MINIREVIEWS

46  Is there a role for liver transplantation in the treatment of hepatocellular carcinoma in non-cirrhotic liver?
    Bredt LC, Felisberto IBG, Felisberto DEG

META-ANALYSIS

52  Different methods of acupuncture for relief of pain due to liver cancer: A network meta-analysis
    Mou HY, Chen J, Chen ZY, Du H

63  Effect of auricular plaster for primary hypertension in older people: A meta-analysis
    Qin Y, Lou Y, Shen XY, Gai Y
ABOUT COVER
Editorial Board Member of World Journal of Meta-Analysis, Zheng Li, PhD, Assistant Professor, Lecturer, College of Health Sciences, Jiangsu Normal University, Xuzhou 221000, Jiangsu Province, China. lizhengcpu@163.com

AIMS AND SCOPE
The primary aim of World Journal of Meta-Analysis (WJMA, World J Meta-Anal) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality meta-analysis and systematic review articles and communicate their research findings online.
WJMA mainly publishes articles reporting research results and findings obtained through meta-analysis and systematic review in a wide range of areas, including medicine, pharmacy, preventive medicine, stomatology, nursing, medical imaging, and laboratory medicine.

INDEXING/ABSTRACTING
The WJMA is now abstracted and indexed in Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE
Production Editor: Hao-Ge Yin; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lei Wang.

NAME OF JOURNAL
World Journal of Meta-Analysis

ISSN
ISSN 2308-3840 (online)

LAUNCH DATE
May 26, 2013

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Saurabh Chandan, Jing Sun

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2308-3840/editorialboard.htm

PUBLICATION DATE
April 28, 2022

COPYRIGHT
© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com
Is there a role for liver transplantation in the treatment of hepatocellular carcinoma in non-cirrhotic liver?

Luis Cesar Bredt, Ingryd Betina Garcia Felisberto, Doroty Eva Garcia Felisberto

Specialty type: Transplantation
Provenance and peer review: Invited article; Externally peer reviewed.
Peer-review model: Single blind
Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Filipec Kanizaj T, Croatia; Granito A, Italy; Rompianesi G, Italy
Received: December 23, 2021
Peer-review started: December 23, 2021
First decision: March 10, 2022
Revised: March 21, 2022
Accepted: April 28, 2022
Article in press: April 28, 2022
Published online: April 28, 2022

Abstract

Whether liver transplantation (LT) plays a role in the treatment of patients with hepatocellular carcinoma (HCC) in non-cirrhotic liver (NCL) is a matter of debate. The recommendations for LT in this setting are extremely fragile and less well-defined than for cirrhosis-associated HCC. All reports of LT for NCL-HCC revealed that long-term outcomes of these patients are poor, and these dismal figures are justified by the advanced tumor stage at the time of LT, suggesting the presence of systemic micrometastatic disease. The decision-making regarding LT for NCL-HCC is difficult, since specific selection criteria are scarce, and basically the potential candidates are those with unresectable only-liver tumor at admission, or unresectable intrahepatic recurrence post-resection. Besides the surgical aspects regarding the tumor resectability, other phenotypic and genetic characteristics of the tumor should be considered for the indication of LT in this scenario. The present minireview aims to discuss and analyze the last series of LT for NCL-HCC, in order to help clinicians in the decision-making process regarding the role of LT in NCL-HCC treatment.

Key Words: Liver transplantation; Non-cirrhotic liver; Liver; Cancer; Hepatocellular carcinoma; Treatment

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.
Core Tip: The present manuscript aims to discuss and analyze the last series of liver transplantation for hepatocellular carcinoma in non-cirrhotic liver, with a special focus on the indications, prognostic factors and long-term outcomes, in order to help clinicians in the decision-making regarding the role of liver transplantation in the non-cirrhotic liver –hepatocellular carcinoma scenario on the basis of these analyses.

Citation: Bredt LC, Felisberto IBG, Felisberto DEG. Is there a role for liver transplantation in the treatment of hepatocellular carcinoma in non-cirrhotic liver? World J Meta- Anal 2022; 10(2): 46-51
URL: https://www.wjgnet.com/2308-3840/full/v10/i2/46.htm
DOI: https://dx.doi.org/10.13105/wjma.v10.i2.46

INTRODUCTION

Hepatocellular carcinoma (HCC) occurs mainly in patients with liver cirrhosis, leading to chronic necroinflammation and hepatocellular regeneration. Nevertheless, HCC can arise in non-cirrhotic liver (NCL) in a proportion of cases that ranges widely from 7% to 54% across the geographic areas and according to the etiology of the liver disease[1-6]. The male predominance is less marked for HCC on NCL (75% men) than HCC on cirrhosis (85% men), and this sex ratio is equal in patients younger than 50 years[7]. These epidemiological data can be extrapolated for fibrolamellar (FL) HCC variant[8,9].

Authors have hypothesized distinct hepatocarcinogenesis in HCC with and without cirrhosis, although it would be an oversimplification to assume that NCL-HCC would occur in a totally healthy liver, because there is a wide range of parenchymal pathology without cirrhosis. In the last decades there was a progressive expansion of non-viral cases and namely of metabolic HCC in non-cirrhotic patients[10]. It has been reported that the role of alcohol intake is an independent predictor in non-cirrhotic subjects with chronic hepatitis B virus infection of HCC development[11] and an extremely variable HCC recurrence risk and survival in successfully treated hepatitis C virus-infected patients[12]. Therefore, the histological background of NCL-HCC can include liver steatosis, hepatitis, genotoxic substances, metabolic diseases, germline mutations, and liver adenomas[13].

In general, NCL-HCC is detected at an advanced stage, and the diagnosis is made when clinical symptoms and signs related to the enlarged lesion appear, such as pain and abdominal discomfort, and a palpable tumor have occurred. Whereas the clinical presentation can be aggressive, distinct from HCC that occurs in a cirrhotic background, the preserved liver function in NCL-HCC scenario allows more extensive liver resections. Despite these high rates of R0 resections, the outcomes are dismal, and may be theoretically justified by the presence of systemic micrometastatic disease[14].

Differently from the extensive experience of referral centers with liver transplantation (LT) for the treatment of HCC in cirrhotic liver, the LT criteria for the treatment of NCL-HCC is not sharply defined, and actually is basically limited to situations in which resection is not possible. Moreover, while the survival rates of the larger group of HCC patients with cirrhosis treated with LT has been extensively published, there are few retrospective series regarding the prognosis and long-term survival evaluation of NCL-HCC after this treatment.

The present minireview aims to discuss and analyze the last series of LT for NCL-HCC, with special focus on the indications, prognostic factors and long-term outcomes, in order to help clinicians for decision-making regarding the role of LT in the NCL-HCC scenario on the basis of these analyses.

TECHNICAL RESECTABILITY DETERMINATION

Despite the enlarged tumor burden, the preserved function of NCL generally offers the chance of performing extended liver resections safely, with totally acceptable perioperative mortality (0%–6%) and morbidity (8%–40%) of these patients[15-17].

One of the cornerstones for the indication of primary or rescue LT for NCL-HCC relies on the tumor’s unresectability. The assessment of resectability differs from HCC in cirrhosis since the liver parenchyma is healthy or only minimally diseased. More extensive resections are feasible, therefore the resectability rates are higher. On the other hand, these tumors are often very bulky at presentation and are prone to vascular invasion of large vessels.

The surgical treatment strategy for both resection and LT should be directed towards R0 resection whenever possible, with both ‘oncological’ (prognostic) and ‘technical’ (surgical) criteria being considered. The technical unresectability does not always mean that the LT is indicated, because unfavorable prognostic criteria may preclude patients from succeeding even with LT.

Initially the first attempt would be the work-up for any evidence of extrahepatic disease, such as metastasis to lymph nodes, lung, or bone, that would be a formal contra-indication for both resection and LT. The evidence of homolateral or contralateral satellite nodules denotes widespread intra-hepatic...
dissemination. It is crucial that an accurate assessment of tumor vascular relationships, the evaluation of the intersection of the hepatic veins with the inferior vena cava must be done, and an eventual tumoral thrombus in the portal vein trunk or branches may preclude the resection. Finally, the quality of the underlying liver parenchyma should be accessed with estimation of the future liver remnant, that would be insufficient despite no underlying cirrhosis[18].

LONG-TERM OUTCOMES AFTER LT FOR NCL-HCC

For all the wide indications of LT, they must have comparable outcomes. If a strict disease does not, then it must cause no undue prejudice to other recipients with a better prognosis[19]. The Milan criteria conception is the ideal example for this statement, and the current benchmark for LT for HCC in cirrhotic patients, because the overall 5-year survival rate of 65%–78% for Milan-in patients[20] is similar to 70%–82% survival for benign indications. In general, a 5-year overall survival rate of > 50% is recommended by the liver-transplant community in the face of liver grafts scarcity[21]. Thus, the indication of LT for NCL-HCC must be comprehensively analyzed.

Liver resection is currently the best upfront therapy for NCL-HCC[22-24]. However, in this section the role of LT in the setting of unresectable HCC at presentation or because of tumor recurrence following resection will be discussed. There is limited literature that reports the long-term survival of the subgroup NCL-HCC patients treated by LT, and the available series (Table 1) have limitations, mainly because of its retrospective and eventually multicenter design, and in some cases the reduced number of patients.

A systematic review that included all very early reported cases of LT for NCL-HCC from 1966 to 1998 revealed poor long-term outcome of these patients. The 5-year survival rates were 11.2% for non-FL-HCC and 39.4% for FL-HCC[24-26]. In the most recent series with 105 NCL-HCC transplant patients reported by Mergental et al[27] a 5-year overall survival of 49% was observed. For 62 patients, LT was the primary treatment with a 5-year overall survival of 43%, and for 43 patients, LT was a rescue treatment after resection, with a 5-year overall survival of 58%. Pathological data showed more favorable tumor characteristics in the rescue-LTs compared to primary-LTs (TNM staging, median size of largest tumor, number of patients Milan-in, and number of patients with serum alpha-fetoprotein level < 100 ng/mL). Rescue-LT within 12 mo after resection was the significant predictor for long-term survival.

A specific question must be addressed regarding FL-HCC, which historically the patients with FL-HCC appear to have a better prognosis, as shown by Houben and McCall[24]. Kakar et al[28] clearly showed that the outcomes of FL-HCC and NC-HCC are similar when same-stage diseases are considered and when the proliferative activities of these tumor variants (Ki-67) are similar[23,26]. Enlarging cohorts, including non-FL and FL-HCC with no distinction, would allow better predictions of the role of LT in patients with NCL-HCC. The analysis of the larger will be a major step forward to a better insight of the indication for LT in this scenario[14].

SELECTION OF CANDIDATES FOR LIVER TRANSPLANTATION

The risk factors for recurrence rate after resection could be very helpful in identifying NCL-HCC candidates for LT[14]. Authors have already hypothesized tumor characteristics that would be potential prognostic factors for recurrence after LT (Table 2). The small number of patients within these series, however, leads the conclusions from these studies to be handled with caution.

According to Mergental et al[29], lymph node invasion and macrovascular invasion were suggested to be the main predictors of recurrence after LT. Later, the same author also showed that a time period of less than 12 mo between the previous resection and tumor recurrence was a significant risk factor for poor survival. This short time span probably would reflect a more aggressive biology[27].

Data on 4373 non-cirrhotic HCC patients who underwent LT for NCL-HCC from a large database were analyzed using logistic regression model and life table methods. The identified factors that significantly related to survival were the total number of tumors, extrahepatic disease, nodal involvement, satellite lesions, vascular invasion, tumor grade and pre-LT treatment[30].

The identified variables for poor prognosis in the published studies are based on the pathological analysis of the explanted livers. Furthermore, the goal would be the evaluation of the predictors before the LT indication, such as tumor imaging at listing, lymph node involvement, the response to previous treatments, and the kinetics of the tumor growth. In the case of rescue-LT patients, the imaging characteristics before resection and the pathological characteristics of the resected tumor are crucial to assess candidates for LT at the time of recurrence[19].

The suggested favorable prognostic factors[19,23,27] such as alpha-fetoprotein level (< 100 ng/mL), tumor number (< 4), tumor diameter (< 5 cm) and no vascular and node involvement assessed on imaging at listing, would refine the selection of patients for LT for NCL-HCC, decreasing therefore, eventual futile procedures.
Table 1 Selected series that addressed the long-term survival of patients with non-cirrhotic liver - hepatocellular carcinoma treated with primary or rescue liver transplantation

<table>
<thead>
<tr>
<th>Ref.</th>
<th>HCC variant</th>
<th>n</th>
<th>Recurrence rate (%)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pichlmayr et al[22], 1995</td>
<td>FL</td>
<td>36</td>
<td>38.0</td>
<td>49.0</td>
</tr>
<tr>
<td>Pinna et al[23], 1997</td>
<td>FL</td>
<td>13</td>
<td>69.2</td>
<td>36.3</td>
</tr>
<tr>
<td>Schlitt et al[25], 1999</td>
<td>FL</td>
<td>25</td>
<td>NR</td>
<td>27.0</td>
</tr>
<tr>
<td>El-Gazzaz et al[26], 2000</td>
<td>FL</td>
<td>9</td>
<td>44.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Mergental et al[27], 2012</td>
<td>NS</td>
<td>105</td>
<td>48.5</td>
<td>53.5</td>
</tr>
</tbody>
</table>

HCC: Hepatocellular carcinoma; OS: Overall survival; FL: Fibrolamellar; NR: Not reported; NS: Not specified.

Table 2 Series of patients with hepatocellular carcinoma in non-cirrhotic liver treated with liver transplantation with reported risk factors for poor prognosis

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pichlmayr et al[22], 1995</td>
<td>&gt; 1 tumor; lymph node invasion</td>
</tr>
<tr>
<td>Pinna et al[23], 1997</td>
<td>Tumor stage; macrovascular invasion; lymph node invasion</td>
</tr>
<tr>
<td>El-Gazzaz et al[26], 2000</td>
<td>Tumor stage</td>
</tr>
<tr>
<td>Mergental et al[27], 2012</td>
<td>Macrovascular invasion; lymph node involvement; time interval between resection and LT &lt; 1 yr</td>
</tr>
</tbody>
</table>

LT: Liver transplantation.

PROGNOSTIC GENETIC INFORMATION ON NCL-HCC

Recently, genetic information regarding NCL-HCC prognosis can ultimately aid the selection of candidates for LT. Clinical data analysis indicated that increased PKM2 expression in NCL-HCC was correlated with tumor vascular invasion and intrahepatic metastasis, and positive PKM2 expression was an independent poor prognostic factor for recurrence[31]. Some studies have found that the level of activity regulator of SIRT1 in NCL-HCC is significantly correlated with tumor size, vascular invasion, and tumor differentiation, consequently with disease-free survival rates[32].

MiRs are 18–25 nucleotide noncoding RNAs that can regulate gene expression. A high expression of hsa-mir-149 was found to be a risk factor for poor prognosis, and an increased hsa-miR-23c expression was associated with improved survival in patients with HCC-NCL[33]. Similarly, miR-21 levels are generally increased in HCC-NCL[33,34].

CONCLUSION

The recommendations for LT in this setting of NCL-HCC are fragile and less well-defined than for cirrhosis-associated HCC. The decision-making for LT is still difficult, since specific selection criteria are scarce. Resection must be the upfront therapy for these patients, and LT must be offered only for patients with recurrence after resection or with unresectable disease at presentation. However, besides technical unresectability, other phenotypic and genetic characteristics of the tumor should be considered for selecting patients for LT in the NCL-HCC scenario, avoiding futile procedures.

FOOTNOTES

Author contributions: All authors contributed equally to this review article; all authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-
REFERENCES


Different methods of acupuncture for relief of pain due to liver cancer: A network meta-analysis

Hong-Yuan Mou, Jing Chen, Zuo-Yun Chen, Hong Du

Abstract

BACKGROUND

Pain in the liver is a common symptom of liver cancer in late stages, and the pain incidence rate exceeds 50%[1]. In serious cancer pain, morphine and other major analgesics have been commonly administrated for clinical treatments, and their effects are accurate, but with a high incidence of side effects, such as nausea, vomiting, constipation, and other conditions. Acupuncture is a traditional Chinese medicine therapy. There have been many randomized controlled trials addressing the safety and usefulness of different methods of acupuncture in alleviating liver cancer pain. However, which of these methods is the most effective method is still unclear.

AIM

To compare the effectiveness of different acupuncture methods for alleviating pain due to liver cancer.

METHODS

Eligible studies were retrieved from eight databases (the Cochrane Library, PubMed, EMBASE, Medline, CNKI, CBM, Chongqing VIP, and Wan Fang Database) up to March 31, 2021 and screened based on the established inclusion and exclusion criteria. The quality of the include studies was evaluated. Stata software was applied for statistical analyses. Publication bias of the included studies was also determined. Finally, the network meta-analysis was carried out to evaluate the efficacy of acupuncture methods for relief of pain due to liver cancer.

RESULTS

A total of eight randomized controlled trials were included in the network meta-analysis. Eight trials (covering 5 treatments and 734 patients) provided data
suitable for analysis. Most trials focused on short-term effects and many were classed as being of poor quality with a high risk of bias, commonly associated with lack of blinding (which was sometimes impossible to achieve). End of treatment results showed that four interventions, including wrist-ankle acupuncture, triple puncture and remaining needle acupuncture, Tian Yuan acupuncture, and block acupuncture, produced a statistically significant reduction in pain when compared with the three-step analgesic ladder therapy. The surface under the cumulative ranking sorting results showed that triple puncture and remaining needle acupuncture had a relatively high effective rate.

**CONCLUSION**
The network meta-analysis results indicate that the overall effectiveness of triple puncture and remaining needle acupuncture is better than the other therapies.

**Key Words:** Pain; Liver cancer; Acupuncture; Network meta-analysis; Effectiveness; Three-step analgesic ladder

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** Seventy-five percent of patients with liver cancer suffer varying degrees of pain. Pain is widely perceived as the fifth vital sign in cancer patients, which seriously affects the quality of their life and threatens their survival. Acupuncture, part of traditional Chinese medicine, involves the application of needles, heat, pressure, and other treatments at specific sites of the body known as acupoints to affect the physical functions of the body. Numerous studies have concluded that acupuncture may be efficacious in relieving cancer-related pain. However, there is still no direct evidence on which method of acupuncture is more effective. The present study aimed to identify the best method of acupuncture for liver cancer-related pain.

**INTRODUCTION**
According to the GLOBOCAN 2012, primary liver cancer is the fifth most common cancer and the third most common cause of cancer mortality worldwide[2]. More than 1 million individuals are diagnosed with this disease each year, and over 250000 patients die annually due to disease progression[3,4]. In China, primary liver cancer is the second most common malignancy, with 360000 incident cases and 350000 deaths a year currently reported[5]. With people’s growing emphasis on health and advances in medical technology, the early screening and treatment of liver cancer have extended the lives of many patients. However, cancer pain brings physical suffering to patients and makes them anxious, desperate, and depressed. In addition, this further aggravates the cancer pain, resulting in a vicious circle. The current clinical treatment for cancer pain is mainly in accordance with the World Health Organization (WHO) recommended three-step analgesic ladder, under which 70%-90% of cancer pain can be relieved[6]. Nevertheless, anesthetic adverse effects, drug resistance, addiction, and other issues associated with the use of opioid analgesics have limited their clinical use. Thus, the identification of an effective treatment for relief of cancer pain with fewer toxic or adverse effects will radically improve quality of life and benefit most patients with cancer pain. Acupuncture analgesia is a traditional Chinese medicine therapy that has the advantages of safety, effectiveness, and no adverse effects and plays an important role in the treatment of cancer pain. Current clinical research shows that acupuncture combined with other therapies can effectively relieve the pain, reduce the adverse effects of Western medicine, and improve the quality of life of patients with primary liver cancer. By using network meta-analysis (NMA), both direct and indirect randomized data can be analyzed, and recommended rankings of different treatments can be provided[7,8]. Therefore, we conducted an NMA to analyze both direct and indirect comparisons of different methods of acupuncture for the relief of pain due to liver cancer. Based on the current evidence, we sorted and explored the advantages and disadvantages of different methods of acupuncture. Compared with traditional meta-analysis, the results of this study may provide a higher quality basis and reference for acupuncture treatment of pain due to liver cancer.
MATERIALS AND METHODS

This NMA was based on the international guidelines for conducting and reporting systematic reviews, as applied to NMA[9,10].

Search strategy
PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure, Wan Fang Database, Chongqing VIP, and Chinese Biomedical Databases were searched from inception to March 31, 2021. Randomized controlled trials (RCTs) associated with pain due to liver cancer and cancer were retrieved. The specific search strategy, which adopted a combination of subject words and free words, was made based on the Cochrane Handbook for Systematic Review of Interventions (version 5.1.0)[11]. (Liver Neoplasms, or Neoplasm or Liver Neoplasm or Hepatic neoplasm or Cancer of Liver or Hepatic Cancer or Liver Cancer or Hepatoma or Hepatocellular Carcinoma or HCC) and (Pain or Suffering or Ache) and (Acupuncture Therapy or Acupuncture or Acupuncture Points or Acupuncture Analgesia or Electro-acupuncture or Moxibustion or Acupotom or Electro-acupuncture or Electro-acupuncture or Needling or Acupoint) was used as the search strategy for Chinese and English databases.

Study selection
Two reviewers independently identified relevant studies based on titles and abstracts. In addition, full-text articles were scanned by these reviewers to identify eligible studies. All disagreements were resolved by consensus and adjudged by a third reviewer if necessary. In the case of duplicate citations, the most updated study was selected for data extraction.

Inclusion and exclusion criteria
The studies included in the review should meet the following criteria: (1) The study design must be RCT; (2) Patients diagnosed with liver cancer irrespective of age and sex were enrolled; diagnostic criteria must be clear and inclusion and exclusion criteria were explicit; (3) All subjects had moderate to severe pain; (4) According to the cancer pain improvement standard of the WHO, the analgesic effects of the treatments were classified into four levels: Complete remission (CR; completely pain-free); partial remission (PR; substantial relief of pain and generally normal sleep); mild remission (MR; moderate relief of pain with residual pain and sleep disturbance); no remission (NR; no relief of pain). Usually, CR and NR are relatively easy to judge, whereas PR and MR are less well defined. CR and PR were considered effective; (5) Participants in the experimental group have received acupuncture treatments; and (6) English or Chinese language studies were included. The following studies were excluded: (1) Self-controlled and non-RCT studies; (2) Preclinical studies, systematic reviews, case reports, and meta-analyses; (3) Reports without sufficient or clear original data; and (4) Duplicate studies and studies reporting the same results.

Data collection and quality assessment
We used the risk of bias tool recommended by the Cochrane Handbook to evaluate the quality of included studies. The items considered were as follows: (1) Random sequence generation; (2) Allocation concealment; (3) Blinding of participants and personnel; (4) Blinding of outcome assessment; (5) Complete outcome data; (6) Selective reporting; and (7) Company funding. The possible answers to items 1–5 were ‘yes’ (representing low risk), ‘no’ (representing high risk), or ‘unclear’ (representing unclear risk). For item 6, ‘yes’ represented high risk, ‘no’ represented low risk, and ‘unclear’ represented unclear risk. Furthermore, grading of recommendation assessment, development, and evaluation (GRADE), which included five aspects (study limitation, indirectness, inconsistency, imprecision, and publication bias), was used to evaluate the quality of evidence contributing to each comparison and the overall ranking of treatment.

Statistical analysis
Stata16.0 software was used to create the network evidence graph that displays the basic information of interventions under each type of outcome indicators. Each node represents an intervention, the size of the node represents the sample size of the intervention, and the connection between the nodes represents the number of included studies under the intervention. As the outcome index of this study was a binary variable, the comparison results are expressed as relative risk. According to the ranking probability of each intervention, the best intervention could be identified.

RESULTS

Literature retrieval
A total of 5889 related studies were searched initially, and 2002 duplicate publications were excluded using Endnote X7 software. Three hundred and sixty-nine studies were initially screened out by
words, the deep presence of pathogenic qi impairs the healthy qi, then the deficiency of qi and blood blocks meridians, and stagnation leads to pain. Deficiency pain is caused by a prolonged illness, in other disorders of qi movement; furthermore, impairment of blood circulation occurs, and finally blood stasis due to liver cancer can be divided into excess pain and deficiency pain. Excess pain means that external stagnation is produced in the body, and then produces ‘poison’, and over time cancer develops. Pain virus theory stagnation. Professor Zhong-Ying Zhou, a master of traditional Chinese medicine, proposed the cancer pathogenesis of cancer pain. Xuezhenglun attaches significance to cancer pain attributed to blood quality studies. It is an analgesic adjunctive method for cancer patients that is worthy of additional high complementary and conservative therapy that balances the flow of vital energy, and in turn helps to acupuncture had the highest effectiveness. In this study, we found that triple puncture and remaining needle acupuncture may be the most effective measure for the treatment of pain in patients with liver cancer (Figures 3-5, Tables 2 and 3).

Nodal analysis
There were no results of nodal analysis and ring inconsistency testing as the network evidence graph does not form a closed ring.

Publication bias and small-sample effect assessment
A funnel plot of treatment response rate is drawn, and each point on the funnel plot is scattered and not completely symmetrical, suggesting that there may be a small publication bias. The funnel plot of the response rate has scatter points distributed at the bottom of the funnel, suggesting the presence of a small sample effect (Figure 6).

DISCUSSION
The aim of this study was to identify the effectiveness or different methods of acupuncture for relief of pain due to liver cancer. In this NMA, the association of each acupuncture and related therapies with relief of pain due to liver cancer was compared using the combination of direct and indirect evidence from eight RCTs with 734 patients. An NMA provides a basis for synthesizing all the available evidence in a consistent framework, obviating the need to make decisions by subjective inferences from disparate data. However, our analysis represents the use of the most practical methods currently available to compare a large number of different types of treatment, thus enabling us to compare different methods of acupuncture with each other. In this study, we found that triple puncture and remaining needle acupuncture had the highest effectiveness.

Acupuncture may be useful in controlling the pain experienced by many cancer patients. It is a complementary and conservative therapy that balances the flow of vital energy, and in turn helps to relieve pain. It is an analgesic adjunctive method for cancer patients that is worthy of additional high quality studies[12-14].

Danxixinfa holds that meridians blocked by qi stagnation and phlegm are involved in the pathogenesis of cancer pain. Xuezhenglun attaches significance to cancer pain attributed to blood stagnation. Professor Zhong-Ying Zhou, a master of traditional Chinese medicine, proposed the cancer virus theory[15], and pointed out that under the action of internal and external factors, cold and heat stagnation is produced in the body, and then produces ‘poison’, and over time cancer develops. Pain due to liver cancer can be divided into excess pain and deficiency pain. Excess pain means that external pathogens invade the body and compete in the body or accumulate in the liver meridians, resulting in disorder of qi movement; furthermore, impairment of blood circulation occurs, and finally blood stasis blocks meridians, and stagnation leads to pain. Deficiency pain is caused by a prolonged illness, in other words, the deep presence of pathogenic qi impairs the healthy qi, then the deficiency of qi and blood

scanning the title and abstract. Thereafter, 49 studies that may have met the criteria were read in detail. Finally, eight RCTs with a total of 734 patients, including four studies on wrist-ankle acupuncture, one on triple puncture and remaining needle acupuncture, one on Tian Yuan acupuncture, and three on block acupuncture, were selected (Figure 1).

Basic characteristics and quality evaluation of the included studies
Of the eight articles selected, all provided statistical analysis of the age and gender of the patients, and five reported the visual analog scale scores. All studies mentioned the random grouping method, and there were no incomplete reporting data or selective reporting results, but the allocation hiding and blind methods were not described in detail. Therefore, the overall quality of the literature was fair (Table 1, Figure 2)

Network meta-analysis results of pain treatment in patients with liver cancer under different measures
The NMA of the response rate under different measures of treatment was tested for consistency, and the results showed that $P > 0.05$, so the consistency model analysis was used. The results of the NMA showed that the response rate to triple puncture and remaining needle acupuncture in treating pain in patients with liver cancer was higher than that to three-step analgesic ladder therapy, wrist-ankle acupuncture, and block acupuncture, and the differences were statistically significant ($P < 0.05$): the response rate to Tianyuan acupoint acupuncture in treating pain in patients with liver cancer was significantly higher than that of three-step analgesic ladder therapy and wrist-ankle acupuncture ($P < 0.05$); the other pairwise comparisons between the interventions showed no statistical significance. The result of ranking the probability that one intervention is the best treatment is as follows: Triple puncture and remaining needle acupuncture (88.8%) > Tianyuan acupoint acupuncture (84.8%) > block acupuncture (45.0%) > wrist-ankle acupuncture (17.7%) > three-step analgesic ladder therapy (14.1%), suggesting that triple puncture and remaining needle acupuncture may be the most effective measure for the treatment of pain in patients with liver cancer (Figures 3-5, Tables 2 and 3).

Nodal analysis
There were no results of nodal analysis and ring inconsistency testing as the network evidence graph does not form a closed ring.

Publication bias and small-sample effect assessment
A funnel plot of treatment response rate is drawn, and each point on the funnel plot is scattered and not completely symmetrical, suggesting that there may be a small publication bias. The funnel plot of the response rate has scatter points distributed at the bottom of the funnel, suggesting the presence of a small sample effect (Figure 6).

DISCUSSION
The aim of this study was to identify the effectiveness or different methods of acupuncture for relief of pain due to liver cancer. In this NMA, the association of each acupuncture and related therapies with relief of pain due to liver cancer was compared using the combination of direct and indirect evidence from eight RCTs with 734 patients. An NMA provides a basis for synthesizing all the available evidence in a consistent framework, obviating the need to make decisions by subjective inferences from disparate data. However, our analysis represents the use of the most practical methods currently available to compare a large number of different types of treatment, thus enabling us to compare different methods of acupuncture with each other. In this study, we found that triple puncture and remaining needle acupuncture had the highest effectiveness.

Acupuncture may be useful in controlling the pain experienced by many cancer patients. It is a complementary and conservative therapy that balances the flow of vital energy, and in turn helps to relieve pain. It is an analgesic adjunctive method for cancer patients that is worthy of additional high quality studies[12-14].

Danxixinfa holds that meridians blocked by qi stagnation and phlegm are involved in the pathogenesis of cancer pain. Xuezhenglun attaches significance to cancer pain attributed to blood stagnation. Professor Zhong-Ying Zhou, a master of traditional Chinese medicine, proposed the cancer virus theory[15], and pointed out that under the action of internal and external factors, cold and heat stagnation is produced in the body, and then produces ‘poison’, and over time cancer develops. Pain due to liver cancer can be divided into excess pain and deficiency pain. Excess pain means that external pathogens invade the body and compete in the body or accumulate in the liver meridians, resulting in disorder of qi movement; furthermore, impairment of blood circulation occurs, and finally blood stasis blocks meridians, and stagnation leads to pain. Deficiency pain is caused by a prolonged illness, in other words, the deep presence of pathogenic qi impairs the healthy qi, then the deficiency of qi and blood
Table 1 Main characteristics of the selected articles

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Cases (observation group/control group)</th>
<th>Treatment measures</th>
<th>Control measures</th>
<th>Evaluating indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeng et al.[18], 2014</td>
<td>30/30</td>
<td>Wrist ankle acupuncture</td>
<td>Three step analgesic ladder therapy</td>
<td>Degree of pain relief</td>
</tr>
<tr>
<td>Liu et al.[18], 2010</td>
<td>51/51</td>
<td>Block acupuncture</td>
<td>Three step analgesic ladder therapy</td>
<td>Degree of pain relief/VAS score</td>
</tr>
<tr>
<td>Liu et al.[18], 2007</td>
<td>30/30</td>
<td>Block acupuncture</td>
<td>Three step analgesic ladder therapy</td>
<td>Degree of pain relief/VAS score</td>
</tr>
<tr>
<td>Liu et al.[21], 2008</td>
<td>51/51</td>
<td>Block acupuncture</td>
<td>Three step analgesic ladder therapy</td>
<td>Degree of pain relief/VAS score</td>
</tr>
<tr>
<td>Sun et al.[22], 2021</td>
<td>80/60</td>
<td>Triple puncture and remaining needle acupuncture</td>
<td>Three step analgesic ladder therapy</td>
<td>Degree of pain relief</td>
</tr>
<tr>
<td>Hu et al.[22], 2004</td>
<td>36/50</td>
<td>Wrist ankle acupuncture</td>
<td>Three step analgesic ladder therapy</td>
<td>Degree of pain relief</td>
</tr>
<tr>
<td>Hu et al.[22], 2005</td>
<td>36/40</td>
<td>Wrist ankle acupuncture</td>
<td>Three step analgesic ladder therapy</td>
<td>Degree of pain relief</td>
</tr>
<tr>
<td>Cai et al.[22], 2009</td>
<td>54/54</td>
<td>Tianyuan acupuncture</td>
<td>Three step analgesic ladder therapy</td>
<td>Degree of pain relief/VAS score</td>
</tr>
</tbody>
</table>

Table 2 Analgesic effect of different acupuncture methods based on network meta-analysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SUCRA</th>
<th>PrBest</th>
<th>MeanRank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three-step analgesic ladder</td>
<td>0.71 (0.59, 0.85)</td>
<td>14.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Triple puncture and remaining needle acupuncture</td>
<td>0.72 (0.54, 0.97)</td>
<td>88.8</td>
<td>55.3</td>
</tr>
<tr>
<td>Tian Yuan acupuncture</td>
<td>1.00 (0.93, 1.08)</td>
<td>84.4</td>
<td>44.7</td>
</tr>
<tr>
<td>Wrist ankle acupuncture</td>
<td>0.95 (0.90, 1.01)</td>
<td>17.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Block acupuncture</td>
<td>1.34 (1.11, 1.62)</td>
<td>45.0</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Table 3 Probability ranking of interventions in different outcome indicators (SUCRA)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SUCRA</th>
<th>PrBest</th>
<th>MeanRank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three-step analgesic ladder</td>
<td>14.1</td>
<td>0.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Triple puncture and remaining needle acupuncture</td>
<td>88.8</td>
<td>55.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Tian Yuan acupuncture</td>
<td>84.4</td>
<td>44.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Wrist ankle acupuncture</td>
<td>17.7</td>
<td>0.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Block acupuncture</td>
<td>45.0</td>
<td>0.0</td>
<td>3.2</td>
</tr>
</tbody>
</table>

makes meridians and viscera lose nourishment, that is, loss of nourishment leads to pain[16]. The main mechanisms of acupuncture in alleviating cancer pain are as follows. First, acupuncture has the function of regulating qi and blood as well as dredging channels and collaterals; hence, pain is relieved with improved blood circulation. Second, it can effectively adjust the body’s immune function to achieve the effects of strengthening body resistance and eliminating pathogenic factors, tonifying deficiency, and purging excess[17]. Western medicine theory holds that the benign stimulation of acupuncture can act on the sympathetic and sensory nerves, and on the relevant autonomic nerve center through the segmental axon reflex of the nerve, thus effectively adjusting the visceral sensory function. In addition, the effective stimulation of acupuncture on acupoints can release endogenous opioid peptides through neurohumoral or meridian conduction, thus achieving acupuncture analgesia[18,19].

From our NMA, we found that triple puncture and remaining needle acupuncture had the highest effectiveness in treating moderate to severe liver cancer pain. Tianyuan acupoint acupuncture mainly uses the exterior and interior acupoint selection method, 12-meridian hedge acupoint selection method,
Sanyin Sanyang Guanheshu acupoint selection method, and twirling reinforcing-reducing method in the Guidelines of Acupuncture Meridians to relieve cancer pain. The exterior and interior acupoint selection method selects acupoints according to the relationship between exterior and interior deficiency of meridians; superficial acupoint is selected for interior disease, and deep acupoint is selected for exterior disease. Because liver cancer is an internal disease, the liver Beishu and Ganshu acupoints on the liver surface, as well as Ququan acupoint, were selected to tonify the liver meridian deficiency syndrome, dredge the qi and blood of the liver meridians, and prevent the conduction of pathogenic factors. The 12-meridian hedge acupoint selection method is proposed according to the hedge relationship of the 12 earthly branches, that is, Zi and Wu hedge, Yin and Shen hedge, Chen and Wu hedge, etc. There is a corresponding relationship between the 12 meridians of the human body and the 12 earthly branches, and there is also a hedge relationship across the 12 meridians of the human body; that is, the hedge between Taiyin Lung Meridian and the Foot-Taiyang Bladder Meridian, the hedge between the Foot-Yangming Stomach Meridian and the Hand-Jueyin Pericardium Meridian, the hedge between the Hand-Shaoyin Heart Meridian and the Foot-Shaoyang Gallbladder Meridian, etc. According to the theory of Sanyin and Sanyang Guanheshu and the tendency of pathogenic conduction of meridians, for the method of acupoint selection of Sanyin and Sanyang Guanshu, the Shu or He acupoint is selected for the disease at Guan acupoint, Guan or Shu is selected for the disease at He acupoint, and Guan or He is selected for the disease at Shu acupoint. The typical acupoints that can be used are Xinyuand Dazhui. Those acupoints are selected for tranquilizing, soothing the liver, relieving depression, activating blood circulation, and relieving pain. Tianyuan acupoint uses rotational tonifying and reducing manipulation with a small amount of stimulation, while the Tianyuan acupoint selection method selects acupoints carefully, so the effect is good. Wrist–ankle acupuncture is a method of acupuncture at specific parts of the wrist or ankle to treat systemic diseases. It is gradually formed and developed under the inspiration of the mid-dermal theory in meridian doctrine. It was officially applied in clinical practice in the early 1970s. Because of its single-acupoint selection, easy operation, and minimal damage to the body, this method is safe without needle sensation. Ququan point is selected for blocking acupuncture, which is the converging point of liver meridian, where the liver meridian qi is full, and acupuncture can soothe the liver, regulate qi and meridians, and relieve pain. Dazhui is the point of the Du meridian, which is a good option for acupoint selection when treating shoulder and back pain and has the functions of activating blood circulation, dredging collaterals, and relieving pain. Liver cancer pain is caused by liver enlargement, tumor invasion of the diaphragm, and stimulation of diaphragmatic nerves into the cervical segment of the spinal cord, resulting in the right shoulder and liver pain, so acupuncture at this point can play a role in soothing the liver, activating blood circulation to relieve pain, and blocking the conduction of pathogenic factors. Acupuncture at Xinshu is used to tranquilize the mind, regulate qi and relieve depression, replenish qi and meridians, and treat cancer pain. Ganshu is the Beishu point of the liver meridian. Acupuncture can notify liver blood, and soothe the liver and meridians to treat cancer pain, and the simultaneous treatment of principal and subordinate symptoms can be achieved. Triple puncture and remaining needle...
Mou HY et al. Acupuncture for liver cancer pain: A meta-analysis

Figure 2 Assessment of quality of the literature. A: Percentile chart of literature risk bias; B: Risk of bias assessment.

DOI: 10.13105/wjma.v10.i2.52 Copyright ©The Author(s) 2022.

Figure 3 Test for inconsistency.

DOI: 10.13105/wjma.v10.i2.52 Copyright ©The Author(s) 2022.

acupuncture, as recorded in LingShu, is called concerted needling. Concerted needling involves insertion directly into one point and then further insertion of two more needles directly beside the first to treat cold qi and is localized but slightly deep. The method of concerted needling and needle retaining for liver cancer pain can prolong the analgesic time. From the recorded description, concerted needling selects the appropriate needle, on the selected acupoints, as follows. First, the first needle is inserted straight down the needle tip in the center of the acupoint, and then 0.5 cun (1 cun is equal to 3.3333333 cm) next to the first needle (up and down or left and right); the needle tip is aligned with the direction of the first needle, and the other two needles are straightly (obliquely) inserted; one acupoint is simultaneously inserted into by three needles, and at the same time, lifting, inserting, and twisting of the needle are performed to achieve the arrival of qi. Three needles are used together, so the name of concerted needling is given, which is mainly suitable for arthralgia with limited lesions, as well as with deep location of lesions and pathogenic factors. According to clinical research reports, the three needles of the concerted needling method not only strengthen the local irritation volume of the acupoint where
the acupuncture is located, but also expand the scope of action of the acupoint where the acupuncture is located. This method is conducive to rapidly stimulating the conduction of meridians and qi so that the induction of acupuncture can reach the disease site directly and the needle sensation spread from shallow to deep, from near to far around the acupoint, rapidly reaching the acupuncture requirements of qi to the disease site. The method also plays a role in relieving tendons through meridians, promoting blood circulation and dredging collaterals, and removing arthralgia and relieving pain. Thus, the purpose of acupuncture treatment based on the principle of “no obstruction, no pain” is achieved [23].

This study had several limitations. First, we failed to evaluate the safety of each acupuncture therapy due to limited data in the primary studies. Future trials should report adverse events clearly to improve the quality of study design. Second, unaddressed concerns still exist regarding the long-term effects of using acupuncture and acupuncture-related therapies for pain due to liver cancer in the clinical setting. Further clinical evaluation of acupuncture for pain due to liver cancer is required and longer follow-up appears warranted. Third, blinding of patients and research was not performed in the included studies that were mainly conducted in China, which may have led to publication bias. Fourth, the included studies in our NMA lacked comparisons on the effectiveness of different acupuncture therapies. Further confirmatory effectiveness trials should compare different types of acupuncture therapies. Finally,
numerous studies that focused on other methods of acupuncture were not included in our study due to the type of design and outcome measures.

CONCLUSION

The evidence from our NMA, in which different methods of acupuncture for pain due to liver cancer were compared with each other within a coherent framework, suggests that the overall effectiveness of triple puncture and remaining needle acupuncture is better than that of other therapies. However, despite the evidence from this study, the methodological limitations associated with many of the trials indicate that high-quality trials of acupuncture treatments are still required.

ARTICLE HIGHLIGHTS

Research background
Seventy-five percent of patients with liver cancer suffer varying degrees of pain. Pain is widely perceived as the fifth vital sign in cancer patients, which seriously affects the quality of their life and threatens their survival. Acupuncture, part of traditional Chinese medicine, involves the application of needles, heat, pressure, and other treatments at specific sites of the body known as acupoints to affect the physical functions of the body. Numerous studies have concluded that acupuncture may be efficacious in relieving cancer-related pain. However, there is still no direct evidence on which method of acupuncture is more effective. The present study aimed to identify the best method of acupuncture for liver cancer-related pain. Further clinical evaluation of acupuncture for pain due to liver cancer is required and longer follow-up appears warranted. The comparisons of the effectiveness of different acupuncture therapies should be conducted.

Research motivation
The aim of our study was to compare the effectiveness of different acupuncture methods for alleviating pain due to liver cancer. In this study, we found that triple puncture and remaining needle acupuncture had the highest effectiveness. The finding of our study may provide evidence for directly comparing different methods of acupuncture for liver cancer related pain.

Research objectives
The present study aimed to identify the best method of acupuncture for liver cancer-related pain. The finding of our study may provide evidence for direct comparisons of different methods of acupuncture for liver cancer related pain.

Research methods
In this network meta-analysis (NMA), the association of each acupuncture and related therapies with relief of pain due to liver cancer was compared using the combination of direct and indirect evidence from eight RCTs with 734 patients. An NMA provides a basis for synthesizing all the available evidence in a consistent framework, obviating the need to make decisions by subjective inferences from disparate data. However, our analysis represents the use of the most practical methods currently available to
compare a large number of different types of treatment, thus enabling us to compare different methods of acupuncture with each other.

**Research results**
We conducted an NMA to analyze both direct and indirect comparisons of different methods of acupuncture for the relief of pain due to liver cancer. Based on the current evidence, we sorted and explored the advantages and disadvantages of different methods of acupuncture. Compared with traditional meta-analysis, the results of this study may provide a higher quality basis and reference for acupuncture treatment of pain due to liver cancer.

**Research conclusions**
The evidence from our NMA, in which different methods of acupuncture for pain due to liver cancer were compared with each other within a coherent framework, suggests that the overall effectiveness of triple puncture and remaining needle acupuncture is better than that of other therapies. However, despite the evidence from this study, the methodological limitations associated with many of the trials indicate that high-quality trials of acupuncture treatments are still required.

**Research perspectives**
Further clinical evaluation of acupuncture for pain due to liver cancer is required and longer follow-up appears warranted. The comparisons of the effectiveness of different acupuncture therapies should be conducted.

---

**ACKNOWLEDGEMENTS**
The authors are grateful for the professional help from their colleagues of Lichuan People’s Hospital and the Central Hospital of EnShi prefecture.

**FOOTNOTES**

**Author contributions:** Mou HY and Chen ZY contributed to the conception and design of the study, acquisition, analysis, and interpretation of the data, and drafting the article; Chen J and Du H interpreted the data and revised the article; All authors read and issued final approval of the submitted version.

**Conflict-of-interest statement:** The authors have no conflict of interest to declare.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Country/Territory of origin:** China

**ORCID number:** Hong-Yuan Mou 0000-0002-1042-4371; Jing Chen 0000-0001-5854-2396; Zuo-Yun Chen 0000-0002-7452-4769; Hong Du 0000-0003-3645-033X.

---

**REFERENCES**


Acupuncture for liver cancer pain: A meta-analysis

WJMA

Mou HY et al. Acupuncture for liver cancer pain: A meta-analysis


20 Li JY, Zhi Y, Lu H, Dong SJ, Liu SJ. 128 cases of Shoulder Periarthritis Treated by Tianyuan acupuncture. Renmin Junyi 2011; 54: 221

21 Li JY, Li JJ. Tian-yuan acupuncture. Renmin Junyi 2010; 38-43

22 Liu XY, Dong RP. 51 cases of liver cancer pain treated by Acupuncture and Acupoint Injection. ShanXi Zhongyiyaos Zazhi 2008; 29: 347-348

Effect of auricular plaster for primary hypertension in older people: A meta-analysis

Yong Qin, Yu Lou, Xiao-Yan Shen, Yun Gai

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chrcanovic BR, Sweden; Chrcanovic BR, Sweden; Kumar A, India; Kumar A, India

Received: December 4, 2021
Peer-review started: December 4, 2021
First decision: December 27, 2021
Revised: January 25, 2022
Accepted: April 24, 2022
Article in press: April 24, 2022
Published online: April 28, 2022

Abstract

BACKGROUND
Hypertension is a critical public health problem globally. Antihypertensive drugs can create an extra burden on hypertension patients' self-regulation leading to an imbalance of blood supply and demand. This study aimed to evaluate the effect of auricular plaster therapy combined with western medicine to treat primary hypertension in older people.

AIM
To carry out a systematic review and meta-analysis for the effect of auricular plaster in elderly hypertension patients.

METHODS
Multiple databases like PubMed, EMBASE, Cochrane Library, Chinese Biomedical Literature on Disc, China National Knowledge Infrastructure, Wan Fang and Chinese Science and Technology Periodical Database were used to search for the relevant studies and full-text articles involved in the evaluation of auricular plaster combined with western medicine and western medicine alone for primary hypertension in older people. All included articles were quality assessed and the data analysis was conducted with the Review Manager (5.4). Forest plots, sensitivity analysis and funnel plots were also performed on the included articles.

RESULTS
In this analysis, fourteen (14) relevant studies were included. The Meta-analysis showed a significant difference in the effective ratio (OR = 3.62; 95% CI, 2.46 to 5.33; P < 0.00001), diastolic blood pressure change (5.68 mmHg; 95% CI, 3.49 to 7.87; P < 0.00001), systolic blood pressure change (MD = 8.78 mmHg; 95% CI, 5.04 to 12.53; P < 0.00001) and symptom score (MD = 3.20; 95% CI, 1.23 to 5.18; P = 0.001) between auricular plaster combined with western medicine group and
western medicine alone group. One bias was detected as selection bias and another two in reporting bias. Sensitivity analysis fulfilled the stability of the results.

CONCLUSION
Our study suggested that auricular plaster combined with western medicine improved primary hypertension better than western medicine alone. Limited by the quality of included studies, further studies should be performed to confirm our findings.

Key Words: Primary hypertension; Older people; Auricular plaster; Meta-analysis

INTRODUCTION
Primary hypertension, referred to as hypertension, is a syndrome with elevated blood pressure as the main clinical manifestation\(^1\),\(^2\). It is an important cause and risk factor for a variety of cardiovascular and cerebrovascular diseases. It affects the structure and function of essential organs such as the heart, brain and kidney and eventually leads to the failure of these organs. It is still one of the leading causes of death in patients with cardiovascular diseases\(^3\),\(^4\). At present, the number of people with hypertension in the world has exceeded 1 billion and 90%-95% of these are diagnosed with primary hypertension\(^5\),\(^6\). Hypertension has become a significant public health problem endangering human health.

Long-term high blood pressure (BP) will cause compression on the systemic blood vessels, leading to vascular blockage or rupture, stroke, heart failure, aortic dissection and other complications\(^7\)-\(^9\). Therefore, reasonable control of blood pressure is the key to treat hypertension and reduce its complications. Patients with hypertension must take prescription medicine for life. Applying antihypertensive drugs will increase the burden of patients' self-regulation leading to the imbalance of blood supply and demand and has certain limitations\(^10\),\(^11\). It is of great clinical significance to explore the non-drug therapy available for hypertension\(^12\).

In recent years, a non-drug therapy called auricular plaster has been reported to treat essential hypertension in China and the number of reports is increasing\(^13\)-\(^15\). Auricular plaster is a common diagnosis and treatment technology of traditional Chinese medicine, also known as auricular point pressing beans or auricular point pressing seeds, which refers to sticking hard and smooth drug seeds or pills, magnetic beads and other things on the surface of the auricular points and fixing them with adhesive tape\(^16\)-\(^18\). The human body has six meridians distributed in and around the ear and the ear is connected with organs through meridians. The auricle is the only body surface area with vagus nerve distribution. Auricular plaster can activate the vagus nerve and regulate the autonomic nervous system by stimulating auricular points with cowherb seeds to reduce blood pressure (BP)\(^19\),\(^20\).

There are many clinical studies on auricular plaster therapy for elderly patients with primary hypertension, but the intervention methods and intervention time were quite different. Our study conducted a systematic review and meta-analysis of related randomized controlled trials (RCT) to evaluate the clinical efficacy of auricular plaster therapy combined with western medicine to treat primary hypertension in older people to provide a reference for clinical decision-making.

MATERIALS AND METHODS

Literature search strategy
We used comprehensive databases (PubMed, EMBASE, Cochrane Library, Chinese Biomedical Literature on Disc, China National Knowledge Infrastructure, Wan Fang and Chinese Science and Technology Periodical Database) to search for previous studies investigating the effects of auricular
plaster therapy for primary hypertension in the elderly. The literature search was performed from inception up to July 2021 using the following keywords: (1) Auricular plaster; (2) Primary hypertension; and (3) Western medicine. Terms were searched as text words and these three themes were combined using the Boolean operator ‘or’ to complete our search strategy. Our literature search was comprehensive with neither language restrictions nor publication status limitations. Two of us identified and reviewed full-text articles deemed relevant by screening the list of titles and abstracts. Disagreements were resolved through consensus between the two reviewers.

Study selection

After the primary selection, the text of the potentially relevant studies was reviewed. The studies included must meet the following inclusion criteria: (1) Comparing research patients who receive combination therapy of auricular plaster and western medicine (test group) and standard western medicine alone (control group); (2) Patients with primary hypertension [systolic BP (SBP) ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg]; (3) Containing indicators evaluating effectiveness between test group and control group; and (4) Available in full text.

Studies were excluded based on the following pre-determined exclusion criteria: (1) Not randomized controlled trials (RCT); (2) Reviews, letters, or protocols; (3) Duplicate articles; and (4) lack of related outcomes.

Data extraction and quality assessment

Two independent reviewers performed the study selection, data extraction and quality assessment. Pre-specified data elements were extracted from each trial using a structured data abstraction form, including baseline characteristics, sample size and interventions used. The risk of bias of included RCTs was assessed using a modified version of the Cochrane Collaboration’s Risk-of-Bias Tool. Two co-authors independently performed the risk-of-bias assessment on all included RCTs. When in a disagreement, the rechecking of the original article was followed by discussion and was used to reach a consensus.

Statistical analysis

Meta-analysis was performed in Review Manager (RevMan) software (version 5.4; Cochrane Collaboration) using the inverse variance method. We assumed that the studies’ variability beyond subject-level sampling error was random, and consequently, we adopted a random-effect model. The Mantel-Haenszel odds ratio (OR) model was used to summarize classification data, summary estimates and a 95% CI was reported for continuous variables as the mean difference (MD). Quantifying the inconsistency and heterogeneity across studies was assessed using Cochran Q and I² statistics. When the heterogeneity was present, the random-effects model was used to calculate the pooled OR or MD, whereas the fixed effects model was used in its absence. We also performed a sensitivity analysis with each endpoint to determine if there was any difference between groups. Publication bias was graphically analyzed with funnel plots. We also applied Egger and Begg’s statistical test. A P value of < 0.05 was considered statistically significant.

RESULTS

Results of the literature search process

An electronic search was performed to identify all potential articles published in the English language by July 2021, and initially, 932 articles were selected. After a careful review of the titles and abstracts, 126 studies were included due to immediate satisfaction with the purpose of the present meta-analysis. Further, 112 articles were excluded due to not fulfilling the inclusion criteria. The remaining 14 studies were assessed and reviewed to satisfy the inclusion criteria and were considered in our meta-analysis [21-34]. Figure 1 represents an outline of the studies’ identification, inclusion and exclusion criteria, thereby summarizing the search process and the reasons for exclusion.

Study characteristics

A total of 1088 patients with primary hypertension were included in this meta-analysis study and all these studies were published from 2012 to 2021. The primary outcome contained effective ratio, DBP change, SBP change and symptom score.

The antihypertensive effect was determined according to the relevant standards in the guiding principles for clinical research of new drugs in traditional Chinese medicine [35]. (1) Strongly effective (meets one of the following conditions): Diastolic blood pressure (DBP) decreased by 10 mmHg or more, and within the normal range; DBP did not fall to the normal range but decreased by 20 mmHg or more; (2) Moderate effective (meet one of the following conditions): DBP decreased to 10-19 mmHg, but still higher than the normal range; Systolic blood pressure (SBP) decreased to 30 mmHg; and (3) Ineffective: Did not meet any of the above criteria. The
effective ratio in our outcome variable was the sum of strongly effective and moderate effective ratios.

Symptom score referred to the curative effect standard in the guiding principles for clinical research of new Chinese medicine in 2002[36]. Headache, vertigo and insomnia were selected to observe the symptoms and the symptoms were scored according to the degree of symptoms from mild to severe. The primary study chosen characteristics are summarized in Table 1.

Results of the quality assessment

According to the Cochrane risk of the bias assessment tool, to assess the bias risk (including selection, performance, detection, attrition and reporting bias among the included randomized trials) (Figures 2 and 3), the methodological quality of included studies was evaluated for the bias risk. There was a high risk of selection bias in one study and reporting bias in two other studies. In the summary risk of bias assessment of the 14 included studies, there is a limited selection bias, performance bias and detection bias. In general, there are only two trials with bias risk and the other six tests have no risk.

Results of heterogeneity test

The effect of auricular plaster on effective ratio was reported in 12 studies. A significant improvement in the effective ratio was identified compared with the control group (OR = 3.62; 95%CI, 2.46 to 5.33; \( P < 0.00001 \)). There was no significant heterogeneity for effective ratio assessment (\( P = 0.74, I^2 = 0\% \)) (Figure 4).

Thirteen trials reported information about DBP change. A random-effect model was used to evaluate the heterogeneity of DBP change due to the significant heterogeneity (\( P < 0.0001, I^2 = 89\% \)). The pooled analysis showed that the test group had a better reduction of DBP than the control group (MD = 5.68 mmHg; 95%CI, 3.49 to 7.87; \( P < 0.00001 \)) (Figure 5).

In evaluating the difference of SBP change between the test group and control group, 13 articles involved 1028 patients. Meta-analysis showed that compared to the control group, the test group had a higher reduction of SBP (MD = 8.78 mmHg; 95%CI, 5.04 to 12.53; \( P < 0.00001 \)), with significant heterogeneity (\( P = 94\% , I^2 = 94\% \)) (Figure 6).

Four studies reported symptom scores. A random-effect model was used to evaluate the heterogeneity among the significant heterogeneity included studies (\( P < 0.00001, I^2 = 89\% \)). The results showed that the test group improved symptom scores better than the control group (MD = 3.20; 95%CI, 1.23 to 5.18; \( P = 0.001 \)) (Figure 7).

Results of sensitivity analysis and publication bias

The included studies will be excluded one by one for sensitivity analysis. The heterogeneity of DBP change was decreased from 89% to 87% when Wu 2013 was excluded suggesting that the meta-analysis results were robust.
A funnel plot was performed to evaluate the publication bias for effective ratio qualitatively. The shape of the funnel plot showed some evidence of symmetry (Figure 8) and the Egger test was not significant ($P = 0.77$), which indicated no significant publication bias existed in this meta-analysis.

## DISCUSSION

Hypertension is one of the most common cardiovascular diseases. In recent years, with the change of modern living habits, the incidence rate of hypertension has been increasing year by year. Hypertension has presented a trend toward younger people. How to control BP safely and reliably has become a problem that medical workers must solve today[37]. How to effectively and stably control BP and avoid large fluctuations such as a sudden fast rise or lowering of blood pressure. Maintaining a steady BP reduces the damage caused by BP fluctuations, prevents the adverse effects caused by excessive BP, reduces the damage of essential organs and effectively controls the disability rate and mortality rate which is the key to the problem[1,38,39].

At present, western medicine is the primary treatment for hypertension and the first-line antihypertensive drugs include diuretics, β Receptor blockers, calcium antagonists, angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists[40,41]. The guidelines point out that diuretics can reduce blood volume and relax peripheral blood vessels; β Receptor blockers can reduce cardiac output; Calcium antagonists can inhibit calcium influx in vascular smooth muscle and reduce myocardial contractility; Angiotensin-converting enzyme inhibitors and angiotensin receptor...
antagonists can block the renin-angiotensin system and dilate arterioles and venules. The mechanism of action of these drugs is to improve the circulatory system from different aspects to reduce BP\cite{42,43}.

In China, auricular plaster is a diagnosis and treatment technology developed based on auricular acupuncture therapy\cite{44}. Cowherb Seeds are complicated and can activate blood circulation and regulate BP. Auricular plaster therapy can regulate BP to a certain extent, significantly improve patients' clinical symptoms with hypertension and improve patients' satisfaction with nursing work\cite{45,46}. Some studies have shown that auricular plaster therapy can regulate the balance of viscera and meridians,
promote the function of the cerebral cortex to return to normal quickly and comprehensively treat the uncoordinated nerve, body fluid and vascular function to achieve the effect of reducing BP\cite{47,48}.

Fourteen studies were included in this systematic review and meta-analysis. The meta-analysis results showed that the effective ratio of auricular plaster therapy in the treatment of hypertension based on conventional western medicine therapy was higher than that of western medicine alone therapy (OR = 3.62; \(P < 0.00001\)), suggesting that auricular plaster therapy had an excellent adjuvant effect on hypertension. The decrease of DBP (MD = 5.68 mmHg; \(P < 0.00001\)), SBP (MD = 8.78 mmHg; \(P < 0.00001\)) and symptom score (MD = 3.20; \(P = 0.001\)) were more evident than that of the control group, suggesting that the combination therapy of auricular plaster and western medicine was better than western medicine alone in improving clinical symptoms. It showed that auricular plaster therapy had significant health benefits in treating hypertension and was worthy of clinical promotion.

This study showed apparent heterogeneity in the assessment of the literature included in the improvement of SBP, DBP and symptom scores. Although sensitivity analysis showed that heterogeneity did not affect the final results, we still analyzed the source of heterogeneity. After further reading and analysis of the included studies, we found that the heterogeneity may be caused by different types of antihypertensive drugs, other antihypertensive mechanisms and different effects on SBP, DBP and clinical symptoms, which suggested that we need to conduct a subgroup analysis on different types of antihypertensive drugs.

There were some limitations in this meta-analysis. Firstly, auricular plaster therapy was a unique traditional medical method in China and the published reports were mainly in Chinese with the quality being relatively poor. Secondly, some of the included studies did not describe the implementation of random allocation and blind methods. In addition, the frequency of auricular plaster, the type and dose of western medicine was also different in the experiment which suggested that more detailed
Qin Y et al. A meta-analysis on auricular plaster

CONCLUSION

In conclusion, auricular plaster combined with western medicine can improve the antihypertensive effect of primary hypertension, reduce BP and improve clinical symptoms. In view of the quality of the hierarchical or subgroup analysis can be done in the future.
included studies, the reliability of the conclusions was reduced. It is still necessary to carry out multi-center, large sample randomized controlled trials, paying attention to the implementation of the randomized method, allocation concealment method and blind method to obtain reliable research data so as to provide the evidence-based basis for clinical treatment of hypertension.

ARTICLE HIGHLIGHTS

Research background
Hypertension is a very common health problem for older people. Recently, a non-drug therapy called auricular plaster has been used to treat hypertension in China and is considered traditional Chinese medicine. There were many clinical studies which reported on auricular plaster therapy for elderly patients with hypertension but the intervention methods and intervention times were quite different.

Research motivation
We speculate about gaining a detailed insight into the effect of auricular plaster therapy on elderly patients with primary hypertension.

Research objectives
This study aimed to evaluate the effect of auricular plaster therapy combined with western medicine to treat primary hypertension in older people.

Research methods
A literature search was carried out to identify reports published through July 1, 2021. The meta-analysis was carried out for the outcomes of the significant difference in the effective ratio, diastolic blood pressure (DBP) change, systolic blood pressure (SBP) change, and symptom score between auricular plaster combined with western medicine group and western medicine alone group. Publication bias was identified by the funnel plots test.

Research results
In this analysis, fourteen (14) relevant studies were included. The Meta-analysis showed a significant difference in the clinical effective ratio (OR = 3.62; 95%CI, 2.46 to 5.33; \(P < 0.00001\)), DBP change (5.68 mmHg; 95%CI, 3.49 to 7.87; \(P < 0.00001\)), SBP change (MD = 8.78 mmHg; 95%CI, 5.04 to 12.53; \(P < 0.00001\)) and symptom score (MD = 3.20; 95%CI, 1.23 to 5.18; \(P = 0.001\)) between auricular plaster combined with western medicine group and western medicine alone group.

Research conclusions
Auricular plaster could be a potential therapy to treat hypertension in elderly patients.

Research perspectives
More prospective sample studies are needed in the future to enhance the speculation of our conclusion.

FOOTNOTES

Author contributions: Qin Y, Lou Y, and Gai Y participated in the conception and design of the study, library searches and assembling relevant literature, critical review of the paper, supervising the writing of the paper and database management; Qin Y, Shen XY, and Gai Y participated in data collection, library searches assembling relevant literature, writing the paper and critical review.

Supported by Leading talent training of Pudong New Area Health Committee, No. PWR12020-02; Exploration on the discipline construction mode of treating and preventing diseases based on specific diseases, No. PWZY-2019-0402; Shanghai collaborative innovation center of traditional Chinese medicine health services.

Conflict-of-interest statement: All authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: This study was conducted as per PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/
REFERENCES


Yu Q, Hu C, Zhao W. Clinical observation of auricular plaster therapy combined with western medicine in the treatment of community primary hypertension. SH JTCM 2018; 52: 44-47


Zhou X, Lin P. Effect of ear point seed pressing on blood pressure of patients with essential hypertension. Henan Traditional Chinese Medicine 2016; 36: 1787-1789


Dong Q, Yan L, Cai L. Clinical effect of auricular-plaster therapy cooperated with antihypertensive drugs in the treatment of grade 1 hypertension disease. China Medical Herald 2017


