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The efficacy of sorafenib in preventing hepatocellular carcinoma recurrence after resection: a systematic review and meta-analysis

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ABSTRACT

Introduction: hepatocellular carcinoma (HCC) recurrence after liver resection remains a major threat for patients' survival. Sorafenib is recommended as an adjuvant treatment for patients after a liver resection. The objective of this meta-analysis was to estimate the therapeutic value of sorafenib in patients who underwent a HCC resection.

Materials and methods: relevant reports were retrieved from electronic databases. All eligible studies were carefully reviewed and the required data were extracted. Outcome with regard to overall survival (OS), recurrence-free survival (RFS), recurrence rate, mortality rate, OS time (months) and RFS time (months) were analyzed.

Results: nine trials were included. The results of the meta-analysis revealed that sorafenib did not exert a significant superior effect on OS (sorafenib as reference: hazard ratio [HR] = 2.15; 95% CI, 0.91-5.08, p = 0.80; control as reference: HR = 0.56;

95% CI, 0.31-1.02; p = 0.059), OS time in months (weighted mean differences [WMD] = 4.96; 95% CI, -1.21-11.13; p = 0.115) and RFS time in months (WMD = 7.58; 95% CI, -1.36-16.53; p = 0.097). Nevertheless, the use of sorafenib was associated with a significantly higher RFS (HR = 0.53; 95% CI, 0.31-0.90; p = 0.018), and a lower recurrence rate (risk ratio [RR] = 0.72; 95% CI, 0.60-0.86; p < 0.001) and mortality rate (RR = 0.74; 95% CI, 0.57-0.95; p = 0.20).

Conclusion: according to the present meta-analysis, sorafenib showed a significant benefit in RFS, recurrence rate and mortality rate. The effect of sorafenib for the prevention of HCC recurrence seems to be encouraging. However, more evidence is still needed before reaching a definitive conclusion.

Keywords: Hepatocellular carcinoma recurrence. Sorafenib. Resection.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer and the third most common cause of cancer-related death worldwide (1). Around 700 thousand new cases are diagnosed per year and the number continues to rise (2). Effective treatment strategies are urgently needed for this life threatening disease. Despite the development of potential curative treatments, including liver transplantation, resection and local ablation, the prognosis of patients is still poor due to tumor recurrence. For patients with early stage HCC, tumor resection may be the best choice due to the organ saving characteristics, lower cost and lower dropout rate (3). Evidence suggests that hepatic resection can provide a five-year survival rate of 50-70% (4,5). However, the recurrence rate after resection is still high. The three-year recurrence rate is 50% and the five-year rate is 70%, which jeopardizes overall survival (OS) in these patients (6).

Many protocols have been proposed and applied in patients after HCC resection, with the aim to prevent HCC recurrence. However, systemic chemotherapy and chemoembolization have been shown to have little effect (7,8). Although the use of immunotherapy and interferon therapies has been suggested to prolong recurrence-free and overall survival (9,10), further evidence is needed before they can be

routinely used in the clinical practice.

Sorafenib, a multiple tyrosine kinase inhibitor, is thought to have antitumor effects. Sorafenib can inhibit HCC tumor cell proliferation and angiogenesis by targeting pathways implicated in the molecular pathogenesis of HCC, such as Raf/MEK/ERK signaling pathway and VEGF receptor 2 (VEGFR-2), VEGFR-3 and PDGFR (11,12). Sorafenib is now recommended as the standard systemic treatment for HCC. This is due to the results of two phase 3, multicenter, randomized controlled trials, which confirmed the positive effect of sorafenib on OS of advanced and unresectable HCC (13,14).

Recently, clinicians have argued that sorafenib can be used in a post-hepatic resection setting to prevent tumor recurrence. Previous animal models have demonstrated that sorafenib prevented metastatic recurrence and improved recurrence free survival (RFS) in mice (15). However, the results in human trials remain controversial. A previous meta-analysis seemed to dispute the effect of sorafenib in preventing HCC recurrence (16). However, only five studies were included and each analysis included no more than four groups of data, which was far from sufficient to draw a definite conclusion. Besides, the former analysis only included studies published up to April 2016. Articles published within the latest three years may provide new information, allowing an update of the meta-analysis. Thus, the present meta-analysis was performed to assess the effect of sorafenib treatment on HCC patients after resection. The aim of the study was to resolve the question whether sorafenib can reduce HCC recurrence and mortality rate and improve RFS and OS after a HCC resection.

MATERIALS AND METHODS

Literature search

The primary sources for the retrieval of relevant publications were PubMed, ScienceDirect and Web of Science. The following subject headings were retrieved: hepatocellular carcinoma, recurrence, resection and sorafenib. The electronic databases were searched from database inception to August 2019 and was restricted to English publications. All titles and abstracts retrieved from the initial search were

screened by two reviewers and the full-text of potentially eligible studies was further reviewed. A manual search of the reference lists of the included publications and relevant review articles was also performed to find additional studies.

Eligible criteria

Studies that investigated the effect of sorafenib on HCC after resection was the field of interest in this meta-analysis. Besides, all of the eligible studies should be human trials with a control group, in which patients only received surgical resection without other systemic therapy and included at least one of the following outcomes: OS, RFS, recurrence rate, mortality rate, OS time (months) and RFS time (months). Studies that did not meet the aforementioned criteria, review articles, case reports and ongoing trials were excluded. For multiple reports with the same cohort of patients, only the latest publication or the one with the most complete data was included.

Data abstraction and quality assessment

All potential studies for inclusion were reviewed by two investigators, using a predefined standardized form. Data, regarding study design, patient characteristics, treatment options, target outcomes and other parameters that were deemed to affect patient outcomes (risk factors, adverse side effects etc.) were extracted. Disagreements were resolved via a discussion until a consensus was reached.

The same two reviewers also performed the quality assessment of the included studies. Methodological quality of the included trials (case control or cohort study) was evaluated using the Newcastle-Ottawa Scale (NOS) (17). Each study was ranked up to 9 with scores based on the NOS; a higher score represented a better methodological quality. For randomized controlled trial (RCT), the seven-point Jadad scale was applied for quality assessment (18).

Statistical analysis

The Stata software version 15.0 (Stata Corporation, College Station, TX, USA) was used for all statistical analyses. Statistical heterogeneity was measured using the Chi-squared Q test and I^2 statistics. The random-effects model was chosen for data

calculation when I^2 > 50% and p < 0.05. Otherwise, a fixed-effects model was used. The hazard ratio (HR) with the corresponding 95% confidence interval (CI) were calculated to assess the correlation of sorafenib treatment with OS and RFS after liver resection. HR > 1 indicated that patients in the comparator group had a poor prognosis. On the contrary, HR < 1 meant that patients in the comparator group had a better prognosis. A pooled risk ratio (RR) with its 95% CI were calculated for dichotomous data, such as recurrence rate and mortality rate. An RR < 1 represented a favorable outcome toward the sorafenib group compared with the control. A w eighted mean difference (WMD) with 95% CI was calculated for continuous variables , such as OS time and RFS time. Sensitivity analysis was performed by removing one study result at a time to test if a certain study could alter the overall effect and to verify the stability of the pooled results. A p-value < 0.05 was considered as statistically significant. This meta-analysis was performed in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (19).

RESULTS

Study selection

The database search identified 957 citations that could potentially be included in the meta-analysis. After the initial screen of the title and abstract, only 16 articles passed through to the full-text review stage. Finally, nine studies were eligible for inclusion (20-28). The cross checking of the reference lists did not identify any additional studies that were suitable for inclusion. Figure 1 illustrates the process of the literature search and study selection.

Study characteristics

Table 1 presents the basic characteristics of each included study. A total of 1,563 patients were included and 721 were treated with sorafenib and 824 subjects were used as a control. Two studies reported a median time to recurrence after resection. Bruix et al. found no significant difference between sorafenib and the control group (p = 0.12), while Wang et al. reported a longer time to recurrence in the sorafenib

group compared with the controls (p = 0.006) (21,24). With regard to sorafenib treatment, seven out of the nine included studies used an initial dose of 400 mg twice a day (21,23-25,27-29) and adjusted doses according to the patients' tolerability and safety. Treatment duration was recorded in six studies (21,23-25,27,28) and differed greatly among trials, which ranged from four to 70.97 months (Table 2). Only two studies reported the occurrence of grade 3 or 4 side effects during sorafenib treatment and both were hand-foot skin reaction (21,22).

Eight included publications were retrospective or prospective cohort or case-control studies (20,22-25,27-29). The NOS score of the eight trials ranged from 6 to 8 with a median of 7.4, indicating that the included studies had a moderate quality. One study was designed as an RCT (21), and the methodological quality Jadad score was 7. Detailed information of the included studies and the results of the distribution are presented in table 3.

Efficacy of sorafenib on OS and RFS

Six studies provided accessible data to evaluate the effect of sorafenib treatment on OS (20,21,25,27-29). The pooled results showed that sorafenib treatment led to a better OS compared with controls (sorafenib as reference: HR = 2.15; 95% CI, 0.91-5.08, p = 0.080; I^2 = 0%; control as reference: HR = 0.56; 95% CI, 0.31-1.02; p = 0.059; I^2 = 77.7%). However, the results did not reach statistical significance (sorafenib as reference: p = 0.080; control as reference: p = 0.059) (Fig. 2A). The sensitivity analysis confirmed that the results of OS were stable, as the opposite result was not found when each study outcome was omitted.

Five trials were included that assessed the correlation between sorafenib treatment and RFS (21,23,24,27,28). The pooled results reported a significantly higher RFS in patients that received sorafenib (HR = 0.53; 95% CI, 0.31-0.90; p = 0.018; I^2 = 73.5%) (Fig. 2B). However, when omitting the studies of Huang, Liao and Wang (23,24,28), although the sorafenib group still showed a trend to have a better RFS, there was no statistically significant difference between the groups with regard to the sensitivity analysis.

Efficacy of sorafenib on recurrence and mortality rate

The analysis of the recurrence rate and mortality rate each included seven studies (20,22-25,27-29). The pooled results showed that sorafenib treatment significantly reduced recurrence rate (RR = 0.72; 95% CI, 0.60-0.86; $p < 0.001$; $I^2 = 30.1\%$) (Fig. 3A) and mortality rate (RR = 0.74; 95% CI, 0.57-0.95; $p = 0.020$; $I^2 = 67.5\%$) (Fig. 3B) in patients after HCC resection compared to controls. The sensitivity analysis suggested that no single study had a significant effect on the pooled RR.

Efficacy of sorafenib on OS and RFS time

OS time and RFS time were reported in three and four publications (21-24,29), respectively. The pooled results suggested that sorafenib treatment tended to prolong OS time (months) (WMD = 4.96; 95% CI, -1.21-11.13; $p = 0.115$; $I^2 = 88.6\%$) (Fig. 3C) and RFS time (months) (WMD = 7.58; 95% CI, -1.36-16.53; $p = 0.097$; $I^2 = 99.5\%$) compared with controls (Fig. 3D) after liver resection. However, this did not reach statistical significance.

DISCUSSION

The current results suggested that sorafenib treatment significantly improved RFS, and reduced recurrence rate and mortality rate in patients with HCC after resection. However, sorafenib as an adjuvant treatment neither significantly improved OS nor prolonged OS and RFS time (months). However, OS, OS time and RFS time seemed to show a better outcome toward the sorafenib group.

Nevertheless, we still could not draw a definite conclusion as to whether sorafenib was effective in preventing HCC recurrence after resection, as the result of RFS in the sensitivity analysis was inconsistent with the pooled outcome. When removing the outcome of Huang Liao and Wang, respectively (23,24,28), the significant effect of sorafenib treatment on RFS disappeared. Sorafenib exerts its anti-tumor effect via the inhibition of kinases, including receptor tyrosine kinases and intracellular Raf serine/threonine kinase isoforms, which are involved in tumor cell proliferation and angiogenesis (30). However, hepatocarcinogenesis is a complex process involving various signaling pathways and the mechanisms of HCC recurrence are still unknown.

Previous studies have suggested that angiogenesis might not be the only mechanism necessary for tumor recurrence after resection. Thus, the antiangiogenic activity of sorafenib is insufficient to prevent relapse (21). The pathogenesis of HCC may be affected by the microenvironment of tumor. In fact, sorafenib affects not only cancer cells but also other cell types such as hepatic stellate cells and macrophages (31). Thus, the dynamic nature of the tumor microenvironment during different tumor stages may affect the efficacy of sorafenib.

Furthermore, studies in a mouse model showed that the efficacy of sorafenib correlated with the expression levels of HIV-1 Tat interactive protein 2 (HTATIP2) in tumors (32). This suggests that sorafenib might have a significant effect only in selected patients with certain activated signaling pathways. The study by Bruix (HR = 0.94; 95% CI, 0.78-1.13) and Zhuang (HR = 0.77; 95% CI, 0.47-1.26) (21,27) did not find a significant correlation between sorafenib treatment and RFS. However, the study by Huang, Liao and Wang demonstrated that sorafenib treatment was associated with a longer RFS (23,24,28). The participants of the latter three studies were selected to represent a cohort with a high risk for recurrence, which might trigger certain pathway that enhance the effect of sorafenib. Thus, molecular biomarkers that allow a more specific subgrouping of patients are warranted, in order to assess the clinical efficacy of sorafenib more precisely.

The results of our meta-analysis showed that the use of sorafenib significantly reduced the HCC recurrence rate and improved RFS. This result was inconsistent with a previous meta-analysis (16). One of the reasons for the discrepancy might be sample size. The present study included twice as many studies as the former analysis, which is more preferable in the meta-analysis setting. In addition, both studies reported a lower mortality rate in the sorafenib group as compared with controls. The reduced mortality rate in sorafenib treatment might represent the prevention of recurrence or the control of tumor growth after recurrence. The antiangiogenic effect of sorafenib functions as a tumor inhibitor, which can impede tumor growth after tumor occurrence (33). Research suggests that sorafenib has an acceptable safety profile and survival benefit in patients suffering HCC recurrence after liver transplantation (34). A previous trial also reported that sorafenib

prolonged the progression of a recurrent tumor in HCC patients after liver transplantation (35), which implied that sorafenib might be useful in a post-recurrence setting. However, whether sorafenib could delay tumor progression after HCC recurrence could not be confirmed due to the limited data provided from the included studies. This aspect should also be studied in the future.

In addition, this study also revealed that sorafenib was generally safe and well tolerated. Grade 3 or 4 adverse side effects only occurred in two studies in less than 2% of the population and many of the adverse events were eliminated after the adjustment of therapy. Other studies only recorded grade 1 or 2 side effects. However, this phenomenon implied that the initial dose of 400 mg twice a day was acceptable for patients after HCC resection. Researchers still argue that the optimal dosage regimen for sorafenib in adjuvant therapy needs to be defined. A previous trial was designed to compare an initial dose of 800 mg/day and 400 mg/day. The results showed that a standard dose and reduced dose did not significantly differ with regard to the duration of treatment or the number of dosing days (36). Thus, the dosage of sorafenib should be chosen based on the condition of the patient or in an attempt to prevent adverse events. If possible, an increase of the dose to the standard dosage regimen should be considered.

The efficiency of sorafenib for HCC patients may be affected by some risk factors. Several included studies reported that treatment prior to resection, tumor size, multiple tumors, intrahepatic metastasis and macrovascular invasion were risk factors associated with the efficacy of sorafenib treatment. Macrovascular invasion is regarded as the most important predictive factor for survival (37). Furthermore, it is also thought to be an independent risk factor for early recurrence after resection (38). According to the American Association for the Study of Liver Diseases, sorafenib therapy is recommended when macrovascular invasion is present in HCC. In addition, Huang et al. showed that sorafenib therapy after resection in HCC patients could significantly reduce recurrence and prolong survival time (28). Recently, some studies have proposed that systemic inflammation might play a role in predicting the outcome of HCC (39). Zhang et al. showed that increased neutrophil-to-lymphocyte ratio or gamma-glutamyl transferase were associated with a worse prognosis in

patients treated with sorafenib after a curative resection for HCC (29). To assess the actual effect of sorafenib as an adjuvant therapy, the influence of risk factors should be eliminated. However, the data of the present analysis was insufficient. Thus, future research is required.

Some limitations need to be taken into consideration. The relatively small number of studies limited the strength of our conclusions and hampered the estimation of publication bias by funnel plots or by the Egger's test. The inclusion of studies with a different study design, including retrospective cohorts, retrospective case-control studies and RCT, might affect the outcome of the analysis. An ideal meta-analysis should include all prospective, double-blinded, randomized controlled trials. However, studies that fulfilled the eligibility criteria for this analysis were quite rare and it was impossible for us to perform a separate subgroup analysis. Therefore, future RCT with a larger population are needed to confirm the current findings. Only a small number of studies were included (nine articles). Thus, defined conclusions of the efficacy of sorafenib for patient with HCC after resection could not be drawn. As the application of sorafenib as an adjuvant treatment for patients after liver resection is still a new method in the clinical practice and all of the included studies were published after 2013, more evidence is required to validate the actual effect of sorafenib treatment.

CONCLUSION

Collectively, sorafenib as an adjuvant treatment in patients with HCC after liver resection could improve RFS and reduce recurrence rate and mortality rate. Sorafenib might be an effective treatment to prevent HCC recurrence after resection. However, the results of this meta-analysis need to be interpreted with caution, as the efficacy of sorafenib might only be exerted in selected patients with certain activated signaling pathways or when HCC is associated with certain risk factors. More studies are expected in the future to update this analysis.

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Table 1. Characteristics of the included studies

Author	*Year*	*Study design*	*Patients*	*Group*	*n*	*Age*	*Male/Female*	*Re tin*
Antoniou (20)	2016	Retrospective	Underwent a curative resection for HCC	Sorafenib	16	62 (55-67.5)	13/3	-
				Control	14	65.5 (53-71)	10/4	-
Bruix (21)	2015	RCT	Underwent a curative resection for HCC with a complete radiological response	Sorafenib	556	58 (24-85)	451/105	38 30 es
				Control	558	60 (19-83)	461/97	35 41
Huang (28)	2019	Retrospective	Underwent a curative resection for HCC with MVI	Sorafenib	16	52.25 ± 11.94	12/4	45
				Control	33	51.52 ± 11.87	30/3	70
Li (22)	2016	Retrospective	Underwent a curative resection for HCC	Sorafenib	12	49.8 ± 6.5	12/0	-
				Control	24	52.8 ± 6.9	24/0	-
Liao (23)	2016	Retrospective	Underwent a curative resection for HCC with high risk of recurrence	Sorafenib	14	47.4 ± 10.6	11/3	-
				Control	28	48.4 ± 11.0	26/2	-

									resection; tumor size	
Wang (24)	2013	Prospective	Underwent a curative liver surgery with high recurrence risk factors	Sorafenib	14	61.4 ± 10.2	-	21.45 ± 1.98	Sorafenib treatment	19 (9.5-30.2)
				Control	17	59.7 ± 11.34	-	13.44 ± 2.66		
Xia (25)	2016	Case-control	Underwent a curative liver surgery with high recurrence risk factors	Sorafenib	34	48 (21-78	25/9	-	Tumor number > 3; MVI; hilar lymph; nodes metastasis; sorafenib;	Sorafenib: median 26 Control: median 25
				Control	68	57 (18-79)	50/18	-		
Zhang (26)	2014	Retrospective	Underwent a curative resection for HCC	Sorafenib	32	54.5 ± 1.6	25/7	-	Sorafenib; multiple tumors; PVT; IM;	
				Control	46	51.7 ± 1.4	42/4	-		

										TNM stage III	
Zhuang (27)	2017	Case-control	Underwent a curative resection for HCC	Sorafenib	27	48.2 ± 9.7	25/2	-		-	14.5 (2.6-44.7)
				Control	54	49.4 ± 9.4	50/4	-			

HCC: hepatocellular carcinoma; MVI: macrovascular invasion; PVT: portal vein thrombosis; IM: intrahepatic metastasis.

Table 2. Characteristics of sorafenib treatment of the included studies

Author	*Year*	*Sample size (sorafenib)*	*Initial dose*	*Duration (month)*	*Discontinuation*	*High severity (grade 3 or 4) side effect*
Antoniou (20)	2016	16	200 mg once daily	-	-	-
Bruix (21)	2015	556	400 mg twice a day	12.5 (2.6-35.8)	Dose modification: 89%; 1-year discontinuation: 49%	Hand-foot skin reaction
Huang (28)	2019	16	400 mg twice a day	45.52 (1.10-70.97)	-	
Li (22)	2016	12		-	-	Hand-foot skin reaction
Liao (23)	2016	14	400 mg twice a day	14.3 (2.6-24.2)	No drug-related adverse events resulted in discontinuation	-
Wang (24)	2013	14	400 mg twice a day	4	-	-
Xia (25)	2016	34	400 mg twice a day	22.9	-	-
Zhang (26)	2014	32	400 mg twice a day	-	-	-

Zhuang (27)	2017	27	400 mg twice a day	7.3 (5.8-8.9)	No patient on sorafenib required treatment discontinuation	-

Table 3. Quality assessment scores according to the Newcastle Ottawa Scale and Jadad scale

Newcastle Ottawa Scale						
Cohort study	Antoniou 2016 (20)	Huang 2019 (28)	Li 2016 (22)	Liao 2016 (23)	Wang 2013 (24)	Zhang 2014 (26)
Selection						
1. Representativeness of the exposed cohort	★	★	★	★	★	★
2. Selection of the non-exposed cohort	★	★	★	★	★	★
3. Ascertainment of exposure	★	★	★	★	★	★
4. Demonstration that the outcome of interest was not present at start of the study	★	★	★	★	★	★
Comparability						
1. Comparability of the cohorts on the basis of the design or analysis	★	★	★	★★	★★	★★
Outcome						
1. Assessment of outcome		★	★	★	★	
2. Was follow-up long enough for outcomes to occur	★	★	★	★		★
3. Adequacy of follow up of cohorts	★	★			★	

Total	7	8	7	8	8	7
Case control study	Xia 2016 (25)		Zhuang 2017 (27)			
Selection						
1. Is the case definition adequate?			★			
2. Representativeness of the cases	★		★			
3. Selection of controls			★			
4. Definition of controls	★		★			
Comparability						
1. Comparability of cases and controls on the basis of the design or analysis	★★		★			
Exposure						
1. Ascertainment of exposure			★			
2. Same method of ascertainment for cases and controls	★		★			
3. Non-response rate	★		★			
Total	6		8			

Jadad scale	Bruix 2015 (21)					
Randomization	★★					
Concealment of allocation	★★					
Double blinding	★★					
Withdrawals and dropouts	★					
Total	7					

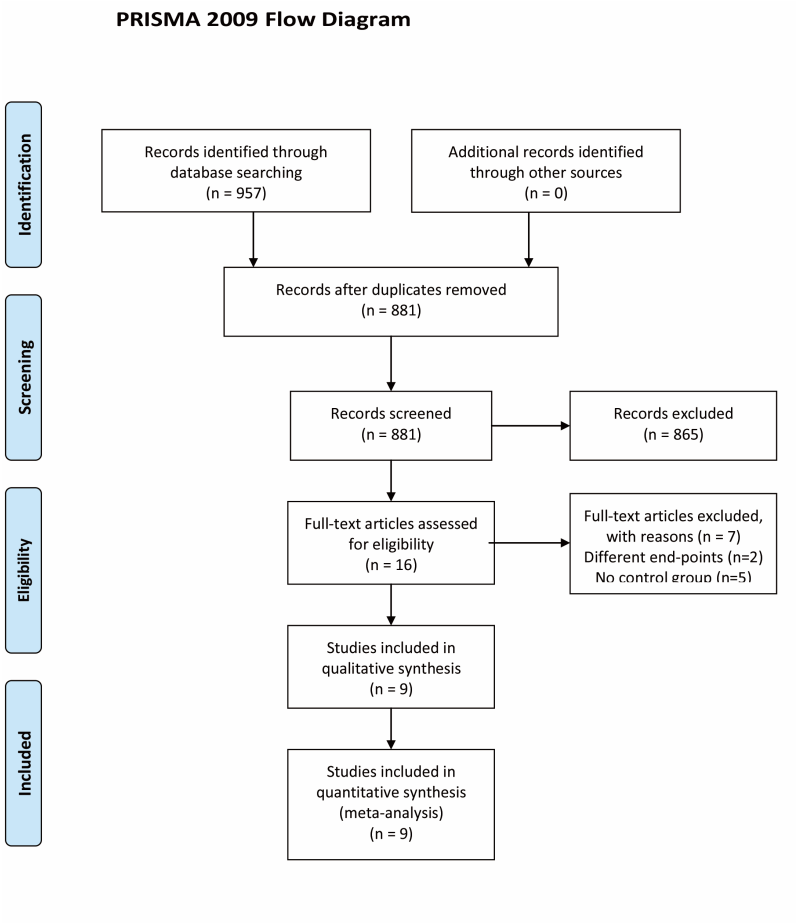

Fig. 1. PRISMA flow diagram of the literature search and study selection.

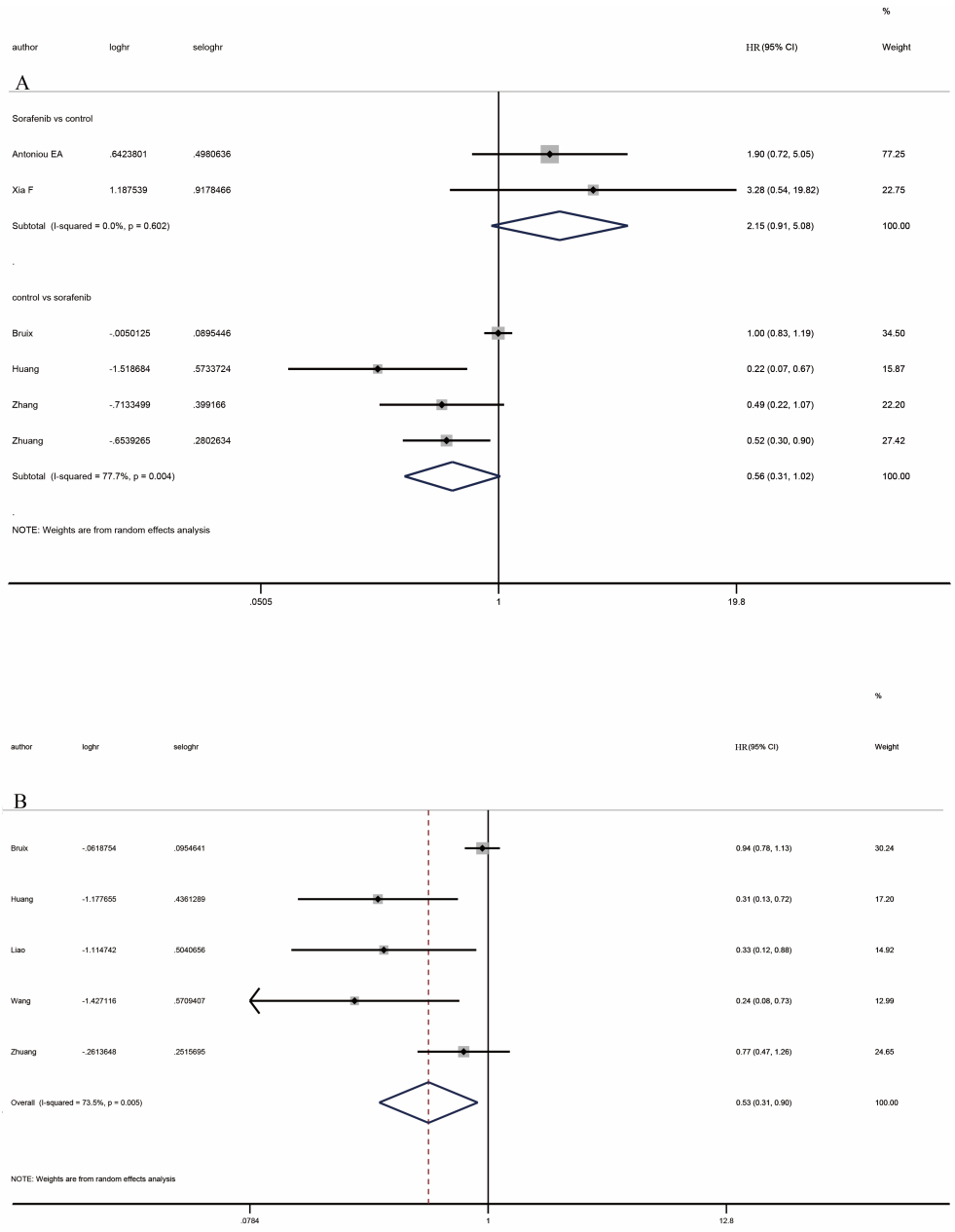

Fig. 2. Comparisons between the sorafenib therapy and control groups with regard to overall survival (A) and recurrence-free survival (B).

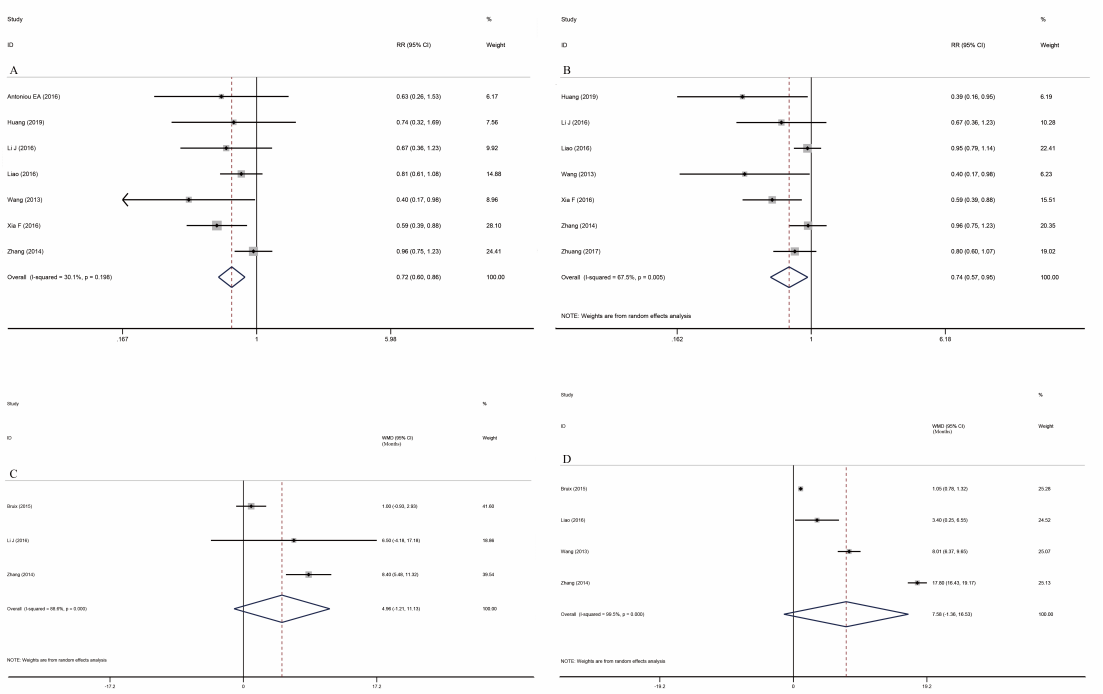

Fig. 3. Comparison between the sorafenib therapy and control groups with regard to recurrence rate (A), mortality rate (B), overall survival time (months) (C) and recurrence-free survival time (months) (D).