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Predictors of low risk for dropout from the liver transplant waiting list for hepatocellular carcinoma in long wait time regions: Implications for organ allocation

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Abstract

All patients with hepatocellular carcinoma meeting United Network for Organ Sharing T2 criteria currently receive the same listing priority for liver transplant (LT). A previous study from our center identified a subgroup with a very low risk of waitlist dropout who may not derive immediate LT benefit. To evaluate this issue at a national level, we analyzed within the United Network for Organ Sharing database 2052 patients with T2 hepatocellular carcinoma receiving priority listing from 2011 to 2014 in long wait time regions 1, 5, and 9. Probabilities of waitlist dropout were 18.3% at 1 year and 27% at 2 years. In multivariate analysis, factors associated with a lower risk of waitlist dropout included Model for End-Stage Liver Disease-Na < 15, Child's class A, single 2- to 3-cm lesion, and α-fetoprotein ≤20 ng/mL. The subgroup of 245 (11.9%) patients meeting these 4 criteria at LT listing had a 1-year probability of dropout of 5.5% vs 20% for all others ($P < .001$). On explant, the low dropout risk group was more likely to have complete tumor necrosis (35.5% vs 24.9%, $P = .01$) and less likely to exceed Milan criteria (9.9% vs 17.7%, $P = .03$). We identified a subgroup with a low risk of waitlist dropout who should not receive the same LT listing priority.

Keywords

clinical research/practice; health services and outcomes research; liver disease malignant; liver transplantation/hepatology; organ allocation; organ procurement and allocation; Organ Procurement and Transplantation Network (OPTN); recipient selection; United Network for Organ Sharing (UNOS)

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

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 2016).

1 | INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) has continued to rise for >2 decades in the United States, largely due to the aging population with cirrhosis due to chronic hepatitis C virus (HCV) infection as well as the new epidemic of nonalcoholic fatty liver disease (NAFLD).[1,2] NAFLD is now the fastest growing etiology of cirrhosis among patients with HCC being considered for liver transplant (LT).[3] The number of HCC waitlist registrations in the United States had risen by nearly 2000 from 2005–2009 to 2010–2014.[4] HCC now accounts for nearly 25% of all LTs performed in the United States, compared with <5% before the implementation of the Model for End Stage Liver Disease (MELD) system of organ allocation for HCC in 2002 and 10%−15% in 2002–2008.[5–7] Given the increasing demands of deceased donor LT for HCC, maximizing LT survival benefit in patients with HCC and ensuring comparable outcomes compared with patients without HCC are of paramount importance.[8] To this end, the United Network for Organ Sharing (UNOS) recently approved a policy requiring patients with HCC with an α-fetoprotein (AFP) level >1000 ng/mL to show reduction to <500 ng/mL with local regional therapy (LRT) before LT could be undertaken. This policy, reflecting the principle of utility, would be expected to improve post-LT outcomes by reducing HCC recurrence.[9,10]

Beyond utility, improving transplant survival benefit also extends to the principle of urgency, or transplanting those in greatest need for LT. At present, all patients with HCC meeting UNOS T2 criteria (1 lesion 2–5 cm or 2–3 lesions ≤3 cm) receive the same listing priority for LT. There have been several proposals to give additional priority to those patients with HCC at high risk of dropout[11–14] but such an approach may end up selecting for LT those with more aggressive tumors who are also at a higher risk for post-LT HCC recurrence,[15] leading to inferior post-LT outcomes.[16,17] Another approach is to consider reducing listing priority for patients with HCC with a low risk of waitlist dropout. A previous study from our center identified a subgroup with a single 2- to 3-cm tumor, AFP <20 ng/mL after first LRT, and a complete response to first LRT who had a very low risk of waitlist dropout (<2% at 2 years).[18] This subgroup, which accounted for 20% of the cohort, would unlikely derive immediate benefit from LT.

At the national level, factors predicting waitlist dropout for HCC have not been well established. A major problem has been the relatively short wait time to LT in many parts of the country, leading to significant regional differences in dropout rates.[13,19] Most previous national database studies assessing waitlist dropout have had a very short median waitlist follow-up period of only 3–6 months.[11,12] Typically, the rate of dropout for patients with HCC tends to be low for the first 6 months on the waitlist and then increases over time.[20] Given the predicted increase in wait times due to recently implemented UNOS policies,[21] these prior studies[8,11,12,14] may not reflect current waitlist dropout risks for patients with HCC. The aim of the present study is to evaluate predictors of dropout for patients listed for LT with T2 HCC in long wait time regions to identify a subset with a low rate of waitlist dropout who may not warrant equal listing priority compared with other patients with T2 HCC.

2 | PATIENTS AND METHODS

2.1 | Study design and patient population

This was a retrospective cohort study of patients aged 18 years and older listed for primary LT in the UNOS database (Standard Transplant Analysis and Research files released March 2016) who received initial MELD exception for stage T2 HCC between January 2011 and December 2014. Only patients listed in long wait time UNOS regions (1, 5, and 9) were initially included so as to capture a study cohort with a relatively long period of waitlist observation expected to undergo LRT while awaiting LT. Patients were excluded from the study if they were listed for multiorgan transplant, ever exceeded Milan criteria by pretransplant imaging, or received a live donor liver transplant.

Study variables collected from the UNOS database at listing with MELD exception included age, sex, 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, treatment with LRT, and time on the waitlist. Presence and absence of LRT were determined based on reporting of LRT in the exception data. Subjects without treatment indicated were classified into the no-LRT group. Explant pathology variables were collected for the subset of patients transplanted since April 2012 when UNOS began capturing HCC explant pathology data. These variables include histologic grade based on the modified Edmondson criteria,[22] tumor stage, and presence of microvascular invasion. Explant tumor staging was based on size and number of only viable tumors.

To improve equity between HCC and patients without HCC and to reduce regional disparities in waitlist outcomes for patients with HCC, UNOS enacted 2 policy changes in 2015: a 6-month mandatory delay in granting MELD exception and a cap of the MELD exception at 34 points.[21] Given the resulting increased wait times throughout the country and the importance of confirming the present findings in the post-2015 HCC MELD exception era, we performed a post-hoc analysis that identified a validation cohort of 2192 subjects from all 11 UNOS regions initially listed for LT with HCC MELD exception from October 2015 to October 2016.

2.2 | Outcomes and statistical analysis

The primary outcome was dropout from the transplant waitlist for any of the following reasons: death without LT, tumor progression, or being too sick to undergo LT. Secondary outcomes included LT and intention-to-treat survival. Patient characteristics were summarized by using medians and IQRs for continuous variables and proportions for categorical variables. The cumulative incidence of dropout and LT were each estimated while accounting for competing risks.[23] Patient follow-up time was measured from the date of first MELD exception to the waitlist outcome (dropout or LT) or last date on the waitlist. For dropout, follow-up terminated on the date of dropout (event), with LT considered a competing event. For LT, patient follow-up ended at the date of LT (event) with dropout was considered a competing event. Patients remaining alive on the waitlist or removed for reasons other than death, tumor progression, or being too sick to undergo transplant were censored at their last date on the waitlist. Univariate competing risk regression using the

Fine and Gray method[24] estimated risk of waitlist dropout with hazard ratios (HRs) and 95% confidence intervals (CIs) for each explanatory variable. Factors with a univariate *P*-value <.1 were evaluated in the multivariable analysis with the final model selected by backward elimination (*P* for removal >.05). The model identified a subpopulation of patients with low risk for waitlist dropout. Cumulative incidence of dropout for this low-risk group was estimated and compared with all other patients. Clinical characteristics were also compared between the 2 groups by using the Pearson χ^2 and Wilcoxon tests, as appropriate.

Intention-to-treat and post-LT survival were estimated by using the Kaplan-Meier method. For intention-to-treat survival, patient follow-up time was measured from the date of first MELD exception to the date of the first event (waitlist death without LT, waitlist removal for being too sick to undergo LT, or post-LT death). Patients were censored on the date of last waitlist follow-up (for those without LT), date of repeat LT, or date of last post-LT follow-up. Statistical analyses were performed with the use of SAS v9.4 (Cary, NC) and Stata/IC 11.1 (College Station, TX).

3 | RESULTS

3.1 | Patient characteristics and LRT

Baseline demographic and clinical characteristics of the 2052 patients comprising the study population are summarized in Table 1. The median age was 60 years (IQR 56–64 years), and 76.8% were men. The most common blood types were O (45.3%) and A (36.3%). The majority of patients were listed in region 5 (52.3%) with 26.8% listed in region 9 and 20.9% listed in region 1. At the time of listing with MELD exception, the median laboratory MELD-Na score was 10 (IQR 8–14). The median Child-Pugh score was 7, and 44.2% of patients were classified as Child class A (5–6), 41.8% were Child class B (7–9), and 14.0% were Child class C (≥10). The median AFP was 11 ng/mL (IQR 5–43), 62.9% had AFP <20 ng/mL, and 2.6% had AFP >1000 ng/mL in 2.6%. Based on tumor burden, 49.5% had a single HCC of 20–3 cm, 23.8% had a single lesion of 3.1–5 cm, and 26.7% had multiple lesions. The majority of patients (77.6%) underwent at least 1 LRT after HCC diagnosis. Transarterial chemoembolization was the most common modality for first LRT.

3.2 | Outcomes while on the waitlist

Of the 2052 patients in the cohort, 1104 (53.9%) underwent LT with a median waiting time of 11.7 months (IQR 6.3–16.0 months). Cumulative probabilities of LT by competing risks analysis were 29.8% (95% CI 27.8–31.9) within 12 months and 63.6% (95% CI 61.2–65.8) within 24 months (Figure 1). Dropout due to tumor progression, being too sick for LT, or death while on the waitlist was observed in 507 (24.7%) with a median time from MELD exception to dropout of 7.4 months (IQR 3.7–12.9 months). Cumulative probabilities of dropout were 10.2% (95% CI 9.0%−11.6%) within 6 months, 18.3% (95% CI 16.6% −20.0%) within 12 months, and 27.0% (95% CI 24.9%−29.1%) within 24 months (Figure 1).

3.3 | Factors associated with dropout

In univariate analysis, risk of dropout was associated with liver disease–related covariates MELD-Na at listing and Child class (Table 2). The 1-year cumulative incidence of dropout for patients with MELD-Na < 15 was 13.4% (95% CI 11.7%−15.3%) vs 29.7% (95% CI 26.0%−33.5%) for those with MELD-Na ≥ 15 ($P < .001$) (Figure 2A). The 1-year cumulative incidence of dropout for Child A patients was 10.7% (95% CI 8.7%−12.9%) compared with 20.6% (95% CI 17.9%−23.5%) for Child B patients and 36.1% (95% CI 30.3%−41.9%) for Child's C patients ($P < .001$) (Figure 2B).

Tumor-related covariates at listing with HCC MELD exception associated with dropout included a solitary tumor of 3.1–5 cm or multiple HCC tumors and AFP level both as a continuous variable and at all cutoffs tested (Table 2). The 1-year cumulative incidence of dropout for patients with a single tumor of 2–3 cm at listing was 14.8% (95% CI 12.6% −17.1%) vs 21.7% (95% CI 19.1%−24.3%) for those with a single tumor of 3.1–5 cm or multiple tumors ($P < .001$) (Figure 2C). The 1-year cumulative incidence of dropout with AFP ≤ 20 ng/mL was 15.2% (95% CI 13.2%−17.2%) vs 23.5% (95% CI 20.5%−26.7%) with AFP > 20 at listing ($P < .001$) (Figure 2D). When limiting the analysis only to patients known to receive at least 1 LRT while awaiting LT (n = 1593), the 1-year cumulative incidence of dropout for patients with both a single 2- to 3-cm tumor at listing and AFP ≤ 20 ng/mL (n = 478) was 7.9% (95% CI 5.6%−10.6%) vs 17.5% (95% CI 15.3%−19.9%) for all other patients (n = 1115) not meeting these 2 tumor-related criteria.

When limiting the analysis only to patients with Child B or C disease (n = 1145), the cumulative incidence of dropout within 1 year of listing for those with AFP ≤ 20 ng/mL was 20.0% (95% CI 17.1%−23.0%) compared with 32.4% (95% CI 27.7%−37.1%) for those with AFP > 20 ng/mL ($P < .001$). When stratified by tumor burden, 1-year cumulative incidence of dropout for Child B/C patients with a single tumor of 2–3 cm at listing was 20.4% (95% CI 17.1%−23.9%) vs 28.6% (95% CI 24.7%−32.5%) for those with a single tumor of 3.1–5 cm or multiple tumors ($P = .001$).

In multivariate competing risk regression, MELD-Na ≥ 15 (HR 1.40 vs MELD-Na < 15, 95% CI 1.10–1.76, $P = .005$) as well as both Child B (HR 1.62 vs Child A, 95% CI 1.30–2.00, $P < .001$) and Child C cirrhosis (HR 2.33 vs Child A, 95% CI 1.68–3.23, $P < .001$) were predictive of dropout. Multiple tumors or a solitary 3.1- to 5-cm tumor (HR 1.46 vs 1 tumor of 2–3 cm, 95% CI 1.22–1.74, $P < .001$) and AFP > 20 ng/mL (HR 1.63 vs AFP ≤ 20, 95% CI 1.36–1.94, $P < .001$) were also significant predictors of dropout (Table 3). The C-statistic for risk of dropout using these 4 predictors in a Cox proportional hazards regression model was 0.69.

3.4 | Subgroup with a low risk of dropout

The 4 listing variables significantly associated with a lower risk of waitlist dropout included MELD-Na < 15, Child class A, single 2- to 3-cm lesion, and AFP ≤ 20 ng/mL. Of the 2052 patients in the study cohort, a subgroup of 245 (11.9%) patients met these 4 criteria. This low-risk subgroup had estimated 1- and 2-year probabilities of dropout of 5.5% and 12.4%, respectively, compared with 20.0% and 29.0% for all other patients ($P < .001$) (Figure 3).

Within blood group O (longest waitlist time), those meeting the same 4 criteria (n = 113) had an even lower 1-year cumulative probability of dropout of 2.8% vs 21.1% for all other blood group O patients (n = 816) ($P < .001$).

Clinical characteristics, receipt of LRT, and histopathologic characteristics were compared between the subgroup with a low risk of dropout vs all other patients (Table 4). While listing age was similar ($P = .31$), the low-risk group had a lower percentage of white and Hispanic patients and patients with hepatitis C virus (HCV) infection and a higher percentage of Asian patients and patients with hepatitis B virus (HBV) infection (all $P < .001$). The subgroup with a low risk of dropout was also significantly more likely to receive LRT (86.5% vs 76.4%, $P < .001$) while awaiting LT. One-year cumulative incidence of dropout in the low-risk subgroup was 4.9% for those receiving LRT (n = 212) compared with 9.9% for those not receiving LRT (n = 33) ($P = .20$). Patients in the low risk of dropout group were more likely to have complete tumor necrosis on explant (35.5% vs 24.9%, $P = .01$) and less likely to have explant tumor burden outside of Milan criteria (9.9% vs 17.7%, $P = .03$). Patients in the low-risk group were also more likely to have well-differentiated tumor grade (38.6% vs 29.8%, $P = .01$).

Intention-to-treat survival from listing with HCC MELD exception for the entire cohort was 80.4% (95% CI 78.5%−82.1%) at 1 year and 63.6% (95% CI 61.0%−66.0%) at 3 years. Intention-to-treat survival at 1 and 3 years from listing in patients meeting all 4 low-risk criteria was 94.0% and 78.8%, respectively, compared with 78.5% to 61.4% for all other patients ($P < .001$). Median post-LT follow-up time was 1.4 years (IQR 0.8–2.6 years). Post-LT survival at 3 years was 84.6% in low risk of dropout patients compared with 82.7% for all other patients ($P = .28$). Cumulative probability of post-LT recurrence at 3 years was 4.1% for the low-risk group compared with 7.6% for all others ($P = .30$).

3.5 | Validation cohort: post-2015 HCC MELD exception era

We performed a post-hoc analysis that identified a validation cohort of 2192 subjects from all 11 UNOS regions initially listed for LT with HCC MELD exception from October 2015 to October 2016. Of these subjects, 367 (16.7%) were at low risk of dropout as defined by our current analysis. The cumulative incidence of dropout for the low-risk group was 5.6% (95% CI 3.6%−8.4%) at 1 year and 9.3% (95% CI 6.2%−13.2%) at 2 years of receiving HCC exception, respectively, vs 17.9% (95% CI 16.1%−19.7%) and 23.7% (95% CI 21.6% −25.8%) within 1 and 2 years of HCC exception, respectively, for all other patients ($P < .001$). The C-statistic was 0.69 for the validation cohort for the multivariable dropout model.

4 | DISCUSSION

Until recently, patients with HCC were given an unfair advantage in the access to LT compared with patients without HCC across most regions in the United States.[13] To narrow this gap to allow for more equitable access to LT for patients with HCC and patients without HCC,[25] a mandatory delay of 6 months for patients with HCC before granting listing priority and a cap of 34 points with MELD exception were implemented in October 2015.[21] A major remaining concern is that not all patients with HCC derive the same LT survival

benefit as patients without HCC,[8] pertaining to the fact that other potentially curative tumor-directed therapies are available to many patients with HCC. This issue is further compounded by the "one size (and number) fits all" mentality for liver allocation, granting equal listing priority to all patients with T2 HCC.[26] This approach has remained unchanged for >15 years, despite ample evidence that the risk of dropout varies not only by wait time region[4,19,27] but also by tumor-related features (eg, tumor burden, AFP, response to LRT)[11–13,18,28,29] and disease severity based on MELD score.[11–13]

Several systems have previously been proposed to give increased priority to listed patients with HCC based on risk factors for waitlist dropout. Freeman et al[11] formulated a continuous score based on the calculated MELD, AFP, and maximal tumor size. Toso et al[12] proposed a common waitlist for both patients with HCC and patients without HCC with priority for patients with HCC given based on age, calculated MELD, tumor size and number, AFP, and etiology of liver disease. Alver et al[14] developed a $MELD_{EQ}$ score consisting of calculated MELD, AFP, and tumor size and number plus additional points allocated for wait time beyond 6 months. A major concern in adopting any of these proposals that gives additional priority to patients with HCC with a high dropout risk (ie, increased urgency) is that such an approach would also select for more aggressive tumors for LT with potentially a higher rate of post-LT HCC recurrence and worse survival (ie, reduced utility).[16,17] While the debate about how best to "square the circle" with regard to organ allocation for patients with HCC at high risk for waitlist dropout is ongoing,[30] another approach to improve LT survival benefit is to reduce LT priority for patients with HCC at low risk for waitlist dropout (ie, reduced urgency). We have previously identified a subgroup of patients listed for LT at our center who had a very low cumulative probability of waitlist dropout of only 1.6% at 2 years if they met all 3 criteria—a single 2- to 3-cm tumor, AFP < 20 ng/mL after the first LRT, and a complete response to first LRT. We concluded that this subgroup at low risk for waitlist dropout did not warrant the same listing priority as others with T2 HCC.[18]

To expand on our work, we report in this study the results of our analysis on waitlist dropout in > 2000 patients with T2 HCC receiving priority listing for LT from 2011 to 2014 in long wait time UNOS regions. We observed dropout rates of 18% at 1 year and 27% at 2 years from listing and identified 4 variables associated with a low risk of waitlist dropout: 2 tumor-related (single tumor 2–3 cm and AFP ≤ 20 ng/mL) variable and 2 related to liver function assessments (Child A and MELD-Na < 15). The subgroup meeting all 4 criteria had a 1-year probability of dropout of only 5.5% vs 20.0% for the remainder of the T2 HCC cohort. Given that blood type was strongly associated with wait time and the MELD score at the time of LT,[31] we then restricted the analysis to patients with blood group O (longest expected wait time) who accounted for 45% of the overall cohort. We found that the blood type O patients meeting these same 4 criteria had an even lower 1-year probability of dropout of 2.8% vs 21% for all other blood types, further reinforcing the impact of these risk factors. We also performed a post-hoc analysis with a validation cohort of nearly 2200 additional patients with HCC from all 11 UNOS regions listed with MELD exception after the UNOS HCC policy changes in October 2015. We found that patients with HCC in this more recent validation cohort meeting these same 4 low-risk criteria continued to have excellent waitlist outcomes, with a cumulative dropout rate of <10% at 2 years from listing.

These 4 variables, which are all easily assessed at the time of LT listing, help identify a subgroup of patients who do not derive immediate benefit from LT. Using these low risk of dropout variables in the MESIAH score[32] results in an estimated 3-year intention to treat survival of ~75%, again suggesting that low-risk patients have decreased urgency for LT. Our findings also nicely coincide with multiple recent studies suggesting that patients with HCC who have a decreased tumor burden, excellent response to LRT, and preserved liver function (ie, Child A, low MELD) have reduced LT survival benefit.[33–36] For example, Lai et al[33] studied > 2100 patients and found that MELD score <13, tumor burden within Milan criteria, and complete response to LRT were all factors that decreased the survival benefit of LT. Consistent with this notion, explant histopathologic analysis of the present "low risk of dropout" subgroup revealed significantly fewer patients beyond Milan criteria (10% vs 18%), a higher proportion with complete tumor necrosis (36% vs 25%), and well-differentiated histologic tumor grade (39% vs 30%). Reducing priority for this low-risk subgroup would be an important step forward to allow for more timely access to LT for other patients with HCC as well as patients without HCC who are in more urgent need for LT.

It is important to note that the 1-year dropout rate of 5.5% for the subgroup with a low risk of dropout was higher than the 1-year dropout rate of 1.3% in the low-risk group observed in our previous single-center study.[18] Additionally, in the previous study, complete tumor necrosis on explant was found in 61% of the low-risk subgroup compared with 36% in the present study. There are several potential reasons for these differences. First, our previous single-center study included a higher proportion of patients with HBV infection, who may as a group have less aggressive tumors than those associated with other etiologies of liver disease.[37,38] The second reason for the differences in the 2 studies may be related to the application of LRT and assessment of treatment response. While the specifics of LRT in terms of the number of treatments received and response to LRT were well characterized in our previous study,[18] data on LRT are limited in the UNOS database. In our previous study, complete radiographic response to first LRT was 1 of the 3 factors defining the criteria for a low risk for dropout. Stratified based on modified RECIST criteria,[39,40] the 1-year cumulative probability of dropout was 9% for complete response, 40% for stable disease, and 85% for progressive disease.[18] Information on the response to LRT was not available in the UNOS database and thus could not be used to further risk stratify listed patients with HCC. Additionally, 22% of patients in the present study were coded in the UNOS database as not receiving any LRT, whereas nearly all the patients in our previous study underwent at least 1 LRT, potentially accounting for the difference in dropout rates in the 2 "low risk of dropout" groups. When we stratified the present analysis to include only patients known to receive at least 1 LRT, dropout at 1 year from listing for patients with both low-risk tumor features (single 2- to 3-cm tumor and AFP ≤ 20) was 8%, vs 18% in all others. This finding suggests that patients with low-risk tumor features are likely to have objective response to LRT, although this could not be confirmed given the limitations of the UNOS database.

While complete radiographic response to LRT clearly decreases waitlist dropout, the benefit of achieving complete response is further supported by published reports showing that LT recipients with complete necrosis on explant without residual viable tumor have a very low risk of HCC recurrence.[41,42] Given these findings, it could be argued that compensated patients with complete pathologic response may not derive significant benefit from LT in the

first place. In the present study, 28% of patients who underwent at least 1 LRT had complete tumor necrosis on explant. This rate of complete response on explant is lower than the 42% in our previous single-enter study[18] but similar to 25% complete response rate in the report by Agopian et al. that included 501 patients who received LRT before LT.[41] Because only a minority of patients undergoing LRT achieve complete pathologic response on explant, we believe that patients with HCC at low risk of dropout should still be given some additional priority for LT but not to the same extent as other patients with HCC. Current proposals are for patients with HCC to be awarded a fixed median MELD at transplant minus 3 (MMAT-3) after a 6-month mandatory waiting period. We would recommend a reduction in assigned priority for the subgroup at low risk of dropout, such as with MMAT-5. In the event of HCC recurrence in this subgroup while on the waitlist, we propose increasing their MELD exception back to MMAT-3, though certainly these proposals require further validation.

The strengths of the present study include the large sample size of >2000 patients with T2 HCC and the use of explant pathologic data that became available since April 2012 to compare actual tumor characteristics in the low risk for dropout subgroup vs all other patients with T2 HCC. There are also a number of limitations of the present study, including the lack of information on response to LRT in the UNOS database. Nevertheless, relying on response to LRT to determine LT priority is problematic as LRT is often applied after a patient has been listed for LT. Implementing a policy for listing priority based on response to LRT would be difficult logistically. Furthermore, a patient with a T2 HCC may be granted MELD exception but could then be subjected to a reduction in MELD exception points based on a favorable response to LRT. If there are already inaccuracies in reporting tumor size by LT centers for patients meeting conventional LT criteria,[43] then there is little doubt that bias in reporting radiographic response to LRT will emerge as well. The focus of the current study is to identify a subgroup at low risk for dropout, but there are still problems concerning the rest of the cohort in that they represent a highly heterogeneous population with a wide range of dropout risks but receive the same priority for LT. Finally, we attempted to create a dynamic model that incorporated changes over time in low-risk patients with HCC awaiting LT but were limited because some characteristics to define the low-risk group are not available longitudinally in the UNOS database, including Child-Pugh components and sodium to calculate MELD-Na. We tested a dynamic model including the following clinical characteristics: single lesion of 2–3 cm, AFP ≤20, and MELD (not MELD-Na) < 15 at (1) initial and second exception applications and (2) baseline, second, and third exception applications, but overall there was no improvement in the model with the addition of data from multiple time points rather than relying on baseline listing variables alone.

In summary, the present study suggests that a combination of tumor characteristics (single lesion of 2–3 cm and AFP ≤ 20 ng/mL) and liver function assessments (Child A cirrhosis and MELD-Na < 15) identifies a subgroup with a low risk of waitlist dropout. These results may have important implications for the organ allocation policy for HCC. Patients fulfilling all 4 criteria are expected to have a very low risk for waitlist dropout and do not appear to derive immediate LT benefit. These patients, in our opinion, should be given reduced listing

priority compared with other patients with T2 HCC to optimize resource utilization and transplant benefits.

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Abbreviations:

AFP	α-fetoprotein
CI	confidence interval
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HR	hazard ratio
LRT	local regional therapy
LT	liver transplant
MELD	Model for End-Stage Liver Disease
MMAT	median MELD at transplant
NAFLD	nonalcoholic fatty liver disease
UNOS	United Network for Organ Sharing

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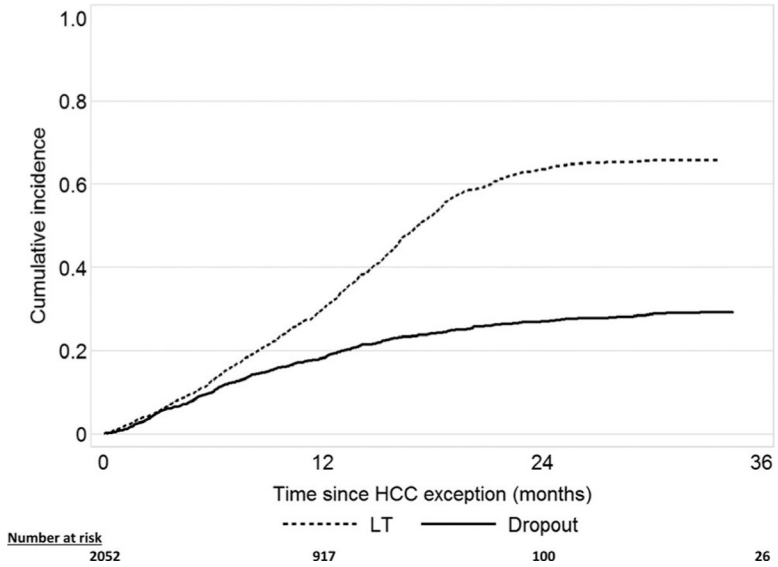

FIGURE 1.

Cumulative incidence of liver transplant (LT) and waitlist dropout due to tumor progression, being too sick to undergo LT, or death

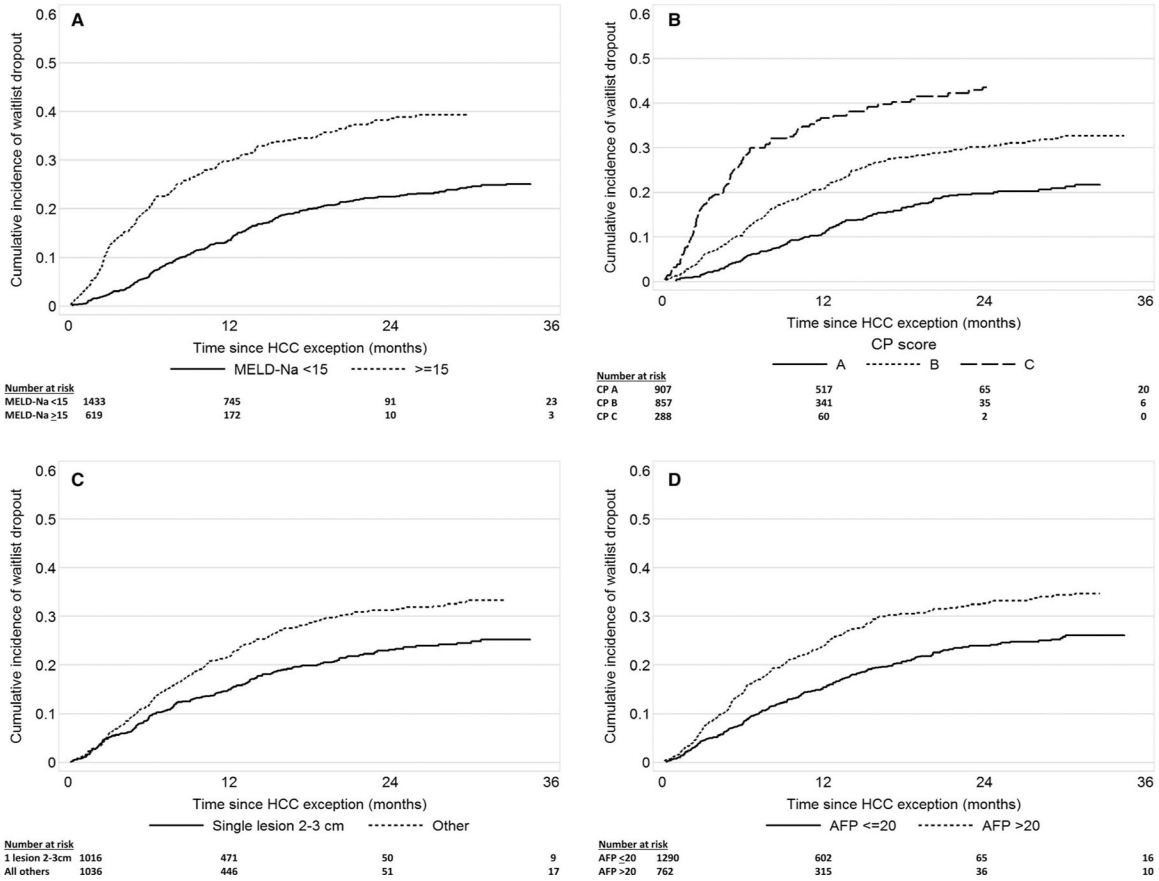

FIGURE 2.

Cumulative incidence of waitlist dropout due to tumor progression, being too sick to undergo livertransplant, or death by listing characteristics. A, MELD-Na < 15 vs ≥ 15. B, Child-Pugh class. C, Tumor size. D, α-Fetoprotein ≤20 vs >20 ng/mL

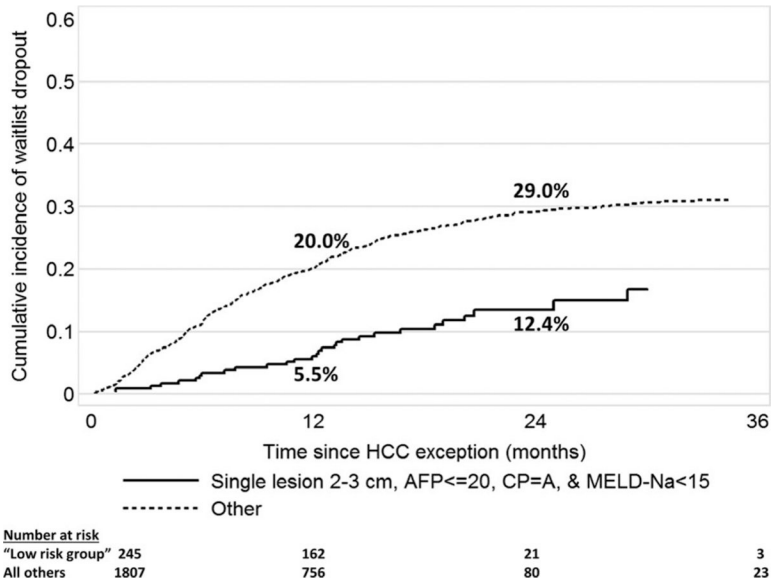

FIGURE 3.

Cumulative incidence of waitlist dropout with low-risk group meeting all of the following at listing: MELD-Na < 15, Child-Pugh class A, single tumor 2–3 cm, and AFP ≤20 ng/mL

TABLE 1

Baseline clinical characteristics of the cohort (N = 2052)

Age, y (IQR)	60 (56–64)
Male, n (%)	1576 (76.8)
Race/ethnicity, n (%)	
White	1176 (57.3)
Hispanic	489 (23.8)
Asian	229 (11.2)
Black	131 (6.4)
Other	27 (1.3)
Etiology of liver disease, n (%)	
Hepatitis C virus	1269 (61.8)
Alcohol	202 (9.8)
Hepatitis B virus	131(6.4)
Nonalcoholic fatty liver disease	129 (6.3)
Autoimmune/cholestatic liver disease	53 (2.6)
Others	268 (13.1)
Body mass index, kg/m^2 (IQR)	27.8 (24.9–31.6)
MELD (IQR)	10 (8–14)
Child class, n (%)	
A	907 (44.2)
B	857 (41.8)
C	288 (14.0)
Listing AFP, ng/mL (%)	
≤20	1290 (62.9)
21–100	428 (20.9)
101–1000	280 (13.6)
>1000	54 (2.6)
Median (IQR)	11 (5–43)
Initial tumor burden, n (%)	
1 lesion 2–3 cm	1016 (49.5)
1 lesion 3.1–5 cm	488 (23.8)
2 lesions	403 (19.6)
3 lesions	145 (7.1)
Received local regional therapy, n (%)	1593 (77.6)

[a] Includes autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis.

TABLE 2

Univariate analysis of predictors of waitlist dropout due to tumor progression or death by competing risks

Predictor	Univariate HR (95% CI)	*P*-value
Patient characteristics at listing with MELD exception		
Age (per year)	1.01 (0.99–1.02)	.07
Female (vs male)	1.01 (0.89–1.24)	.89
Body mass index (kg/m^2)		
<18.5 (vs 18.5–24.9)	1.07 (0.30–3.82)	.92
25.0–29.9 (vs 18.5–24.9)	0.85 (0.68–1.06)	.16
30.0–34.9 (vs 18.5–24.9)	0.90 (0.70–1.15)	.40
≥35 (vs 18.5–24.9)	1.18 (0.88–1.57)	.26
MELD-Na (per point)	1.07 (1.05–1.08)	<.001
MELD-Na ≥ 15 (vs < 15)	1.99 (1.67–2.38)	<.001
Child C (vs A)	3.36 (2.54–4.43)	<.001
Child B (vs A)	1.92 (1.54–2.39)	<.001
Tumor characteristics at listing with MELD exception		
1 lesion 3.1–5 cm (vs 1 lesion 2–3 cm)	1.43 (1.15–1.78)	.001
2 lesions (vs 1 lesion 2–3 cm)	1.33 (1.06–1.66)	.01
3 lesions (vs 1 lesion 2–3 cm)	1.40 (1.01–1.94)	.04
AFP > 10 vs ≤ 10 ng/mL	1.33 (1.11–1.58)	<.001
AFP > 20 vs ≤ 20 ng/mL	1.50 (1.26–1.79)	<.001
AFP > 100 vs ≤ 100 ng/mL	1.66 (1.35–2.05)	<.001

TABLE 3

Multivariate analysis of predictors of waitlist dropout due to tumor progression or death by competing risks (n = 2052)

Predictor	Multivariate HR (95% Cl)	*P*-value
MELD-Na ≥ 15 (vs < 15)	1.40 (1.10–1.76)	.005
Child C (vs A)	2.33 (1.68–3.23)	<.001
Child B (vs A)	1.62 (1.30–2.00)	<.001
1 lesion 3.1–5 cm or 2–3 lesions (vs 1 lesion 2–3 cm)	1.46 (1.22–1.74)	<.001
AFP > 20ng/mL (vs ≤ 20)	1.63 (1.36–1.94)	<.001

TABLE 4

Waitlist and explant characteristics between the low risk of dropout group and all other patients

Listing characteristic	**Low risk of dropout n = 245**	**All others n = 1807**	***P*-value**
Ethnicity, n (%)			<.001
White	152 (62.0)	1024 (57.3)	
Hispanic	40 (16.3)	449 (24.8)	
Asian	44 (18.0)	185 (10.2)	
Black	8 (3.3)	123 (6.8)	
Other	1 (0.4)	26 (1.4)	
Disease etiology, n (%)			<.001
HCV infection	126 (51.4)	1143 (63.3)	
Alcohol	18 (7.3)	184 (10.2)	
HBV infection	34 (13.9)	97 (5.4)	
NAFLD	16 (6.5)	113 (6.3)	
Autoimmune	8 (3.3)	45 (2.5)	
Other	43 (17.6)	225 (12.5)	
Received LRT, n (%)			<.001
Yes	212 (86.5)	1381 (76.4)	
No	33 (13.5)	426 (23.6)	
Explant characteristics	**N = 122**	**N = 724**	
Explant path stage, n (%)			
No residual tumor	43 (35.5)	180 (24.9)	.01
Within Milan criteria	67 (54.9)	416 (57.5)	
Beyond Milan criteria	12 (9.9)	128 (17.7)	.03
Microvascular invasion, n (%)	14 (11.6)	88 (12.2)	.84
Histologic grade, n (%)			.01
Well differentiated	27 (38.6)	142 (29.8)	
Moderately differentiated	36 (51.4)	323 (61.3)	
Poorly differentiated	7 (10.0)	51 (9.9)	

[a] Includes autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis.

[b] Explant pathology data available in patients who underwent liver transplant since April 2012.

[c] Missing 3 observations.

[d] Of those with viable tumor on explant.