Prognostic Impact of Surgical Margin in Hepatectomy On Patients with Hepatocellular Carcinoma: A Meta-Analysis of Observational Studies

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Abstract

Objective

This study aims to comprehensively evaluate the prognostic impact of the surgical margin in hepatectomy on patients diagnosed with hepatocellular carcinoma (HCC).

Methods

A comprehensive and systematic search for eligible articles published in English before July 2021 was conducted in PubMed, Cochrane Library, Web of Science, and Embase electronic databases. Notably, overall survival (OS) and disease-free survival (DFS) were the primary endpoints.

Results

In total, 37 observational studies with 12,295 cases were included in this meta-analysis. The results revealed that a wide surgical margin (≥1 cm) was associated with better OS (hazard ration (HR), 0.70; 95% confidence interval (CI), 0.63-0.77) and DFS (HR, 0.66; 95% CI, 0.61-0.71) compared to a narrow surgical margin (<1 cm). Subgroup analyses were conducted based on median follow-up time, gender, country, hepatitis B surface antigen (HBsAg) status, tumor number, and liver cirrhosis. The prognostic benefit of a wide surgical margin was consistent in most subgroups, however, analysis of studies from Western countries showed that margin width was not associated with prognosis.

Conclusion

In summary, a wide surgical margin prolongs the long-term prognosis of HCC patients compared to a narrow surgical margin.

Introduction

Although hepatocellular carcinoma (HCC) has the 5th highest incidence across the globe, it is currently the 3rd leading cause of cancer-related deaths [1, 2]. So far, liver transplantation and hepatic resection are the treatment strategies for HCC. Although hepatectomy is the first-line therapeutic intervention, the prognosis of patients is unsatisfactory due to the high risk of recurrence and metastasis [3].

The long-term prognosis of patients with HCC is influenced by several factors, and the surgical margin is considered a potential prognostic factor [4, 5]. Curative hepatectomy is complete resection of all visible tumors without residual tumor cells at the resection margin [6]. As such, an adequate resection margin is vital in preventing tumor recurrence [7]. Nonetheless, minimizing the removal of the nonmalignant parenchyma tissue and protecting the residual liver of liver resection is necessary for many HCC patients

with liver cirrhosis or other liver diseases. This is because the capacity for liver regeneration is damaged among these patients and excessive liver tissue removal leads to severe consequences including liver failure [8, 9]. Thus, controversies on the width of the surgical margin have been reported under the premise of R0 resection. Many studies reveal that the width of the resection margin less than 1 cm is a risk factor for the long-term prognosis of HCC patients after surgery [4, 10]. Nevertheless, a number of articles found that a wide surgical margin did not improve the prognosis of HCC patients after hepatectomy [11, 12].

Therefore, this meta-analysis seeks to assess the correlation between surgical margins (wide surgical margin group, ≥1 cm; narrow surgical margin group, <1 cm) and long-term prognosis of HCC patients after hepatectomy.

Methods

Literature search strategy

This meta-analysis adhered to the guidelines from the Preferred Reporting Items for Systematic Review and Meta-Analysis [13]. A comprehensive and systematic literature search for articles published in English before July 2021 was conducted in four online electronic databases including PubMed, Cochrane Library, Web of Science, and Embase. The search terminologies included: “Hepatocellular Carcinoma” OR “Liver Cell Carcinomas” OR “Hepatoma” OR “HCC” AND “Resection Margin” OR “Surgical Margin” OR “Margin Width”. Besides, reference lists of all retrieved papers were inspected to identify potentially eligible but uncaptured literature in the primary search.

Inclusion criteria

Studies were if they met the following criteria: (1) The cancer type was primary HCC and hepatectomy was performed on patients; (2) Patients received different surgical margins in the experiment (a wide surgical margin, ≥1 cm) and control (a narrow surgical margin, <1 cm) groups; (3) The study was original, including retrospective and prospective observational studies (OBS); (4) Extractable outcomes were in the studies.

Exclusion criteria

The exclusion criteria for this meta-analysis included: (1) HCC was recurrent; (2) The patients received palliative hepatectomy or had extrahepatic metastases; (3) The study did not divide the experimental group and the control group into larger than 1cm and smaller than 1cm; (4) Duplicate article or repeat analyses using similar data.

Data extraction and quality evaluation

Data extracted from eligible studies included study characteristics (author, country, publication year, study design, median follow-up time, and mentioned outcome measures), demographic data of parents (age,

gender, and the number of patients), and clinicopathological features (liver cirrhosis, virus status, tumor number and size, and serum alpha-fetoprotein (AFP)), and survival outcomes.

The quality of incorporated OBSs was evaluated using the Newcastle-Ottawa Scale (NOS) based on three aspects i.e., patient selection, comparability of groups, and outcome evaluation. The scores of papers >6 were considered high-quality.

Statistical analysis

To evaluate the relationship between surgical margins and HCC prognosis, the overall survival (OS) and disease-free survival (DFS) in the wide margin group versus the narrow group was compared using a pooled hazard ratio (HR) with its corresponding 95% confidence interval (CI). The degree of heterogeneity across included literature was assessed using the I^2 statistic. Considering the potential heterogeneity, random-effect models were applied in all analyses. To assess the robustness of conclusions, a sensitivity analysis was conducted. P-value < 0.05 was considered statistically significant.

Results

Data collection and characteristics

A total of 6,864 records were initially identified by the literature search. Out of these, 4,743 records were excluded because of duplication, and 2,050 records were eliminated after evaluating their titles or abstracts. The remaining 71 records were carefully inspected by full-text reading. Finally, 37 articles [4, 5, 7, 10–12, 14–44] were included. The comprehensive search and selection process is shown in Fig. 1.

The comprehensive characteristics of the included studies are summarized in Table 1. The included articles were published between 1993 and 2021. A total of 12,295 patients from Western and Asian countries were enrolled in 37 OBSs; 2 studies of these were prospective, while the rest were retrospective. The majority of articles were from Asia, with China representing the most (24 articles). The demographic and clinicopathological characteristics of patients are presented in Supplementary Table 1. Based on a qualitative assessment by NOS criteria, the results revealed that all included OBSs were of higher quality (Supplementary Table 2).

Table 1
Characteristics of all the studies included in the meta-analysis.

Author	Year	Country	Number of patients		Median follow-up (months)	Study design	Survival outcomes
			Wide resection margin (>1cm)	Narrow resection margin (<1cm)			
Belli	2011	Italy	56	9	29.0	Retrospective	DFS
Chang	2012	China	478		29.5	Retrospective	DFS
Chen	2003	China	174	68	11.8	Retrospective	OS
Chen	2015	China	114	82	NA	Retrospective	OS
Chen	2021	China	176	238	>60.0	Retrospective	OS
Dong	2016	China	351	235	46.8	Retrospective	DFS
Han	2019	China	302	147	56.3	Retrospective	OS, DFS
Hirokawa	2014	Japan	10	10	46.0	Retrospective	DFS
Hsiao	2017	China	154	67	NA	Retrospective	OS
Huang	2013	China	528	512	42.0	Retrospective	OS, DFS
Huang	2015	China	71	159	72.0	Retrospective	OS, DFS
Laurent	2005	France	61	41	23.0	Retrospective	OS, DFS
Lee	1996	China	38	10	>60.0	Retrospective	OS
Lee	2007	Korea	44	56	31.0	Retrospective	OS, DFS
Lee	2012	China	142	156	73.0	Retrospective	OS, DFS
Lee	2018	Korea	186	233	37.5	Retrospective	OS, DFS
Lee	2019	China	143	391	66.3	Retrospective	OS, DFS
Lise	1998	Italy	72	15	29.0	Retrospective	OS, DFS
Liu	2016	China	186	37	26.1	Retrospective	DFS
Liu	2020	China	134	106	55.2	Retrospective	OS, DFS
Park	2018	Korea	61	31	28.0	Retrospective	OS, DFS
Poon	2000	China	138	150	27.0	Prospective	OS, DFS
Sasaki	2006	Japan	176	241	>120.0	Retrospective	DFS

OS, overall survival; DFS, disease-free survival; NA, not available.

Author	Year	Country	Number of patients		Median follow-up (months)	Study design	Survival outcomes
			Wide resection margin (>1cm)	Narrow resection margin (<1cm)			
Shi	2019	China	177	99	44.0	Retrospective	OS, DFS
Shimada	2008	Japan	32	85	62.0	Retrospective	OS
Shin	2018	Korea	55	61	66.7	Retrospective	DFS
Su	2021	China	45	114	61.2	Retrospective	OS, DFS
Takano	2000	Japan	244	56	NA	Retrospective	OS
Torii	1993	Japan	25	34	25.0	Retrospective	OS
Tsilimigras	2020	Multicenter	78	326	28.5	Retrospective	OS, DFS
Wang	2010	China	404	34	21.0	Retrospective	OS
Yang	2014	China	126	959	NA	Retrospective	OS, DFS
Zeng	2020	China	155	544	NA	Retrospective	OS, DFS
Zhang	2014	China	216	86	26.0	Prospective	DFS
Zhang	2021	China	305	120	26.0	Retrospective	DFS
Zhou	2020	China	92	217	NA	Retrospective	OS, DFS
Zhou	2021	China	325	492	NA	Retrospective	OS

OS, overall survival; DFS, disease-free survival; NA, not available.

Correlation between surgical margin and OS

A total of 28 studies reported on OS outcomes and pooling analysis of these data revealed that a wide surgical margin is associated with better OS (HR, 0.70; 95% CI, 0.63-0.77) compared to a narrow surgical margin (Fig. 2). Subgroups analyses were conducted to explore the potential factors that might affect the impact of the surgical margin on the prognosis (Table 2). This was based on the reported median follow-up time, the studies into 3-year OS and 5-year OS subgroups. The result showed that patients who received a wide resection margin had better mid-and long-term prognosis than those who received a narrow resection margin. Moreover, the gender factor in the subgroups was analyzed and the findings revealed that narrow surgical margin was a risk factor for OS of patients regardless of men and women. For patients from China or Non-Chinese Asian countries, a wide resection margin was associated with better OS than a narrow resection margin. However, a pooled analysis of three studies from western countries showed that margin width was not associated with prognosis. Additionally, the wide surgical margin group obtained greater OS than that of the narrow surgical margin group in subgroups of hepatitis B surface antigen status (HBsAg) positive/negative and single/multiple tumors.

Table 2
Subgroup analysis of the resection margin on the prognosis of patients with HCC.

	Overall survival (OS)			Disease-free survival (DFS)		
	No. of studies	HR	95%CI	No. of studies	HR	95%CI
3-year survival	5	0.67	0.54-0.82	8	0.57	0.48-0.67
5-year survival	23	0.70	0.63-0.79	19	0.70	0.65-0.76
Male	18	0.68	0.59-0.78	18	0.66	0.60-0.72
Female	9	0.75	0.64-0.89	9	0.66	0.55-0.78
China	19	0.70	0.62-0.78	17	0.67	0.62-0.72
Non-Chinese Asian countries	6	0.68	0.51-0.91	4	0.64	0.46-0.88
Western countries	3	0.54	0.26-1.12	4	0.45	0.30-0.66
HBsAg positive	10	0.71	0.65-0.78	11	0.64	0.57-0.72
HBsAg negative	14	0.66	0.57-0.78	14	0.70	0.64-0.77
Single tumor	9	0.80	0.71-0.92	10	0.67	0.59-0.77
Multiple tumors	7	0.60	0.49-0.73	7	0.66	0.57-0.78
Liver cirrhosis	-	-	-	4	0.71	0.60-0.84
Non-liver cirrhosis	-	-	-	18	0.64	0.58-0.71

HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval.

Correlation between surgical margin and DFS

A pooled analysis of DFS data from 27 studies including 9,443 patients revealed that a wide surgical margin was related to better DFS (HR, 0.66; 95% CI, 0.61-0.71) (Fig. 3). Further, subgroup analyses were performed based on reported median follow-up time (3-year DFS/5-year DFS), gender (male/female), country (China/Non-Chinese Asian countries/Western countries), HBsAg status (positive/negative), tumor number (single/multiple), liver cirrhosis (patients with/without). As a consequence, a wide surgical margin provided patients with better DFS compared to a narrow surgical margin (Table 2).

Sensitivity analysis

After excluding the included studies in sequence, sensitivity analysis outcomes confirmed the excellent robustness of the conclusion that a wide surgical margin could benefit the OS and DFS of patients (Supplementary Fig. 1. and Supplementary Fig. 2.).

Discussion

The findings of this meta-analysis revealed that surgical margins correlate with the prognosis of HCC patients; besides, a wide surgical margin (≥1 cm) could improve long-term prognosis compared to a narrow surgical margin (<1 cm). This is in line with the results reported in previous articles [39, 40]. Through subgroups analyses, we found that the above outcome showed a similar phenomenon in different subgroups except for studies from Western countries. In this analysis, a wide surgical margin did not prolong the OS of patients compared to a narrow surgical margin. This is potentially attributed to the inclusion of a few studies (five articles).

No consensus has been reached in academia on whether gender is an independent risk factor for the prognosis of HCC patients after hepatectomy [45]. Although there is no direct evidence that gender is a risk factor for HCC prognosis, men have higher smoking rates, alcohol consumption rates, and tumor burden than women [46]. A different study found that women have a better long-term prognosis than men, but without statistical difference among patients with HCC lesions maximum size<3 cm or with solitary HCC [47].

Notably, regional factors were also considered in subgroup analysis. The etiology of HCC in different regions is remarkably different. Asian countries, specifically East Asia are dominated by viral hepatitis, whereas HCC etiology in Western countries is mostly related to alcohol [48]. Subgroup analyses revealed that despite HCC patients with/without hepatitis B virus (HBV) and liver cirrhosis, a wide surgical margin prolonged the prognosis of patients than a narrow surgical margin. HBV-liver cirrhosis-HCC progression is a vital approach for HCC occurrence. High HBsAg level, lack of antiviral treatment, severe liver cirrhosis are risk factors affecting this process [49–51]. Despite in single or multiple HCC populations, the wide surgical margin group could still yield a better prognosis than narrow surgical margin group. Nevertheless, a study on a single HCC revealed that a wide surgical margin was not a prognostic factor, however, after propensity score matching (PSM), a wide surgical margin could still prolong the prognosis of patients [44]. This is possibly because PSM could reduce the confounding bias of OBS and improve the research efficacy by omitting the unmatched study subjects.

Microvascular invasion (MVI) is the presence of tumor emboli in vascular spaces rowed by endothelial cells from the tumor capsule into the liver parenchyma (either hepatic vein or portal vein branches) [52]. Research confirms that MVI is an independent risk factor for postoperative recurrence and metastasis of HCC, this significantly affects the long-term prognosis of patients [53, 54]. Based on the distribution and number of MVI, MVI is classified into the following grades, M0: no MVI; M1 (low risk): MVI <5 and the distance from adjacent liver tissues ≤1 cm; and M2 (high risk): MVI >5 or the distance from adjacent liver tissues >1 cm [55]. Researchers attempted to develop a preoperative model integrating laboratory examinations and imaging examinations to predict MVI. However, its accuracy requires additional validation by large-scale prospective multi-center studies [56]. At present, MVI can only be diagnosed by postoperative histopathological examination; this significantly limits the application of MVI in guiding diagnosis and treatment. From MVI to macrovascular invasion, the malignant degree of HCC cells

gradually increases and destroys the surrounding tissues; the chance of radical surgery is lost if a macrovascular invasion is formed [57]. Therefore, effective surgical plans and postoperative adjuvant treatment can be adopted if timely interventions are implemented at the MVI stage of HCC. This thus minimizes metastasis and HCC recurrence as well as significantly improves the prognosis of patients.

To survive and metastasize, cancer cells must evade the immune system. After cancer cells invade the bloodstream, the classic hematological mechanism believes that platelets, leukocytes, and endothelial cells mediate the related process of metastasis and recurrence [58]. New research indicates that MVI provides another path for HCC recurrence and metastasis; besides, HCC cell clusters obtain endothelial coating by protruding the vessels, this enables evasion of the immune surveillance mechanism and thereby preventing the activation of the coagulation cascade [59–62]. Thus, if a liver resection with a narrower surgical margin is performed on patients, theoretically, the residual micrometastasis increases the risk of recurrence [37]. Besides, 90% of MVI occurs in the range less than 1cm from the edge of the tumor. If a wider margin is achieved, the incidence of MVI can be reduced, hence significantly preventing tumor recurrence and metastasis [63]. However, due to data unavailability, we were unable to analyze the influence of MVI on the results in subgroup analysis.

The surgical margin should however not be blindly enlarged for preventing the recurrence and metastasis of HCC after surgery. Due to the excessively wide surgical margin, more normal liver parenchyma will be removed, causing serious postoperative complications including liver failure, and eventually death [8, 9, 11, 12]. Poon et al. [12] revealed that the relatively healthy liver parenchyma should not be sacrificed for obtaining the wider margin, particularly in cirrhotic patients with limited hepatic functional reserves. Another study [25] showed that a wide surgical margin could not improve the OS of patients compared to a narrow surgical margin. This was because of different baselines of the experimental group and the control group; this was largely reflected in liver cirrhosis, large and multiple tumors.

Previous research evaluated the relationship between surgical margins and prognosis by systematic review and meta-analysis [64, 65]. The findings [64] are inconsistent with ours and suggested that prognostic benefit was not achieved in patients receiving a resection margin≥1 cm. A few articles (5 articles) included is a potential reason. This study lacked sensitivity analysis, therefore, the reliability and stability of its findings are uncertain.

Zhong et al. [65] results are consistent with our findings, however, this study has limitations. First, although the number of included studies is more than that of previous studies, it is still a few compared to our study (37 articles versus 7 articles). Besides, subgroup analysis was not performed. It, therefore, remains unknown whether this conclusion (the prognostic benefit of a wide margin) will be interfered with by other factors.

Our study has worth-mentioning limitations. First, due to limited related studies, we could not perform a comprehensive analysis of different resection margin lengths. Secondly, the study population is from Asia, therefore the results cannot be directly applied to the population in Western countries. Thirdly, most of the included literature is retrospective, thereby hinting a possibility of the potential risk of information

bias. Fourthly, due to the unavailability of relevant data, we did not perform additional subgroup analyses including MVI.

Conclusion

In conclusion, our meta-analysis revealed that a wide surgical margin (≥1 cm) potentially prolongs the long-term prognosis of HCC patients than a narrow surgical margin (<1 cm). We conducted various subgroup analyses, and the results remained consistent in most factors of median follow-up time, gender, country, hepatitis B surface antigen status, tumor number, and liver cirrhosis.

Abbreviations

HCC, hepatocellular carcinoma; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen; OBS, observational study; AFP, alpha-fetoprotein; NOS, Newcastle-Ottawa Scale; HBV, hepatitis B virus; PSM, propensity score matching; MVI, microvascular invasion.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Ping Chen designed the research process. Jiaxuan Xu and Lihu Gu searched the database for corresponding articles and drafted the meta-analysis. Jiaze Hong extracted useful information from the articles above. Yuexiu Si used statistical software for analysis. Yujing He polished this article. All authors had read and approved the manuscript and ensured that this was the case.

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Figures

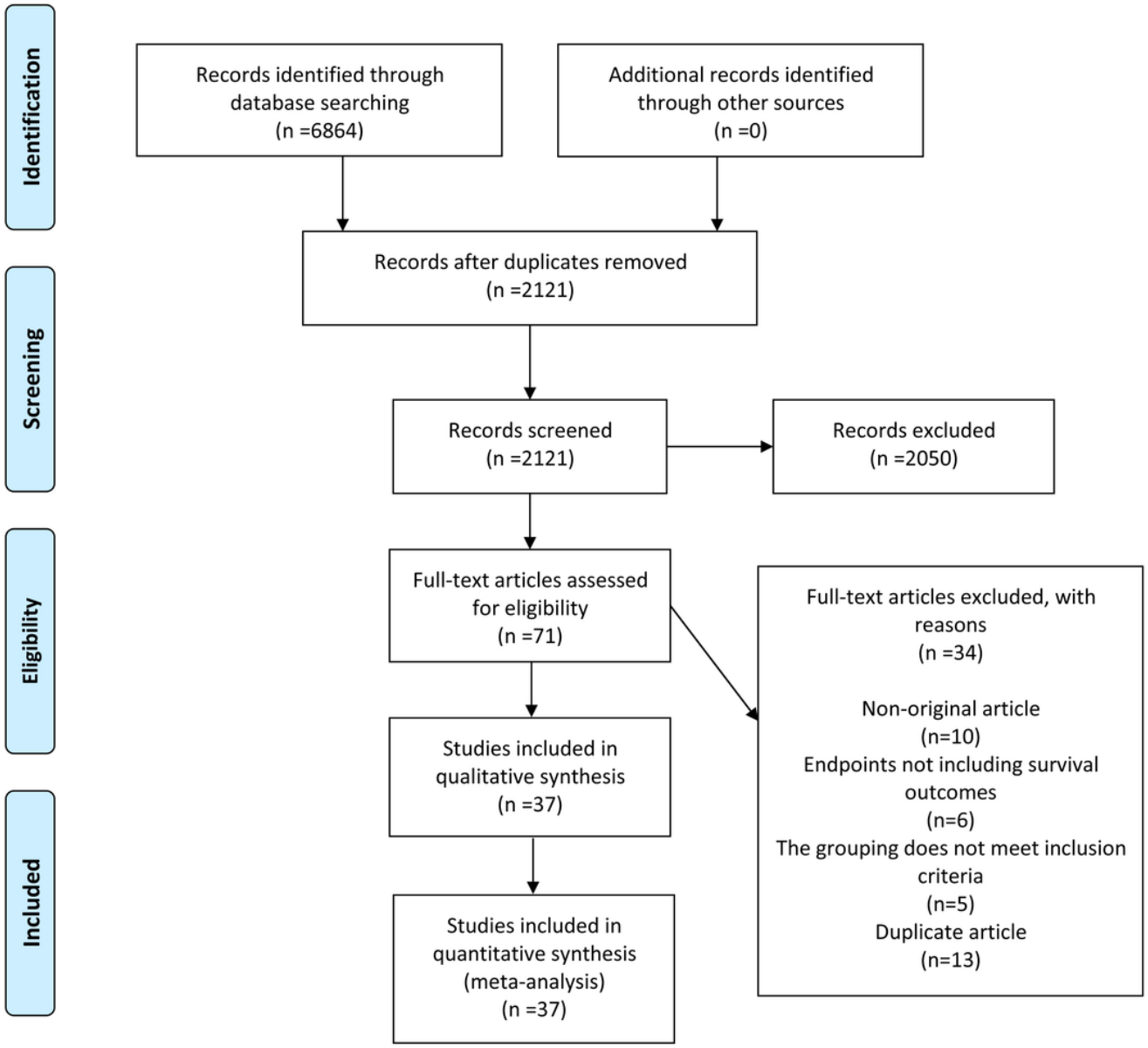

Figure 1

A schematic flow for selecting the articles included in the meta-analysis.

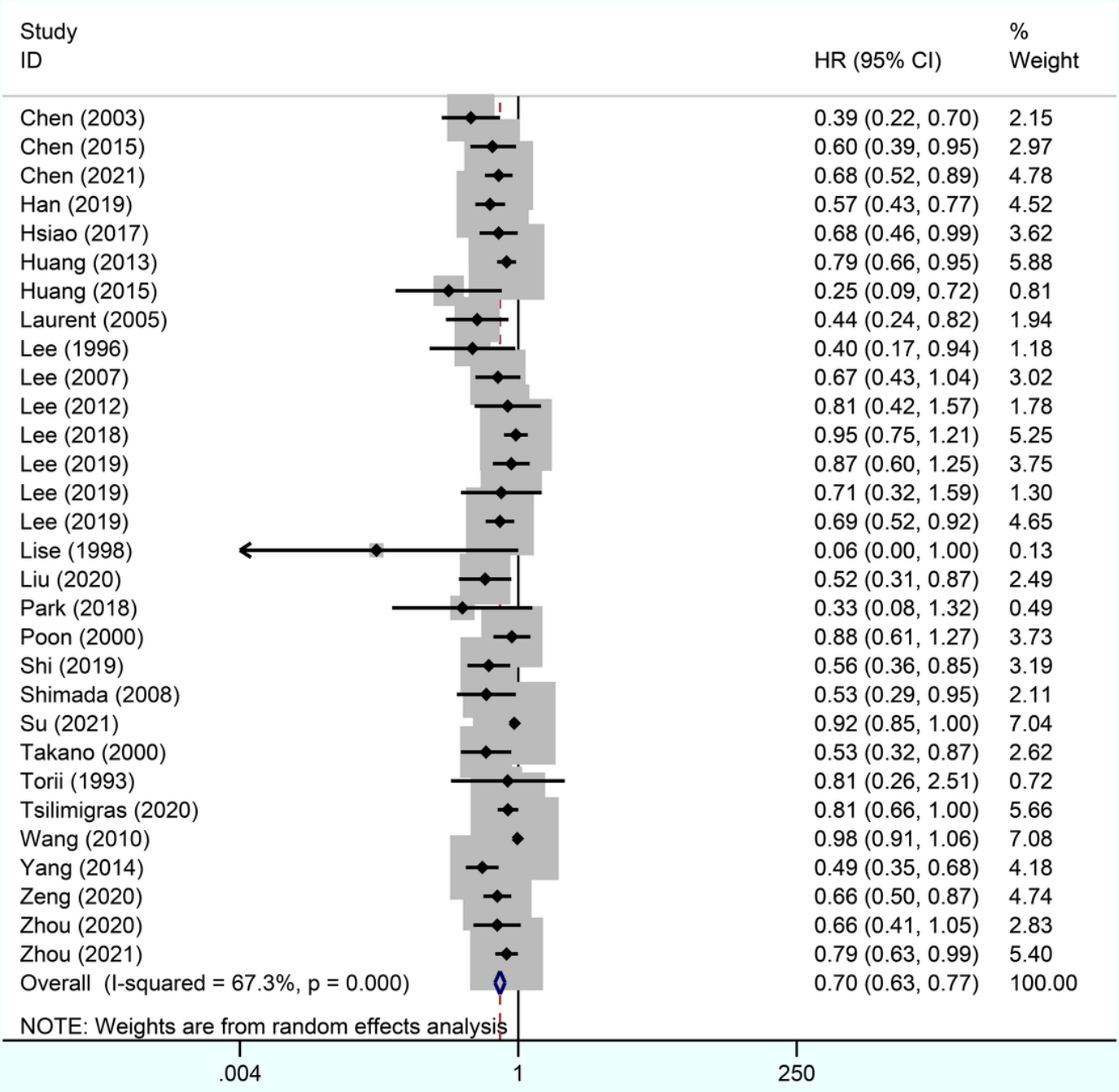

Figure 2

Forest plot of OS of HCC patients receiving wide surgical margin.

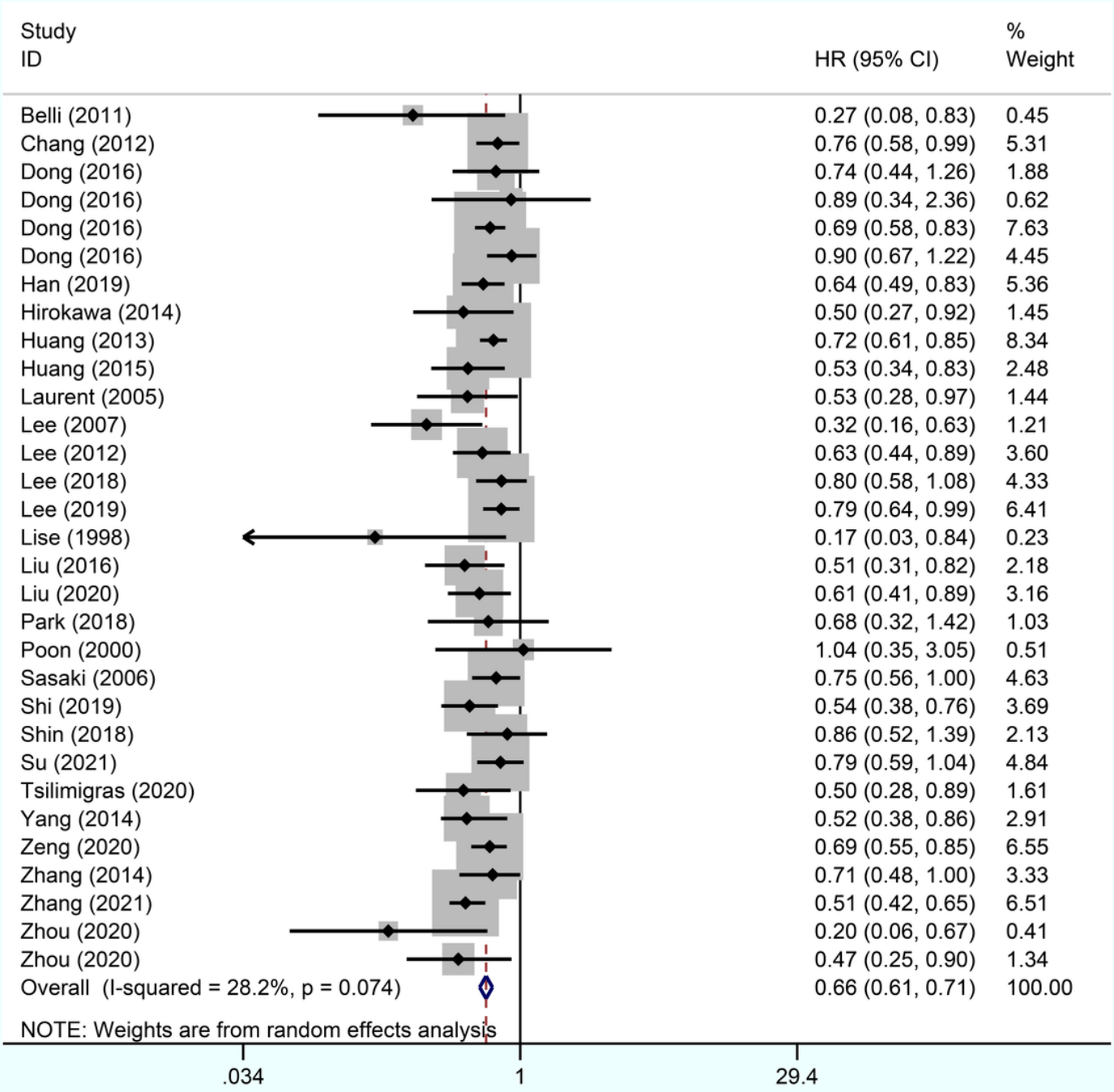

Figure 3

Forest plot of DFS of HCC patients receiving wide surgical margin.

Supplementary Files

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- SupplementaryTable1.docx
- SupplementaryTable2.docx
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