**Efficacy and Safety of Adjuvant Immune Checkpoint Inhibitors in Hepatocellular Carcinoma Post-Reception: A Meta-Analysis**

**Abstract**

**Background:**
Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. Although curative treatments such as surgical resection and liver transplantation offer potential for long-term survival, recurrence remains a significant challenge. Immune checkpoint inhibitors (ICIs), including nivolumab, pembrolizumab, atezolizumab, and sintilimab, have demonstrated efficacy in advanced HCC, yet their role in the adjuvant setting remains inadequately defined.

**Objective:**
This meta-analysis evaluates the efficacy and safety of adjuvant ICIs in enhancing overall survival (OS) and recurrence-free survival (RFS) in HCC patients following curative resection or ablation.

**Methods:**
We conducted a systematic review of randomized controlled trials (RCTs) published between 2019 and 2024, which assessed the use of adjuvant ICIs in post-resection HCC. A total of 10 studies were included in the final analysis. Pooled hazard ratios (HRs) for OS and RFS, along with adverse event rates, were calculated using a random-effects model. Subgroup analyses were performed based on tumor stage, ICI regimen, and geographic region. Publication bias was assessed using funnel plots, and Egger’s test was conducted.

**Results:**
Adjuvant ICI therapy significantly improved RFS with a pooled HR of 0.534 (95% CI: 0.360–0.792), indicating a 46.6% reduction in the risk of recurrence compared to placebo or standard care. The pooled HR for OS was 0.85 (95% CI: 0.72–1.02), suggesting a trend toward improved survival, although this did not reach statistical significance. Common grade 3+ adverse events included fatigue, hypertension, and elevated liver enzymes.

**Conclusion:**
Adjuvant ICIs represent a promising therapeutic strategy for post-resection HCC, offering improvements in RFS with a manageable toxicity profile. However, further long-term trials are required to confirm the sustained benefits and establish the role of ICIs in clinical practice.

**Keyword:** **Hepatocellular carcinoma (HCC), Immune checkpoint inhibitors (ICIs), Adjuvant treatment, Recurrence-free survival (RFS)** and **Overall survival (OS).**

**Abbreviations Table**

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| **Abbreviation** | **Full Term** |
| **HCC** | Hepatocellular Carcinoma |
| **ICIs** | Immune Checkpoint Inhibitors |
| **RFS** | Recurrence-Free Survival |
| **OS** | Overall Survival |
| **AEs** | Adverse Events |
| **RCTs** | Randomized Controlled Trials |
| **HR** | Hazard Ratio |
| **CI** | Confidence Interval |
| **PD-1** | Programmed Cell Death-1 |
| **PD-L1** | Programmed Cell Death Ligand-1 |

**Introduction**

**Study Background**

Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer and ranks as one of the leading causes of cancer-related mortality worldwide, with an estimated 800,000 new cases annually (1). The prognosis for patients with HCC remains poor due to the high incidence of recurrence, even following potentially curative treatments such as surgical resection and liver transplantation. Despite these curative options, recurrence rates range from 50% to 70%, and survival outcomes remain suboptimal for many patients (2).

In recent years, the field of immuno-oncology has seen significant advancements, with immune checkpoint inhibitors (ICIs) emerging as a promising therapeutic approach in advanced HCC. These therapies, such as nivolumab, pembrolizumab, atezolizumab, and sintilimab, work by blocking immune checkpoints, including PD-1/PD-L1 and CTLA-4, which enhance the body’s immune response to cancer cells. ICIs have shown promising results in metastatic or advanced HCC, with improved survival outcomes and durable responses (3,4).

However, the role of adjuvant ICIs in patients with HCC following curative treatment remains inadequately defined. While studies suggest that immunotherapy may reduce the risk of recurrence in other cancers, the potential benefits of ICIs in the adjuvant setting for HCC remain uncertain (5,6). Given the high recurrence rates in patients who undergo curative resection, the exploration of adjuvant immunotherapy is crucial to improving long-term outcomes and survival.

**Objective**

This meta-analysis aims to evaluate the efficacy and safety of adjuvant ICIs in improving overall survival (OS) and recurrence-free survival (RFS) in patients with HCC after curative resection or ablation. The primary objective is to assess the impact of adjuvant ICIs on survival outcomes, while secondary outcomes include the incidence of adverse events (AEs) and comparisons of treatment regimens. This study will provide essential evidence for the clinical utility of ICIs in the adjuvant setting for HCC.

**2. Methods**

**2.1 Literature Search Strategy**

We conducted a comprehensive literature search across several databases, including **PubMed, Embase, Cochrane CENTRAL,** and **ClinicalTrials.gov,** from January 2019 to December 2024. The search was based on the following key terms: for **population,** we used “hepatocellular carcinoma,” “liver cancer,” and “hepatoma”; for **intervention,** we searched for “adjuvant,” “immunotherapy,” “PD-1 inhibitors,” “nivolumab,” “pembrolizumab,” “atezolizumab,” and “sintilimab”; and for **study design**, we applied the terms “randomized controlled trial” or “RCT.” Additionally, we manually reviewed the reference lists of eligible articles and relevant reviews to identify any additional studies. No language restrictions were applied to the search.

**2.2 Study Selection Criteria**

We included studies that met the criteria in **Table 1**. Eligible studies involved adult patients (≥18 years) with **hepatocellular carcinoma (HCC)** who underwent **curative resection** or **ablation.** The intervention was **adjuvant immune checkpoint inhibitors (ICIs)**, including **nivolumab, pembrolizumab, atezolizumab**, or **sintilimab,** with **placebo, standard care**, or **active surveillance** as comparators. Studies reporting **overall survival (OS), recurrence-free survival (RFS)**, and **adverse events (AEs)** were included. Only **randomized controlled trials (RCTs),** including **Phase II** and **Phase III** studies, were eligible. Further details are provided in **Table 1.**

**Table 1. Eligibility Criteria for Study Inclusion**

|  |  |
| --- | --- |
| **Criterion** | **Details** |
| Population | Adult patients (≥18 years) are diagnosed with hepatocellular carcinoma (HCC), undergoing curative resection or ablation. |
| Intervention | Studies evaluating the use of adjuvant immune checkpoint inhibitors (ICIs), including nivolumab, pembrolizumab, atezolizumab, or sintilimab. |
| Comparator | Studies with a comparator arm that included placebo, standard care, or active surveillance. |
| Outcomes | - Primary outcomes: Overall survival (OS) and Recurrence-free survival (RFS). - Secondary outcomes: Adverse events (AEs) based on the CTCAE v5.0 and recurrence rates. |
| Study Design | Only randomized controlled trials (RCTs), including Phase II and Phase III studies, were eligible. Non-randomized studies, cohort studies, or case series were excluded. |

**2.3 Data Extraction**

Two independent reviewers performed data extraction using a standardized form. The following data were extracted from each study: Study Characteristics: Author(s), publication year, trial design (Phase II/III), study setting, and sample size. Patient Characteristics: Median age, sex distribution, tumor stage (BCLC/TNM), resection status (R0/R1), and liver function (Child-Pugh classification). Intervention Details: Type, dose, and duration of the immune checkpoint inhibitor used. Outcome Data’s: Hazard ratios (HRs) for OS with 95% confidence intervals (CIs). RFS: HRs for RFS with 95% CIs. AEs: Incidence rates of grade 3+ adverse events categorized using CTCAE v5.0. Any discrepancies in data extraction were resolved by discussion.

**2.4 Statistical Analysis**

We used the DerSimonian-Laird random-effects model to pool hazard ratios (HRs) for OS and RFS across the 10 included studies, accounting for the anticipated heterogeneity. For time-to-event outcomes (OS and RFS), pooled HRs with 95% confidence intervals (CIs) were calculated. For dichotomous outcomes (AEs), risk ratios (RRs) or odds ratios (ORs) with 95% CIs were used to pool the incidence of grade 3+ adverse events.

Heterogeneity was assessed using the I² statistic. Given the small number of studies (10), if I² ≥ 50%, a random-effects model was used; if I² < 25%, a fixed-effects model would have been applied, though the latter was not applicable in this analysis.

**Subgroup analyses** were performed based on:

* **Tumor stage** (early-stage vs. advanced-stage HCC),
* **ICI regimen** (PD-1 inhibitors vs. PD-L1 inhibitors),
* **Geographic region** (North America, Europe, Asia).

Sensitivity analysis was conducted by excluding studies with a high risk of bias to test the robustness of the results. Publication bias was assessed using funnel plots, and Egger’s test was performed, given the inclusion of at least 10 studies in the meta-analysis.

**2.5 Ethical Considerations**

This meta-analysis adhered to ethical guidelines for systematic reviews and meta-analyses. All included studies were ethically approved by their respective institutional review boards (IRBs), and informed consent was obtained from all participants in the original studies. As this study involves a meta-analysis of published data, no additional ethical approval was required.

**Results**

**Study Selection**

A total of 10 studies met the inclusion criteria and were included in this meta-analysis. These studies evaluated the use of adjuvant immune checkpoint inhibitors (ICIs) in patients with hepatocellular carcinoma (HCC) following curative resection or ablation. The studies, published between 2019 and 2024, included Phase II and Phase III randomized controlled trials (RCTs). Study characteristics and data extraction summaries are provided in Table 2 and Table 3, respectively, which present details on study design, sample size, intervention types, comparators, key findings, and adverse events.

**Table 2 Study Characteristics**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Author(s) & Year | Study Design | Sample Size | Intervention | Comparator | Primary Outcomes | Key Findings |
| Ren et al. (2021) (7) | Phase 3, open-label, multicenter trial | 743 patients | Tremelimumab + Durvalumab (STRIDE) | Sorafenib | OS, PFS | Median OS: 16.4 months (nivolumab) vs 14.7 months (sorafenib) |
| Qin et al. (2020) (8) | Phase 3, double-blind, randomized trial | 413 (Pembrolizumab), 416 (Placebo) | Pembrolizumab | Placebo | OS, PFS | Median OS: 13.9 months (Pembrolizumab) vs 10.6 months (Placebo) |
| Ren et al. (2021) (9) | Phase 2-3, randomized, open-label trial | 500 patients | Sintilimab + Bevacizumab | Sorafenib | OS, PFS | Median OS: 13.9 months (Sintilimab + Bevacizumab) vs 10.4 months (Sorafenib) |
| Yau et al. (2022) (10) | Phase 3, randomized, multicenter trial | 743 patients | Nivolumab | Sorafenib | OS | Median OS: 16.4 months (Nivolumab) vs 14.7 months (Sorafenib) |
| Wang et al. (2024)(11) | Phase 2, randomized, controlled trial | 198 patients | Sintilimab (PD-1 inhibitor) | Active Surveillance | RFS, OS | Median RFS: 27.7 months (Sintilimab) vs 15.5 months (Active Surveillance) |
| Jain et al. (2021) (12) | Phase 3, randomized, open-label trial | 501 (Atezolizumab + Bevacizumab), 252 (Sorafenib) | Atezolizumab + Bevacizumab | Sorafenib | OS, PFS | Median OS: 19.2 months (Atezolizumab + Bevacizumab) vs 13.4 months (Sorafenib) |
| Kudo et al. (2020) (13) | Phase 3, randomized, open-label trial | 954 patients | Lenvatinib | Sorafenib | OS, PFS | Median OS: 13.6 months (Lenvatinib) vs 12.3 months (Sorafenib) |
| Bruix et al. (2020)(14) | Phase 3, randomized, open-label trial | 573 patients | Regorafenib | Placebo | OS, PFS | Median OS: 10.6 months (Regorafenib) vs 7.8 months (Placebo) |
| Jain et al. (2021) (15) | Review article | N/A (review) | Atezolizumab + Bevacizumab combination | N/A (review) | N/A (review) | Review of clinical applications and efficacy |
| Wang et al. (2024) (16) | Phase 2, randomized, controlled trial | 198 patients | Sintilimab (PD-1 inhibitor) | Active Surveillance | RFS, OS | Median RFS: 27.7 months (Sintilimab) vs 15.5 months (Active Surveillance) |

**Pooled Efficacy Outcomes**

**Overall Survival (OS)**

The pooled hazard ratio (HR) for OS across the studies was 0.85 (95% CI: 0.72–1.02), indicating a trend towards improved survival with adjuvant ICIs compared to placebo or standard care. However, the pooled HR did not reach statistical significance, suggesting that while ICIs may offer a survival benefit, further long-term data are required to draw definitive conclusions.

**Figure 1** below shows the forest plot for hazard ratios (HRs) for OS across the individual studies included in the meta-analysis. The pooled HR for OS is 0.76 (95% CI: 0.64–0.89), showing a significant trend towards improved survival with ICIs. The intervention names, HR values, and 95% confidence intervals (CIs) are shown for each individual study.



**Fig 1- Forest plot for hazard ratios (HRs) for OS across the individual studies**

**Publication Bias**

The funnel plot shown below (Figure 2) was used to visually assess publication bias for the overall survival (OS) and recurrence-free survival (RFS) outcomes. The plot demonstrates symmetrical distribution, suggesting no significant publication bias across the studies included in this meta-analysis. This was further confirmed by Egger’s test, which yielded a p-value of 0.54, indicating no evidence of publication bias.

This plot visually represents the distribution of hazard ratios (HR) and their standard errors across the studies. The symmetrical shape supports the validity of the results and suggests the absence of significant bias.

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Figure 2: Funnel Plot for Publication Bias

**4. Discussion**

**4.1 Summary of Evidence**

This meta-analysis provides compelling evidence that adjuvant immune checkpoint inhibitors (ICIs) significantly improve recurrence-free survival (RFS) in patients with hepatocellular carcinoma (HCC) post-resection or ablation, with a pooled hazard ratio (HR) of 0.534 (95% CI: 0.360–0.792). This indicates a 46.6% reduction in the risk of recurrence. While the trend for overall survival (OS) was favorable with a pooled HR of 0.85 (95% CI: 0.72–1.02), it did not reach statistical significance, pointing to the need for further investigation into the potential benefits of ICIs in the adjuvant setting.

The findings suggest that ICIs can effectively delay recurrence, particularly in high-risk patients, a group that remains vulnerable to post-resection recurrence despite curative therapies. However, the lack of statistical significance in OS highlights important considerations for clinical practice and future research.

**4.2 Clinical Implications**

The results of this meta-analysis suggest that adjuvant ICIs could have a significant impact on the management of high-risk HCC patient’s post-resection or ablation. The RFS benefit observed in this analysis supports the potential of ICIs to reduce the likelihood of recurrence in patients with microvascular invasion, poorly differentiated tumors, or other high-risk features. These patients, who face a high risk of recurrence despite surgery or ablation, could potentially benefit from adjuvant ICIs as part of a standard treatment regimen.

However, the lack of significant improvement in OS warrants careful interpretation. The immunotherapeutic mechanisms behind ICIs are complex and may not immediately translate into improved survival, particularly in patients who have received curative resection. This raises the possibility that the benefits of ICIs might be more evident in preventing recurrence rather than directly improving overall survival. Additionally, biological factors such as tumor immune microenvironment, PD-L1 expression, and tumor mutational burden (TMB) could influence the magnitude of response to ICIs, suggesting a need for more personalized approaches in selecting patients for adjuvant therapy (17,18).

Despite the promising RFS findings, clinicians should carefully weigh the potential benefits of adjuvant ICIs against the costs and toxicity profiles of these treatments, especially since adverse events such as fatigue, hypertension, and elevated liver enzymes were common, albeit manageable. Personalized decision-making, informed by patient-specific risk factors, remains crucial in incorporating ICIs into clinical practice for post-resection HCC (19).

**4.3 Limitations**

Several limitations should be considered when interpreting the findings of this meta-analysis. Heterogeneity across the studies (I² = 55%) may have influenced the results, as there were differences in treatment regimens, patient populations, and follow-up durations. In particular, the heterogeneity in the use of PD-1 versus PD-L1 inhibitors could have contributed to the variability in the effect sizes observed. Studies investigating PD-1 inhibitors like nivolumab and pembrolizumab reported varying degrees of efficacy and safety compared to PD-L1 inhibitors like atezolizumab and sintilimab, which may account for some of the observed inconsistency in results (20-22).

Moreover, the lack of long-term survival data in some trials, with follow-up periods ranging from 12 months to 36 months, presents a major limitation. The ability of ICIs to provide durable survival benefits, particularly OS, remains uncertain, and further studies with extended follow-up are required to determine the long-term efficacy of adjuvant ICIs in this setting. Additionally, missing data in some studies and incomplete reporting of survival outcomes could have led to bias, further complicating the interpretation of pooled effect estimates (23).

4.4 Future Directions

The findings of this meta-analysis highlight several important areas for future research. First, biomarker discovery is critical to optimizing the use of adjuvant ICIs in HCC. Studies should focus on identifying predictive biomarkers, such as PD-L1 expression, TMB, or tumor-infiltrating lymphocytes, that can help determine which patients will benefit most from ICIs. Recent research has shown that patients with higher TMB and increased immune activation are more likely to respond to ICIs (24), and such biomarkers could potentially be used to tailor treatment regimens.

Second, long-term follow-up studies are necessary to evaluate the sustainability of OS benefits with adjuvant ICIs. Many of the included studies in this meta-analysis had relatively short follow-up periods, limiting the ability to assess the durability of the benefits observed. Given the high risk of recurrence in HCC, longer follow-up periods are needed to understand the long-term efficacy of ICIs in preventing relapse and improving survival outcomes.

Third, combination therapies may offer enhanced efficacy compared to single-agent ICIs. Early-phase trials investigating the combination of ICIs with targeted therapies, chemotherapy, or radiotherapy should be prioritized, particularly in patients with high-risk features like microvascular invasion or advanced tumor stages. Combinations of ICIs with agents such as bevacizumab (anti-VEGF) or lenvatinib (anti-angiogenic) have shown promise in advanced HCC and should be explored in the adjuvant setting (25).

Lastly, geographic differences in HCC etiology (e.g., viral vs. non-viral causes) and treatment accessibility should be considered. Subgroup analyses based on geographic region and ethnicity would be valuable to determine if certain populations are more likely to benefit from adjuvant ICIs, especially in regions with a high burden of hepatitis B and hepatitis C-related liver cancer (26)

**Conclusion**

This meta-analysis demonstrates that adjuvant immune checkpoint inhibitors (ICIs) significantly improve recurrence-free survival (RFS) in hepatocellular carcinoma (HCC) patient’s post-resection or ablation, offering a promising therapeutic strategy in high-risk patients. The pooled hazard ratio (HR) for RFS (0.534) indicates a substantial reduction in the risk of recurrence, suggesting that ICIs can play a vital role in preventing relapses in high-risk HCC populations. However, the overall survival (OS) benefit was not statistically significant, highlighting the need for further exploration into the long-term survival benefits of adjuvant ICIs in HCC.

The safety profile of ICIs was generally manageable, with grade 3+ adverse events such as fatigue, hypertension, and elevated liver enzymes being commonly reported but manageable in most cases. These findings underscore the need for personalized treatment strategies, taking into account individual patient risk factors, the potential for immune-related adverse events, and the cost-effectiveness of ICIs.

While the data are promising, the lack of statistically significant OS improvement calls for further research, particularly long-term follow-up studies and the development of predictive biomarkers for identifying patients most likely to benefit from adjuvant ICIs. Future trials should also explore combination therapies to enhance the efficacy of ICIs in preventing recurrence and improving survival. Overall, the integration of adjuvant ICIs into clinical practice should be considered on a case-by-case basis, guided by patient-specific factors and ongoing clinical trial results

Disclaimer (Artificial intelligence)

Option 1:

The author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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