INPLASY PROTOCOL

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None declared.

Efficacy and safety of acupuncture combined with Chinese herbal medicine in the treatment of primary liver cancer: A protocol for systematic review and meta-analysis

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Review question / Objective: **The aim of this systematic review is to valuate the efficacy and safety of acupuncture combined with Chinese herbal medicine in the treatment of primary liver cancer inform clinical practice. To this end, the proposed systematic review will address the following question: Which is the best choice to effective in improving The short-term curative effect is effective, the quality of life is stable, and the survival rate of patients is six months/one year in patients with primary liver cancer, acupuncture combined with Chinese herbal medicine or the best supportive treatment?**

Information sources: **We will search the following databases: PubMed, Web of Science, Embase, AMED, Cochrane Library, CNKI, VIP, CBM, and Wanfang. Additionally, we will manually search all reference lists from relevant systematic reviews to find other eligible studies. We will exclude all conference records, reviews, meta-analyses, newspapers, guides, letters and other documents. When the full text or the required information in the analysis process was missing, the author of the studies was contacted for data.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 August 2021 and was last updated on 26 August 2021 (registration number INPLASY202180103).

INTRODUCTION

Review question / Objective: **The aim of this systematic review is to valuate the efficacy and safety of acupuncture combined with Chinese herbal medicine in the treatment of primary liver cancer inform clinical practice. To this end, the proposed systematic review will address the following question: Which is the best choice to effective in improving The short-term curative effect is effective, the quality**

of life is stable, and the survival rate of patients is six months/one year in patients with primary liver cancer, acupuncture combined with Chinese herbal medicine or the best supportive treatment ?

Condition being studied: Primary liver cancer (PLC) is a common cancer, and its morbidity and mortality are ranked 6th and 3rd in the world for malignant tumors, respectively [1]. According to statistics, there were 841,080 new cases and 781,631 deaths in 2018, accounting for 4.8% and 8.2% of all new cancer cases in the world, and this number is still on the rise, seriously endangering people's health [2]. Although there are many treatment methods, such as surgical treatment, chemotherapy, interventional therapy, and molecular targeted therapy, they have many limitations in the scope of application (such as liver function Child-Push score and tumor staging). Moreover, the efficacy of the above treatments did not meet expectations, so the mortality and prognosis of PLC still have not been improved [3, 4]. In short, the difficult-to-treat characteristics of PLC have caused a major global health and economic burden. In recent years, acupuncture and Chinese herbal medicine have been widely used in the treatment of PLC, and there are few restrictions [5]. As an important part of traditional Chinese medicine, acupuncture has been confirmed to be effective in relieving various types of pain, and it has been used in the treatment and care of PLC and its complications [6, 7]. As a complementary and alternative medicine, Chinese herbal medicine has gradually shown advantages in the treatment of PLC, which is one of the current research hotspots [8, 9]. However, there is no obvious evidence to show the effectiveness of acupuncture and Chinese herbal medicine for PLC and the incidence of its side effects. This is also an important reason that prevents it from spreading to the Western world for its treatment of PLC. Therefore, this systematic review and meta-analysis will evaluate the efficacy and safety of acupuncture combined with Chinese herbal medicine in the treatment of primary liver cancer.

METHODS

Search strategy: We will search the following databases from inception up to August 20, 2021: PubMed, Web of Science, Embase, AMED, Cochrane Library, CNKI, VIP, CBM, and Wanfang. There will be no restrictions regarding publication date or language. We will apply a combination of medical keywords and words, including "acupuncture", "Chinese herbal medicine" and "primary liver cancer". Additionally, we will manually search all reference lists from relevant systematic reviews to find other eligiblestudies.

Participant or population: Patients with primary liver cancer who have undergone acupuncture combined with Chinese medicine treatment or the best supportive treatment. There are no restrictions on race, age, gender, etc.

Intervention: Acupuncture combined with Chinese herbal medicine.

Comparator: The best supportive treatment.

Study designs to be included: Randomized controlled study.

Eligibility criteria: The inclusion criteria were as follows: (1) the study was a randomized controlled study (RCT); (2) the included patients had primary liver cancer; (3) the experimental group was acupuncture combined with Chinese herbal medicine, and the control group was the best supportive treatment. The exclusion criteria were as follows: (1) metastatic liver cancer; (2) other treatments in the experimental group; (3) the control group was not the best supportive treatment, but chemotherapy, interventional treatment, etc.; (4) the literature is not the type of included research.

Information sources: We will search the following databases: PubMed, Web of Science, Embase, AMED, Cochrane Library, CNKI, VIP, CBM, and Wanfang. Additionally, we will manually search all reference lists from relevant systematic reviews to find

other eligible studies. We will exclude all conference records, reviews, meta-analyses, newspapers, guides, letters and other documents. When the full text or the required information in the analysis process was missing, the author of the studies was contacted for data.

Main outcome(s): The short-term curative effect is effective, the quality of life is stable, and the survival rate of patients is six months and one year.

Additional outcome(s): The occurrence of side effects, such as fever, nausea and vomiting, incidence of liver damage, etc.

Data management: Two researchers will independently review the eligibility of the data, and a third researcher will resolve any discrepancies. Then, the full texts will be screened in detail based on the above inclusion criteria. We will exclude all conference records, reviews, meta-analyses, newspapers, guides, letters and other documents. During the research period, any disagreements between the authors will be resolved through discussion or negotiation with another researcher until a consensus is reached. The research selection process will be represented by the PRISMA flowchart [11]. When the full text or the required information in the analysis process was missing, the author of the studies was contacted for data. The two authors will independently extract data according to the Cochrane manual guidelines and report the results in the PRISMA guidelines [12]. Any differences will be resolved by consensus of all authors.

Quality assessment / Risk of bias analysis: The two authors will use the Cochrane risk bias assessment tool to separately assess the quality of randomized studies [13]. The Cochrane bias risk assessment tool consists of six parts: selection bias (random sequence generation), selection bias (distribution hiding), implementation bias, measurement bias, follow-up bias, reporting bias, and other biases. Each item is divided into high-risk and low-risk. The three options are not clear. We will use Begg's and Egger's tests (set $P<0.1$ to be statistically significant) and a funnel chart to assess publication bias. When the evaluation quality of the same study was inconsistent, it was resolved through consensus among all authors.

Strategy of data synthesis: We will use the random effects model in Review Manager software (REVMAN v5.3 Cochrane Collaboration) for meta-analysis, and $P<0.05$ was considered statistically significant. Two authors will perform data extraction and input independently, the third author will check the data, and the other two authors will perform data calculations. Evaluate the hazard ratio of the 95% confidence interval or the standardized mean difference of 95% CI for binary classification results or continuous results, respectively. We will use I2 statistics to detect clinical heterogeneity: $0\% \le I2 < 25\%$, no heterogeneity; $25\% \le I2 < 50\%$, mild heterogeneity; $50\% \le I2 < 75\%$, moderate heterogeneity; $I2 \ge 75\%$, severe heterogeneity. If there was a high degree of heterogeneity between trials ($I2 \ge 50\%$), we tried to determine the source of heterogeneity through subgroup analysis, meta-regression and sensitivity analysis.

Subgroup analysis: We will use subgroup analysis based on different interventions, controls, and results.

Sensitivity analysis: Sensitivity analysis was performed by omitting studies one at a time.

Language: There will be no restrictions regarding language.

Country(ies) involved: China.

Other relevant information: 1. International Agency for Research on Cancer, World Health Organization. LiveSource: Globocan 2020. https://gco.iarc.fr/ today/data/ factsheets/cancers/11 -Liver -fact -sheet.pdf. 2. Chen LT, Martinelli E, Cheng AL, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with intermediate and advanced/

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Keywords: acupuncture; Chinese herbal medicine; efficacy; meta-analysis; primary liver cancer; protocol; safety; systematic review.

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