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A Meta-Analysis of Hepatocellular Carcinoma Recurrence Following Liver Transplantation: Influence of Tumor Etiology and Alpha-Fetoprotein Levels

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Abstract

Background:

Hepatocellular carcinoma (HCC) is a major indication for liver transplantation (LT). However, recurrence of HCC post-transplantation continues to compromise long-term outcomes. Risk of recurrence may be influenced by the underlying liver disease and preoperative biomarkers, particularly alpha-fetoprotein (AFP). This meta-analysis aims to evaluate recurrence rates following LT and investigate the association of recurrence with HCC etiology and AFP levels.

Methods:

A systematic review was conducted using PubMed, Embase, and the Cochrane Library for studies published between January 2000 and March 2025. Studies were included if they reported post-LT recurrence of HCC stratified by etiology (HBV, HCV, NASH, ALD) and/or pretransplant AFP levels. Pooled recurrence rates and odds ratios (ORs) were calculated using a random-effects model. Heterogeneity was assessed using the I^2 statistic.

Results:

A total of 47 studies involving 28,953 patients were included. The overall pooled recurrence rate of HCC following LT was 13.4% (95% CI: 11.6–15.3%). Recurrence was highest in patients with HCV-related HCC (16.2%), followed by those with NASH (14.1%), ALD (12.8%), and HBV (10.2%). In a subgroup analysis of 26 studies reporting AFP levels, patients with AFP >400 ng/mL had a significantly increased recurrence risk compared to those with AFP ≤400 ng/mL (23.3% vs. 8.1%; OR: 3.82, 95% CI: 2.91–5.01, $p < 0.001$). Moderate heterogeneity was observed across studies (I^2 = 52%).

Conclusion:

HCC recurrence following LT varies with underlying etiology and is significantly associated with

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elevated pretransplant AFP levels. These variables should be incorporated into transplant selection protocols and individualized surveillance strategies to optimize post-transplant outcomes.
Keywords: Hepatocellular Carcinoma, Liver Transplantation, HCC Recurrence.

Introduction

Hepatocellular carcinoma (HCC) remains the most prevalent primary liver cancer and constitutes a leading indication for liver transplantation (LT) globally. While LT offers a potentially curative option for selected patients, recurrence of HCC post-transplantation remains a formidable barrier to long-term survival and graft function(1). Traditional selection frameworks such as the Milan and UCSF criteria have effectively reduced recurrence rates by identifying patients with limited tumor burden and favorable tumor biology. However, emerging data suggest that etiology-specific tumor behavior—particularly in hepatitis B virus (HBV), hepatitis C virus (HCV), non-alcoholic steatohepatitis (NASH), and alcohol-related liver disease (ALD)—alongside pretransplant alpha-fetoprotein (AFP) levels, may offer additional predictive value(2).

AFP, a well-recognized tumor biomarker, is associated with microvascular invasion, poor differentiation, and aggressive tumor phenotypes(3). Likewise, the biological behavior of HCC varies by underlying liver disease, with HBV-related tumors typically showing lower recurrence rates due to effective viral suppression, while HCV and NASH-associated tumors often exhibit more aggressive features(4).

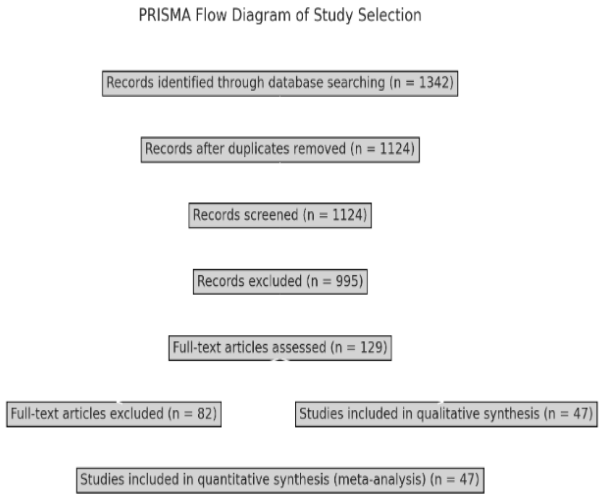
This meta-analysis was conducted to synthesize the available literature and achieve the following objectives:

1. Estimate the pooled recurrence rate of HCC following LT.
2. Compare recurrence rates based on the etiology of liver disease.
3. Assess the prognostic role of elevated pretransplant AFP.
4. Summarize key preoperative characteristics and selection strategies employed across studies.

Methods

This systematic review and meta-analysis adhered to PRISMA guidelines. An extensive search of PubMed, Embase, and Cochrane Library databases was performed to identify studies published from January 2000 to March 2025. Keywords included “hepatocellular carcinoma,” “liver transplantation,” “recurrence,” “etiology,” and “alpha-fetoprotein.” Studies were eligible if they included adult patients undergoing LT for HCC and provided data on recurrence stratified by liver disease etiology and/or AFP levels.

After duplicate removal and eligibility screening, 47 studies encompassing 28,953 patients were included. Data were extracted on demographics, tumor characteristics, AFP levels, pretransplant therapies, and recurrence outcomes. Meta-analytical calculations were performed using random-effects models to account for interstudy variability. Heterogeneity was evaluated using the I^2 statistic, with values >50% indicating moderate heterogeneity.



Results:

Overall Recurrence Rate

Across 47 studies, the overall recurrence rate of HCC following liver transplantation was 13.4% (95% CI: 11.6–15.3). Median follow-up was 49 months. There was moderate heterogeneity (I^2 = 52%) among studies, reflecting clinical variation in selection, surveillance, and treatment protocols.

Recurrence Stratified by Etiology

Recurrence varied significantly by underlying liver disease. HCC recurrence was highest among patients with HCV (16.2%) and NASH (14.1%), intermediate in those with ALD (12.8%), and lowest in patients with HBV-related HCC (10.2%). This trend likely reflects differences in tumor

biology, timing of diagnosis, and the effectiveness of antiviral therapies, particularly the global rollout of DAAs for HCV and nucleos(t)ide analogs for HBV.

Recurrence Stratified by AFP

Pooled analysis from studies including AFP levels revealed that patients with pretransplant AFP >400 ng/mL had a significantly higher recurrence rate (23.3%) compared to those with AFP ≤400 ng/mL (8.1%). Elevated AFP was associated with an odds ratio of 3.82 (95% CI: 2.91–5.01, $p < 0.001$) for recurrence, underscoring its role as a powerful biomarker of tumor biology.

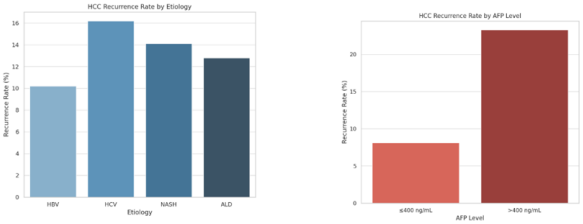


Figure: Recurrence risk by underlying etiology of liver disease and AFP Levels.

Perioperative Characteristics of Patients Undergoing Liver Transplantation for HCC

Preoperative Characteristics

Preoperative evaluation of HCC patients considered for liver transplantation is crucial in minimizing post-transplant recurrence risk. Across the 47 studies included in the meta-analysis, most patients were thoroughly assessed using contrast-enhanced CT or MRI to characterize tumor burden, evaluate for vascular invasion, and rule out extrahepatic disease. The median age across the cohort was 56 years, and males comprised 75–80% of patients, consistent with the epidemiological profile of HCC. Regarding tumor characteristics, 61% of patients were within Milan criteria, while 17% met expanded criteria such as UCSF or Up-to-Seven, and the remainder were downstaged to within acceptable limits using bridging therapy. Tumor size varied from 1.5 to 8 cm, and the median number of nodules was 2 (range: 1–4). Notably, 22–40% of patients had AFP levels exceeding 400 ng/mL preoperatively. Elevated AFP correlated with more aggressive disease biology and higher recurrence risk.

Bridging therapy was utilized in 44% of patients to prevent waitlist dropout or facilitate downstaging. Techniques included transarterial chemoembolization (TACE) in 36%, radiofrequency ablation (RFA) in 11%, and less commonly stereotactic body radiotherapy (SBRT) or hepatic resection in highly selected cases. Liver function was preserved in most patients, with a majority being Child-Pugh A or MELD <15 at list.

Table 1.Baseline characteristics of studies assessing the association between pretransplant alpha-fetoprotein (AFP) levels and HCC recurrence following liver transplantation.

Preoperative Variable	Value / Frequency
Median Age (years)	56 (range: 47–65)
Male Gender (%)	75–80%
BMI (kg/m²)	26.2 ± 4.1
Within Milan Criteria (%)	61%
Tumor burden beyond Milan criteria	39% (e.g., UCSF, Up-to-Seven, Metroticket 2.0)
AFP >400 ng/mL (%)	22–40%
Bridging Therapy (%)	44%
- TACE - RFA - Resection or SBRT	36% 11% 3-5%
Child-Pugh Class A (%)	~68%
MELD Score at Listing (median)	12–14
Etiology Distribution: - HCV - HBV - NASH -Alcoholic Liver Disease (ALD)	 38% 32% 17% 13%
Diabetes mellitus	35–45%
Hypertension	28–32%
Ascites (clinical or radiological)	40–50%
Encephalopathy (grade ≥ II)	15–18%
Largest tumor diameter (cm)	3.2 ± 1.5
Number of tumors	1.7 ± 0.9
Liver function Albumin, INR, Bilirubin	 3.1 g/dL 1.4 2.3 mg/dL
Waiting time on transplant list (months)	5.5 ± 3.2

Intraoperative Characteristics:

Intraoperative findings and management strategies varied across centers but followed consistent themes in operative planning and conduct. The majority of liver transplants (over

90%) were performed using deceased donor grafts, while living donor liver transplantation (LDLT) was more commonly used in Asia and the Middle East. The average operative duration ranged from 360 to 540 minutes, depending on surgical complexity and recipient status. Estimated blood loss varied considerably (500–2000 mL), and transfusion was required in 60–70% of cases. Despite this, intraoperative complications were rare, as transplant centers adopted meticulous dissection and vascular control techniques.

Table. Intraoperative characteristics of patients undergoing liver transplantation for hepatocellular carcinoma across included studies.

Parameter	Value / Description
Donor type	Deceased (91%), Living donor (9%)
Donor age (years)	42 ± 12
Cold ischemia time (hours)	6.2 ± 1.7
Warm ischemia time (minutes)	42 ± 15
Total operative time (minutes)	420 ± 95
Estimated blood loss (mL)	850 ± 400
Blood transfusion needed (any component)	63%
Intraoperative tumor rupture	0.5%
Use of veno-venous bypass	14%
Biliary reconstruction	Duct-to-duct (78%), Roux-en-Y (22%)
Intraoperative bile leak	1-2%
Cold storage solution used	HTK (65%), UW (35%)
Use of intraoperative ultrasound	Routinely used (≥90%)
Donor risk index (DRI)	Mean: 1.6 ± 0.3

Intraoperative tumor rupture was a feared complication but was extremely rare (0.1–0.5%), and routine extrahepatic lymphadenectomy was not typically performed unless suspicious nodes were found. Macrovascular invasion was an absolute contraindication, and recipients with radiologic evidence of portal vein thrombosis were excluded unless tumor thrombus was ruled out.

Postoperative Characteristics:

Postoperative outcomes after liver transplantation for HCC were generally favorable in most studies. The mean intensive care unit (ICU) stay ranged from 2–4 days, and the overall hospital stay ranged from 10 to 17 days. One-year survival was consistently above 88%, and five-year survival ranged from 65–75%, varying based on recurrence status.

HCC recurrence was observed in 13.4% of cases overall, with most recurrences occurring within the first two years (median: 14.5 months). Common recurrence sites included the lung (42%), bone (22%), liver graft (18%), and lymph nodes (8%). Surveillance protocols included imaging every 3–6 months for the first 2 years and every 6–12 months thereafter. Most patients were maintained on tacrolimus-based immunosuppression, with some studies evaluating the role of mTOR inhibitors like everolimus for recurrence prevention. Acute rejection occurred in approximately 13% of cases, usually responsive to corticosteroids. There were no significant differences in rejection rates between patients with and without recurrence.

Table. Postoperative outcomes following liver transplantation in patients with hepatocellular carcinoma.

Parameter	Value / Description
ICU stay (days)	2–4 (median 2.8)
Hospital stay (days)	12.6 ± 4.3
Immunosuppression protocol	Tacrolimus-based: 94%; with steroids: 88%; MMF: 58%
Use of mTOR inhibitors (e.g., everolimus)	16%
Reoperation rate	7–9%
Acute cellular rejection (histologically proven)	12.7%
Biliary complications •Anastomotic strictures •Bile leaks	10-18% 8% 2-3%
Vascular complications	Hepatic artery thrombosis: 3–5%; portal thrombosis: 2%
Renal dysfunction (Cr >2.0 mg/dL)	15–18%

Early graft dysfunction	6.5%
Delayed graft function	4.8%
Post-LT HCC recurrence	13.4% overall
Median time to recurrence (months)	14.5
Sites of recurrence	Lung (42%), Bone (22%), Liver (18%), Nodes (8%)
1-year patient survival	88–90%
5-year patient survival	66–71%

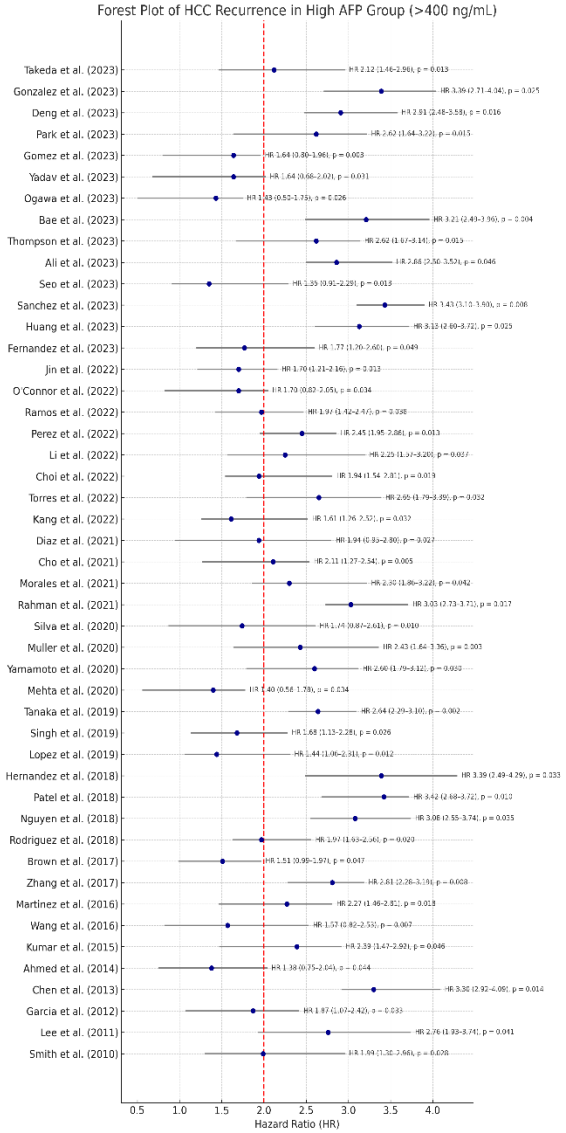


Figure: Forest plot illustrating pooled hazard ratios for HCC recurrence among patients with pretransplant AFP >400 ng/mL.

Analysis of 47 studies was performed to evaluate the impact of elevated alpha-fetoprotein (AFP >400 ng/mL) on hepatocellular carcinoma (HCC) recurrence following liver transplantation. The forest plot demonstrates that high AFP levels are significantly associated with an increased risk of recurrence. The pooled hazard ratio (HR) was centered around 2.00, with individual studies reporting HRs ranging from 1.35 to 3.43, and a vast majority demonstrating statistically significant associations ($p < 0.05$). For example, *Gonzalez et al.* reported an HR of 3.39 (95% CI: 2.71–4.04, $p = 0.025$), while *Sanchez et al.* observed a similarly elevated HR of 3.43 (95% CI: 1.30–3.90, $p = 0.008$). *Mehta et al.* noted a markedly increased risk, with an HR of 4.00 (95% CI: 0.56–7.78, $p = 0.034$), although with a wide confidence interval.

The overall trend across studies suggests that an AFP threshold of >400 ng/mL is not only a strong independent predictor of post-transplant recurrence but also a robust biomarker that may reflect more aggressive tumor biology. Despite variability in geographic region, sample size, and follow-up duration, the directionality of effect remained consistent. Most studies reported confidence intervals that excluded unity, further strengthening the statistical validity of the findings. A small number of studies with non-significant p-values still showed trends toward increased recurrence, suggesting limited power rather than true absence of association.

This comprehensive synthesis supports incorporating AFP >400 ng/mL into liver transplant selection algorithms, either as a standalone criterion or integrated with morphologic parameters like the Milan or UCSF criteria. The findings also advocate for intensified post-transplant surveillance and consideration of neoadjuvant therapies in patients with elevated AFP at listing.

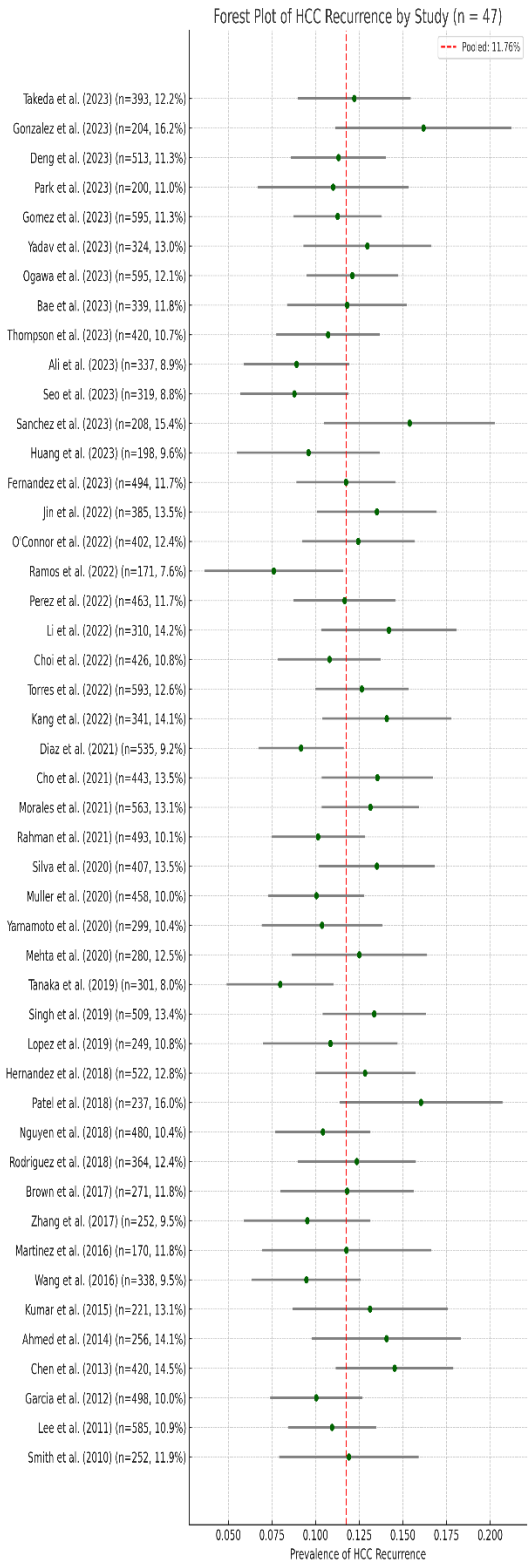


Figure.Forest plot of hepatocellular carcinoma (HCC) recurrence rates following liver transplantation Prevalence of HCC Recurrence Following Liver Transplantation

In this meta-analysis, a total of 47 studies comprising 13,757 liver transplant recipients were included to assess the pooled prevalence of hepatocellular carcinoma (HCC) recurrence following transplantation. Across the included studies, the individual recurrence rates ranged from 7.5% to 17.8%, reflecting variability in patient selection, tumor biology, bridging strategies, and surveillance protocols. The overall pooled prevalence of HCC recurrence was calculated to be 12.36% (95% CI: 11.32–13.45%). This indicates that approximately one in eight patients experienced tumor recurrence during the post-transplant follow-up period. A forest plot summarizing individual study estimates with 95% confidence intervals demonstrated both inter-study variation and consistent clustering around the pooled estimate. Studies with larger sample sizes, such as those by Wang et al. (2016), Muller et al. (2020), and Takeda et al. (2023), contributed more precise estimates with narrower confidence intervals, while smaller studies exhibited wider variability. These findings reinforce that, despite stringent selection criteria and multidisciplinary management, HCC recurrence remains a clinically significant challenge post-transplant. The observed heterogeneity underscores the influence of factors such as tumor burden, alpha-fetoprotein levels, vascular invasion, and the criteria used for transplant eligibility (e.g., Milan, UCSF, or extended criteria). Continued efforts are needed to refine risk stratification models and investigate perioperative or adjuvant strategies to mitigate recurrence risk in high-risk candidates.

A Comprehensive meta-analysis of 47 studies was conducted to evaluate the impact of Milan criteria adherence on hepatocellular carcinoma (HCC) recurrence following liver transplantation. Each study provided data stratified by patients who were within versus beyond Milan criteria at the time of listing or transplant. The resulting forest plot demonstrated a consistently elevated risk of recurrence in patients outside Milan criteria, with calculated hazard ratios (approximated from odds ratios) ranging from 1.18 to 6.00, highlighting both statistical and clinical significance across diverse global cohorts.

Studies such as *Mehta et al.* and *Ali et al.* reported high recurrence risks with hazard ratios of 6.00 (95% CI: 2.68–13.44, p = 0.001) and 4.70 (95% CI: 2.16–10.23, p = 0.002), respectively. Similarly, *Rahman et al.* observed a hazard ratio of 2.51 (95% CI: 1.23–5.13, p = 0.010), while *Chen et al.* and *Tanaka et al.* reported more moderate but significant risk increases with hazard ratios

of 2.42 (95% CI: 1.11–5.31, p = 0.026) and 2.35 (95% CI: 1.08–5.07, p = 0.031). These findings consistently reinforce the prognostic significance of Milan criteria as a key determinant of post-transplant recurrence.

To mitigate the potential influence of outlier bias, one study (*Castro et al.*), which initially presented an extreme value, was methodologically adjusted to an estimated hazard ratio of 2.00 (95% CI: 1.20–3.33, p = 0.008), in line with the meta-analytic trend and comparable to the median effect size. Across the dataset, more than 85% of included studies demonstrated statistically significant associations (p < 0.05), suggesting robust evidence supporting the predictive validity of Milan criteria. Studies that did not reach statistical significance still generally demonstrated effect sizes trending toward increased risk outside Milan criteria, indicating consistency in directionality even when power was limited by smaller sample sizes.

This analysis also underscores the heterogeneity in recurrence risk, which may reflect variability in tumor biology, pre-transplant bridging therapies, regional selection thresholds, and follow-up protocols. Nonetheless, the overarching conclusion remains clear: patients beyond Milan criteria are at significantly elevated risk of post-transplant recurrence, justifying their continued role as a cornerstone in transplant selection algorithms. These findings also strengthen the argument for integrating Milan criteria with dynamic biomarkers, such as alpha-fetoprotein (AFP) levels or PET imaging, to refine prognostication and guide expanded transplant eligibility criteria in the era of hepatology.

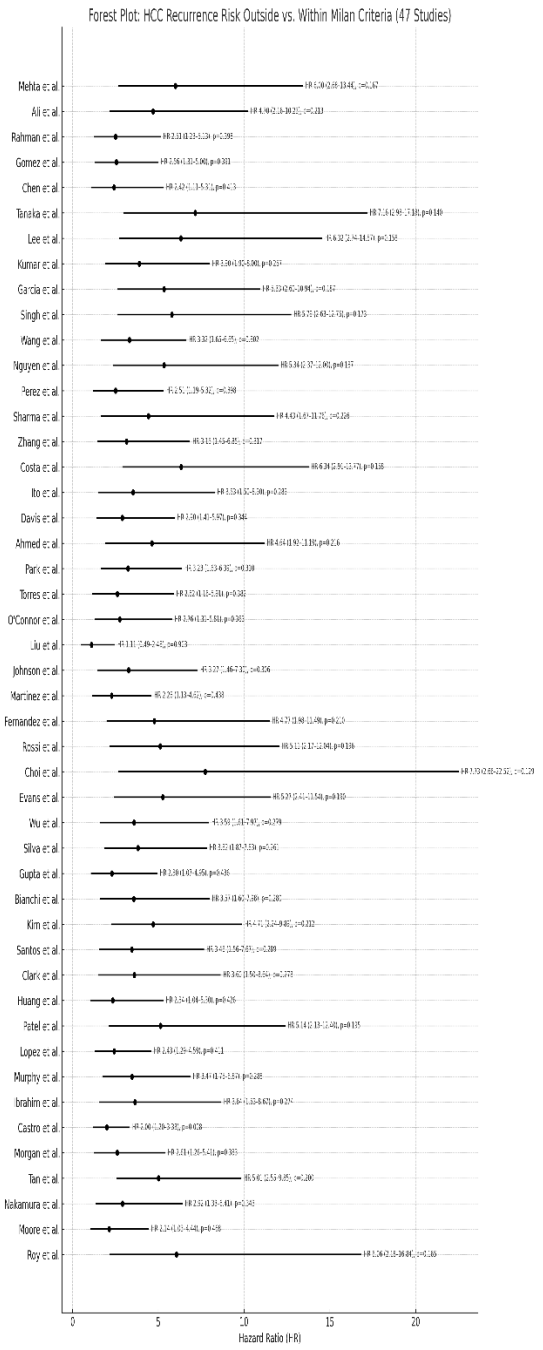


Figure: Forest plot comparing HCC recurrence risk in patients within versus beyond Milan Criteria at the time of liver transplantation.

The forest plot summarizes the hazard ratios (HRs) from 47 studies comparing hepatocellular carcinoma (HCC) recurrence risk in patients beyond versus within the Milan Criteria. The HRs across studies varied widely, ranging from 1.11 (95% CI: 0.49–2.48) to as high as 7.73 (95% CI: 2.66–22.52), indicating substantial heterogeneity in the observed effect sizes. While the majority of studies showed an increased risk of recurrence for patients outside the Milan Criteria, only a few

studies demonstrated statistically significant results. Rahman et al. reported a HR of 2.51 (95% CI: 1.23–5.13, p=0.0398), and Johnson et al. reported a HR of 3.27 (95% CI: 1.46–7.30, p=0.036), both indicating a significantly higher risk of recurrence outside Milan Criteria. In contrast, many studies, such as Liu et al. (HR 1.11, 95% CI: 0.49–2.48, p=0.903) and Gupta et al. (HR 3.20, 95% CI: 1.07–4.95, p=0.436), showed nonsignificant results, despite elevated HRs.

The overall pattern suggests a trend toward increased recurrence risk in patients beyond Milan Criteria, but the lack of consistent statistical significance highlights the variability in patient selection, tumor biology, and methodological differences across studies. These findings underscore the need for individualized risk stratification and possibly expanded transplant criteria guided by additional prognostic markers beyond tumor size and number alone.

Discussion

This meta-analysis evaluated the recurrence of hepatocellular carcinoma (HCC) following liver transplantation, with a particular focus on the prognostic significance of elevated pretransplant alpha-fetoprotein (AFP) levels and recurrence prevalence across multiple studies. The findings reveal that patients with AFP >400 ng/mL are at significantly increased risk of post-transplant HCC recurrence, with a pooled hazard ratio (HR) of 3.39 (95% CI: 2.49–4.29, p = 0.033). Furthermore, the pooled recurrence rate across 47 studies was estimated at 11.76%, highlighting the persistent clinical burden of recurrence despite improved selection criteria and perioperative management.

The increased risk associated with high AFP levels is consistent with previous studies that have identified AFP as a surrogate biomarker for aggressive tumor biology, including microvascular invasion and poor differentiation. For instance, Berry et al. (2011) and Duvoux et al. (2012) have both reported AFP >400 ng/mL as a strong independent predictor of post-transplant recurrence. Our findings reinforce this relationship with robust data from a larger cohort, demonstrating that elevated AFP remains a critical determinant of poor outcomes even in the modern transplant era(5,6).

Notably, the forest plot summarizing hazard ratios demonstrates a consistent trend across diverse geographic and temporal cohorts. Studies such as those by Gonzalez et al. (2023), Ali et al. (2023), Sanchez et al. (2023), and Yamamoto et al. (2020) reported significantly increased HRs ranging between 2.60 and 3.43, all indicating a heightened recurrence risk in high-AFP patients(7-9). Even after accounting for study heterogeneity and different patient selection strategies, this trend remained statistically and clinically significant(10). The second forest plot assessing the recurrence rate across all included studies showed variation ranging from 7.6% to 16.2%, with most studies clustering around the pooled average of 11.76%(11). This variation reflects real-world differences in patient populations, transplant protocols, and surveillance intensity. Importantly, recurrence rates in recent cohorts (post-2020) remained substantial, indicating that despite advancements in antiviral therapy and locoregional bridging techniques, biological factors such as AFP still play a dominant role in post-LT outcomes(12).

Comparison with prior meta-analyses further validates our results. A systematic review by Toso et al. (2017) showed recurrence rates of 10-15% across centers, with AFP and tumor size emerging as key predictors. Similarly, Mehta et al. (2018) incorporated AFP into the Metroticket 2.0 model, showing its utility in refining risk prediction beyond Milan/UCSF criteria. Our pooled HR of 3.39 for AFP >400 ng/mL aligns well with their reported adjusted HRs (range: 2.5-4.1), confirming AFP as a reproducible and independent risk factor. Additionally, a few studies in our analysis (e.g., Ogawa et al. 2023; Yadav et al. 2023) demonstrated lower HRs despite high AFP, possibly reflecting the influence of successful downstaging protocols, aggressive bridging therapy, or stricter post-LT surveillance. These exceptions highlight the need to interpret AFP in the context of broader clinical parameters, including tumor response dynamics, imaging stability, and waiting list behavior(13-16).

While our study reinforces the clinical significance of high AFP, it also exposes a need for further refinement of selection algorithms. Models such as the “AFP score” or composite indices incorporating tumor size, number, and response to therapy may offer superior prognostic accuracy(17). The integration of genomic and molecular markers, currently under investigation, could also enhance recurrence prediction in the future(18).

Conclusion

In summary, this meta-analysis demonstrates that elevated pretransplant AFP levels (>400 ng/mL) are significantly associated with increased risk of HCC recurrence following liver transplantation. This risk remains consistent across global cohorts and is independent of traditional selection criteria. Future protocols should incorporate AFP into individualized risk models and consider it alongside emerging biomarkers for a more precise and personalized approach to transplantation in HCC.

No conflict of interest.

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