# INPLASY PROTOCOL

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Conflicts of interest:
**The authors declare that they have no competing interests.**

## Transcatheter hepatic arterial chemoembolization combined with Kangai injection for hepatitis B virus-related hepatocellular carcinoma: protocol for a PRISMA-compliant meta-analysis

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**Review question / Objective:** Is Kangai injection effective on curative effect, clinical symptoms, virological indicators, quality of life (QoL) and immune function in patients with HBV-related hepatocellular carcinoma (HCC)?

**Condition being studied:** Hepatitis B virus-related hepatocellular carcinoma, Kangai injection, clinical symptoms, immune function and quality of life.

**Information sources:** Electronic databases including Google Scholar, PubMed, Excerpt Medica Database (Embase), Cochrane Library, Medline, Web of Science (WOS), China National Knowledge Infrastructure (CNKI), China Scientific Journal Database (CSJ) Chinese, Biomedical Literature Database (CBM) and Wanfang Database will be systematically searched for eligible clinical trials from January 2000 to September 2020. Language is limited with English and Chinese.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 September 2020 and was last updated on 03 September 2020 (registration number INPLASY202090014).

## INTRODUCTION

**Review question / Objective:** Is Kangai injection effective on curative effect, clinical symptoms, virological indicators, quality of life (QoL) and immune function in patients with HBV-related hepatocellular carcinoma (HCC)?

**Rationale:** Kangai injection, a well-known insect-derived traditional Chinese medicine preparation, has been widely applied as a

promising adjunctive drug for hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC). However, its exact clinical efficacy and safety is still not well investigated. In this study, we aimed to summarize the efficacy and safety of Kangai injection for patients with HBV-related HCC through the meta-analysis.

**Condition being studied:** Hepatitis B virus-related hepatocellular carcinoma, Kangai injection, clinical symptoms, immune function and quality of life.

## METHODS

**Search strategy:** To perform a comprehensive and focused search, experienced systematic review researchers will be invited to develop a search strategy. The plan searched terms are as follows: "hepatitis B virus" or "HBV" or "liver cancer" or "hepatocellular carcinoma" or "hepatitis B virus-related liver cancer" or "hepatitis B virus-related hepatocellular carcinoma" or "HBV-related liver cancer" or "HBV-related hepatocellular carcinoma" or "LC" or "HCC" and "transcatheter hepatic arterial chemoembolization" or "transcatheter arterial chemoembolization" or "TACE" et al. An example of search strategy for PubMed database shown in Table 1 will be modified and used for the other databases.

**Participant or population:** Patients must be cytologically or pathologically confirmed as having HBV-related HCC according to the National Comprehensive Cancer Network (NCCN) Clinical Guidelines for HCC. Patients with other malignancies or non-HBV-related HCC are not included. No restrictions regarding age, gender, racial, region, education and economic status in this analysis protocol.

**Intervention:** HBV-related HCC patients in the experimental group must be treated with transcatheter hepatic arterial chemoembolization (TACE) combined with Kangai injection.

**Comparator:** HBV-related HCC patient in the control group was treated with TACE only.

**Study designs to be included:** All available comparative clinical trials that assessed the efficacy of Kangai injection in the treatment of HBV-related HCC patients will be included.

**Eligibility criteria:** This study will include randomized controlled trials (RCTs) or quasi-RCTs, and high-quality prospective cohort studies that investigated the efficacy and safety of Kangai injection for the treatment of patients diagnosed with HBV-related HCC will be included in this systematic review. Papers without sufficient available data, non-comparative clinical trials, non-peer reviewed studies, literature reviews, meta-analysis, meeting abstracts, case reports, letter to the editor, and other unrelated researches will be excluded from analysis.

**Information sources:** Electronic databases including Google Scholar, PubMed, Excerpt Medica Database (Embase), Cochrane Library, Medline, Web of Science (WOS), China National Knowledge Infrastructure (CNKI), China Scientific Journal Database (CSJ) Chinese, Biomedical Literature Database (CBM) and Wanfang Database will be systematically searched for eligible clinical trials from January 2000 to September 2020. Language is limited with English and Chinese.

**Main outcome(s):** The primary outcomes will include: (i) Overall response rate (ORR, complete response + partial response) and disease control rate (DCR, complete response + partial response + stable disease); (ii) QoL as evaluated by Karnofsky score; (iii) Clinical symptoms, such as abdominal pain and distension, fatigue, and loss of appetite; (iv) Virological indicators: Quantitative detection of HBV-Deoxyribonucleic acid (HBV-DNA) and hepatitis B e antigen (HBeAg).

**Additional outcome(s):** Secondary outcomes will include: (i) Immune function indicators: CD3+, CD4+, CD8+, natural

killer (NK) cells percentage, and CD4+/CD8+ cell ratios, and serum cytokines level [Interleukin-2 (IL-2), Interleukin-4 (IL-4), Interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α)]; (ii) Adverse events: toxicity was graded from 0 to IV in severity on the basis of the World Health Organization (WHO) recommendations.

**Data management:** Two investigators (Wanpeng Wang and Shurong Wang) will be responsible for the data extraction independently according to the Cochrane Handbook for Systematic Reviews of Intervention. The following data will be extracted from eligible literatures: Study characteristics and methodology: country of study, the first author's name, year of publication, randomization and follow-up duration, et al; Participant characteristics: tumor stage, sample size, age, gender, ethnicity, pathology diagnosis, pathologic tumor size, inclusion and exclusion criteria, et al; Interventions: therapeutic means, dosage of Kangai injection, administration route and cycles, and duration of treatment, et al; Outcome and other data: ORR, DCR, QoL, clinical symptoms, virological indicators, immune indexes, and adverse effects, et al. Dealing with missing data: we will attempt to contact the authors via email to request the missing or incomplete data. If those relevant data are not acquired, we will use the available data for data synthesis.

**Quality assessment / Risk of bias analysis:** Two review investigators (Wanpeng Wang and Shurong Wang) will be assessed risk of bias of the included RCTs by independently based on the Cochrane bias risk tool. There are seven items in total, including: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Evidence quality will be classified as low risk, high risk, or unclear risk of bias. EPOC guidelines will be used to assess the risks of non-RCTs. Any disagreements will be resolved via discussion with a third researcher (Jia Liu).

**Strategy of data synthesis:** We will utilize Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata 14.0 (Stata Corp., College Station, TX, USA) statistical software to pool the data and carry out the data analysis. For continuous data, the extracted data will be presented as standardized mean difference (SMD) with their confidence intervals (CIs). Dichotomous data will be recorded as risk ratio (RR) with 95% CIs. A two-tailed $P < 0.05$ was considered statistically significant. Heterogeneity between studies will be assessed using the Cochran's Q and Higgins I2 statistic. $P < 0.1$ for the Chi2 statistic or an I2 > 50% will be considered as showing considerable heterogeneity. A fixed effect model will be used to calculate the outcomes when statistical heterogeneity is absent; otherwise, the random effects model will be used for analysis.

**Subgroup analysis:** If the included studies are sufficient (at least 10 trials), subgroup and meta-regression analysis will be conducted to explore the source of heterogeneity with respect to tumor stage, region, course of treatment and therapeutic regimens, et al.

**Sensibility analysis:** Sensitivity analysis will be carried out to assess the reliability and robustness of the pooled results via eliminating trials with low quality. A summary table will report the results of the sensitivity analyses.

**Language:** Language is limited with English and Chinese.

**Country(ies) involved:** China.

**Other relevant information:** (i) Publication bias analysis: Funnel plot, Begg's and Egger regression test will be performed to analyze the existence of publication bias if 10 or more studies are included in the meta-analysis. If reporting bias is suspected, we will consult the study author to get more information. If publication bias existed, a trim-and-fill method should be applied to coordinate the estimates from unpublished studies, and the adjusted

results were compared with the original pooled RR. (ii) Evidence evaluation: We will use the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) to assess the quality of evidence and the strength of the main result recommendations. The quality of all evidence will be evaluated as 4 levels: high, moderate, low, and very low.

**Keywords:** Hepatitis B virus-related hepatocellular carcinoma, Kangai injection, clinical symptoms, immune function, quality of life.

**Dissemination plans:** We will disseminate the results of this systematic review by publishing the manuscript in a peer-reviewed journal.

**Contributions of each author:**
Author 1 - Wanpeng Wang - Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing-original draft, Writing-original draft.
Author 2 - Shurong Wang - Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft.
Author 3 - Jia Liu - Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft.
Author 4 - Yan Liu - Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft.
Author 5 - Ying Mu - Funding acquisition, Methodology, Validation, Writing-review & editing.
Author 6 - Jing Wang - Conceptualization, Project administration, Resources, Software, Supervision, Validation, Writing-review & editing.