

# INPLASY

## Efficacy and Safety of Tyrosine Kinase Inhibitors in Advanced Hepatocellular Carcinoma Patients with Child-Pugh A and B Cirrhosis: A Meta-Analysis

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### ADMINISTRATIVE INFORMATION

**Support** - No funding.

**Review Stage at time of this submission** - Completed but not published.

**Conflicts of interest** - None declared.

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**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 October 2024 and was last updated on 30 October 2024.

### INTRODUCTION

**Review question / Objective** The objective of this review is to assess the efficacy and safety of guideline-recommended tyrosine kinase inhibitors (TKIs), including sorafenib, lenvatinib, regorafenib, and cabozantinib, in advanced hepatocellular carcinoma (HCC) patients stratified by Child-Pugh classification (Child-Pugh A [CPA] and Child-Pugh B [CPB]). The review seeks to determine whether there is a difference in outcomes between these two groups, focusing on treatment efficacy (ORR, DCR) and safety (grade  $\geq 3$  treatment-related adverse events).

**Rationale** Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, and tyrosine kinase inhibitors (TKIs) are widely used for managing advanced HCC. While TKIs are effective, liver function significantly influences treatment tolerability and outcomes. Previous studies have primarily evaluated individual TKIs like sorafenib, often excluding

patients with compromised liver function (Child-Pugh B [CPB]). This review aims to address this gap by synthesizing data on multiple TKIs in patients with different liver function statuses (Child-Pugh A [CPA] vs. Child-Pugh B [CPB]). By providing a comprehensive analysis, this study will inform clinical decisions and potentially expand treatment options for CPB patients.

**Condition being studied** This review focuses on hepatocellular carcinoma (HCC), a common and deadly primary liver cancer, particularly in patients with advanced stages of the disease. The study specifically considers the role of liver function, as classified by the Child-Pugh system, in influencing the safety and efficacy of tyrosine kinase inhibitors (TKIs) for advanced HCC treatment.

### METHODS

**Search strategy** The literature search will be conducted across major databases, including PubMed, Web of Science, and Cochrane Library,

to identify studies relevant to the efficacy and safety of tyrosine kinase inhibitors (TKIs) in advanced hepatocellular carcinoma (HCC) patients stratified by Child-Pugh classification (Child-Pugh A [CPA] vs. Child-Pugh B [CPB]). The following search terms and combinations will be employed:

#### PubMed

("Tyrosine Kinase Inhibitors"[Mesh] OR "tyrosine kinase inhibitor\*" [tiab] OR TKI [tiab] OR sorafenib [tiab] OR lenvatinib [tiab] OR regorafenib [tiab] OR cabozantinib [tiab] OR axitinib [tiab] OR sunitinib [tiab] OR apatinib [tiab] OR vandetanib [tiab] OR tivozanib [tiab] OR nintedanib [tiab]) AND ("Carcinoma, Hepatocellular"[Mesh] OR "hepatocellular carcinoma" [tiab] OR HCC [tiab] OR "liver cancer" [tiab] OR hepatoma [tiab]) AND ("Child-Pugh Class B" [tiab] OR "Child-Pugh B" [tiab] OR "Child Pugh B" [tiab] OR "Child-Pugh score B" [tiab] OR "Child-Pugh grade B" [tiab] OR "Child-Pugh classification B" [tiab]) AND ("Advanced" [tiab] OR "advanced stage" [tiab] OR "stage III" [tiab] OR "stage IV" [tiab] OR unresectable [tiab])

#### Web of Science

TS=("tyrosine kinase inhibitor\*" OR TKI OR sorafenib OR lenvatinib OR regorafenib OR cabozantinib OR axitinib OR sunitinib OR apatinib OR vandetanib OR tivozanib OR nintedanib) AND TS=("hepatocellular carcinoma" OR HCC OR "liver cancer" OR hepatoma) AND TS=("Child-Pugh B" OR "Child Pugh B" OR "Child-Pugh class B" OR "Child-Pugh grade B" OR "Child-Pugh score B" OR "Child-Pugh classification B") AND TS=("advanced" OR "advanced stage" OR "stage III" OR "stage IV" OR unresectable)

#### Cochrane Library

("Hepatocellular Carcinoma" OR "Liver Cancer" OR HCC) AND ("Tyrosine Kinase Inhibitors" OR TKIs OR sorafenib OR lenvatinib OR regorafenib OR cabozantinib OR ramucirumab) AND ("Child-Pugh A" OR "Child-Pugh B" OR "Liver Cirrhosis" OR "Liver Function") AND (efficacy OR survival OR outcomes)

For all databases, the search will be limited to English or Spanish language studies. Additional inclusion criteria include a focus on TKI monotherapy, with exclusion criteria applied to studies involving combination therapies (e.g., TKI combined with immune checkpoint inhibitors). The reference lists of relevant articles will be screened to identify any additional eligible studies.

**Participant or population** The review will focus on patients with advanced hepatocellular carcinoma

(HCC) who are categorized by liver function status as either Child-Pugh A (CPA) or Child-Pugh B (CPB).

**Intervention** The interventions to be evaluated include guideline-recommended tyrosine kinase inhibitors (TKIs), specifically sorafenib, lenvatinib, regorafenib, and cabozantinib, used in the treatment of advanced hepatocellular carcinoma (HCC).

**Comparator** The primary comparison will be between Child-Pugh A (CPA) and Child-Pugh B (CPB) patient groups to assess variations in efficacy and safety outcomes associated with TKI therapy in these populations.

**Study designs to be included** This review will include observational studies (retrospective and prospective cohorts), randomized controlled trials, and case-control studies that evaluate the efficacy and safety of TKIs in CPA and CPB patients with advanced HCC.

**Eligibility criteria** Inclusion criteria:

Studies must involve patients with advanced HCC treated specifically with TKI monotherapy. Studies should report data on Child-Pugh A and Child-Pugh B classifications. Outcome data on efficacy (ORR, DCR) or safety (grade  $\geq 3$  adverse events) must be provided.

Exclusion criteria:

Studies that focus on combination therapies (e.g., TKIs with immune checkpoint inhibitors) rather than TKI monotherapy. Studies not addressing primary liver cancer or lacking clear Child-Pugh classification data. Studies that do not report on the relevant outcomes of interest (efficacy and safety).

**Information sources** The review will use information from databases such as PubMed, Web of Science, and Cochrane Library. Additionally, reference lists of identified studies and relevant review articles will be manually screened to identify further eligible studies.

**Main outcome(s)** The primary outcomes are efficacy (measured by overall response rate [ORR] and disease control rate [DCR]) and safety (measured by the incidence of grade  $\geq 3$  treatment-related adverse events) of TKIs in CPA and CPB patients.

**Data management** Data will be managed using Microsoft Excel for initial organization and extraction. Relevant study characteristics, patient

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demographics, intervention details, and outcomes will be systematically recorded in a structured data extraction form. Meta-analysis will be conducted using statistical software (e.g., R software).

**Quality assessment / Risk of bias analysis** The quality of included studies will be assessed using the Cochrane Risk of Bias tool for randomized controlled trials and the Newcastle-Ottawa Scale (NOS) for observational studies. Risk of bias assessment will be performed independently by two reviewers, with any discrepancies resolved by discussion or a third reviewer.

**Strategy of data synthesis** Data will be synthesized using a meta-analysis approach if sufficient homogeneous data are available. Random-effects or fixed-effects models will be applied depending on heterogeneity levels, assessed by Cochran's Q and  $I^2$  statistics. Odds ratios (ORs) with 95% confidence intervals (CIs) will be calculated for dichotomous outcomes, and a narrative synthesis will be conducted if meta-analysis is not feasible.

**Subgroup analysis** Subgroup analyses may be conducted based on specific TKIs (e.g., sorafenib vs. lenvatinib) and different baseline characteristics, such as patient age, sex, and prior treatment history, if the data allow.

**Sensitivity analysis** Sensitivity analyses will be performed by excluding studies with high risk of bias, small sample sizes, or significant outliers to assess the robustness of the primary findings.

**Language restriction** ENGLISH; SPANISH.

**Country(ies) involved** China.

**Keywords** Hepatocellular carcinoma; Tyrosine kinase inhibitors; Child-Pugh classification; Liver cirrhosis; Advanced HCC; Efficacy; Safety.

#### **Contributions of each author**

Author 1 - Xionglin Liu - Xionglin Liu conducted the literature search, data collection, and analysis. Xionglin Liu drafted the manuscript.

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