Serum Alpha-Fetoprotein Level Independently Predicts Posttransplant Survival in Patients With Hepatocellular Carcinoma

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We aimed to determine whether combining serum alpha-fetoprotein (AFP) level with hepatocellular carcinoma (HCC) tumor burden would allow better stratification of posttransplant survival for patients with HCC undergoing liver transplantation. Adjusting for donor and recipient characteristics, we calculated the risk of posttransplant mortality associated with serum AFP level or HCC tumor burden for all first-time adult liver transplants performed in the United States between 2002 and 2011 (n = 45,267). Serum AFP level, rather than tumor burden, was the tumor characteristic most strongly associated with posttransplant survival. Although recipients with HCC and a serum AFP level \( \leq 15 \) ng/mL at the time of transplantation had no excess posttransplant mortality [adjusted hazard ratio (AHR) = 1.02, 95% confidence interval (CI) = 0.93-1.12], patients with a serum AFP level of 16 to 65 ng/mL (AHR = 1.38, 95% CI = 1.23-1.54), patients with a serum AFP level of 66 to 320 ng/mL (AHR = 1.65, 95% CI = 1.45-1.88), and patients with a serum AFP level > 320 ng/mL (AHR = 2.37, 95% CI = 2.06-2.73) had progressively worse posttransplant mortality in comparison with recipients without HCC. Patients with a tumor burden exceeding the Milan criteria (who are usually excluded from transplantation) had excellent posttransplant survival if their serum AFP level was 0 to 15 ng/mL (AHR = 0.97, 95% CI = 0.66-1.43). In contrast, patients within the Milan criteria (who are routinely considered to be transplant candidates) had poor survival if their serum AFP level was substantially elevated (for a serum AFP level > 66 ng/mL, AHR = 1.93, 95% CI = 1.74-2.15). Changes in serum AFP level while patients were on the waiting list corresponded closely to changes in posttransplant mortality. In conclusion, the absolute serum AFP level and changes in the serum AFP level strongly predict posttransplant survival independently of the tumor burden. We hope that these data, in combination with other factors, can be used to inform future studies and ongoing discussions aimed at improving the eligibility criteria for liver transplantation for patients with HCC. Liver Transpl 19:634–645, 2013. © 2013 AASLD.

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Additional Supporting Information may be found in the online version of this article.

Abbreviations: AFP, alpha-fetoprotein; AHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; STAR, Standard Transplant Analysis and Research; UCSF, University of California San Francisco; UNOS, United Network for Organ Sharing.

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Liver transplantation is the treatment that offers the best prospects of long-term survival for patients with cirrhosis and hepatocellular carcinoma (HCC). It is the only treatment that can eliminate the underlying cirrhosis as well as HCC as long as it has not metastasized outside the liver. In contrast, other treatments are limited by the fact that even if complete removal, ablation, or necrosis of the HCC is achieved, the patient will continue to suffer from cirrhosis and, therefore, continue to be at risk of developing progressive liver dysfunction, liver failure, or a new HCC.

The number of persons in the United States in need of liver transplantation far exceeds the number of donor organs. This relative shortage will continue to worsen because the prevalence of cirrhosis and HCC is increasing, but the number of donors is stable. As a result of this relative shortage, criteria have to be in place to determine who is eligible for liver transplantation. One of the most important changes in these eligibility criteria in the United States occurred in February 2002 when patients with early-stage HCC were determined to be eligible for liver transplantation with an artificially high priority Model for End-Stage Liver Disease (MELD) score to ensure that they could undergo liver transplantation before their tumor burden grew. Currently, patients with stage II HCC (a single tumor 2-5 cm in diameter or 2-3 tumors 1-3 cm in diameter) are assigned a MELD score of 22 if they have a lower actual MELD score. The main rationale for the adoption of this policy was that patients with stage II HCC were thought to have posttransplant survival comparable to that of patients without HCC. The adoption of this policy led to a dramatic increase in the proportion of first-time adult recipients of deceased donor transplants who had HCC (from 4.6% in 1997-2002 to 26% in 2002-2007). However, during the first 5 years after the introduction of the HCC MELD exception policy, posttransplant survival was worse for patients with HCC versus patients without HCC.

Currently, the tumor size and the tumor number are the only tumor characteristics used to determine eligibility for liver transplantation. However, we and others have recently shown that the serum alphafetoprotein (AFP) level is an excellent predictor of posttransplant survival. We reasoned that combining the serum AFP level with the tumor size/number might allow better predictions of posttransplant survival and, therefore, could be used to inform a more appropriate selection of patients eligible for liver transplantation. We aimed to describe posttransplant survival in patients with HCC who underwent transplantation in the United States from 2002 to 2011 according to relevant subgroups defined by the tumor size, tumor number, and serum AFP level.

PATIENTS AND METHODS

Data Collection

Transplant centers and organ procurement organizations in the United States are required to submit
by UNOS as the variable _final_meld_peld_lab_score_, (2) underlying cause of liver disease [categorized as hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol, primary biliary cirrhosis, primary sclerosing cholangitis, cryptogenic cirrhosis, nonalcoholic steatohepatitis, autoimmune hepatitis, tumor other than HCC, acute hepatic necrosis, hemochromatosis, or other], (3) age, (4) sex, (5) race/ethnicity, (6) diabetes, and (7) body mass index (BMI).

The donor characteristics were as follows: (1) age, (2) sex, (3) race/ethnicity, (4) height, (5) cold ischemia time, (6) cause of death (categorized as trauma, anoxia, cerebrovascular accident, or other), (7) presence of HBV core antibodies, (8) presence of HCV antibodies, (9) living donor, (10) split liver donor, (11) deceased cardiac donor, and (11) organ location (categorized as local, regional, or national). These characteristics included all the components of the donor risk index.13

Among patients with HCC, we ascertained the following tumor-related characteristics:

1. Tumor size and number at transplant based on computed tomography or magnetic resonance imaging performed before liver transplantation as part of MELD exception applications.
2. Serum AFP level at transplant [categorized with the values of the 25th (6 ng/mL), 50th (15 ng/mL), 75th (65 ng/mL), and 90th percentiles (320 ng/mL)]. For patients who had multiple serum AFP levels, we also analyzed the effects of changes in the serum AFP level between the time of listing and the time of transplantation on posttransplant survival.
3. Time on the waiting list after the diagnosis of HCC, which was calculated from the number of exception applications (≤3 months if there was only 1 exception application or >3 months if there was more than 1 exception application). We decided not to use the total time on the waiting list because patients might have been diagnosed with HCC after they were listed for transplantation.
4. Pretransplant locoregional treatment for HCC with transcatheter chemoembolization, radiofrequency ablation, chemical ablation, resection, or cryotherapy.

For the purpose of sensitivity analyses, we also modeled the maximum serum AFP level or tumor burden recorded while patients were on the waiting list (as opposed to the values at transplant).

The aforementioned tumor-related characteristics were reported to UNOS on HCC exception applications. Therefore, they were available only for patients with HCC who applied for an HCC-related MELD exception. The majority of the patients who received an HCC MELD exception had available tumor burden data (10,001/10,282 or 97%) because they had to submit HCC exception applications. The serum AFP level was available for 8659 of these patients because it was reported only after May 10, 2003. However, only a small proportion of patients in the HCC/no exception group (1172/3196 or 37%) had available tumor burden data because they had completed HCC exception applications (although they did not ultimately receive an HCC MELD exception).

**Statistical Analysis**

The Kaplan-Meier method was used to calculate posttransplant survival 1, 2, 3, 4, 5, and 6 years after transplantation. The follow-up time was defined as the time in years from transplantation until death from any cause or until last known follow-up (the variable _ptime_ in the UNOS STAR file). Patients who remained alive were censored at the time at which they were last traced alive.

Cox proportional hazards regression was used to compare patients with HCC to patients without HCC with respect to survival after liver transplantation after adjustments for potential confounders, which included all the recipient and donor characteristics listed previously.14 To account for regional differences, subjects were stratified by 52 donation service areas in all multivariate analyses. For patients with HCC, Cox proportional hazards regression was used to compare patients with different tumor characteristics (tumor size, tumor number, and serum AFP level) with respect to survival after liver transplantation after adjustments for potential confounders. We performed a subgroup analysis subdividing patients according to their HCV status in order to determine whether associations between the serum AFP level and posttransplant survival were different in patients with or without an HCV infection. We also performed a subgroup analysis subdividing patients with HCC according to whether or not they received pretransplant locoregional treatment.

The primary cause of posttransplant death was determined via UNOS with the variable _COD_, and deaths due to malignancy were identified; whether the malignancy was HCC or some other malignancy was not reported.

We limited our main analyses of the effects of the tumor size/number and serum AFP level on survival to patients with HCC who received an HCC MELD exception because they represented a well-characterized group of patients for whom data on the tumor size/number and serum AFP level were (almost) universally available. In contrast, only a small subset of patients in the HCC/no exception group (1172/3196 or 37%) had these data available. Because the HCC/no exception group was a poorly defined group with a very high proportion of missing data, we analyzed it separately in a supplementary analysis that combined all patients with available tumor data, regardless of whether they received an HCC exception or not, after an additional adjustment for the receipt of an HCC exception (Supporting Table 1).

Stata SE-11 software (StataCorp, College Station, TX) was used for all statistical calculations. The study was approved by the Institutional Review Board at Veterans Affairs Puget Sound Health Care System.
RESULTS

Patients with HCC were more likely to have a viral HBV or HCV infection and were less likely to have other underlying liver diseases in comparison with patients without HCC (Table 1). There were no appreciable differences between patients with HCC and patients without HCC with respect to the recipient BMI or any donor characteristics except for the presence of HBV core and HCV antibodies, which were slightly more common for patients with HCC. Living donor transplantation was less common in patients with an HCC MELD exception (1.1%) versus patients without HCC (5.5%) or patients with HCC without an exception (5.1%). Patients with an HCC MELD exception had a lower MELD score (12.3 vs. 10.2) or patients without HCC (23.1 ± 9.5).

Unadjusted and adjusted posttransplant survival was worse for the HCC/no exception group [adjusted hazard ratio (AHR) = 1.39, 95% confidence interval (CI) = 1.28-1.51] versus the HCC/MELD exception group [AHR = 1.28, 95% CI = 1.20-1.37] in comparison with the group with no HCC (Table 2 and Fig. 1A).

There was a dramatic decrease in posttransplant survival as the serum AFP level increased in patients with an HCC MELD exception (Table 2 and Fig. 1B). Although patients with a serum AFP level of 0 to 15 ng/mL at the time of transplantation had survival similar to that of patients without HCC (AHR = 1.02, 95% CI = 0.93-1.12), progressively worse survival was observed in patients with an AFP level of 16 to 65 ng/mL (AHR = 1.38, 95% CI = 1.23-1.54), patients with an AFP level of 66 to 320 ng/mL (AHR = 1.65, 95% CI = 1.45-1.88), and patients with an AFP level >320 ng/mL (AHR = 2.37, 95% CI = 2.06-2.73). Six-year survival progressively declined from 71.9% in patients without HCC to 69.9% (AFP level = 0-15 ng/mL), 60.4% (AFP level = 16-65 ng/mL), 57.4% (AFP level = 66-320 ng/mL), and 50.6% (AFP level >320 ng/mL) in patients with HCC and increasing serum AFP levels. When we used the maximum serum AFP level recorded while patients were on the waiting list instead of the level at the time of transplantation, similar results were obtained (data not shown). When patients with HCC were subdivided according to whether they received pretransplant locoregional treatment for HCC or not, a very similar association between serum AFP levels and posttransplant mortality was observed in the 2 groups, as indicated by the very similar AHRs (Table 2). Also, similar AHRs for the association between serum AFP levels and posttransplant survival were observed in HCV-positive patients and HCV-negative patients (Supporting Table 1). Finally, when we combined HCC patients with an HCC MELD exception and HCC patients without an HCC MELD exception, we found very similar associations between serum AFP levels and posttransplant survival (Supporting Table 2).

Posttransplant survival also decreased as the tumor size increased up to 5.0 cm and less so as the tumor number increased (1 versus 2-3), but these associations were not as strong as those observed for increasing serum AFP levels (Table 2). In comparison with patients without HCC, the AHR for patients with HCC increased progressively with increasing tumor size, with an AHR of 1.55 (95% CI = 1.32-1.81) for patients with a tumor size >4 to 5 cm when the maximum recorded tumor burden was used. The group of patients with a tumor size >5 to 6.5 cm was paradoxically associated with good posttransplant survival (AHR = 0.99, 95% CI = 0.55-1.81), and this likely indicated that this was a highly select group of patients exceeding the Milan criteria. Similar associations were observed when we used the maximum tumor burden recorded while patients were on the waiting list rather than the tumor burden at transplant (data not shown).

In comparison with patients without HCC, patients with HCC within the Milan criteria (a single tumor ≤5.0 cm in diameter or 2-3 tumors <3 cm in diameter; AHR = 1.30, 95% CI = 1.21-1.39), patients with HCC beyond the Milan criteria but within the University of California San Francisco (UCSF) criteria (A single tumor ≤6.5 cm in diameter or 2-3 tumors <4.5 cm in diameter and a total tumor size ≤8.0 cm; AHR = 1.26, 95% CI = 0.94-1.67), and patients with HCC beyond the UCSF criteria (AHR = 1.57, 95% CI = 1.00-2.48) all had worse posttransplant survival (Table 2).

We further categorized patients according to both the tumor burden (within or outside the Milan and UCSF criteria) and the serum AFP level (0-15, 16-65, or >66 ng/mL) at transplant in order to gain insight into how these 2 tumor characteristics could be combined to create meaningful categories with respect to posttransplant survival (Table 2 and Fig. 1C). Patients with a serum AFP level of 0 to 15 ng/mL had excellent survival even if their tumor burden exceeded the Milan criteria (6-year survival = 71.8%; AHR = 0.97, 95% CI = 0.66-1.43). When the tumors exceeded the UCSF criteria, there was a substantial increase in mortality even for patients with a serum AFP level of 0 to 15 ng/mL (6-year survival = 46.0%; AHR = 1.50, 95% CI = 0.75-3.02). In contrast, patients with a serum AFP level >66 ng/mL had significantly reduced posttransplant survival in comparison with patients without HCC even if their tumor burden was within the Milan and UCSF criteria.

We then analyzed predictors of posttransplant survival only among patients with HCC in order to be able to simultaneously model the serum AFP level and tumor burden at transplant as well as other recipient and donor characteristics (Table 3). The serum AFP level was the tumor characteristic most strongly associated with posttransplant survival in both adjusted and unadjusted analyses: the AHR increased progressively in a dose-response fashion from 1 in the reference category (0-6 ng/mL) to 2.27 (95% CI = 1.91-2.69) in patients with an AFP level >320 ng/mL. The
| Table 1. Recipient and Donor Characteristics of First-Time Adult Liver Transplants Performed in the United States (2002-2011) Presented Separately for Patients With HCC and Patients Without HCC |
|---------------------------------------------------------------|
| **Recipient characteristics**                                 |
|                                                               |
| **No HCC** (n = 31,789)                                      |
| **HCC/MELD Exception** (n = 10,282)                          |
| **HCC/No Exception** (n = 3196)                              |
|                                                               |
| **MELD score**                                               |
| 23.1 ± 9.5                                                   |
| 12.3 ± 4.5                                                   |
| 20.3 ± 10.2                                                  |
| **MELD score (%)**                                           |
| <19                                                          |
| 11,879 (37.4)                                                |
| 9342 (90.9)                                                  |
| 1634 (51.1)                                                  |
| ≥19                                                          |
| 19,850 (62.4)                                                |
| 932 (9.1)                                                    |
| 1556 (48.7)                                                  |
| Missing                                                      |
| 60 (0.2)                                                     |
| 8 (0.1)                                                      |
| 6 (0.2)                                                      |
| **Underlying liver disease (%)**                             |
| HCV                                                          |
| 38.3                                                         |
| 67.3                                                         |
| 61.8                                                         |
| HBV                                                          |
| 3.8                                                          |
| 8.8                                                          |
| 7.8                                                          |
| Alcoholic liver disease                                      |
| 15.2                                                         |
| 7.3                                                          |
| 10.0                                                         |
| Primary biliary cirrhosis                                    |
| 4.8                                                          |
| 1.2                                                          |
| 1.0                                                          |
| Primary sclerosing cholangitis                               |
| 6.7                                                          |
| 0.7                                                          |
| 0.9                                                          |
| Cryptogenic                                                  |
| 8.4                                                          |
| 3.6                                                          |
| 5.0                                                          |
| Nonalcoholic steatohepatitis                                 |
| 5.9                                                          |
| 3.0                                                          |
| 3.6                                                          |
| Autoimmune hepatitis                                         |
| 3.7                                                          |
| 1.3                                                          |
| 1.1                                                          |
| Cholangiocarcinoma                                           |
| 0.8                                                          |
| 0.2                                                          |
| 0.2                                                          |
| Other tumor                                                  |
| 0.9                                                          |
| 0.2                                                          |
| 0.8                                                          |
| Acute hepatic necrosis                                       |
| 4.4                                                          |
| 0.2                                                          |
| 0.3                                                          |
| Hemochromatosis                                              |
| 0.6                                                          |
| 0.7                                                          |
| 0.8                                                          |
| Other                                                        |
| 6.5                                                          |
| 5.6                                                          |
| 6.7                                                          |
| **Male (%)**                                                 |
| 62.8                                                         |
| 77                                                           |
| 80.4                                                         |
| **Race/ethnicity (%)**                                       |
| White                                                        |
| 75.8                                                         |
| 67.4                                                         |
| 65.1                                                         |
| Black/African American                                       |
| 8.7                                                          |
| 8.5                                                          |
| 8.7                                                          |
| Hispanic                                                     |
| 11.9                                                         |
| 13.5                                                         |
| 16.3                                                         |
| Other (mostly Asian)                                         |
| 3.6                                                          |
| 10.5                                                         |
| 9.9                                                          |
| Diabetes (%)                                                 |
| 19.8                                                         |
| 25.4                                                         |
| 26.1                                                         |
| **Age (years)**                                              |
| 51.8 ± 10.4                                                  |
| 56.8 ± 7.6                                                   |
| 56.5 ± 7.9                                                   |
| **BMI (kg/m²)**                                              |
| 28.2 ± 5.9                                                   |
| 28.2 ± 5.2                                                   |
| 28.1 ± 5.5                                                   |
| **Waiting time (months)**                                   |
| 8.2 ± 15.3                                                   |
| 9.5 ± 17.1                                                   |
| 9.2 ± 16.8                                                   |
| **Donor characteristics**                                   |
|                                                               |
| **Male (%)**                                                 |
| 59.0                                                         |
| 59.8                                                         |
| 59.2                                                         |
| **Race/ethnicity (%)**                                       |
| White                                                        |
| 70.0                                                         |
| 67.1                                                         |
| 65.3                                                         |
| Black/African American                                       |
| 14.9                                                         |
| 15.8                                                         |
| 15.6                                                         |
| Hispanic                                                    |
| 12.0                                                         |
| 13.0                                                         |
| 14.6                                                         |
| Other (mostly Asian)                                         |
| 3.1                                                          |
| 4.1                                                          |
| 4.5                                                          |
| **Height (cm)**                                              |
| 171.7 ± 10.9                                                 |
| 171.6 ± 10.8                                                 |
| 171.6 ± 10.9                                                 |
| **HBV core antibody–positive (%)**                           |
| 0.1                                                          |
| 0.1                                                          |
| 0.4                                                          |
| **HCV antibody–positive (%)**                                |
| 2.5                                                          |
| 3.8                                                          |
| 3.7                                                          |
| **Age (years)**                                              |
| 41.4 ± 17.1                                                  |
| 42.0 ± 17.1                                                  |
| 43.0 ± 17                                                    |
| **Cold ischemia time (hours)**                              |
| 7.2 ± 3.8                                                    |
| 7.1 ± 3.5                                                    |
| 7.3 ± 3.7                                                    |
| **Split liver donor (%)**                                   |
| 6.6                                                          |
| 2.7                                                          |
| 6.2                                                          |
| **Deceased cardiac donor (%)**                              |
| 4.1                                                          |
| 4.8                                                          |
| 5.2                                                          |
| **Cause of death (%)**                                       |
| Trauma                                                       |
| 36.2                                                         |
| 35.9                                                         |
| 32.9                                                         |
| Anoxia                                                       |
| 15.2                                                         |
| 17.4                                                         |
| 16.8                                                         |
| Cerebrovascular accident                                     |
| 40.7                                                         |
| 43.0                                                         |
| 42.7                                                         |
| Other                                                        |
| 2.5                                                          |
| 2.6                                                          |
| 2.4                                                          |
| **Living donor (%)**                                         |
| 5.5                                                          |
| 1.1                                                          |
| 5.1                                                          |
| **Organ location (%)**                                       |
| Local                                                        |
| 71.8                                                         |
| 79.0                                                         |
| 70.6                                                         |
| Regional                                                    |
| 22.1                                                         |
| 16.6                                                         |
| 20.7                                                         |
| National                                                    |
| 6.1                                                          |
| 4.3                                                          |
| 8.7                                                          |

*The data are presented as means and standard deviations.
| Patients (n) | Person-Years | Hazard Ratio | AHR* |
|-------------|--------------|--------------|------|
| 1 Year | 2 Years | 3 Years | 4 Years | 5 Years | 6 Years |
| No HCC (reference category) | 31,789 | 100,359 | 1 | 1 | 88.4 | 84.3 | 81.2 | 78.3 | 75.2 | 71.9 |
| HCC/no exception | 3196 | 7490 | 1.59 (1.48-1.70) | 1.39 (1.28-1.51) | 84.9 | 76.4 | 70.5 | 65.9 | 61.4 | 57.2 |
| HCC/MELD exception Patients | 10,282 | 29,181 | 1.19 (1.14-1.25) | 1.28 (1.20-1.37) | 89.6 | 82.0 | 77.0 | 72.9 | 68.8 | 65.2 |
| HCC with Milan criteria at transplant† | 9614 | 27,603 | 1.19 (1.13-1.25) | 1.30 (1.21-1.39) | 89.6 | 82.0 | 77.0 | 72.9 | 68.8 | 65.2 |
| HCC beyond Milan criteria but within UCSF criteria at transplant‡ | 289 | 650 | 1.29 (1.01-1.66) | 1.26 (0.94-1.67) | 91.7 | 81.6 | 72.7 | 65.9 | 62.8 | 62.8 |
| HCC beyond UCSF criteria at transplant‡ | 98 | 190 | 1.51 (1.00-2.30) | 1.57 (1.00-2.48) | 89.2 | 74.3 | 61.8 | 57.4 |
| Serum AFP level at transplant | | | | | | | | | | | |
| 0-15 ng/mL | 4783 | 12,568 | 0.93 (0.86-0.99) | 1.02 (0.93-1.12) | 91.8 | 86.9 | 82.6 | 78.4 | 73.9 | 69.9 |
| 16-65 ng/mL | 1998 | 4984 | 1.35 (1.23-1.48) | 1.38 (1.23-1.54) | 88.7 | 79.1 | 74.2 | 69.8 | 65.3 | 60.4 |
| 66-320 ng/mL | 1160 | 3002 | 1.51 (1.35-1.69) | 1.65 (1.45-1.88) | 88.4 | 77.6 | 70.0 | 65.1 | 60.4 | 57.4 |
| >320 ng/mL | 718 | 1895 | 2.04 (1.81-2.31) | 2.37 (2.06-2.73) | 82.2 | 68.7 | 61.8 | 57.4 |
| Serum AFP level at transplant with pretransplant locoregional HCC treatment | | | | | | | | | | | |
| 0-15 ng/mL | 2915 | 6965 | 0.91 (0.82-0.99) | 1.05 (0.94-1.17) | 92.1 | 87.1 | 82.8 | 78.0 | 73.5 | 69.8 |
| 16-65 ng/mL | 1246 | 2902 | 1.35 (1.20-1.52) | 1.39 (1.21-1.60) | 89.2 | 78.5 | 74.2 | 69.0 | 64.9 | 58.3 |
| 66-320 ng/mL | 686 | 1673 | 1.40 (1.20-1.63) | 1.55 (1.31-1.85) | 88.0 | 76.9 | 71.4 | 67.8 | 64.2 | 61.5 |
| >320 ng/mL | 353 | 884 | 2.23 (1.89-2.63) | 2.50 (2.08-3.00) | 81.8 | 66.7 | 58.6 | 55.9 | 47.9 | 46.8 |
| Tumor size/number at transplant | | | | | | | | | | | |
| <2 cm/1 | 1588 | 3372 | 1.01 (0.86-1.15) | 1.14 (0.99-1.32) | 90.4 | 83.7 | 79.3 | 74.9 | 71.6 | 68.6 |
| <2 cm/2-3 | 1058 | 2083 | 1.34 (1.16-1.52) | 1.32 (1.21-1.40) | 89.2 | 78.5 | 74.2 | 69.0 | 64.9 | 58.3 |
| 2-3 cm/1 | 3142 | 6383 | 1.64 (1.40-1.93) | 1.74 (1.44-2.09) | 89.0 | 78.5 | 68.3 | 62.0 | 56.4 | 53.0 |
| 2-3 cm/2-3 | 1608 | 3216 | 2.04 (1.81-2.31) | 2.37 (2.06-2.73) | 82.2 | 68.7 | 61.8 | 57.4 |
| >3-4 cm/1 | 1423 | 4290 | 1.04 (1.16-1.14) | 1.19 (1.08-1.31) | 90.5 | 84.0 | 78.7 | 74.6 | 70.0 | 66.4 |
| >3-4 cm/2-3 | 795 | 2312 | 1.38 (1.24-1.52) | 1.55 (1.37-1.75) | 87.5 | 78.4 | 74.6 | 70.4 | 65.5 | 61.6 |
| >5-6.5 cm/1 | 85 | 245 | 1.05 (0.63-1.75) | 0.99 (0.55-1.81) | 93.2 | 84.6 | 81.9 | 71.7 | 71.7 | 71.7 |
| >3-4.5 cm/2-3 | 204 | 566 | 1.39 (1.05-1.86) | 1.36 (0.98-1.88) | 91.1 | 80.2 | 69.1 | 63.5 | 59.3 | 59.3 |
| Milan criteria/ AFP level | | | | | | | | | | | |
| Within/0-15 ng/mL | 4592 | 12,116 | 0.93 (0.86-1.00) | 1.03 (0.94-1.12) | 91.8 | 86.9 | 82.7 | 78.5 | 74.0 | 70.0 |
| Within/16-65 ng/mL | 1916 | 4804 | 1.33 (1.21-1.46) | 1.36 (1.22-1.53) | 88.6 | 79.2 | 74.6 | 70.5 | 66.1 | 61.0 |
| Outside/0-15 ng/mL | 1794 | 4698 | 1.72 (1.57-1.87) | 1.93 (1.74-2.15) | 85.9 | 74.2 | 66.9 | 62.2 | 57.4 | 54.7 |
| Outside/16-65 ng/mL | 191 | 453 | 0.94 (0.66-1.33) | 0.97 (0.66-1.43) | 93.2 | 86.2 | 81.7 | 75.4 | 71.8 | 71.8 |

TABLE 2. Posttransplant Survival in Patients With HCC Presented According to Tumor Size and Number and Serum AFP Level, Compared to Posttransplant Survival in Patients Without HCC in the United States (2002-2011)
associations between the serum AFP level and posttransplant survival were very similar between patients with HCV infections and patients without HCV infections, as indicated by the similar AHRs (Table 3).
In contrast, there was little increase in the AHR associated with an increasing tumor burden after adjustments for all donor and recipient characteristics, including the serum AFP level (Table 3). Other recipient characteristics that were significantly associated with decreased survival included age, HCV, a MELD score ≥ 19, and black race.

Patients with multiple serum AFP levels recorded during their time on the waiting list were divided into those who underwent locoregional treatment for HCC on the waiting list and had serum AFP levels before and after treatment (n = 1422) and those who did not undergo treatment for HCC on the waiting list (n = 2213; Table 4). The effects of changes in the serum AFP level on posttransplant survival were similar in the 2 groups. Patients whose serum AFP level decreased (from >320 to ≤320 or 16-320 to 0-15 ng/mL) had no excess posttransplant mortality. This suggests that down-staging of the serum AFP level is associated with down-staging for posttransplant mortality. In contrast, patients whose serum AFP level increased (from 0-15 to ≥16 ng/mL or from 16-320 to >320 ng/mL) had very significantly elevated posttransplant mortality. Among the transplant recipients who died, malignancy was a much more common cause of death for those with pretransplant HCC and a MELD exception (31.2%) versus those without HCC (9.1%). Furthermore, an increasing serum AFP level was associated with an increasing proportion of deaths due to malignancy, and this suggests that the excess mortality associated with an increasing serum AFP level was related to recurrent HCC (Table 5). However, these malignancies were not further subdivided into recurrent HCC or other de novo malignancies in the available UNOS data.

**DISCUSSION**

Our results demonstrate a very strong dose-response relationship between the serum AFP level and posttransplant mortality. Although recipients with HCC and a serum AFP level < 15 ng/mL at transplant had no excess posttransplant mortality (AHR = 1.03, 95% CI = 0.93-1.12), those with a serum AFP level of 16 to 65 ng/mL (AHR = 1.38, 95% CI = 1.23-1.54), a serum AFP level of 66 to 320 ng/mL (AHR = 1.65, 95% CI = 1.45-1.88), or a serum AFP level > 320 ng/mL (AHR = 2.37, 95% CI = 2.06-2.73) had progressively worse posttransplant mortality in comparison with recipients without HCC. Thus, posttransplant survival decreases significantly even at serum AFP levels that are generally considered low or normal (ie, serum AFP levels ≥ 16 ng/mL). Furthermore, changes in serum AFP levels while patients were on the waiting list corresponded accurately to changes in posttransplant mortality. Patients who exceeded the Milan criteria had excellent posttransplant survival if they had low serum AFP levels (0-15 ng/mL), whereas patients within the Milan criteria had poor posttransplant survival if they had elevated serum AFP levels (≥66 ng/mL).

Because the serum AFP level shows a stronger association with posttransplant survival than the tumor size and number, it does not seem reasonable that the tumor burden, as expressed in the Milan criteria, should be the only tumor characteristic that determines transplant eligibility. Even the most widely quoted recommendations about ways to potentially improve the Milan criteria (eg, the UCSF criteria and the Metroticket system) are based on the tumor size and number and do not incorporate the serum AFP level.

Our study was not designed to determine what the threshold expected survival or survival benefit should be for liver transplant eligibility. Rather, our results can be used to determine what the threshold AFP level should be to achieve a given posttransplant survival rate for patients with HCC within or outside the Milan criteria. A recent national conference on liver allocation for patients with HCC in the United States recommended that a future allocation policy for candidates with HCC “should select HCC candidates so that there are similar posttransplant outcomes for HCC and non-HCC recipients.” If such a stringent recommendation were to be adopted, then a serum AFP level < 15 ng/mL would have to be used as the threshold in order for patients with HCC to have posttransplant survival similar to that of patients without HCC. This would result in the exclusion of approximately 45% of the patients with HCC currently undergoing transplantation, which is perhaps an unacceptable scenario. If a less stringent criterion, such as a predicted 5-year posttransplant survival rate of at least 60% for patients with HCC, were to be used, then patients with HCC within the Milan criteria with a serum AFP level > 66 ng/mL (approximately 22% of such patients) would have to be excluded because their 5-year survival in this study was 57.4%, whereas the rate for patients without HCC was 75.2%. In contrast, our results show that some patients with HCC beyond the Milan criteria, who are generally excluded from transplantation, can achieve excellent posttransplant survival similar to that of patients without HCC if their serum AFP level is 0 to 15 ng/mL.

Using UNOS AFP data from May 2003 to January 2008, Toso et al. reported that a serum AFP level > 400 ng/mL was associated with worse posttransplant survival. They concluded that eligibility criteria could be extended beyond the Milan criteria [up to a total tumor volume of 115 cm³, which included practically everyone (99.7%) in their data set] as long as the serum AFP level was ≤ 400 ng/mL. In a previous UNOS-based study of liver transplant recipients extending only up to 2007, we also reported that a serum AFP ≥ 455 ng/mL was significantly (P < 0.05) associated with increased mortality. Serum AFP categories between 16 and 455 ng/mL were also associated with increased mortality in that study, but the associations did not reach statistical significance. In light of our current expanded results, this was most likely due to the smaller sample sizes of these
| Patients [n (%)] | Person-Years | Hazard Ratio [95% CI for Patient Death] | AHR [95% CI] for Patient Death* |
|----------------|-------------|----------------------------------------|---------------------------------|
| **Serum AFP level†** | | | |
| 0-6 ng/mL | 2758 (31.9) | 7258 | 1 | 1 |
| 7-15 ng/mL | 2025 (24.3) | 5310 | 1.03 (0.90-1.18) | 0.98 (0.84-1.14) |
| 16-65 ng/mL | 1998 (23.1) | 4984 | 1.49 (1.31-1.69) | 1.37 (1.18-1.58) |
| 66-320 ng/mL | 1160 (13.4) | 3002 | 1.65 (1.43-1.91) | 1.61 (1.37-1.89) |
| >320 ng/mL | 718 (8.3) | 1896 | 2.24 (1.92-2.59) | 2.27 (1.91-2.69) |
| **Serum AFP level for recipients with HCV infection** | | | |
| 0-6 ng/mL | 1366 (23.4) | 3473 | 1 | 1 |
| 7-15 ng/mL | 1428 (24.5) | 3714 | 0.95 (0.79-1.13) | 0.95 (0.78-1.15) |
| 16-65 ng/mL | 1638 (28.1) | 4043 | 1.37 (1.17-1.61) | 1.37 (1.14-1.64) |
| 66-320 ng/mL | 889 (13.4) | 2236 | 1.55 (1.30-1.85) | 1.61 (1.32-1.97) |
| >320 ng/mL | 507 (8.7) | 1268 | 2.29 (1.90-2.75) | 2.31 (1.88-2.86) |
| **Serum AFP level for recipients without HCV infection** | | | |
| 0-6 ng/mL | 1392 (49.2) | 3785 | 1 | 1 |
| 7-15 ng/mL | 597 (21.1) | 1596 | 1.13 (0.90-1.42) | 0.98 (0.75-1.32) |
| 16-65 ng/mL | 271 (9.6) | 766 | 1.63 (1.32-2.21) | 1.37 (1.14-1.63) |
| 66-320 ng/mL | 271 (9.6) | 766 | 1.63 (1.32-2.21) | 1.37 (1.14-1.63) |
| >320 ng/mL | 211 (7.5) | 628 | 1.88 (1.43-2.47) | 2.11 (1.53-2.92) |
| **Tumor size/number** | | | |
| <2 cm/1 | 1588 (15.9) | 3372 | 0.96 (0.83-1.11) | 1.07 (0.89-1.28) |
| <2 cm/2-3 | 1058 (10.6) | 3345 | 1 | 1 |
| 2-3 cm/1 | 3142 (31.4) | 9383 | 1.15 (1.01-1.30) | 1.11 (0.96-1.29) |
| 2-3 cm/2-3 | 1608 (16.1) | 4902 | 1.23 (1.09-1.39) | 1.14 (0.98-1.34) |
| >3-4 cm/1 | 1423 (14.2) | 4290 | 1.30 (1.11-1.50) | 1.18 (0.98-1.43) |
| >4-5 cm/1 | 795 (7.9) | 2312 | 1.30 (1.11-1.50) | 1.18 (0.98-1.43) |
| >5-6.5 cm/1 | 85 (0.8) | 194 | 0.97 (0.58-1.61) | 0.81 (0.44-1.49) |
| >3-4.5 cm/2-3 | 204 (2.0) | 456 | 1.29 (0.96-1.73) | 1.05 (0.74-1.49) |
| Greater tumor burden | 98 (1.0) | 190 | 1.41 (0.92-2.15) | 1.19 (0.74-1.91) |
| **MELD score** | | | |
| 6-9 | 3092 (30.9) | 8610 | 1 | 1 |
| 10-12 | 2606 (26.1) | 7438 | 0.96 (0.86-1.07) | 0.94 (0.83-1.08) |
| 13-15 | 2160 (21.6) | 6305 | 0.99 (0.89-1.12) | 1.02 (0.88-1.18) |
| 16-18 | 1237 (12.4) | 3560 | 1.00 (0.87-1.15) | 0.94 (0.79-1.12) |
| >19 | 898 (9.0) | 2513 | 1.16 (1.00-1.35) | 1.26 (1.05-1.52) |
| **Time on waiting list after HCC diagnosis** | | | |
| ≤3 months | 5931 (58.2) | 18,272 | 1 | 1 |
| >3 months | 4255 (41.8) | 10,283 | 0.96 (0.88-1.04) | 1.09 (0.96-1.24) |
| **Pretransplant locoregional treatment for HCC‡** | | | |
| No | 4985 (48.9) | 16,131 | 1 | 1 |
| Yes | 5201 (51.1) | 12,424 | 1.00 (0.92-1.09) | 1.07 (0.96-1.20) |
| **HCV infection** | | | |
| No | 3275 (32.7) | 9852 | 1 | 1 |
| Yes | 6726 (67.3) | 18,591 | 1.22 (1.12-1.34) | 1.19 (1.05-1.34) |
| **Age** | | | |
| 18-52 years | 2637 (26.4) | 8959 | 1 | 1 |
| 53-56 years | 2270 (22.7) | 6223 | 1.20 (1.07-1.36) | 1.14 (0.99-1.33) |
| 57-62 years | 2817 (28.2) | 7199 | 1.18 (1.05-1.32) | 1.18 (1.02-1.37) |
| 63-67 years | 1515 (15.1) | 4146 | 1.34 (1.19-1.53) | 1.36 (1.15-1.61) |
| ≥68 years | 762 (7.6) | 1917 | 1.68 (1.44-1.96) | 1.72 (1.42-2.09) |
| **BMI** | | | |
| <24.7 kg/m² | 2421 (25.5) | 6963 | 1 | 1 |
| ≥24.7–27.6 kg/m² | 2340 (24.6) | 6764 | 0.86 (0.76-0.96) | 0.79 (0.68-0.91) |
| ≥27.6–31.2 kg/m² | 2385 (25.1) | 6708 | 0.83 (0.73-0.93) | 0.80 (0.69-0.93) |
previous studies and, more importantly, the much shorter follow-up period. Our current results, extending to June 2011, revealed the association of a much lower serum AFP threshold with increased mortality (ie, \(< 21.6\) ng/mL) and a much stronger dose-response relationship for serum AFP levels \(< 21.6\) ng/mL. Analyzing UNOS data extending to February 2008, Mailey et al. also reported the association of a much lower AFP threshold (\(< 20.0\) ng/mL) with excess posttransplant mortality in patients with HCC. Given our findings from updated UNOS data, we disagree with Toso et al.’s recommendation to consider transplantation in patients beyond the Milan criteria as long as the serum AFP level is \(< 400\) ng/mL because this would lead to unacceptably low posttransplant survival. Rather, our results suggest expanding the Milan criteria only for patients with a serum AFP level of 0 to 15 ng/mL, especially because patients who underwent transplantation in the United States between 2002 and 2011 with HCC exceeding the Milan criteria were a highly select group, in that such patients are generally excluded from transplantation. If eligibility criteria were expanded in the future to routinely offer transplantation to patients with more extensive tumors, it is possible that worse survival would be observed than what we describe here for the 2002-2011 period. In addition, any expansion of the Milan criteria should probably be initially restricted to patients within the UCSF criteria (a single tumor \(\leq 6.5\) cm in diameter or 2-3 tumors \(\leq 4.5\) cm in diameter and a total tumor size \(\leq 8.0\) cm) because we observed worse survival in patients beyond the UCSF criteria even with an AFP level of 0 to 15 ng/mL.

The associations between serum AFP levels and posttransplant survival were remarkably robust in clinically relevant subgroup analyses. Very similar associations were observed in HCV-positive patients and HCV-negative patients and in patients with HCC who received pretransplant locoregional treatment and patients who did not.

Our results suggest that patients who initially have high serum AFP levels can still be expected to have excellent posttransplant survival if their serum AFP levels subsequently decline either spontaneously or as a result of treatment. In contrast, a rising serum AFP level is associated with poor posttransplant survival and should be monitored closely before decisions are made about whether to offer transplantation or not. Thus, changes in serum AFP levels correspond to changes in posttransplant mortality and can also be used to guide decisions about liver transplant eligibility.

In common with all studies based on national UNOS data, our study is limited by the absence of data on the posttransplant recurrence of HCC and HCC-specific deaths. We are assuming that the excess mortality experienced by transplant recipients with HCC and elevated serum AFP levels is related to the recurrence of HCC because an elevated serum AFP level is not known to be a marker of any other adverse conditions and because we have adjusted for all important predictors of posttransplant survival. This is supported by our finding that an increasing serum AFP level was

### Table 3. Continued

| Patients [n (%)] | Person-Years | Hazard Ratio [95% CI] for Patient Death | AHR [95% CI] for Patient Death |
|-----------------|--------------|---------------------------------------|---------------------------------|
| \(\geq 31.2-35.2\) kg/m\(^2\) | 1408 (14.8) | 3798 | 0.97 (0.84-1.11) | 0.95 (0.81-1.12) |
| \(\geq 35.2\) kg/m\(^2\) | 958 (10.1) | 2378 | 1.06 (0.91-1.23) | 1.05 (0.88-1.26) |
| Sex             |              |            |                    |                          |
| Female          | 2363 (23.0) | 6663 | 1 | 1 |
| Male            | 7919 (77.0) | 22,518 | 0.94 (0.85-1.03) | 0.97 (0.86-1.10) |
| Race/ethnicity  |              |            |                    |                          |
| White           | 6930 (67.4) | 19,682 | 1 | 1 |
| Black/African American | 877 (8.5) | 2217 | 1.33 (1.16-1.51) | 1.22 (1.03-1.44) |
| Hispanic        | 1393 (13.5) | 3926 | 0.88 (0.77-0.99) | 0.91 (0.77-1.07) |
| Other (mostly Asian) | 1082 (10.5) | 3356 | 0.70 (0.61-0.82) | 0.70 (0.57-0.86) |
| Diabetes        |              |            |                    |                          |
| No              | 7482 (74.1) | 21,634 | 1 | 1 |
| Yes             | 2613 (25.9) | 6942 | 1.14 (1.04-1.25) | 1.22 (1.09-1.37) |

*Adjusted for recipient characteristics (serum AFP level, MELD score, size and number of tumors, race, sex, age, BMI, diabetes, HCV infection, waiting list time, and pretransplant locoregional treatment for HCC) and donor characteristics [age, sex, race/ethnicity, height, cold ischemia time, presence of HBV core or HCV antibodies, organ location (local, regional, or national), cause of death, living donor, split liver donor, and deceased cardiac donor].

†There were fewer patients with serum AFP level measurements because these measurements began to be reported on May 10, 2003.

‡Includes patients who underwent transarterial chemoembolization (n = 3222), radiofrequency ablation (n = 1147), chemical ablation (n = 138), resection (n = 43), cryoablation (n = 23), or a combination of these modalities (n = 628).

§Estimated from the number of HCC exception applications (which have to be updated every 3 months).
| AFP Level at Listing (ng/mL) | No locoregional treatment for HCC on the waiting list | Hazard Ratio AHR* | 1 Year | 2 Years | 3 Years | 4 Years | 5 Years | 6 Years | Posttransplant Survival (%) |
|-----------------------------|------------------------------------------------------|-------------------|--------|---------|---------|---------|---------|---------|-----------------------------|
| 0-15                        | 0-15                                                 | 1                 | 1      | 88.4    | 84.3    | 81.2    | 78.3    | 75.2    | 71.9                        |
| >16                         | >16                                                  | 1.76 (1.24-2.49)  | 1.89 (1.30-2.75) | 86.1 | 76.3 | 66.6 | 57.9 | 51.1 | 43.8 |
| 16-320                      | 0-15                                                 | 0.85 (0.58-1.26)  | 1.02 (0.67-1.55) | 94.7 | 89.0 | 83.6 | 77.6 | 64.5 | 64.5 |
| >320§                       | >320§                                                 | 1.76 (1.24-2.49)  | 1.89 (1.30-2.75) | 86.1 | 76.3 | 66.6 | 57.9 | 51.1 | 43.8 |
| 0-15                         | 0-15                                                  | 1.06 (0.72-1.55)  | 1.32 (0.86-2.02) | 94.7 | 89.0 | 83.6 | 77.6 | 64.5 | 64.5 |
| >16                         | >16                                                  | 1.76 (1.24-2.49)  | 1.89 (1.30-2.75) | 86.1 | 76.3 | 66.6 | 57.9 | 51.1 | 43.8 |
| 16-320                      | 0-15                                                 | 0.85 (0.58-1.26)  | 1.02 (0.67-1.55) | 94.7 | 89.0 | 83.6 | 77.6 | 64.5 | 64.5 |
| >320§                       | >320§                                                 | 1.76 (1.24-2.49)  | 1.89 (1.30-2.75) | 86.1 | 76.3 | 66.6 | 57.9 | 51.1 | 43.8 |

*Adjusted for recipient characteristics (actual MELD score, underlying liver disease, age, sex, race/ethnicity, diabetes, and BMI) and donor characteristics [age, sex, race/ethnicity, height, cold ischemia time, presence of HBV core or HCV antibodies, organ location [local, regional, or national], cause of death, living donor, split liver donor, and deceased cardiac donor].

†Includes patients whose AFP level increased from a listing value of 0 to 15 ng/mL to a transplant value >320 ng/mL (n = 2 for no treatment and n = 2 for treatment).

§Includes patients whose AFP level decreased from a listing value of >320 ng/mL to a transplant value of 0 to 15 ng/mL (n = 24 for no treatment and n = 21 for treatment).

‡Includes patients who underwent transarterial chemoembolization (n = 986), radiofrequency ablation (n = 300), chemical ablation (n = 44), cryoablation (n = 8), resection (n = 1), or a combination of these modalities (n = 83) while they were on the waiting list and had serum AFP levels before and after these treatments.
associated with an increasing proportion of posttransplant deaths attributable to malignancy. Our study was based on data submitted to UNOS by each transplant center in the United States rather than data collected specifically for the purpose of this study. Hence, we cannot verify the accuracy of the data. We suspect that there was great accuracy in reporting the presence and stage of HCC as part of the MELD exception applications because these applications determine the priority score of patients with HCC and their position on the liver transplant waiting list. At the same time, we believe that the greatest strength of this study is the derivation of data from UNOS for every transplant recipient in the United States; this means that our results reflect the entire US experience rather than the experience of a single transplant center or a group of centers with special interest or expertise in HCC.

We hope that our results will be used in the future to improve liver transplant eligibility criteria for patients with HCC by combining the serum AFP level with the tumor burden.

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