Title

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Journal

Liver Transplantation, 28(5)

ISSN

1527-6465

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Publication Date

2022-05-01

DOI

10.1002/lt.26392

Peer reviewed

HHS Public Access

Author manuscript

Liver Transpl. Author manuscript; available in PMC 2023 May 01.

Published in final edited form as:

Liver Transpl. 2022 May ; 28(5): 763–773. doi:10.1002/lt.26392.

Lower Alpha-Fetoprotein Threshold of 500 ng/mL for Liver Transplantation May Improve Posttransplant Outcomes in Patients With Hepatocellular Carcinoma

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Abstract

Under current United Network for Organ Sharing (UNOS) policy, patients with hepatocellular carcinoma (HCC) and alpha-fetoprotein (AFP) levels ≥1000 ng/mL are required to show a reduction in AFP level to <500 ng/mL before liver transplantation (LT). However, effects of AFP reduction on post-LT HCC outcomes among patients with HCC with moderately elevated AFP levels between 100 and <1000 ng/mL are unclear. Adults in the UNOS registry who underwent LTs from January 2005 to September 2015 with initial AFP levels of 100 to 999 ng/mL at listing for Model for End-Stage Liver Disease exceptions were included. Primary predictor was AFP level at LT, categorized as <100, 100 to 499, or ≥500 ng/mL, and patients with only 1 recorded pre-LT AFP value (AFP 1-value). Survival was compared using the Kaplan-Meier curve method. Factors associated with post-LT survival and HCC recurrence were assessed in a multivariable Cox regression model. Among 1766 included patients, 50.2% had AFP 1-value, followed by 24.7%, 18.9%, and 6.2% with AFP levels <100, 100 to 499, and ≥500 ng/mL, respectively. The 5-year post-LT survival rate was lowest in the AFP ≥500 category, at 56.1%, compared with 72.7%, 70.4%, and 65.6% in the AFP <100, 100 to 499 ng/mL, and AFP 1-value categories, respectively. In multivariable analysis, AFP ≥500 ng/mL at LT was associated with a greater risk of post-LT death (hazard ratio [HR], 1.5; 95% confidence interval [CI], 1.1–2.1) and HCC recurrence (HR, 1.9; 95% CI, 1.1–3.1) when compared with the AFP <100 ng/mL category; other significant variables included donor risk index, age, race/ethnicity, Child-Turcotte-Pugh class, and tumor diameter. Among AFP levels ≥500 ng/mL at LT, 40.4% had AFP levels ≥1000, but no difference in post-LT survival or recurrence was seen between those patients with AFP levels < or ≥1000

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Max L. Goldman, Kali Zhou, Jennifer L. Dodge, Francis Yao, and Neil Mehta contributed to the concept and design; acquisition, analysis, or interpretation of data; and critical revision of the manuscript for important intellectual content. Max L. Goldman, Kali Zhou, Jennifer L. Dodge, Francis Yao, and Neil Mehta approved the final version of the manuscript. Kali Zhou and Jennifer L. Dodge participated in the statistical analysis. Max L. Goldman and Kali Zhou contributed to drafting the manuscript. Neil Mehta is the guarantor of the article.

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ng/mL. Mandating AFP <500 ng/mL at LT for all patients, not only for those with initial AFP levels ≥1000 ng/mL, may improve post-LT outcomes and can be considered in future UNOS policy.

Hepatocellular carcinoma (HCC) is the fifth most common solid malignancy worldwide, with nearly 40,000 new cases and more than 27,000 deaths annually in the United States.[1] Liver transplantation (LT) offers patients with early-stage HCC (solitary tumor ≤5 cm or up to 3 tumors ≤3 cm) an excellent posttransplant survival rate of >70% at 5 years and a low rate of HCC recurrence.[1–3] However, ongoing national organ shortages and increasing transplant waitlist times have necessitated efforts to optimize LT selection criteria for patients with HCC without causing excessive harm to others on the transplant waiting list. Although prioritization of recipients for donor livers in the United States is dependent on the Model for End Stage Liver Disease (MELD) score and exception point allocation, qualification for LT in HCC is currently based almost exclusively on tumor size and number. However, mounting evidence suggests that other factors may be more indicative of aggressive tumor biology in HCC, thereby playing a more pivotal role in predicting overall patient survival after LT.[4,5] A better understanding of such biologic markers, and their association with tumor characteristics and outcomes in distinct patient populations, would allow for improved allocation of donor livers to those most likely to attain the greatest survival benefit with LT.

Alpha-fetoprotein (AFP) is 1 such marker, which when elevated has been associated with significantly worse post-LT outcomes.[6–10] AFP is an independent predictor of tumor recurrence in the posttransplant setting and has separately been found to be elevated in conjunction with vascular invasion and poor tumor differentiation on explant.[11–13] Some investigations have even demonstrated a stronger association between AFP level and post-LT survival relative to tumor size and number alone.[6] AFP levels >1000 ng/mL prior to LT, despite tumor burden within the Milan criteria,[2] are associated with a significant risk of HCC recurrence and worsened posttransplant survival, with 5-year recurrence-free survival rates of only 52.7%, relative to 80.3% for those with AFP levels <1000 ng/mL.[11,14] On the other hand, AFP levels <100, and even as low as 16 to 20 ng/mL, are associated with improved post-LT outcomes relative to those patients with higher AFP levels.[6,11] A recent national study further demonstrated that AFP reduction from >1000 to <500 ng/mL with locoregional therapy (LRT) prior to LT results in significantly improved 5-year post-LT survival rates and HCC recurrence probabilities, with AFP decreases to <100 ng/mL associated with the best post-LT outcomes.[15] Although national policy currently requires those patients with AFP levels >1000 ng/mL to demonstrate a decrease to <500 ng/mL prior to LT, a paucity of both evidence and management guidelines exist regarding the impact of AFP reductions and related post-LT outcomes of those with moderately elevated AFP levels between 100 and 999 ng/mL at the time of listing for MELD exception. We therefore sought to investigate the effects of AFP level changes from baseline 100 to 999 ng/mL to different pre-LT thresholds on post-LT survival and HCC recurrence.

Patients and Methods

PATIENT POPULATION AND STUDY DESIGN

We performed a retrospective cohort study of adult LT recipients aged 18 years or older who received their first LT for HCC from January 2005 through September 2015 and had a listing AFP of 100 to 999 ng/mL at the time of initial MELD exception. Eligible patients were identified from the national United Network for Organ Sharing (UNOS)/Organ Procurement and Transplant Network database Standard Transplant Analysis and Research File released June 2019. Only patients with radiographic tumor burden either within Milan criteria or UNOS downstaging criteria (1 lesion 5.1–8.0 cm, 2–3 lesions with at least one 3.1–5.0 cm and total tumor diameter ≤8.0 cm, or 4–5 lesions each ≤3.0 cm with total tumor diameter ≤8.0 cm)[16] were considered. Patients were also excluded if they had been listed for multiorgan transplants, received a living donor transplant, and if intrahepatic cholangiocarcinoma was found on explant or serum AFP levels at the time of LT were missing.

Demographic and clinical variables at the time of initial HCC MELD exception and at LT were collected from the UNOS database and included age, sex, race/ethnicity, underlying etiology of liver disease, Model for End-Stage Liver Disease–sodium (MELD-Na) score, Child-Turcotte-Pugh (CTP) class, radiographic tumor size and number, AFP levels, administration of pre-LT LRT if performed, time from MELD exception to LT, and donor risk index (DRI).[17] For those patients who underwent LT after April 2012 (when UNOS initiated collection of HCC explant pathology), explant features were evaluated for histological grade of differentiation based on the Edmondson and Steiner criteria (grade 1, well-differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated),[18] pathological tumor stage based on the size and number of only viable tumors, and presence of microvascular or macrovascular invasion.

Patients with multiple AFP values recorded while listed were stratified into the following 3 AFP level comparison groups by AFP level at the time of or within 90 days prior to LT: <100, 100 to 499, and >500 ng/mL (hereafter referred to collectively as AFP categories). Patients with only 1 recorded pre-LT AFP value of 100 to 999 ng/mL at listing formed a fourth study group (hereafter referred to as AFP 1-value).

STATISTICAL ANALYSIS

The primary outcome was posttransplant survival, defined as the time from LT until the date of death, with patients censored at retransplant or last documented follow-up. The secondary outcome was posttransplant HCC recurrence, defined as the date of confirmed HCC recurrence after LT or death from HCC, with patients censored at retransplant, non-HCC death, or last documented follow-up. To identify patients with post-LT HCC recurrence, liver malignancy follow-up and cause of death variables underwent physician review (N.M.). Records indicating posttransplant recurrence of pretransplant malignancy or a cause of death indicating HCC or metastatic malignancy were classified as having HCC recurrence.

Demographic and clinical variables were summarized using median and interquartile range (IQR) for continuous variables and proportions for categorical variables. Comparison of these variables between the AFP groups was performed using the Kruskal-Wallis and Pearson chi-square tests, respectively. Linear trends in the annual proportion of cases within each AFP category were evaluated using linear regression. Logistic regression was used to evaluate characteristics associated with each of the following explant events as odds ratios (ORs): (1) microvascular invasion, (2) liver tumors beyond Milan criteria, and (3) poor tumor differentiation on explant. The Kaplan-Meier curve (KM) method was used to estimate posttransplant survival and HCC recurrence probabilities stratified by AFP at LT and compared using the log-rank test. Cox proportional hazards regression was also used to evaluate clinical factors at LT associated with risk of death and HCC recurrence in separate models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated, and factors with a univariate P value <0.10 were included in the multivariable analysis with the final model selected by backward elimination (P for removal >0.05). We conducted a sensitivity analysis with the inclusion of transplant era (before versus after 2010) in our models. Statistical analyses were performed using Stata/IC 14.2 (StataCorp, College Station, TX).

Results

COHORT SELECTION

A total of 1766 patients with a listing AFP level between 100 and 999 ng/mL met the inclusion criteria and were further categorized by their AFP levels at LT (Fig. 1). Of the entire cohort, the majority (82.6%) had a listing AFP level between 100 and 499 ng/mL. Approximately half (50.2%) of all patients had only 1 AFP measurement while on the waiting list, and the remainder (n = 879) had a median of 3 (IQR, 2–4) available AFP measurements. Those patients with at least 2 waitlist AFP measurements were further categorized by AFP level at LT. A total of 49.6% (n = 436) of those with at least 2 AFP measurements had an AFP level <100 ng/mL at LT, whereas 38.0% (n = 334) had an AFP level between 100 and 499, and 12.4% (n = 109) had an AFP level ≥500 ng/mL at LT. Among those patients with AFP Levels ≥500 ng/mL, 40.3% had AFP levels ≥1000 ng/mL at LT.

PATIENT AND TUMOR CHARACTERISTICS AT LISTING

Demographic and tumor characteristics of the cohort at time of listing for MELD exception are presented in Table 1. The median age at listing was 57 years (IQR, 53–62 years) and did not differ by AFP category. The majority of patients (71.6%) were men, and the most common racial/ethnic groups were Caucasian (58.3%), Hispanic (15.5%), Black (14.8%), and Asian (10.2%). Hepatitis C virus (HCV) accounted for 64.6% of all HCC etiologies transplanted, followed by 19.7% cryptogenic/other and 6.4% hepatitis B virus (HBV). The overall median MELD-Na at listing was 10 (IQR, 8–15). Those patients with AFP levels at LT ≥500 ng/mL or with AFP 1-values were more likely to be CTP class C (17.0%−17.4%) at listing relative to the lower AFP categories (8.7% for AFP levels 100–499 ng/mL and 7.8% for AFP levels <100 ng/mL; P < 0.001). Median total tumor diameter was highest in

the AFP 1-value category (3.0 cm; IQR, 2.3–4.0 cm) and lowest in the AFP ≥500 ng/mL category (2.4 cm; IQR, 1.8–3.5 cm; $P < 0.001$).

TRENDS IN AFP CATEGORY OVER TIME

There were notable changes in the proportion of patients in each AFP category by year of LT during the time period 2005 to 2015 (Fig. 2). The proportion of patients having only 1-value of AFP prior to LT declined sharply, from 66.2% in 2005 to 28.4% in 2010 (mean decrease of −4.5% per year; $P < 0.001$). In contrast, the proportion with AFP levels <100 ng/mL at LT increased from 14.9% to 46.1% (mean increase of 3.1% per year; $P < 0.001$). The proportion of patients with AFP levels 100 to 499 ng/mL also increased, although to a lesser degree (mean increase of 1.2% per year; $P = 0.02$), whereas the proportion of patients with AFP levels ≥500 ng/mL at LT remained low (<9.0%) and stable over time (mean increase of 0.2% per year; $P = 0.14$).

TRANSPLANT CHARACTERISTICS

Significant differences were seen in waitlist time from initial listing for MELD exception to LT and receipt of LRT among the 4 AFP categories, particularly among those patients with AFP 1-values (Table 1). As expected, the median waitlist time in the AFP 1-value category was relatively short at 1 month (IQR, 0.5–1.8 months), and only 51.4% received LRT. Median waitlist times increased with sequentially lower AFP levels at LT categories: 5.6 months (IQR, 3.8–8.6 months) with AFP levels ≥500 ng/mL, 5.6 months (IQR, 4.0–8.5 months) with AFP levels 100 to 499 ng/mL, and 7.0 months (IQR, 4.6–11.3 months) with AFP levels <100 ng/mL ($P < 0.001$). Correspondingly, the proportion of patients receiving LRT increased with longer waitlist time and decreasing AFP category. A total of 68.8%, 83.2%, and 91.3% received LRT with a respective AFP level at LT of ≥500 ng/mL, 100 to 499 ng/mL, and <100 ng/mL ($P < 0.001$). Of note, 29.4% of those in the AFP ≥500 ng/mL category were CTP class C at LT compared with 21.1% with AFP 1-value, 19.2% with AFP levels 100 to 499 ng/mL, and 17.9% with AFP levels <100 ng/mL ($P = 0.13$). At LT, the median total tumor diameter was lowest in the AFP at LT <100 ng/mL category, followed by AFP levels 100 to 499 ng/mL, AFP levels ≥500 ng/mL, and finally AFP 1-value ($P < 0.001$). Median DRI was 1.4 (IQR, 1.1–1.7) and did not differ by AFP category ($P = 0.32$).

AFP CATEGORY AND EXPLANT CHARACTERISTICS

Of 489 patients who received transplants after 2012 with available explant characteristics, 15.1% had microvascular invasion, 18.0% were beyond the Milan criteria at explant, and 14.2% had poorly differentiated tumor type (Supporting Table 1). AFP category was not associated with either microvascular invasion or having a poorly differentiated tumor. However, 34.4% of patients with AFP levels >500 ng/mL were beyond the Milan criteria on explant compared with only 11.1% and 19.2% in the AFP <100 ng/mL and 100–499 ng/mL categories, respectively. In comparison with those patients with AFP levels ≥500 ng/mL, those patients with AFP levels <100 ng/mL at LT had a 76% reduction in the odds of explant understaging (OR, 0.24; 95% CI, 0.10–0.57).

POST-LT SURVIVAL AND HCC RECURRENCE RATES BY AFP CATEGORY

The median follow-up time after LT was 5.0 years (IQR, 2.1–8.0 years), during which time 673 patients (38.1%) died with median time from LT to death of 2.1 years (IQR, 0.9–4.6 years). A total of 286 patients (16.2%) had post-LT HCC recurrence with a median time from LT to recurrence of 1.5 years (IQR, 0.7–3.1 years). KMs for post-LT survival and HCC recurrence, stratified by AFP at LT category, are shown in Fig. 3A. The KM 5-year survival rate was lowest in the AFP ≥500 ng/mL category at 56.1% compared with 72.7%, 70.4%, and 65.6% in the AFP <100 ng/mL, 100 to 499 ng/mL, and AFP 1-value categories, respectively. The difference in post-LT survival was significant when compared across all 4 categories (overall log-rank $P = 0.003$). In addition, the survival difference was significant when comparing the AFP ≥500 ng/mL versus the AFP <100 ng/mL and 100 to 499 ng/mL categories ($P < 0.05$). Similarly, HCC recurrence at 5 years was highest in the AFP ≥500 ng/mL category (24.2%), followed by the AFP 100 to 499 ng/mL (18.7%), AFP 1-value (18.3%), and AFP <100 ng/mL (13.1%) categories (log-rank $P = 0.007$).

We also compared outcomes, stratified by overall changes in AFP level (ie, rising versus declining), among patients who received LRT with more than 1 AFP value and AFP levels ≥100 ng/mL at LT to examine the impact of AFP response to LRT. Those patients with AFP levels <100 ng/mL at LT were excluded from this additional analysis, as each of these patients had a declining AFP, based on the initial cohort inclusion criteria, and therefore a direct comparative analysis stratified by rising versus declining AFP could not be performed. Recurrence was noted to be significantly higher in those patients with rising AFP levels despite LRT, and all patients with AFP levels ≥500 ng/mL at LT and recurrence were noted to have rising AFP levels ($P = 0.01$). However, no difference in survival was observed ($P = 0.10$; Supporting Figs. 1 and 2).

Finally, in an analysis of patients with elevated AFP levels ≥500 ng/mL, there was no significant difference in either survival or recurrence rates between those with AFP levels at LT 500 to 999 ng/mL and AFP levels at LT ≥1000 ng/mL (survival log-rank $P = 0.89$; recurrence log-rank $P = 0.52$; Fig. 3B). The 5-year survival was 55.7% and 56.7%, and recurrence was 24.2% and 24.4% for AFP levels at LT 500 to 999 ng/mL and AFP levels at LT ≥1000 ng/mL, respectively. A significantly higher proportion of patients with AFP levels ≥500 ng/mL at LT and HCC recurrence had received LRT (90.9%) in comparison with those without recurrence (63.2%; $P = 0.01$). A separate analysis comparing the 47 patients (43.1%) with AFP levels ≥500 ng/mL who received transplants from 2005 to 2009 and the 62 (56.9%) who received transplants after 2010 demonstrated no significant difference in post-LT recurrence rates (14.9% and 24.2%, respectively; $P = 0.23$). The 5-year survival rate for those patients with AFP levels ≥500 ng/mL at LT who received transplants before 2010 was 44.7% compared with 62.9% for those who received transplants thereafter, trending toward, but not reaching, the threshold of significance ($P = 0.06$).

PREDICTORS OF POST-LT MORTALITY AND HCC RECURRENCE

Table 2 summarizes the predictors of post-LT mortality and HCC recurrence in multivariable models. The significant univariate predictors of mortality included AFP category, age, race/ethnicity, liver disease etiology, MELD-Na score, CTP class, tumor diameter, tumor number,

waitlist time, and DRI (Supporting Table 2). Both an AFP level at LT ≥500 ng/mL and AFP 1-value were significantly associated with mortality in univariate models in comparison with AFP level at LT <100 ng/mL. In multivariable analysis, however, only AFP level at LT ≥500 ng/mL was significantly associated with a 1.50-fold (95% CI, 1.07–2.10; P = 0.02) increased hazard of post-LT mortality relative to an AFP level at LT <100 ng/mL. There was no difference in mortality risk for those patients with AFP levels 100 to 499 ng/mL and those with AFP 1-values relative to those patients with AFP levels <100 ng/mL. Other predictors of increased post-LT mortality included being CTP class B or CTP class C (versus CTP class A), older age, higher DRI, and higher tumor diameter. Asian populations had a lower post-LT mortality rate (HR, 0.66; 95% CI, 0.48–0.89; P = 0.007) relative to Caucasian populations. The addition of transplant era to the multivariate model demonstrated a significant association between era and mortality (HR for post-2010 LT, 0.67; 95% CI, 0.57–0.79) but minimal impact on the relationship between AFP at LT ≥500 ng/mL and mortality (HR, 1.43; 95% CI, 1.03–2.01).

Regarding post-LT recurrence, significant univariate predictors at LT included AFP category, age, CTP class, and tumor diameter. Notably, receipt of LRT, waitlist time, tumor number, DRI, and MELD-Na were not associated with recurrence. An AFP level at LT of 100 to 499 ng/mL, ≥500 ng/mL, and AFP 1-value, relative to having an AFP level <100 ng/mL, were all associated with a higher likelihood of recurrence in univariate models. Results of multivariable analysis demonstrated that, relative to an AFP level <100 ng/mL, there was a 1.52-fold (95% CI, 1.04–2.22; P = 0.03) increase in post-LT recurrence with an AFP level 100 to 499 ng/mL and a significantly higher 1.88-fold (95% CI, 1.13–3.14, P = 0.02) increase with an AFP level ≥500 ng/mL. Older age, male sex, and larger tumor diameter were associated with a greater probability of recurrence, whereas both Asian and Black populations had a decreased recurrence risk relative to Caucasian populations. The addition of transplant era did not change our final multivariate model for recurrence.

Discussion

Given the national organ shortages, the appropriate allocation of livers for transplant requires prioritization of patients who are likely to derive maximal survival benefit from transplantation.[1,3,4,19–21] In addition to morphologic variables such as total tumor burden, which may not fully reflect tumor biology, AFP has regained attention as an important prognostic marker of posttransplant outcomes in HCC.[5–7,9,11,13,22–25] In this large, national study involving 1766 patients with HCC with intermediate AFP level 100 to 999 ng/mL at the time of listing with HCC MELD exception, we demonstrated significantly inferior survival and higher rates of recurrence among patients with AFP levels ≥500 ng/mL at LT. These findings support continued debate about lowering the AFP level threshold for exclusion from LT to ≥500 ng/mL for all patients rather than only for those patients with AFP levels >1000 ng/mL under current UNOS HCC policy.

Compared with the previously published 5-year post-LT survival rate of 49% among patients with AFP levels >1000 ng/mL, we observed a similar 5-year post-LT survival rate of only 56.1% among patients with AFP levels >500 ng/mL at LT.[15] In contrast, 5-year post-LT survival among those patients with AFP levels <500 ng/mL was markedly higher at >70.0%.

Furthermore, compared with those patients with AFP levels <100 ng/mL, those with AFP levels ≥500 ng/mL at LT had a 50.0 % increase in mortality and nearly double the risk of HCC recurrence. Importantly, we demonstrated that the worsened outcomes in the group with AFP levels ≥500 ng/mL were not driven by the 40.4% of individuals in this cohort with AFP levels ≥1000 ng/mL at LT, as post-LT outcomes were similar between those patients with AFP levels between 500 and 999 ng/mL (who are eligible for LT) and those patients with AFP levels ≥1000 ng/mL at LT (who are excluded under current policy).

Our findings add to the mounting evidence supporting the prognostic value of AFP waitlist changes with regard to post-LT outcomes in HCC independent of tumor burden.[6,11,14,26–29] In our multivariable model, an AFP level ≥500 ng/mL at LT was independently associated with significantly reduced survival and increased risk of HCC recurrence, distinct from older studies in which radiographic tumor diameter mitigated the prognostic effect of AFP.[9,29] Depending on regional organ availability, transplantation in those patients with AFP levels ≥500 ng/mL at LT—and significantly lower post-LT survival—may negatively impact the survival of others on the transplant waiting list. An international consensus report has advocated for minimum survival thresholds for transplant recipients with HCC to qualify for LT, such that post-LT survival in HCC approximates that of other indications for LT, thereby limiting undue harm to others awaiting transplant.[3] For instance, Volk et al. found that a 5-year post-LT survival threshold above 61% was needed for the benefit of transplantation in HCC to outweigh the harm caused by delaying transplant for other waitlist candidates.[30] Although LT still confers the best chance of survival for many high-risk patients with HCC, given the shortage of available livers for transplant, the collective benefit to all potential transplant recipients may be improved by reserving donations for those patients with HCC with the best chance of survival. Conversely, further criteria for MELD exception point allocation in HCC are likely to negatively impact individual survival in higher risk HCC cohorts. Future studies may elucidate updated survival thresholds under which the relative harm to other waitlist patients outweighs the survival benefits of transplantation in those patients with significantly elevated AFP levels, especially given the increased use of more “marginal grafts” for higher risk patients with HCC.

The findings in this study also support the growing importance of LRT and subsequent assessment of AFP response as a surrogate marker of tumor biology.[16,24,31] Although more patients with AFP levels <500 ng/mL relative to AFP levels ≥500 ng/mL at LT received LRT (83.2% and 68.8%, respectively), LRT alone was not found to be significantly associated with post-LT survival or HCC recurrence in multivariable analysis. A likely explanation is that AFP response to LRT is a more relevant prognostic indicator of post-LT outcomes than receipt of LRT itself.[31] This is supported by an observed increase in post-LT HCC recurrence among those patients with rising AFP levels despite LRT. During the mandated 6-month waiting period, AFP levels that remain elevated above 500 ng/mL, that rise, or that fail to respond to waitlist interventions may indicate either aggressive or unassessed tumor biology. Furthermore, given that those patients with AFP levels ≥1000 ng/mL must now demonstrate a decrease to <500 ng/mL prior to LT, patients in the interval AFP range of 500 to 999 ng/mL at LT are now composed solely of those with either relatively stable elevated or rising AFP levels, likely signifying a poor biochemical response to waitlist interventions and a high risk of HCC recurrence. In our analysis, a significantly higher

proportion of those patients with HCC recurrence and high AFP levels ≥500 ng/mL at LT had received LRT, relative to those without recurrence, likely indicating unresponsive/aggressive tumor biology among patients with AFP levels ≥500 ng/mL despite LRT. As use of LRT administration was already highly prevalent during the study period—and is likely even higher under current policy—lowering the AFP threshold for UNOS exclusion from LT to ≥500 ng/mL could identify those patients with biologically aggressive tumors, thereby improving population-level post-LT outcomes.

In addition, our findings support improved post-LT outcomes with an extended time to LT, as part of an "ablate-and-wait" strategy.[15,32] Rapid LT precludes a minimal observation period to adequately assess tumor biology by observing waitlist AFP changes over time. Whereas a higher AFP level at LT was independently associated with worsened post-LT outcomes, those patients with AFP levels <100 ng/mL at LT had significantly longer times to LT on average, relative to those without such marked AFP reductions. The percentage of patients with AFP levels <100 ng/mL at LT also doubled between 2010 and 2015 relative to those who received transplants in the preceding 5-year period, with an average annual increase of 3.1% of patients with AFP levels <100 ng/mL at LT. This might suggest that waitlist times and use of LRT have increased over time and allowed for improved selection of appropriate transplant candidates. These factors likely contributed to the significantly improved post-LT survival observed in those patients who received transplants during the second half of our study period relative to those patients who received transplants prior to our study period. Our results support the mandatory 6-month waitlist period between listing and MELD exception and suggest that those patients with AFP levels ≥500 ng/mL should either be further observed prior to LT to assess response to waitlist interventions or have limited access to deceased donor LT because of their predicted poor post-LT outcomes.

A notable limitation of the present study is the inability to accurately capture every HCC recurrence event for patients in the UNOS databases, where recurrence reporting is not mandated.[33] However, event capture rate was maximized through systematic author review of follow-up data and cause-of-death variables. In addition, post-LT survival, rather than recurrence, was selected as the primary outcome to mitigate any resulting bias. Given the national, retrospective nature of this study, we were also unable to control for certain variables including the inconsistent application of LRT during the observation period or capture of explant pathology on the majority of included patients. Similarly, there was a lack of a mandated 6-month waiting period during the included timeframe, with a significant number of included patients in this study having only 1 documented AFP value. Future studies on those transplanted after the October 2015 UNOS policy change or in individual centers that have consistently applied LRT for a predefined waiting period may be able to further contribute to the findings of this study. Finally, despite the inclusion of 1766 patients from a nationally representative sample, the relatively small sample size of 109 patients with AFP levels ≥500 ng/mL at LT might have limited our ability to detect additional meaningful differences among the cohorts.

In conclusion, we have demonstrated that among those patients with AFP levels 100 to 999 ng/mL at LT listing, a reduction in the AFP level to <100 ng/mL before LT was associated with the best post-LT outcomes. Our results support targeted AFP reduction with LRT and

assessment of biochemical response to waitlist interventions prior to LT in clinical practice. Importantly, an AFP level that remains elevated or rises to ≥500 ng/mL at LT portends the highest risk for HCC recurrence and post-LT mortality, fostering debate on potential policies mandating an AFP level <500 ng/mL at LT for all patients, not only for those with initial AFP levels ≥1000 ng/mL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by the University of California, San Francisco Clinical and Translational Science Institute Research Funding Award and by the University of California, San Francisco Liver Center (P30 DK026743).

Kali Zhou received grants from Gilead.

Abbreviations:

AFP	alpha-fetoprotein
CI	confidence interval
CTP	Child-Turcotte-Pugh class
DRI	donor risk index
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HR	hazard ratio
IQR	interquartile range
KM	Kaplan-Meier curve
LT	liver transplantation
LRT	locoregional therapy
MELD	Model for End-Stage Liver Disease
MELD-Na	Model for End-Stage Liver Disease–sodium
NASH	nonalcoholic steatohepatitis
OR	odds ratio
UNOS	United Network for Organ Sharing

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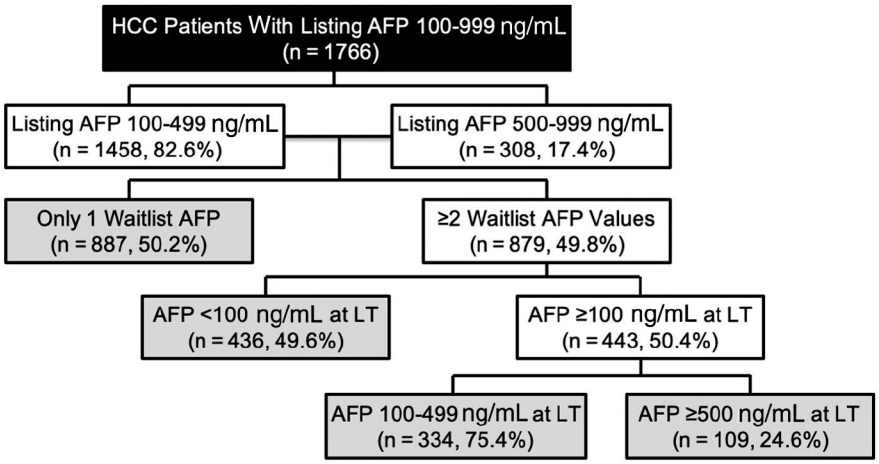

Fig. 1.

AFP category at listing and LT for patients with initial listing AFP levels between 100 and 999 ng/mL. Gray boxes represent primary predictor categories.

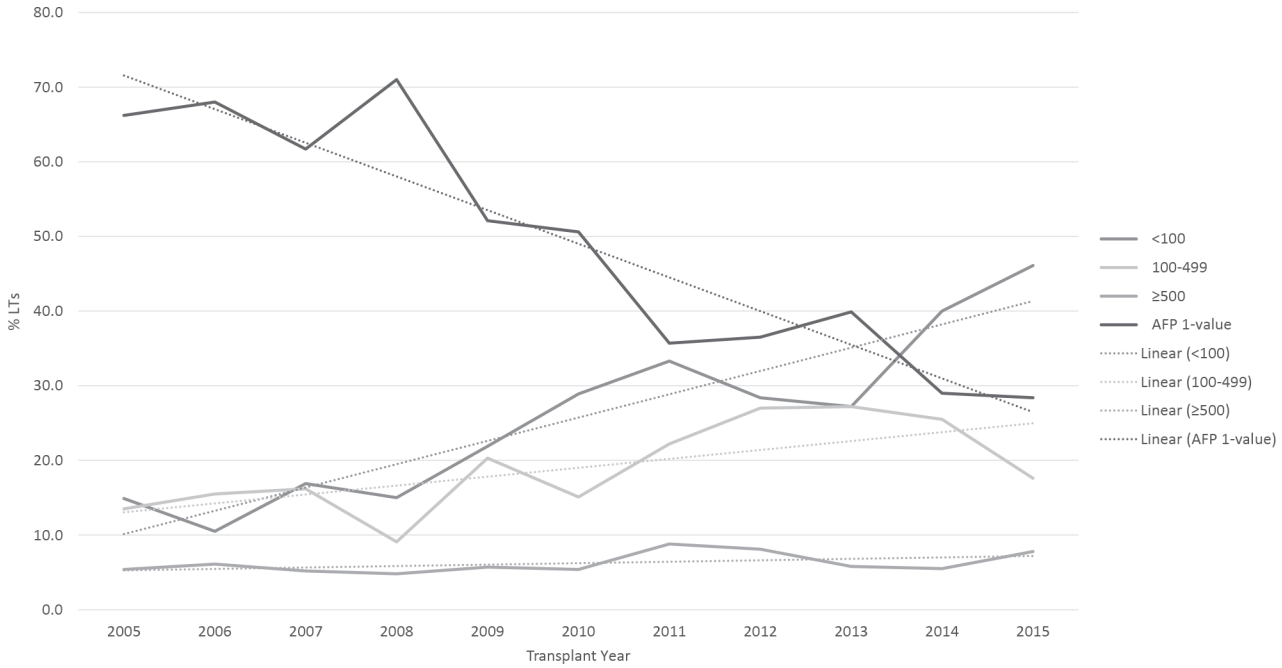

Fig. 2.
Temporal trend in proportion within each AFP category at LT (2005–2015).

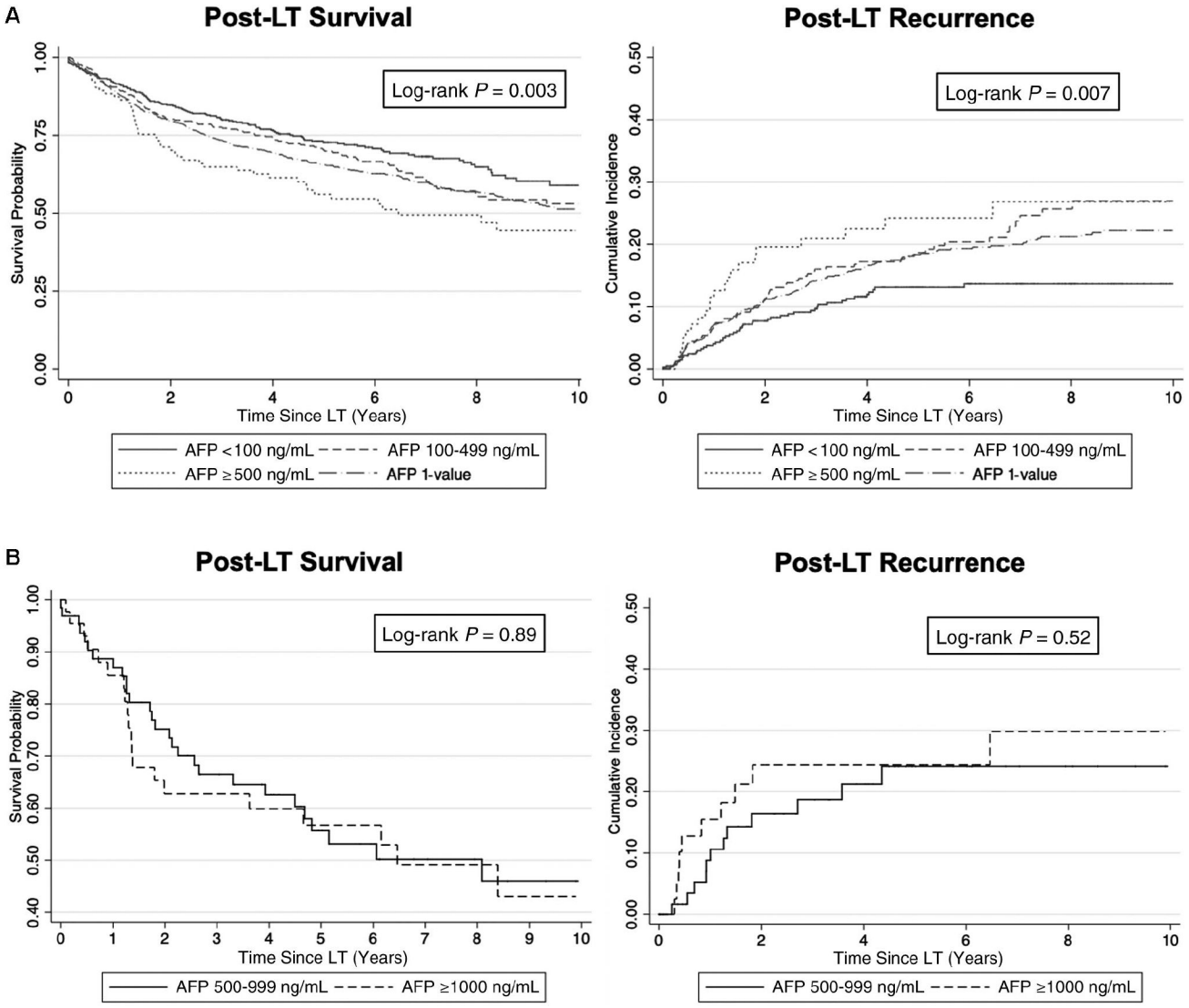

Fig. 3.

KMs for post-LT survival and HCC recurrence rates comparing (A) all AFP at LT categories (n = 1766) and (B) AFP levels 500 to 999 and AFP levels ≥1000 ng/mL at LT (n = 109).

TABLE 1.

Characteristics of Patients With Initial Listing AFP Levels Between 100 and 999 ng/mL Stratified by AFP at LT Category

	AFP at LT Category					
Patient Characteristics	**Overall, n = 1766**	**<100, n = 436**	**100 to 499, n = 334**	**≥500, n = 109**	**1-Value, n = 887**	***P* Value**
Demographics/clinical						
Male sex, %	71.6	70.2	68.9	72.5	73.3	0.40
Race/ethnicity, %						<0.001
Caucasian	58.3	54.1	52.1	54.1	63.3	
Asian	10.2	14.9	9.0	14.7	7.9	
Hispanic	15.5	16.1	19.8	17.4	13.3	
Black	14.8	12.8	17.7	13.8	14.8	
Other	1.2	2.1	1.5	0.0	0.8	
Etiology, %						0.05
HCV	64.6	66.7	70.1	64.2	61.4	
HBV	6.4	7.8	4.5	8.3	6.2	
Alcohol	4.1	13.7	5.4	3.8	4.6	
Autoimmune	2.8	1.8	2.1	0.0	3.0	
NASH	2.5	1.3	1.2	2.8	2.8	
Cryptogenic/other	19.7	17.0	16.8	21.1	21.9	
At listing						
Age, years	57 (53–62)	58 (53–61)	58 (53–62)	57 (51–61)	57 (53–63)	0.19
AFP ng/mL	226 (144–386)	197 (133–339)	206 (142–319)	518 (306–672)	222 (146–393)	<0.001
MELD-Na	10 (8–15)	10 (8–13)	10 (8–14)	10 (8–15)	10 (8–16)	<0.001
CTP class, %						<0.001
A	41.8	47.9	44.6	33.9	38.6	
B	45.0	44.3	46.7	48.6	44.4	
C	13.2	7.8	8.7	17.4	17	
Total tumor diameter, cm	2.9 (2.2–3.8)	2.7 (2.1–3.6)	2.8 (2.1–3.7)	2.4 (1.8–3.5)	3.0 (2.3–4.0)	<0.001
Total tumor number	1 (1–2)	1 (1–1)	1 (1–2)	1 (1–2)	1 (1–2)	0.10
At transplant						
Age, years	58 (54–63)	59 (55–62)	59 (54–63)	58 (53–61)	57 (53–63)	0.01

Patient Characteristics	AFP at LT Category					*P* Value
	Overall, n = 1766	**<100, n = 436**	**100 to 499, n = 334**	**≥500, n = 109**	**1-Value, n = 887**	
AFP ng/mL	172 (100–335)	29 (10–60)	200 (140–280)	887 (633–1694)	222 (146–393)	<0.001
Waitlist time, months	2.9 (1.0–6.4)	7.0 (4.6–11.3)	5.6 (4.0–8.5)	5.6 (3.8–8.6)	1.0 (0.5–1.8)	<0.001
Received LRT, %	68.4	91.3	83.2	68.8	51.4	<0.001
MELD-Na	11 (9–1 7)	11 (8–17)	11 (9–17)	14 (9–18)	11 (9–1 7)	0.26
CTP class, %						0.13
A	35.4	39.2	35.3	30.3	34.2	
B	44.2	42.9	45.5	40.4	44.8	
C	20.4	17.9	19.2	29.4	21.1	
Total tumor diameter, cm	2.6 (1.5–2.7)	1.5 (0.0–3.0)	2.3 (1.0–3.4)	2.6 (1.3–3.9)	3.0 (2.2–4.0)	<0.001
Total tumor number	1 (1–2)	1 (1–1)	1 (1–2)	1 (1–2)	1 (1–2)	<0.001
DRI	1.4 (1.1–1.7)	1.4 (1.1–1.7)	1.5 (1.2–1.7)	1.5 (1.2–1.7)	1.4 (1.1–1.7)	0.32

NOTE: Continuous variables are presented as median (IQR).

TABLE 2.

Multivariable Predictors of Post-LT Mortality and HCC Recurrence

Predictor Variables	HR	95% CI	*P* Value
Post-LT mortality			
AFP at LT category			
<100 ng/mL	Reference		
100 to 499 ng/mL	1.07	0.83–1.38	0.53
≥500 ng/mL	1.50	1.07–2.10	0.02
1-value	1.13	0.91–1.39	0.27
CTP class at LT			
A	Reference		
B	1.33	1.11–1.59	0.002
C	1.64	1.33–2.03	<0.001
Age, per year	1.03	1.01–1.03	<0.001
Race/ethnicity			
Caucasian	Reference		
Black	1.08	0.87–1.35	0.70
Hispanic	0.84	0.67–1.06	0.14
Asian	0.66	0.48–0.89	0.007
Other	1.27	0.65–2.46	0.49
DRI	1.37	1.13–1.66	0.001
Tumor diameter at LT, per cm	1.11	1.06–1.17	<0.001
Post-LT HCC recurrence			
AFP at LT category			
<100 ng/mL	Reference		
100 to 499 ng/mL	1.52	1.04–2.22	0.03
≥500 ng/mL	1.88	1.13–3.14	0.02
1-value	1.22	0.87–1.71	0.26
Age at listing, per year	1.02	1.00–1.03	0.03
Sex			
Male	Reference		
Female	0.71	0.53–0.95	0.02
Race/ethnicity			
Caucasian	Reference		
Black	0.63	0.42–0.94	0.02
Hispanic	0.93	0.67–1.28	0.65
Asian	0.51	0.31–0.83	0.008
Other	0.58	0.14–2.36	0.45
Tumor diameter at LT, per cm	1.15	1.07–1.23	<0.001