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A Novel Model Measuring the Harm of Transplanting Hepatocellular Carcinoma Exceeding Milan Criteria

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No empirical studies have defined the posttransplant survival that would justify expansion of the Milan criteria for liver transplantation of hepatocellular carcinoma. We created a Markov model comparing the survival benefit of transplantation for a patient with >Milan HCC, versus the harm caused to other patients on the waiting list.

In the base-case analysis, the strategy of transplanting the patient with >Milan HCC resulted in a 44% increased risk of death and a utility loss of 3 quality-adjusted years of life across the pre- and posttransplant periods for a nationally representative cohort of patients on the waiting list. This harm outweighed the benefit of transplantation for a patient with >Milan HCC having a 5-year posttransplant survival of less than 61%. This survival threshold was most sensitive to geographic variations in organ shortage, with the threshold varying from 25% (Region 3) to >72% (Regions 1, 5, 7 and 9).

In conclusion, expansion of the Milan criteria will require demonstrating high survival rates for the newly eligible patients—approximately 61% at 5 years after transplantation. In regions with less severe organ shortage, a more aggressive approach to transplanting these patients may be justified.

Key words: Ethics, hepatocellular carcinoma, liver transplantation, public policy

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Introduction

Early experience with liver transplantation for hepatocellular carcinoma (HCC) was disappointing, with many patients developing early tumor recurrence (1). Then in 1996, Mazaferro et al. (2) showed that when patients were carefully selected, transplantation of early HCC was associated with a 75% survival after 4 years (3). This led to the development of the Milan criteria for transplant eligibility: a single lesion <5 cm or three lesions each <3 cm, without gross vascular invasion or metastatic disease (4). When these criteria are applied, posttransplant survival is similar to patients transplanted without HCC (2). In the United States, patients with solitary HCC from 2 to 5 cm or 2–3 lesions <3 cm receive extra priority model for end-stage liver disease (MELD) points for transplantation, increasing their likelihood of receiving an organ (5).

Unfortunately, up to 70% of patients with HCC are diagnosed at advanced stages of the disease (6), and are not suitable candidates for transplantation by Milan criteria. For most of these patients, the currently available treatment options are associated with little chance of cure (5,7). Furthermore, the incidence of HCC in the United States is increasing (8). This has led some authors to call for awarding priority MELD points to patients with tumors exceeding Milan criteria. Yao et al. (9) have proposed a new set of criteria, the University of California at San Francisco (UCSF) criteria: solitary tumor 6.5 cm or less, no more than three lesions with the largest being 4.5 cm or less, and a total tumor diameter 8 cm or less, without gross vascular invasion.

Given the shortage of organs for transplantation, the question of whether to award priority points to patients with HCC exceeding Milan but within UCSF criteria (Milan-UCSF+) is controversial (10,11). The 5-year posttransplant survival for patients with Milan-UCSF+ HCC has been reported as anywhere from 38% to 93% (see Table 1). Such variability across studies may be due to differential patient selection and small numbers of patients in each study. Further research is needed to refine these estimates, but the question will still remain: what is the lowest acceptable posttransplant survival at which transplantation with standard quality organs would still be justified? In other words, what proportion of patients would have to survive 5 years after transplantation in order for transplanting these patients to be a good use of scarce organs? No studies have

Table 1: Five-year survival after liver transplantation for patients with HCC exceeding Milan criteria

Author, year	Number of patients	Etiology of liver disease	HCC staging	Staging method	Neoadjuvant therapy	5-year survival	Ref.
Marrero 2007	346	57% HCV 14% HBV 7% Alcohol 22% Other	Milan-UCSF+	Radiologic	Variable	38%	(38)
Decaens 2004	44	38% HCV 20% HBV 32% Alcohol 10% Other	Milan-UCSF+	Radiologic	Yes	46%	(39)
Onaca 2007	24	49% HCV 13% HBV 10% Alcohol 28% Other	1 tumor 5–6 cm	Pathologic	Variable	55%	(25)
Roayaie 2002	43	49% HCV 23% HBV 14% Alcohol 14% Other	1 tumor 5–7 cm	Pathologic	Yes	55%	(40)
Duffy 2007	185	55% HCV 17% HBV 13% Alcohol 15% Other	Milan-UCSF+	Radiologic	Yes	64%	(41)
Yao 2001	18	50% HCV 19% HBV 9% Alcohol 22% Other	Milan-UCSF+	Pathologic	Yes	74%	(42)
Yao 2006	32	Not listed	Milan-UCSF+	Radiologic	Yes	93%	(43)

addressed this question in an empirical manner. We propose that this threshold can be estimated by balancing the survival benefit and gains in life expectancy from transplantation for the Milan-UCSF+ HCC patient, against the harm caused by delaying transplantation for the other patients on the waiting list. How much harm would be caused by expanding the Milan criteria? The aim of this study was to examine how transplantation of a patient with Milan-UCSF+ HCC affects survival of patients on the waiting list across the pre- and posttransplant periods (overall survival). Using this approach we then determined the 5-year post-transplant survival threshold, below which transplantation for patients with HCC is no longer justified.

Methods

Definition of survival benefit and harm

The survival benefit of liver transplantation for the patient with Milan-UCSF+HCC can be calculated by subtracting the area under the survival curve without transplantation from the area under the survival curve with transplantation (12). The harm caused to others on the waiting list, if the Milan-UCSF+HCC patient is transplanted with a standard quality organ, depends on the additional time these patients must wait for a transplant to occur and their rate of death while waiting.

From a utilitarian perspective, optimal organ allocation will maximize the life expectancy of the entire cohort of patients with benign and malignant liver disease. Thus, if the benefit to the Milan-UCSF+HCC patient is greater than the cumulative harm to the rest of the transplant waiting list, then the HCC patient should receive the transplant.

Decision model

We constructed a Markov model, which examines the decision whether or not to transplant a patient with Milan-UCSF+ HCC, beginning just prior to this patient receiving the organ. The impact of this decision on the Milan-UCSF+ HCC patient and other patients on the waiting list was weighted as follows:

$$\text{Milan} - \text{UCSF} + \text{HCC} = 1/(N + 1),$$

$$\text{Other patients} = 1 - 1/(N + 1),$$

where N = the number of patients on the waiting list before the Milan-UCSF+ HCC patient is listed. For example, if there were three other patients on the list then the weighting would be:

$$\text{Milan} - \text{UCSF} + \text{HCC} = 1/(3 + 1) = 0.25,$$

$$\text{Other patients} = 1 - 1/(3 + 1) = 0.75.$$

Thus, the cumulative harm to patients on the waiting list is proportional to the number of patients on the list.

Study endpoints

Both the Milan-UCSF+ patient and the waiting list patients were followed for 10 years in the model. Thus the survival benefit for the Milan-UCSF+ patient and the harm to the waiting list patients were measured over the 10 years, which included the pre- and posttransplant periods. This time horizon was chosen in an effort to balance the need for allocation policies, which maximize long-term survival and the limited long-term survival data for patients with Milan-UCSF+ HCC.

Model assumptions

Prior to the beginning of the model, the patient with Milan-UCSF+ HCC was assumed to have received an increase in MELD exception points every 3 months, as is current practice with patients meeting Milan criteria (13). The model begins once the Milan-UCSF+ HCC patient is first in line for the next available organ. If this patient is transplanted, then the other patients on the waiting list all wait for one extra organ arrival cycle and are subjected to the extra risk of death during this time period. This scenario is displayed in Figure 1. The increase in harm caused by transplanting the Milan-UCSF+ HCC patient therefore depends on the number of patients on the waiting list, their waiting list and posttransplant mortality rates and the organ arrival rate.

Because the death rates and transplantation rates vary substantially by MELD scores, the waiting list patients were divided into subgroups with MELD scores of 11–20, 21–30 and >30. Separate Markov processes were developed for each of these groups as previously described (14), as well as for patients with HCC within Milan criteria who currently receive automatic MELD upgrades to 22 and extra points every 3 months thereafter (13). Patients with MELD scores <11 were excluded, since their mortality rates and transplant rates are negligible (15). Patients with MELD exceptions other than HCC were not explicitly modeled, since they represent a small and heterogeneous group for whom limited outcome data is available (16).

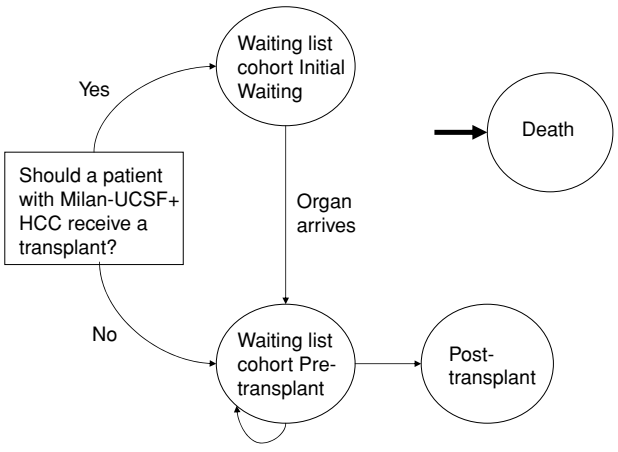

Figure 1: Influence diagram describing the structure of the model. If the patient with hepatocellular carcinoma exceeding Milan criteria but within University of California San Francisco criteria (Milan-UCSF+ HCC) receives a transplant, all the patients in the waiting list cohort start off in an initial waiting state and progress to the pretransplant state once the first organ arrives. If the Milan-UCSF+ patient does not receive a transplant, then all the waiting list patients start off in the pretransplant state. The solid black arrow indicates that death can occur from any state.

The Markov cycle length was 1 day, and survival was adjusted for quality of life based on utilities as described below. Discounting of quality-adjusted life expectancy was performed at a rate of 3% per year. All analyses were performed using TreAge Pro v2006 1.2 (TreAge Software, Williamstown, MA).

Data sources

National averages for waiting list size, organ arrival rates, mortality rates on the list, dropout rates, time to transplantation and posttransplant survival were obtained from the most recent report of the Organ Procurement and Transplantation Network (www.optn.org) (17). Table 2 displays all of the variables used in the model, the base-case values, ranges and sources of data. Annual probabilities were converted to daily probabilities using a linear decay function (18).

Waiting list variables

The waiting list size and organ arrival rate in the base-case analysis was the national average per blood group and donation service area (DSA), excluding patients with MELD scores <11. Dropout from the waiting list was modeled separately for HCC patients within Milan criteria, since most deaths occur after waiting list removal. The median time-to-transplant was used to calculate the probability of getting a transplant rather than the median waiting times, since the latter excludes time spent on the list as inactive status (17). The same posttransplant survival rates were used for all waiting list patients, as these do not vary substantially by MELD score (12) and it is unclear whether MELD predicts posttransplant survival over the long term (19). All calculated variables were similar to those used in previously published models of the liver transplant organ allocation system (14,20). For the distribution of MELD scores on the waiting list, registration MELD scores were used in the base-case analysis (12) and a cross-section of the average waiting list (21) was analyzed on sensitivity analysis.

Milan-UCSF+ HCC variables

In the scenario where the patient with Milan-UCSF+ HCC does not receive a transplant, we assumed that patient would receive standard care including transarterial chemoembolization (TACE), with 5-year survival rates of 10% in the base-case analysis (7,22–24). In the scenario where the patient with Milan-UCSF+HCC receives a transplant, the 5-year survival was varied as the primary endpoint of the study. Since most HCC recurrences occur within the first 2 years (25), we assumed a low mortality rate between years 5 and 10 posttransplantation of 2% per year.

Utilities

Quality of life for pre- and posttransplant patients was determined by a systematic review of the literature using the search algorithm (quality of life OR utilities) AND liver transplantation (n = 390). Articles prior to a 1998 systematic review (26) were excluded, yielding 210 abstracts, which were reviewed. Studies were selected for data abstraction if they used utility assessment techniques and determined quality of life pre- and posttransplantation within the same patient population (n = 3 studies) (27–29). Since no studies have directly compared the quality of life for Milan-UCSF+HCC patients versus other patients on the waiting list, they were assumed to be equivalent for the base-case analysis. In the sensitivity analysis, we analyzed a range of plausible assumptions based on the quality of life literature in patients with cirrhosis (27–29).

Model calibration and sensitivity analysis

We examined model predictions for transplant rates and survival in order to ensure the model structure was calibrated and aligned with expected rates. This involved comparison of the 90-day outcomes for patients in the model, with the 90-day outcomes of a waiting list cohort reported by the OPTN (17). The small numbers of patients in the OPTN cohort limited reliable comparison for all but the MELD 11–20 group (n = 6369), among whom 90%

Table 2: Variables utilized in constructing the model

Variable	Base-case values	Range	Source
Waiting list size (N)[1]	58	11–86	(17)
Organs arriving per year[1]	30	18–38	(17)
Waitlist mortality (deaths/1000 patient-years) MELD 11–20	135	100–150	(17)
Waitlist mortality (deaths/1000 patient-years) MELD 21–30	693	550–900	(17)
Waitlist mortality (deaths/1000 patient-years) MELD >30	3500	2992–5000	(17)
Waitlist mortality (deaths/1000 patient-years) HCC (within Milan)	237	150–300	(17)
HCC (within Milan) death or dropout (probability/year)	31%	20–50%	(44–46)
HCC (within Milan) death after dropout (probability/year)	46%	20–71%	(45,47)
Median time-to-transplant (days) MELD 11–20	1000	500–1200	(17)
Median time-to-transplant (days) MELD 21–30	100	56–162	(17)
Median time-to-transplant (days) MELD >30	24	12–88	(17)
Median time-to-transplant (days) HCC (within Milan)	90	32–145	(17)
Proportion of list with MELD 11–20[2]	63%	55–70%	(12,17)
Proportion of list with MELD 21–30	19%	10–20%	(12,17)
Proportion of list with MELD >30	8%	5–10%	(12, 17)
Proportion of list with HCC (within Milan)	10%	5–15%	(17,44)
Posttransplant survival waiting list patients (probability/5 years)	72%	70–75%	(32)
Pretransplant quality-of-life utility	0.53	0.51–0.61	(27–29)
Posttransplant quality-of-life utility	0.62	0.61–0.63	(27–29)
Pretransplant quality-of-life utility for patients with Milan-UCSF+ HCC	0.53	0.45–0.6	(27–29)
5-year survival of Milan-UCSF+ HCC patients treated by TACE only	20%	1–30%	(7,22–24)
Time horizon (years)	10	5–15	N/A

[1]Per donation service area and blood group. MELD = model for end-stage liver disease; HCC = hepatocellular carcinoma; TACE = transarterial chemoembolization; Milan-UCSF+ = patients with HCC beyond Milan criteria but meeting University of California San Francisco criteria.
[2]Proportions are excluding patients with MELD <11.

were still waiting, 6% were transplanted and 4% had died or dropped out after 90 days. This compared well with the model output for the waiting list cohort with MELD 11–20, among whom 90% were still waiting, 5.5% were transplanted and 4.5% had died or dropped out after 90 days, indicating that the model was well calibrated.

The base-case analysis was performed using national averages, and two-way sensitivity analysis was performed comparing the ranges of all variables with the range of possible posttransplant survival for the Milan-UCSF+ HCC patient. Because organ arrival rates at DCAs across the country are correlated with size of the waiting list (15), it is difficult to present and interpret the sensitivity analysis on these variables. Therefore, we captured these variables by repeating the analysis for each region of the country. In some regions the model output led to a survival threshold higher than that of the general transplant population. This is called the 'aggregation problem' of resource allocation, whereby in some circumstances a higher aggregate survival could be achieved by sacrificing a few to save the majority (30). Since public opinion and ethical theory overwhelmingly reject this violation of equity (30,31), we set an upper limit for the survival threshold at 72% at 5 years, which is the average survival for the general transplant population (32). We also repeated the analysis by blood group, another proxy for variations in organ shortage.

Finally, we considered the impact of changes in allocation policy, such as capping the MELD exception points at 30 for patients with Milan-UCSF+ HCC. Such a policy would mean that these patients would never be transplanted ahead of patients with lab MELD scores above 30. This analysis was performed by excluding patients with MELD >30 from the waiting list cohort.

Please refer to our supplemental methods at http://www.blackwell-synergy.com/doi/abs/10.1111/j.1600-6143.2007.02138.x. (publisher's hosting address).

Results

In the base-case analysis, with a waiting list size of 58 per blood group and DSA based upon national averages, the strategy of transplanting the patient with Milan-UCSF+HCC increased the risk of a death occurring among the waiting list cohort by 44%. This higher mortality risk translated into a loss of three quality-adjusted life-years (QALYs) for the entire cohort. The amount of harm varied by region of the country depending on severity of organ shortage, from a 16% mortality risk and 1.1 QALYs lost in Region 3 to a 100% mortality risk and 4.9 QALYs lost in Region 5. While this aggregate harm was substantial, the harm to individual patients was much smaller and varied by MELD score, as shown in Table 3. These harms to the waiting list cohort were offset by the survival benefit of transplantation for a Milan-UCSF+ patient, whose 5-year posttransplant survival exceeded 61%, assuming a 5-year

Table 3: Harm caused to individual patients on the waiting list when the patient with Milan-UCSF+ HCC receives an organ[1]

Patient subgroup	Increase in mortality risk (per patient)	Quality-adjusted days of life lost (per patient)
HCC within Milan	0.4%	10
MELD 11–20	0.1%	3
MELD 21–30	1.1%	27
MELD >30	4.2%	108

[1]Based on national averages for organ arrival rate.

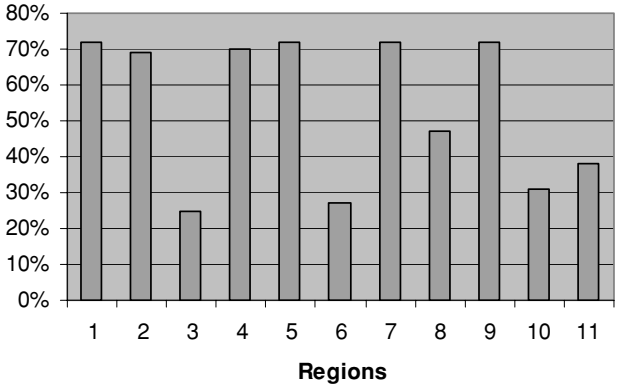

Figure 2: Five-year survival threshold by United Network for Organ Sharing (UNOS) region of the country, below which the benefit of liver transplantation for patients with Milan-UCSF+ HCC is outweighed by the harm caused to other patients.

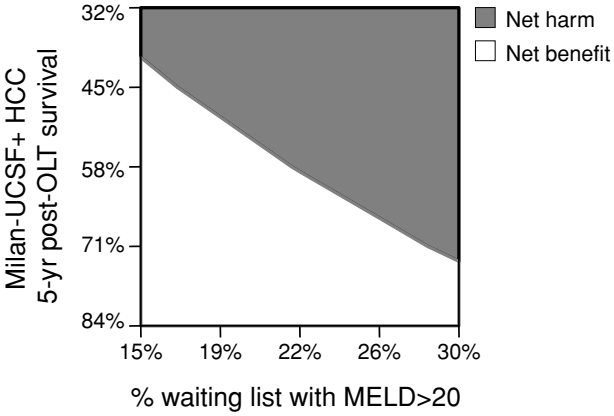

Figure 3: Sensitivity analysis demonstrating the impact of proportion of patients on the waiting list with model for end-stage liver disease (MELD) scores >20, on the 5-year post-transplant survival threshold for patients with Milan-UCSF+ HCC. The survival threshold is the intersection between the black- and white-shaded areas and equals the posttransplant survival at which the benefit of transplantation is outweighed by the harm caused to other patients.

survival with TACE alone of 10%. In other words, expanding Milan criteria would require a 5-year posttransplant survival of 61% in order to outweigh the harm caused to other patients on the waiting list.

On sensitivity analysis, this threshold value for the 5-year posttransplant survival showed significant variability depending on the severity of organ shortage. For example, in the region with the least severe organ shortage (Region 3), a 5-year survival as low as 25% could be permitted before the cumulative harm to the waiting list patients outweighed the survival benefit for the Milan-UCSF+ HCC patient. In the regions with the most severe organ shortage (Regions 1, 5, 7 and 9), a 5-year survival greater than or equal to the general transplant population (72%) was necessary to maintain this balance. Figure 2 shows the survival thresholds for each region of the country. The results were also sensitive to the distribution of MELD scores on the waiting list, another function of geographic variation. When the waiting list was composed of only 15% of patients with MELD scores >20, the 5-year survival threshold for transplanting the Milan-UCSF+HCC patient decreased to 38% as shown in Figure 3. Finally, the results were sensitive to blood group, another proxy for organ shortage. When the waiting list was composed of only blood group O, the survival threshold for transplanting the Milan-UCSF+HCC patient was 68% at 5 years compared with 38% at 5 years when the waiting list was composed of only patients with blood group AB.

The results were fairly robust to uncertainty surrounding the clinical variables which are unaffected by geographic disparities. The 5-year survival of a Milan-UCSF+ HCC patient treated with TACE alone (set at 10% in the base-case analysis) was the most influential in affecting the threshold for 5-year survival, causing the survival threshold for justifying transplantation to vary from 51% to 72%, as shown in Figure 4. Thus, as multimodality treatments for HCC continue to improve, a higher posttransplant survival will be required to justify the harm caused to other patients on the waiting list. Varying the time horizon from 5 to 15 years caused the survival threshold to vary from 72% (time horizon of 5 years) to 54% (time horizon of 15 years). Finally, the uncertainty about quality of life for patients with Milan-UCSF+ HCC resulted in only minor changes in the survival threshold, from 57% to 65% across a range of plausible assumptions. None of the other variables affected the posttransplant survival threshold by more than 5%.

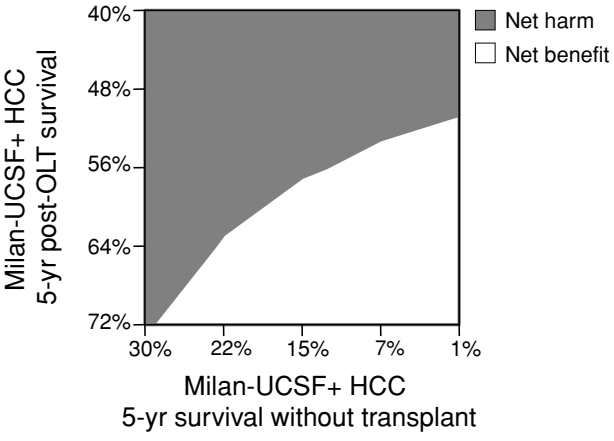

Figure 4: Sensitivity analysis demonstrating the impact of survival with nontransplant therapies (such as transarterial chemoembolization) on the 5-year posttransplant survival threshold for patients with Milan-UCSF+ HCC.

We then analyzed the potential impact of changing UNOS rules so that patients with Milan-UCSF+ HCC would have their MELD exception points capped at 30. When waiting list patients with MELD scores >30 were excluded from the model, the survival threshold for transplanting the Milan-UCSF+ HCC patient dropped substantially to 35% at 5 years.

Discussion

We examined the posttransplant survival needed to justify expanding Milan criteria for transplantation of patients with HCC. While the issue has raised significant debate, to our knowledge this is the first quantitative examination of the tradeoffs between the benefits of transplanting patients with HCC exceeding Milan criteria and the harms incurred by delaying transplantation for other patients on the waiting list. We found that for the average patient with HCC exceeding Milan criteria, a 5-year posttransplant survival of 61% or more would be needed for the benefit of transplantation to be outweighed by the harm caused to other patients on the waiting list. These results fill an important gap in the debate over expanding the Milan criteria for transplanting HCC. Although more research is still needed to improve the prediction of survival of patients with HCC after liver transplantation, this study provides empiric evidence for a survival threshold below which MELD exception points for transplantation should not be awarded.

Although allocation policy is usually debated on the national level, most organ distribution is local. We found wide variations by region of the country in the lowest acceptable posttransplant survival for a patient with HCC, from 25% to 72% at 5 years depending on the severity of organ shortage. Our results were also sensitive to the proportion of patients on the waiting list with MELD scores >20, also a function of geographic variations in organ shortage. These findings are consistent with a recent analysis demonstrating a 4-fold difference in liver transplantation rates across regions (15). In regions with more organs available for transplantation, the harm caused by taking one extra organ is smaller. A reorganization of the transplant regions might reduce these disparities (33), but this may not be politically feasible. One approach to dealing with these disparities would be to expand Milan criteria in some regions but not others. We propose that a selective expansion of criteria may be justified in regions with less severe organ shortage. This demonstration project could yield important data for improving the prediction of posttransplant survival in these patients. Alternatively, MELD exception points for patients with HCC exceeding Milan but within UCSF criteria could be capped at 30. This would mean that the probability of transplantation for these patients would depend upon the number of other patients on the waiting list with lab MELD scores of >30, and dropout from the list would be high in areas of the country with the most severe organ shortage. Either of these approaches would limit harm to other patients on the waiting list, though they could also be seen as exacerbating current geographic inequalities in access to transplantation. The ethical implications of these proposals warrant further discussion by the transplant community.

While this is the only study to address this question, there are several limitations and caveats to consider. First, this study only looked at the harm of assigning MELD exception points for patients with Milan-UCSF+ HCC. We did not consider transplantation with marginal quality organs, which is an alternative that deserves further study. Second, the study assumed that long-term posttransplant survival does not vary substantially by pretransplant MELD score. If expanding the Milan criteria caused the waiting list cohort to be transplanted at higher MELD scores, their posttransplant survival could be slightly lower, resulting in harm not measured by the model. Third, as with any modeling study our findings are limited by the quality of the available literature. However, aside from geographic variations in organ shortage our findings were robust to sensitivity analysis for almost all variables. The most influential variable was the survival after TACE alone for a patient with Milan-UCSF+ HCC. As multimodal treatments for HCC continue to improve (23,34), a higher posttransplant survival will be needed to justify liver transplantation in these patients. Despite recent advances in nontransplant therapies, only a third of candidates for curative therapy are being treated (35). Deciding not to transplant these patients does not mean giving up on them; more aggressive treatment is still warranted. Finally, translating these results into clinical practice is limited by the current ability to accurately predict survival after transplantation for individual patients with HCC exceeding Milan criteria. A recent study showed that only 44% of tumors are accurately staged on pretransplant imaging (36), thus limiting the ability of tumor stage to predict prognosis. In the future, new methods for predicting survival such as the use of genomics or proteomics will hopefully improve upon this accuracy (37). For now, the limited supply of organs forces physicians to make rationing decisions using the available data. This study provides an analytic framework for making these difficult decisions.

In conclusion, we show that transplanting patients with HCC exceeding Milan criteria would cause significant harm to the other patients on the waiting list. This finding does not mean that expansion of Milan criteria should not be performed, nor that individual centers should cease their efforts to improve transplant outcomes for these patients. Rather, our results suggest that in terms of national policy, expansion of criteria would require 5-year posttransplant survival rates of approximately 61% in order to outweigh the harm to other patients. Since most centers currently report survival rates below this threshold, it may be premature at this time to expand Milan criteria on a national level.

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