

# Sorafenib in the treatment of Hepatocellular carcinoma (HCC) patients with microvascular infiltration: a systematic review and meta-analysis

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## Research article

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# Abstract

Microvascular invasion has been shown to be an independent risk factor for liver cancer recurrence. Timely treatment can reduce the recurrence rate and prolong the total survival time. However, the effectiveness of sorafenib in treating HCC patients with microvascular invasion remains controversial. As of December 30, 2019, a comprehensive literature search has been conducted in PubMed, EMBASE, MEDLINE, web of science and Cochrane Library. A meta-analysis was conducted to assess the impact of sorafenib on mortality in HCC patients with microvascular involvement. Two researchers independently reviewed and cross-checked independent reports with sufficient information. Four studies were selected and reported 950 cancer events and 505 cancer deaths. The results showed that sorafenib could improve the survival rate of liver cancer patients with microvascular invasion (RR= 1.369;95% confidence interval (CI) ,1.193-1.570; P < 0.001). However, given the potential for residual confounding, the results should be interpreted with caution. Further prospective studies still need to confirm the prognostic benefits of sorafenib.

## Introduction

Liver cancer is the second leading cause of cancer death worldwide. Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death, the fifth most common cancer in men and the seventh most common cancer in women. [1, 2]. Partial hepatectomy is the preferred treatment for patients with early hepatocellular carcinoma (HCC) [3], but about 70% of patients relapse within 5 years after hepatectomy [4], and about 30% of patients with recurrent HCC perform poorly at the time of mid-term diagnosis [5]. Hepatocellular carcinoma with microvascular tumor invasion (MVI) is very common, and microvascular invasion is often associated with early recurrence of tumors and reduced survival. [6–8]. Microvascular invasion occurs in approximately 15–60% of HCC patients. Relevant studies have shown that microvascular invasion is an independent risk factor for early recurrence [9–12]. Although there are some studies that show that some complementary therapies can help [13, 14], there is still no commonly accepted adjuvant therapy after hepatectomy[15].

Sorafenib is an effective multi-kinase inhibitor that inhibits tumor angiogenesis and proliferation by interfering with the binding of serine/threonine kinases to receptor tyrosine kinases [16]. In addition, sorafenib is known to have effects on both tumor cells and endothelial cells[17]. Despite multiple studies, no reliable predictive biomarkers have been identified for the response of HCC patients to sorafenib, including sorafenib targets such as MAPK/ERK or VEGF. However, sorafenib is considered an effective treatment for advanced liver cancer, and this treatment has been maintained for nearly a decade. [18].

In view of the global prevalence of liver cancer and the high mortality of cancer patients, it is of great clinical significance to explore sorafenib in the treatment of liver cancer in daily practice. In addition, they are crucial in the area of public health, as a modest increase in cancer risk translates into a huge social burden. These conditions prompted us to study the effect of sorafenib on cancer mortality more precisely. We carefully read the relevant original reports and combined their data to try to obtain meaningful clues.

# Methods

## 1. Search strategy

The two studies independently searched the Medline, Embase, PubMed, Cochrane Libraries, and Web of science databases for all relevant articles. Medical subject heading terms used in the search included "liver cancer", "Hepatocellular carcinoma (HCC)", "Hepatic carcinoma", "hepatoma", "sorafenib", "microvascular invasion". The study's title and abstract were independently reviewed by the two authors, excluding studies that did not answer relevant research questions. The full text of the remaining articles, including references, was examined to determine if they contained relevant information. When incomplete information was available, attempts were made to contact the corresponding author of the study for more information. Figure 1 shows the literature screening process..

## 2. Selection criteria

If the cohort and case-control studies or randomized controlled trial of sorafenib therapy associated with microvascular invasion of hepatocellular carcinoma (HCC), in which the experimental group for the use of sorafenib therapy, treatment group does not contain sorafenib, and study the related risk ratio (hr)/relative risk (RR)/odds ratio (or) and corresponding 95% confidence intervals (CIs), or provides ample research data will be incorporated in the analysis. Inclusion is not limited by language, time, nationality and other factors. If the study object is the same population, select a more complete study to be included in the analysis.

## 3. Data extraction

In the Endnote version X9, references are merged together for ease of administration. Two authors independently completed the literature search and evaluated the full text. For the selected literature, two authors read the title, abstract and full text of the article. Authors in each eligible studies to extract the relevant data, to extract the study's lead author, publication date, country, research methods, data sources, research time, fixed number of year of follow-up, the study of the characteristics of the object (age, gender, exposure, the definition of a test dose and duration of the relevant risk assessment (including hr, RR or) and 95% confidence interval and relevant confounding factors. The authors did all this work independently. Because subjects in some studies used combination therapy, we defined the experimental group as treatment with sorafenib and the control group as non-treatment with sorafenib.

## 4. Quality assessment

The Newcastle Ottawa scale[19] was used to evaluate the quality of the cohort study. In this scale, the study was divided into three categories: subject selection (4 stars), study group comparability (2 stars), result / exposure assessment (3 stars). The quality adopts star system, the highest 9 stars, 0–5 stars are low quality, 6–9 stars are high quality. The characteristics of the study are shown in Table 1.

## 5. Statistical analysis

The statistical analysis in this article used the 15th generation of STATA software (STATA, College Station, TX, USA). The probability values (P values) of all statistical results were bilateral, and  $P < 0.05$  was considered statistically significant. Higgins and Thompson's  $I^2$  was used to assess heterogeneity between studies. When  $I^2 > 50\%$  is represented as large heterogeneity,  $I^2 < 50\%$  indicates small heterogeneity. [20], DerSimonian and Laird random effect model (REM) is used as pooling method, otherwise, fixed effect model (FEM) is used as pooling method.

## 6. Results

Four related studies were reviewed [21–24], with a total of about 950 HCC patients with microvascular invasion. Sorafenib significantly improved survival in HCC patients with microvascular invasion compared to those without sorafenib treatment (RR = 1.369, 95% confidence interval (CI) 1.193, 1.570;  $P < 0.001$ ). There was no significant heterogeneity between the 4 included studies ( $P = 0.352 > 0.01$ ;  $I^2 = 8.2\%$ ). The relevant results are shown in Fig. 2. The results of publication bias show that there is no publication bias ( $z = 1.02 > 0.05$ ,  $Pr > |z| = 0.308$ ), The funnel is shown in Fig. 3. Through the sensitivity analysis, it can be concluded that there is no significant difference among the four studies, with good consistency (Fig. 4).

## Discussion

HCC is one of the most common cancers in the world [25]. In the past few decades, with the progress of technology, the treatment of liver cancer has made great progress. Surgical resection remains the first-line treatment for early and intermediate HCC. The recurrence rate after tumor resection is high, but the long-term survival rate of patients is low [26, 27]. Microvascular invasion is a manifestation of tumor invasion of endothelial cells. Microvascular invasion often leads to poor prognosis. [28, 29]. Hepatectomy is a safe and effective method to treat liver cancer, however, microvascular invasion greatly increases the risk of cancer recurrence after hepatectomy. Several studies have demonstrated that radiofrequency ablation and TACE are effective for recurrence after hepatectomy and for patients with hepatocellular carcinoma with venular invasion. [30–32]. An animal study in mice found that sorafenib prevented the recurrence and metastasis of liver tumors. [33]. One study found that the effect of sorafenib adjuvant chemotherapy in patients with liver cancer with MVI was positive after surgery. [34]. Therefore, theoretically, the antiangiogenesis, apoptosis and proliferation effects of sorafenib make it an ideal drug choice after hepatectomy, but there are few related studies.

Although the mechanism of sorafenib's action is not very clear, related studies suggest that sorafenib may be an enzyme inhibitor, whose effect is to inhibit vascular endothelial hyperplasia and thus inhibit microvascular invasion. For example, sorafenib can block serine/threonine kinases (c-RK and b-RAF) and receptor tyrosine kinases (vascular endothelial growth factor receptors 2 and 3, platelet-derived growth factor receptor levels, FMS tyrosine kinase 3) [35], VEGF is a major factor in the mechanism of tumor angiogenesis. An animal study showed that sorafenib could significantly inhibit the growth and migration of cancer cells [33]. Wang et al. demonstrated that sorafenib as an adjuvant therapy for liver cancer can

prevent early recurrence after hepatectomy[36]. The study found that the use of sorafenib can significantly reduce the recurrence rate and improve the survival rate of patients with liver cancer. [37–40]. However, the results of some studies are not identical. The results show that although sorafenib can reduce the mortality of patients after radical hepatectomy and reduce the operation time, it can not reduce the risk of tumor recurrence.[41].

At present, there are few relevant studies on the efficacy of sorafenib on liver cancer patients with venereal metastasis, and the sample size of existing studies is relatively small, so we decided to conduct a systematic analysis based on relevant studies. This review systematically reviewed the efficacy of sorafenib in the treatment of hepatocellular carcinoma patients with venule invasion in four studies. We conduct relevant literature searches in multiple databases and hope to collect articles as comprehensively as possible. And through rigorous scientific methods to extract valid data in relevant articles. Because of the potential confounding factors in relevant studies, we tried to exclude relevant interfering factors to collect as accurate data as possible. A systematic analysis of four studies involving 950 patients with hepatocellular carcinoma with venular invasion by our team found that the use of sorafenib significantly improved the survival rate of patients with low hepatocellular carcinoma with venular invasion compared with patients without sorafenib. (RR = 1.369; 95%ci, 1.193–1.570; P < 0.001), and there was no significant heterogeneity between studies ( $I^2 = 8.2\%$ ). Since there was no significant heterogeneity between studies, we did not further explore the sources of heterogeneity. Our systematic analysis also has certain limitations, for example, the adjustments included in the study may be incomplete and inconsistent. Confounders such as the patient's own status (tumor stage and related complications) and the lack of detail on sorafenib use (dose and duration) in most studies will affect the overall analysis. In addition, treatment information is obtained through prescriptions in the patient's medical records, so the difference between the prescribed dose and the actual dose may affect the outcome.

## Conclusion

In summary, the use of sorafenib reduced the mortality of HCC patients with venereal invasion, and most other exploratory analyses confirmed this effect. However, Considering the presence of confounding factors, the conclusions should be interpreted with caution. At the same time, due to the limitation of relevant research design, this outcome is somewhat controversial. Therefore, more clinical trials are needed to prove whether sorafenib is effective in the treatment of hepatocellular carcinoma patients with venular invasion.

## Abbreviations

HCC☐Hepatocellular carcinoma☐TACE☐Transarterial chemoembolization ☐RR☐Relative risk ☐MVI☐ Microvascular invasion☐AASLD☐American Association for the Study of Liver Diseases.

## Declarations

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## Availability of data and materials

Not applicable.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Written informed consent was obtained from the patient and patient's next-of-kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## Competing interests

The authors declare that they have no competing interests.

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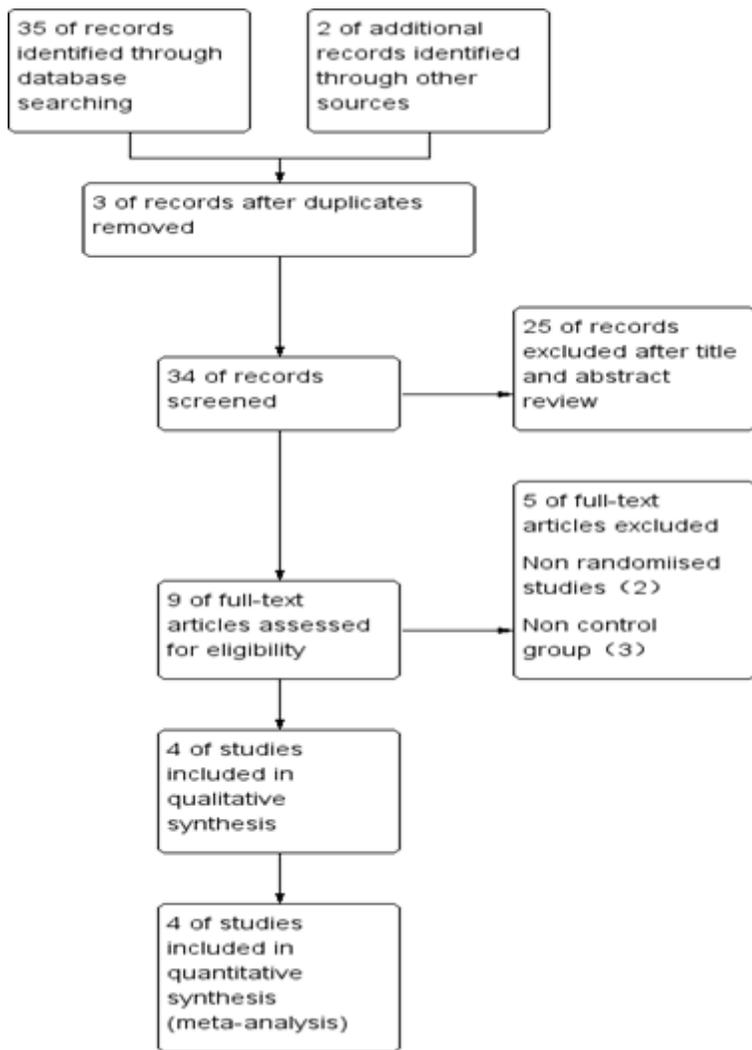
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## Tables

**Table1: Characteristics of included studies in the meta-analysis**

Study (year)	Design	Location	Study population	Total subject	NOS score	Definition of exposure and control	Median follow-up, M	Adjusting factors
Yun Huang [2019]	Cohort	China	HCC patients with microvascular infiltration	49	6	Ex: Use sorafenib	22.2 months	Study exposure
Zhenwei Peng [2019]	Cohort	China	HCC patients with microvascular infiltration	127	6	Ex: Sorafenib with TACE	34.5 months	Study exposure and TACE
Xiuping Zhang [2019]	Cohort	China	HCC patients with microvascular infiltration	728	7	Ex: Use sorafenib	No report	Study exposure
Xinyu Bi [2019]	Cohort	China	HCC patients with microvascular infiltration	46	6	Ex: Use sorafenib	No report	Study exposure

## Figures



**Figure 1**

The flow chart of literature selection

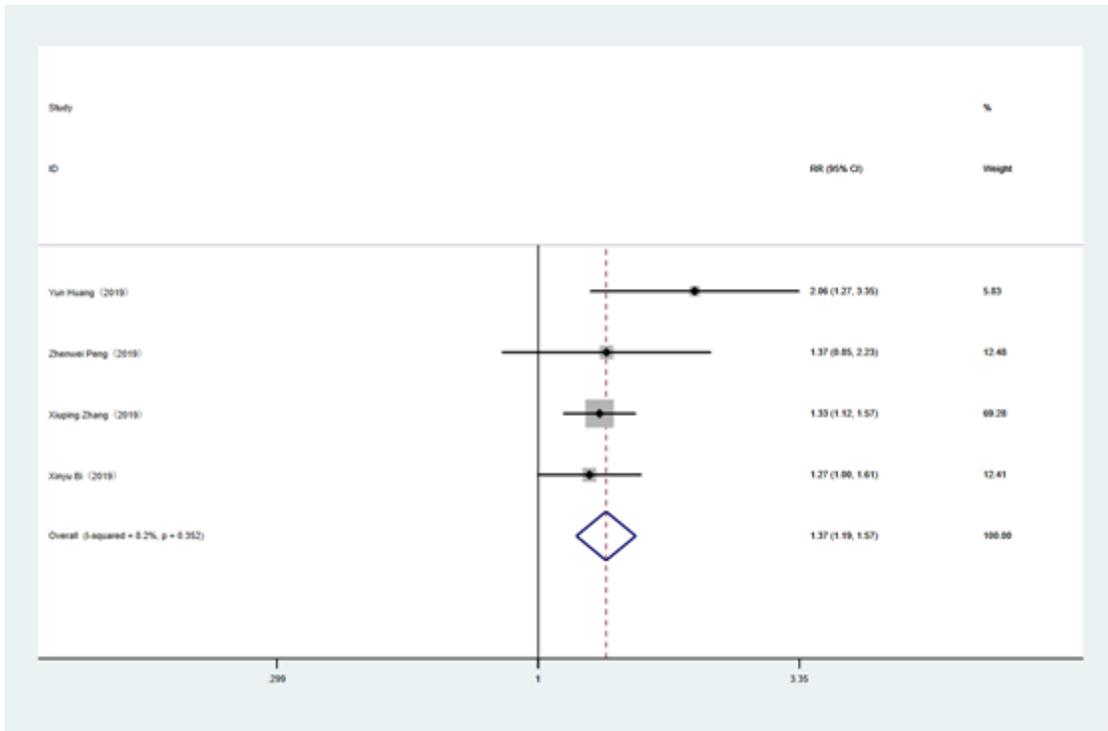


Figure 2

Forestplot of the relationship between the use of sorafenib and the outcome of treatment in patients with HCC with microvascular invasion.

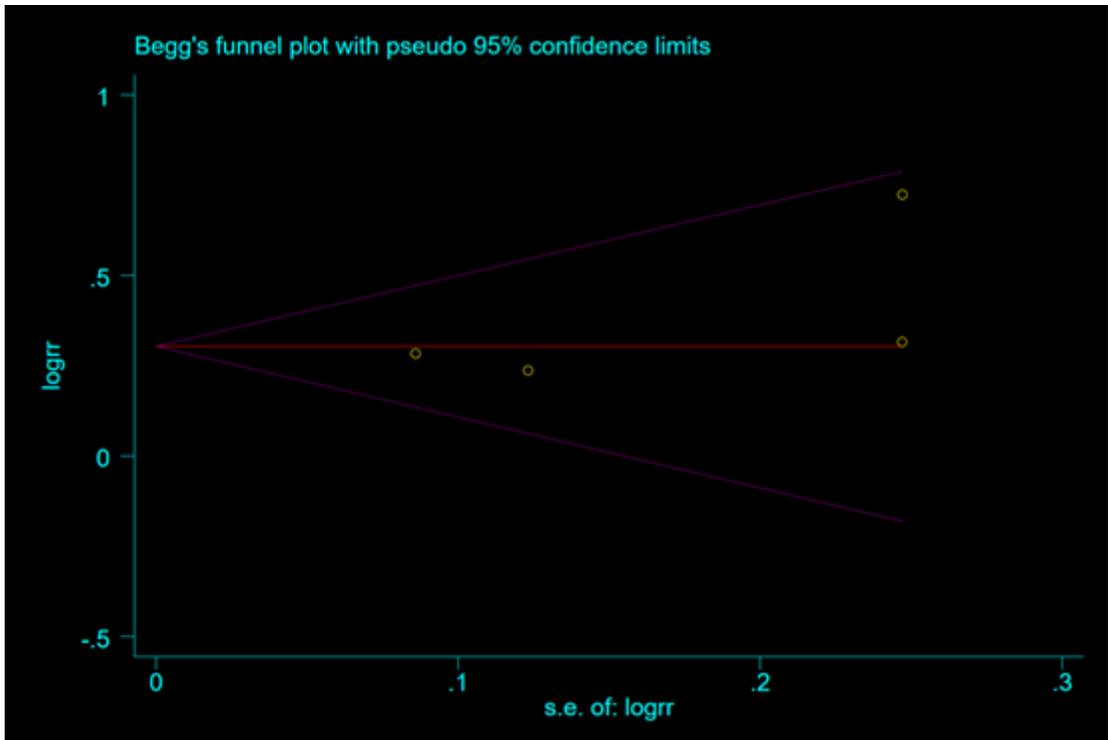


Figure 3

Begg's funnel polt

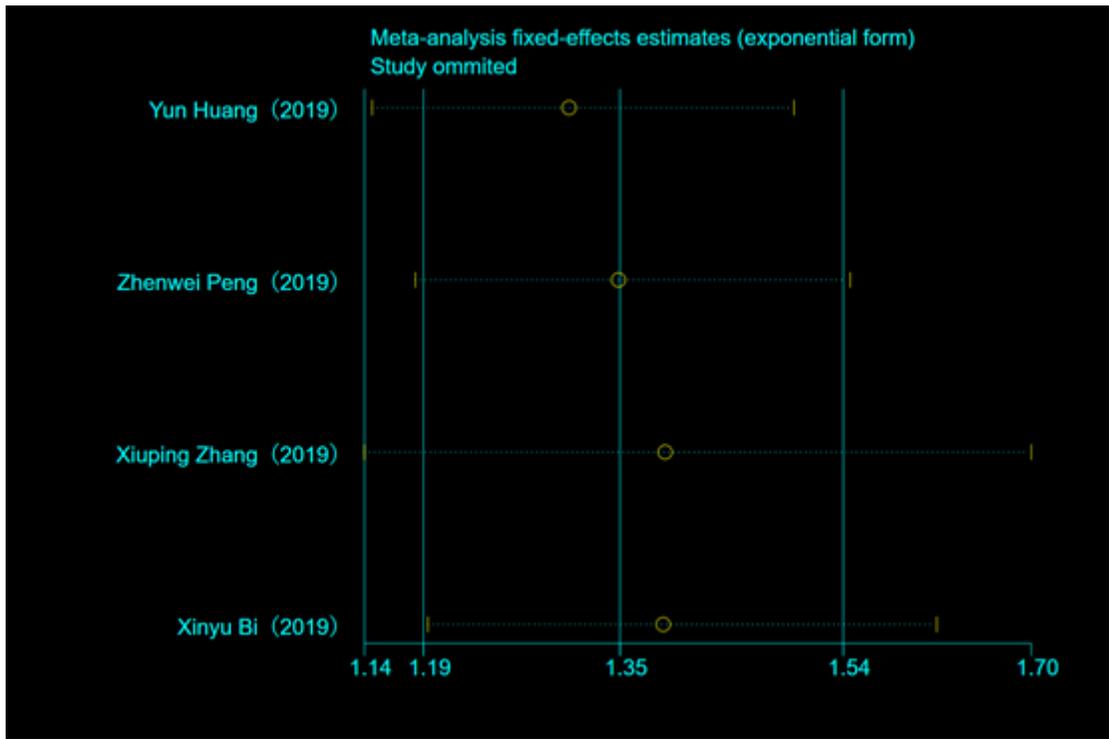


Figure 4

sensitivity analysis

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