT.

In this large UNOS-based study involving over 6700 patients with HCC meeting the Milan criteria by imaging before LT, we developed and validated a dropout risk score from LWR based on 4 listing variables – AFP, tumor size/number, MELD-Na score and Child-Pugh score – that was able to stratify 1-year waitlist dropout risk ranging from 7% in those with a risk score of ≤7 (lowest risk quartile) to 40% with a score >23 (highest risk quartile). The novel aspect of our study is the application of this dropout risk score in SWR and MWR to evaluate post-LT outcomes, and the identification of a threshold in this risk score that predicts worse post-LT survival. Those with a very high dropout risk score of >30 who received LT in SWR and MWR had a significantly lower 5-year post-LT survival of only 60% compared to 72% in all other HCC patients. We also found that this same group had post-LT HCC recurrence nearly doubled that of patients with a lower dropout risk score of ≤30. On the other hand, we found no significant differences in post-LT outcomes when lower dropout risk score cutoffs were tested. These findings provide the proof of concept about tumor aggressiveness – those with the highest risk of waitlist dropout also have worse survival if transplanted quickly.

Identifying a threshold in the dropout risk score that predicts worse outcome after LT offers greater clarity in how to effectively use this risk score to shape future organ allocation policies. We have demonstrated no significant decrease in post-LT survival in patients below this threshold, and therefore a graded listing priority system can be created based on the anticipated dropout risk in these patients without compromising post-LT outcome (Table 4).

We envision several distinct categories of HCC patients within Milan criteria who are awaiting LT. Approximately 20–25% of patients have a dropout risk score of ≤7 reflecting compensated liver disease with low risk tumor features. It has previously been shown that patients with well-compensated liver disease and the same favorable tumor characteristics including single tumor 2–3 cm and low AFP ≤20 have very low risk for waitlist dropout even if the waiting time is prolonged. These patients should receive a lower priority in our proposed model (21, 28). On the other hand, LT should not be undertaken in the 10–15% of HCC patients with very high dropout risk score of >30 assuming that the high score is not driven entirely by decompensated liver disease based on high MELD-Na and Child-Pugh score (with low AFP and minimal tumor burden), in which case immediate LT may be warranted. These patients with the highest risk score >30 have a predicted 5-year survival of only 60%. According to Clavien et al. for the international consensus conference on LT for HCC, LT should be reserved for HCC patients who have a predicted 5-year survival comparable to non-HCC patients (>70%) (29). Allowing immediate LT would likely reduce access to LT for patients with a better post-LT prognosis (29, 30). These patients should be observed for a longer period of time and only those showing response to LRT (if feasible based on liver function) and reduction in AFP would be considered acceptable candidates for LT. Under different circumstances, LT may be acceptable if a living donor is available or in a region with organ surplus (31, 32). The remaining 60% of patients with intermediate dropout risk (dropout risk score of 8–30) represent the subgroup that may derive the greatest LT benefit. These patients should be classified into different categories in listing priority based on the risks of waitlist dropout – granting a higher priority to those with a higher risk for dropout (Table 4).

Similar to previous studies (13–16), both initial tumor burden and AFP are significant predictors of waitlist dropout in our model. In the present study, patients with multiple tumors or a solitary tumor 3.1–5 cm in diameter are at higher risk for waitlist dropout when compared to those with a solitary tumor 2–3 cm in diameter, confirming the same findings from one of the first publications on waitlist dropout 2 decades ago (33). High AFP predicts not only waitlist dropout but also a greater risk of HCC recurrence after LT (34–36). A new national policy has recently been implemented in which patients with HCC and an AFP >1000 ng/ml are required to show a decrease in AFP to <500 with LRT before they can proceed with LT (37). We have recently validated this policy based on analysis of UNOS data, in which the 5-year post-LT survival for those with AFP >1000 at LT was 49% compared to 67% with decrease in AFP from >1000 to 101–499 and nearly 90% for those with an AFP reduction from >1000 to ≤100 at LT (38). These findings highlight the importance of allowing a period of observation for change in AFP in addition to tumor response to LRT prior to LT (39).

The present study has also clearly demonstrated that those with decompensated cirrhosis based on MELD-Na score or Child-Pugh score have a greater risk of waitlist dropout. The most likely explanation is that many patients with liver dysfunction are not eligible for LRT or have received suboptimal LRT for their HCC because of the risk for further hepatic decompensation (for chemoembolization or radioembolization) or risk of bleeding due to the presence of ascites or coagulopathy (for percutaneous ablation). As a result, these patients are at greater risk for tumor progression to beyond transplant criteria. In our dropout model,

the vast majority of the subgroup at highest risk for dropout (risk score >30) had a combination of both aggressive tumor features and decompensated liver disease, and only 12.7% had risk score of >30 solely as a result of high MELD-Na and Child-Pugh score. We feel that sicker patients, based on MELD-Na score or Child-Pugh score or both, should receive greater listing priority than those with well-compensated cirrhosis. Until such a system is in place, the only viable options are living donor LT or the use of extended criteria donors to potentially shorten the waiting time for LT.

There are a number of limitations of this study, most notably the inability to study the performance of this dropout risk score over time. Some of the components of this risk score are not available longitudinally in the UNOS database, including Child-Pugh components and sodium to calculate MELD-Na. Response to LRT data is not specifically recorded in the UNOS database and there may be differences in how tumor burden is reported at each MELD exception application. Given the lack of granularity of data, we could not accurately assess a dynamic model of this dropout risk score that incorporates changes due to LRT. However, the primary goal of this dropout risk score was to identify up front thresholds to predict patients who can undergo rapid LT. Our results showed that post-LT survival became significantly worse only in the subgroup at highest risk of dropout. The secondary aim was to prioritize wait list rank at the time of LT listing. We did also demonstrate that the risk score based on only baseline tumor and liver function variables were highly predictive of dropout. When we censor follow-up at 3 months, essentially eliminating dynamic changes in tumor burden and disease progression, we in fact observed an increase in the performance of the dropout risk score, with C-index of 0.78 (95% CI 0.73–0.82). Another limitation of our study is that post-LT HCC recurrence may be under-reported in the UNOS database and thus we chose overall survival instead of HCC recurrence as the primary endpoint in assessing post-LT outcomes. Our results require validation, perhaps in a large database from another country. Finally, the dropout risk score is based on well-established risk factors and did not include any new prognostic markers. The message here is that these well-known risk factors are underutilized in shaping organ allocation policy. There is still a pressing research need to identify novel biomarkers that improve prognostication among HCC patients being considered for LT.

In summary, when confronting the daunting question of whether “high risk for waitlist dropout equals poor post-LT outcome”, our results help shed light on how we may improve prioritization of HCC patients for LT based on the predicted risks of waitlist dropout. We have demonstrated that post-LT outcomes become significantly worse only in the subgroup at highest risk of dropout (dropout risk score >30). These patients should not undergo LT, at least not immediately, unless dropout risk is driven entirely by decompensated liver disease. Below this threshold in the dropout risk score, however, giving higher listing priority for LT to those at a higher risk for waitlist dropout should not result in reduced post-LT survival. These findings may be important in shaping future organ allocation policies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data Availability:

For this study, the only source of data was the publicly available UNOS STAR file which contains the national database for HCC patients in the United States undergoing liver transplantation.

Abbreviations:

MELD	Model for End Stage Liver Disease
HCC	hepatocellular carcinoma
LT	liver transplantation
AFP	alpha-fetoprotein
UNOS	United Network for Organ Sharing
LWR	long wait regions
MWR	mid wait regions
SWR	short wait regions
LRT	local regional therapy
ITT	intention-to-treat
IQR	inter-quartile range
HR	hazard ratio
CI	confidence interval
AIC	Akaike information criterion

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- Increasing tumor burden, AFP, Child-Pugh and MELD score predict HCC waitlist dropout
- Novel HCC dropout risk score stratifies 1-year dropout risk from 7% up to 40%
- HCC patients with the highest dropout risk score >30 have poor transplant survival
- In all others with HCC, calculated dropout risk can safely guide waitlist priority

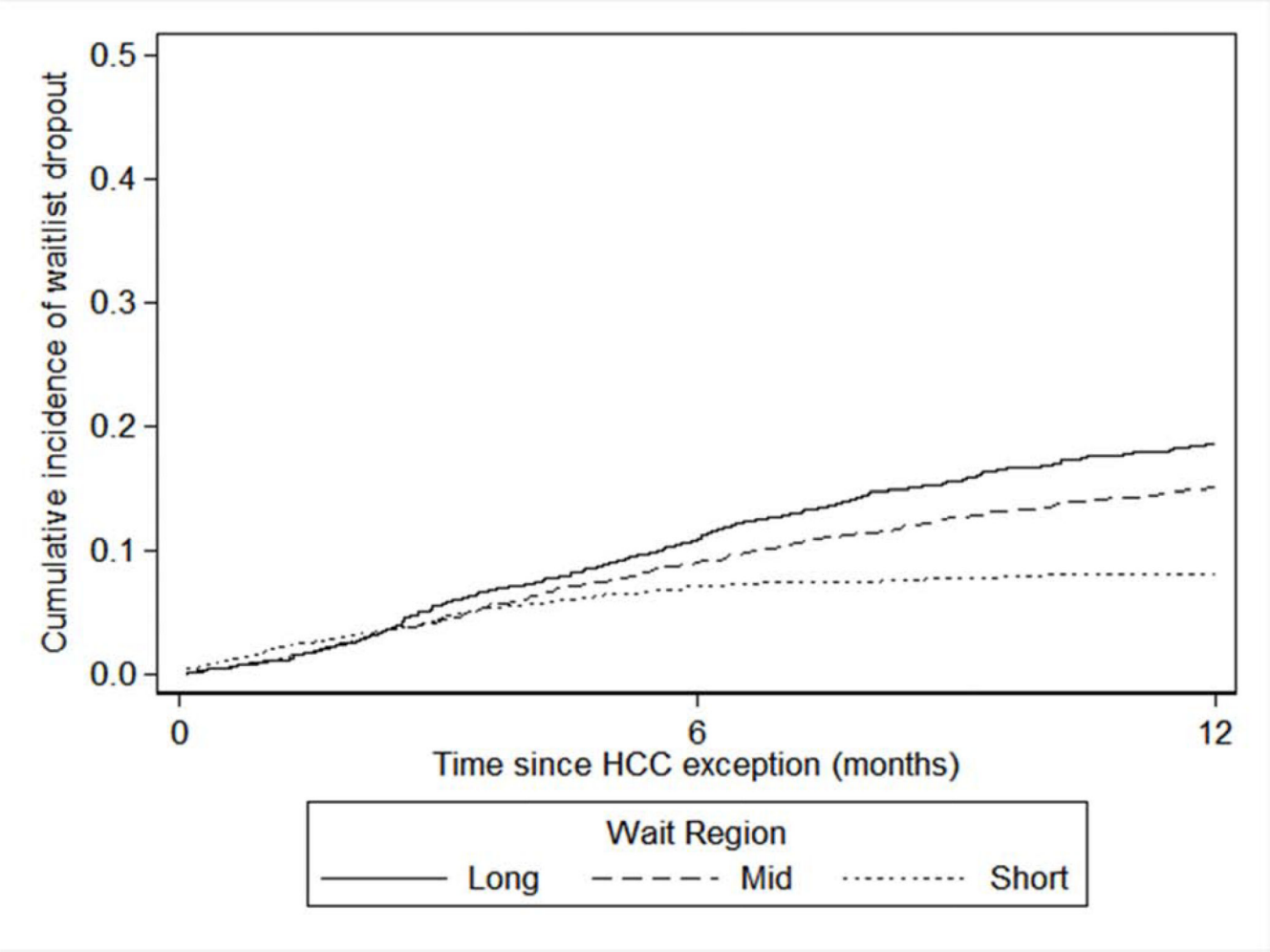
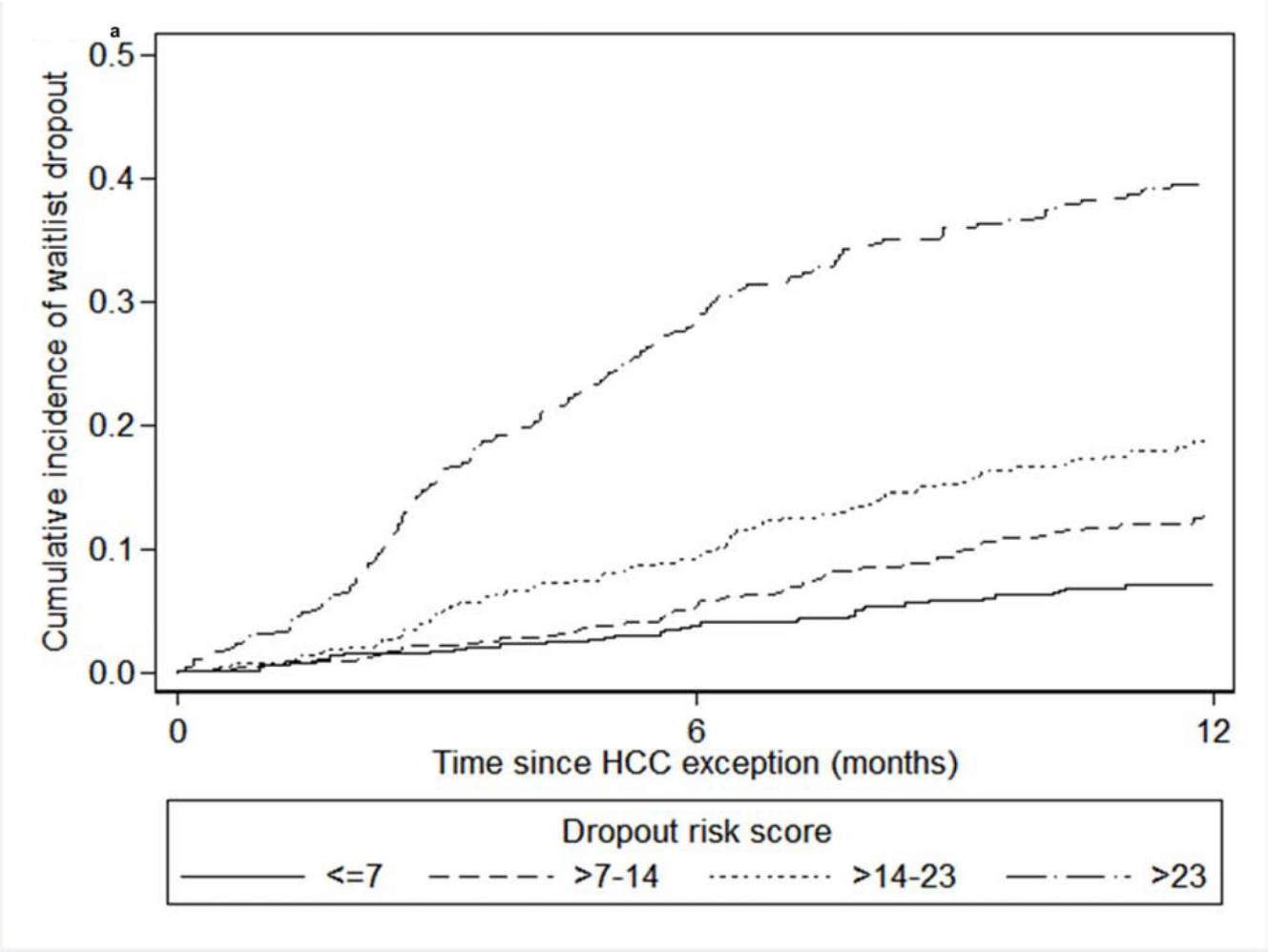


Figure 1.
Cumulative incidence of waitlist dropout within 1 year of listing with HCC MELD exception in long (LWR), mid (MWR), and short wait regions (SWR). The cumulative incidence of dropout was estimated while accounting for competing risks.



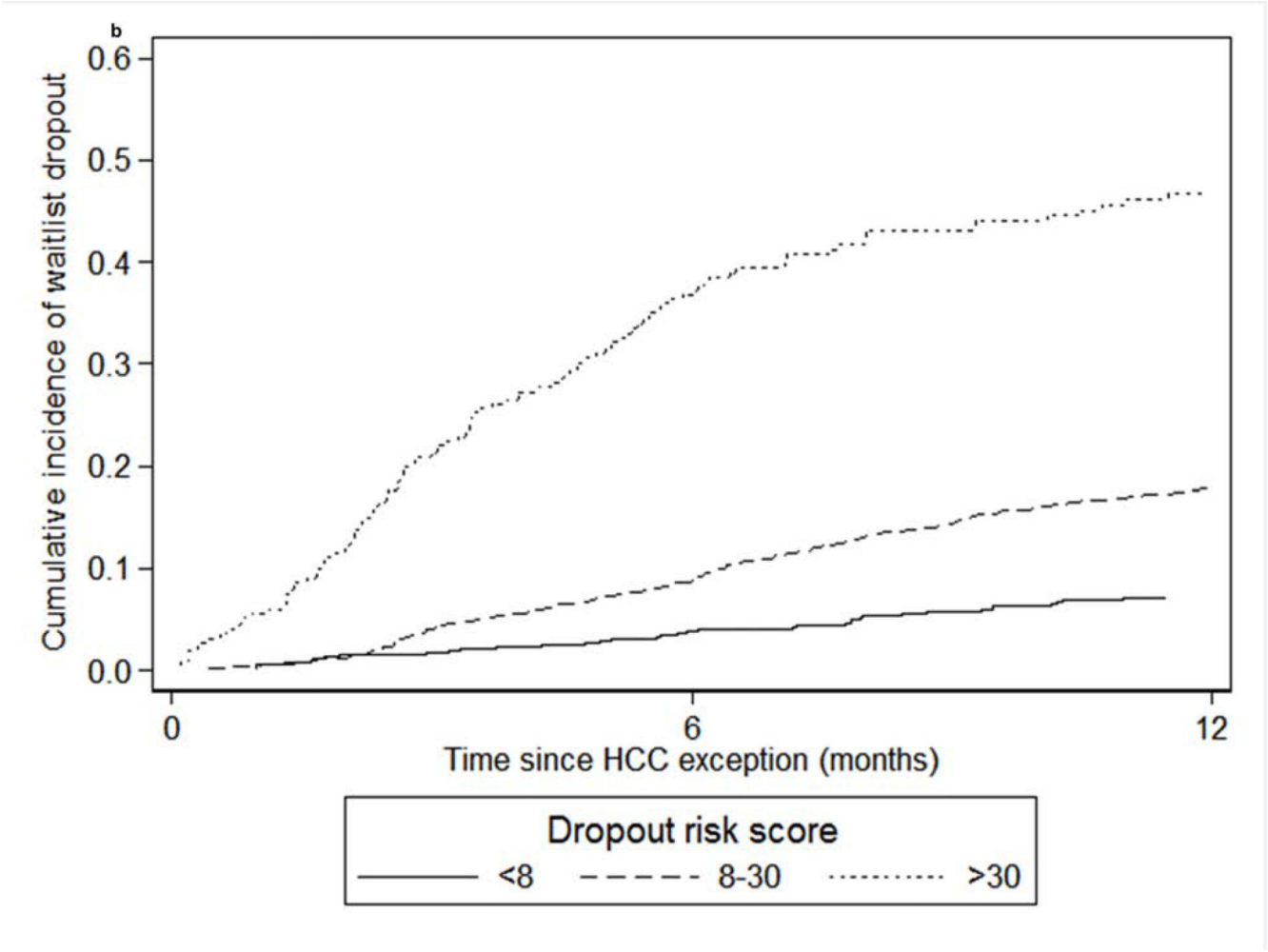


Figure 2.

Cumulative incidence of waitlist dropout in long wait regions (LWR) stratified by **(A)** dropout risk score quartiles and **(B)** risk score >30 versus 8–30 versus ≤7. The C-index was 0.74 for the development LWR cohort. The cumulative incidence of dropout was estimated while accounting for competing risks.

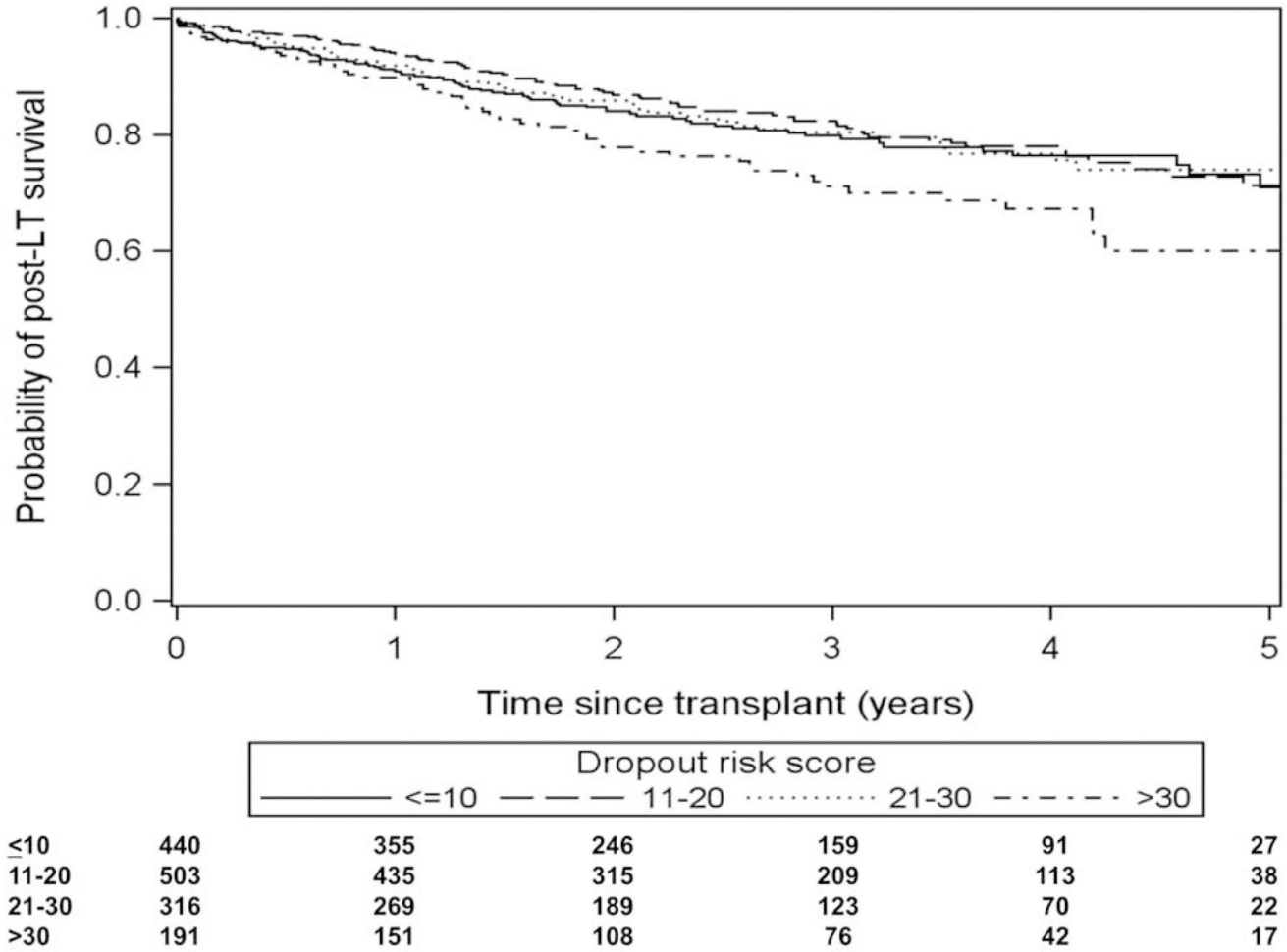
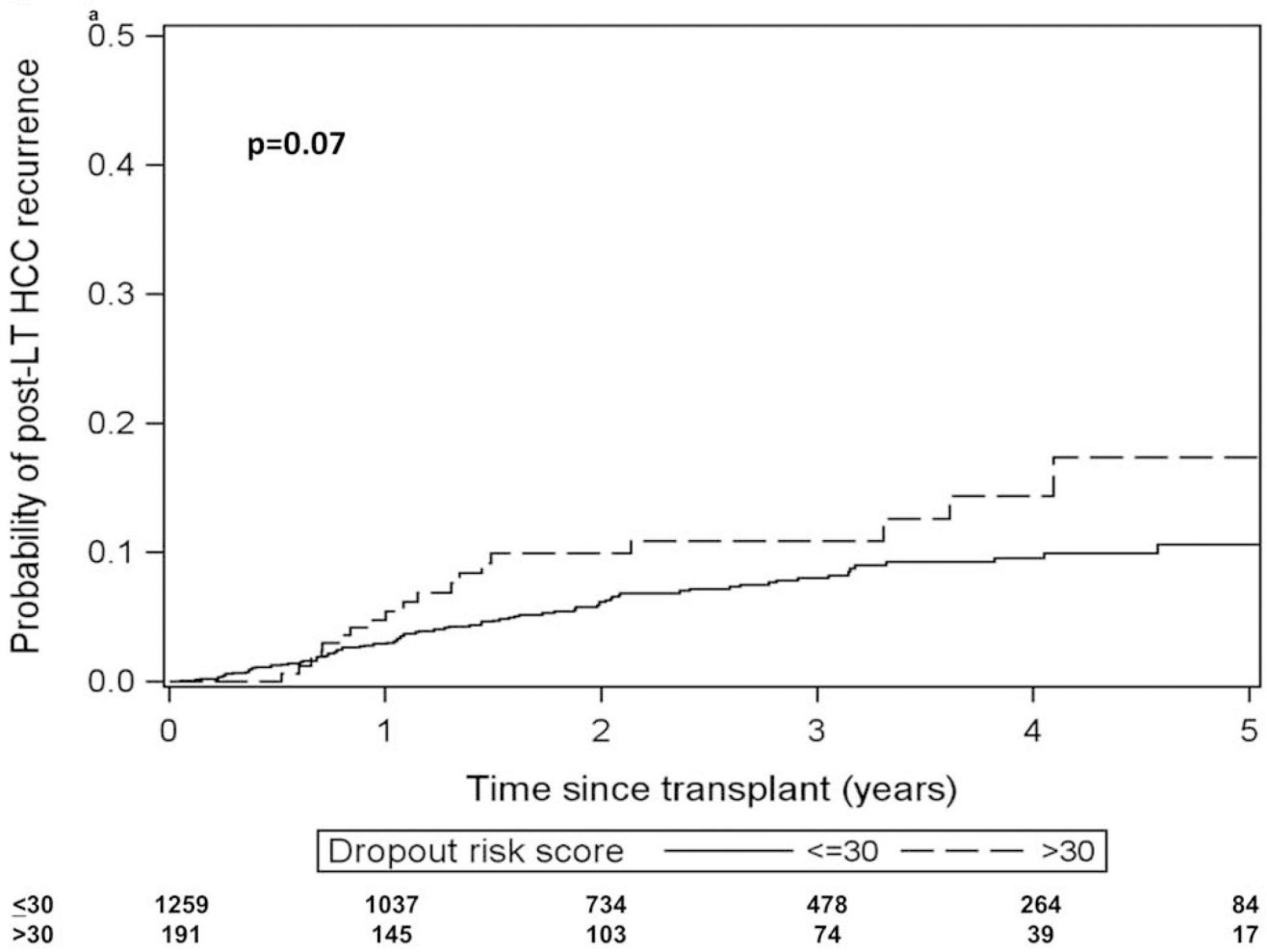


Figure 3.

Kaplan-Meier post-LT survival for the SWR testing cohort stratified by dropout risk score categories and compared using the log-rank test.



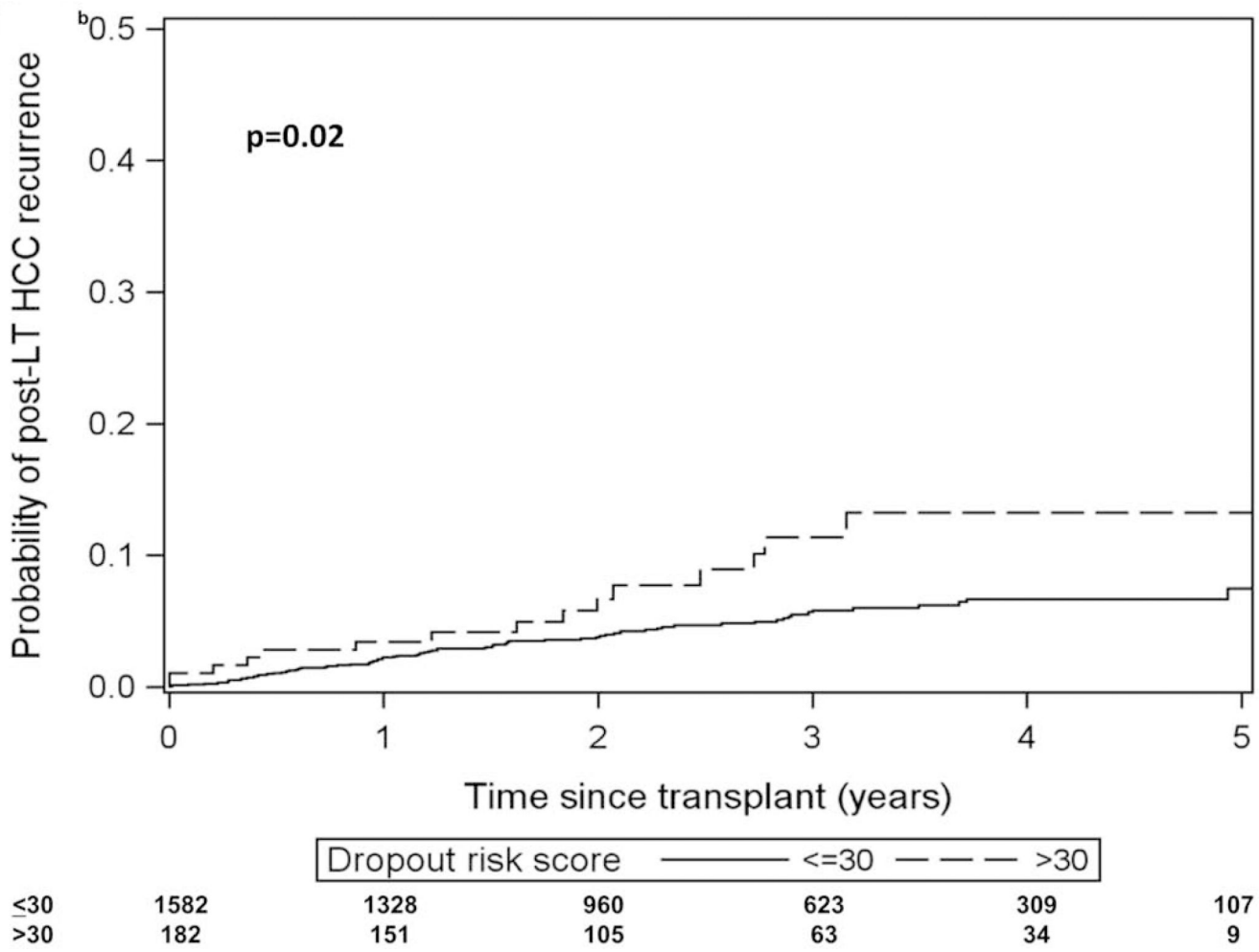


Figure 4.

Kaplan-Meier post-LT recurrence stratified by dropout risk score >30 versus ≤30 for **(A)** SWR and **(B)** MWR and compared using the log-rank test.

Table 1.

Baseline and Waitlist Characteristics of the Development (LWR) and Validation (SWR, MWR) Cohorts

	Development Cohort	Validation Cohorts		
	Long Wait* Region (n=2092)	**Short Wait* Region (n=1735)**	**Mid Wait* Region (n=2894)**	**p-value**
Age (IQR)	60 (56–64)	59 (55–63)	59 (55–63)	<0.001
Male (%)	1610 (77.0)	1331 (76.7)	2208 (76.3)	0.58
Race/Ethnicity (%)				<0.001
Caucasian	1177 (56.3)	1334 (76.9)	1939 (67.0)	
Hispanic	489 (23.4)	142 (8.2)	384 (13.3)	
African	141 (6.7)	191 (11.0)	355 (12.3)	
Asian	259 (12.4)	45 (2.6)	178 (6.1)	
Etiology (%)				<0.001
HCV	1282 (61.3)	1006 (58.0)	1782 (61.6)	
Alcohol	195 (9.3)	125 (7.2)	197 (6.8)	
NAFLD	156 (7.5)	195 (11.2)	218 (7.5)	
HBV	140 (6.7)	40 (2.3)	143 (4.9)	
Other	319 (15)	369 (21.3)	554 (19.1)	
BMI (IQR)	28 (25–32)	29 (25–32)	28 (25–32)	<0.001
MELD-Na at Listing (IQR)	10 (8–16)	11 (8–16)	10 (8–16)	<0.001
Child's Class at Listing (%)				<0.001
A	997 (47.7)	564 (32.5)	1118 (38.6)	
B	822 (39.3)	845 (48.7)	1330 (46.0)	
C	273 (13.0)	326 (18.8)	446 (15.4)	
AFP ng/ml at Listing (IQR)	12 (5–49)	12 (5–45)	13 (5–45)	0.22
Initial Tumor Burden (%)				0.19
1 lesion 2–3 cm	1022 (48.9)	835 (48.1)	1486 (51.3)	
1 lesion 3.1–5 cm	499 (23.8)	384 (22.1)	654 (22.6)	
2–3 lesions	571 (27.3)	516 (29.7)	754 (26.0)	
Received LRT (%)	1683 (80.4)	1139 (65.6)	2325 (80.3)	<0.001
# LRT received overall (IQR)	1 (1–2)	1 (0–1)	1 (1–1)	<0.001
# LRT among treated (IQR)	1 (1–2)	1 (1–1)	1 (1–2)	<0.001
Type of LRT received (%)				<0.001
Chemoembolization	1320 (63.1)	937 (54.0)	1977 (68.3)	
Ablation	695 (33.2)	288 (16.6)	592 (20.4)	
Radioembolization	35 (1.7)	12 (0.7)	49 (1.7)	
External Radiation	19 (0.9)	6 (0.4)	19 (0.7)	

	Development Cohort	Validation Cohorts		
	Long Wait* Region (n=2092)	**Short Wait* Region (n=1735)**	**Mid Wait* Region (n=2894)**	**p-value**
Waitlist dropout ** **(%)**	522 (25.0)	146 (8.4)	478 (16.5)	<0.001
Time (mo) to Dropout (IQR)	7.1 (3.4–12.8)	3.0(1.2–5.0)	5.5 (3.1–9.6)	<0.001
Liver Transplant (%)	1135 (54.2)	1516 (87.4)	1975 (68.2)	<0.001
Time (mo) to LT (IQR)	11.6 (6.2–16.0)	2.2 (1.0–4.0)	6.4 (3.3–10.2)	<0.001

* Long wait time is UNOS regions 1, 5, and 9, mid wait time 2, 4, 6, 7, and 8 and short wait time 3, 10, and 11

** Due to tumor progression, liver related death, or being too sick for transplant.

Table 2.

Multivariable Analysis of Predictors of Waitlist Dropout in Long Wait Regions and Creation of the Dropout Risk Score

Predictor	Multivariable HR (95% CI)	p-value	Dropout Risk Score Points
MELD-Na score	1.07 (1.03–1.10)	<0.001	**1** *
Child-Pugh score	1.19 (1.11–1.29)	<0.001	**3** **
AFP at Listing (ng/ml)			
≤20	Ref		**0**
21–40	1.41 (1.0–1.97)	0.048	**5**
41–500	1.84 (1.44–2.35)	<0.001	**9**
501–1000	3.55 (2.00–6.29)	<0.001	**20**
>1000	4.40 (2.78–6.96)	<0.001	**23**
Listing Tumor Burden			
1 lesion 2–3 cm	Ref		**0**
2–3 lesions	1.38 (1.08–1.77)	0.01	**5**
1 lesion 3.1–5 cm	1.48 (1.14–1.92)	0.003	**6**

* Per 1 unit increase from 10 (MELD-Na values <=10 receive 0 points, 11 receives 1 point, 12 receives 2 points, etc.)

** Per 1 unit increase from 5 (Child-Pugh score of 5 receives 0 points, 6 receives 1 point, etc.)

Dropout risk score = (MELD-Na -10) + ((CP - 5) *3) + (5 if AFP 21–40) + (9 if AFP 41–500) + (20 if AFP 501–1000) + (23 if AFP >1000) + (6 if 1 tumor 3.1–5cm) + (5 if 2–3 tumors)

The dropout risk score was created based on the final multivariable model coefficients. Model coefficients were scaled to the coefficient for MELD-Na and rounded to the nearest integer. This produced a simplified point scale reflecting the relative impact of model co-variables. The integer value for each model component was then summed to calculate the dropout risk score.

Table 3.

Baseline liver-disease and tumor characteristics by dropout risk score ≤ 30 vs > 30

Characteristics at listing	Dropout score <=30 (n=5886)	Dropout score >30 (n=835)	p-value
Median MELD-Na score (IQR)	10 (8–14)	21 (18–24)	<0.001
Median Child-Pugh score (IQR)	7(6–8)	10(9–11)	<0.001
Median AFP (ng/ml) (IQR)	11 (5–38)	40 (7–251)	<0.001
AFP, n (%)			
≤20	3798 (64.5)	343 (41.1)	<0.001
21–40	691 (11.7)	76 (9.1)	
41–500	1269 (21.6)	249 (29.8)	
501–1000	69 (1.2)	57 (6.8)	
>1000	59 (1.0)	110 (13.2)	
Tumor burden, n (%)			
1 lesion ≤3cm	3077 (52.3)	266 (31.9)	<0.001
1 lesion 3.1–5cm	1269 (21.6)	268 (32.1)	
2–3 lesions	1540 (26.2)	301 (36.0)	

Table 4.

Example of potential US MELD exception policy refinement based on HCC dropout risk score

Dropout risk score	% of HCC patients	Current MELD exception after 6 month wait	Proposed MELD exception after 6 month wait
≤7	20–25%	MMAT -3	MMAT-5 *
8–20	40–50%		MMAT-3
21–30	20–25%		MMAT
>30	10–15%		No MELD exception

Abbreviations: MMAT, Median MELD at Transplant

* In the event of HCC recurrence in low dropout risk candidates awaiting LT, we would propose increasing MELD exception from MMAT-5 back up to MMAT-3