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Efficacy and safety of neoadjuvant therapy for hepatocellular carcinoma with portal vein thrombosis: A meta-analysis

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Abstract. Hepatocellular carcinoma (HCC) with coexisting portal vein tumor thrombus (PVTT) is associated with poor patient outcomes. The efficacy and safety of neoadjuvant therapy in patients with HCC with PVTT remain a subject of debate. In the present study, a comprehensive search of electronic databases, including PubMed, Web of Science, Embase and the Cochrane Library, was conducted to identify studies evaluating the outcomes of neoadjuvant therapy in patients with HCC and PVTT. The primary outcomes assessed were overall survival (OS) and relapse-free survival (RFS), with complication rates as a secondary outcome. A total of six studies comprising 750 patients were included in the present meta-analysis. The neoadjuvant therapy group exhibited significantly superior OS [hazard ratio (HR), 0.39; P<0.001] and RFS (HR, 0.31; P<0.001) compared with the primary hepatectomy control group. Compared with the control group, neoadjuvant radiotherapy improved OS (HR, 0.34; P<0.001) and RFS (HR, 0.24; P=0.004). While the neoadjuvant intervention subgroup exhibited an improved OS compared with controls (HR, 0.37; P=0.001), no significant difference in RFS was observed (HR, 0.11; P=0.095). Geographical analysis revealed that the Chinese subgroup demonstrated a significantly improved OS and RFS (HR, 0.41 for both; P<0.001), compared with the control group. However, the Japanese and Korean subgroups showed no improvement in OS (HR, 0.25; P=0.057) compared with the control group, and the results did not reach statistical significance. There were no significant differences between the groups in terms of blood transfusion, blood loss, operation time, bile leakage, ascites, peritoneal infection, postoperative bleeding, complications or mortality (all P>0.05). Overall, neoadjuvant therapy significantly improved survival outcomes in patients with HCC and PVTT without increasing complication rates, supporting its efficacy and manageable safety profile.

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Abbreviations: HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; OS, overall survival; RFS, relapse-free survival; HR, hazard ratio; BCLC, Barcelona Clinic Liver Cancer; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MeSH, Medical Subject Headings; RCT, randomized controlled trial; NOS, Newcastle-Ottawa scale; TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy

Key words: HCC, PVTT, neoadjuvant therapy, hepatectomy, meta-analysis

Introduction

According to global cancer statistics for 2022, Liver cancer is the sixth most commonly diagnosed cancer worldwide and the third leading cause of cancer-associated mortalities (1). In 2022, ~860,000 new cases and 750,000 mortalities were reported globally (1). The prevalence of liver cancer is higher in regions such as East Asia and South Africa (1). Hepatocellular carcinoma (HCC) accounts for ~75% of all primary liver cancer cases (2), with 70-80% of patients being diagnosed at an advanced stage, often with large size tumors and concomitant poor liver function. Among these cases, the incidence of portal vein tumor thrombus (PVTT) ranges between 13 and 45% (3,4), and these patients face the poorest prognosis, often developing severe complications such as portal hypertension, hepatocellular jaundice and refractory ascites (5). The median survival time for patients with HCC and PVTT who receive only supportive care is 2.7 months (5).

Currently, the optimal treatment strategy for technically resectable HCC with PVTT remains a subject of debate. Both the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases recommend the Barcelona Clinic Liver Cancer (BCLC) staging system for managing and prognosticating HCC (6). According to this system, patients with HCC and PVTT are classified as advanced (BCLC stage C) and are eligible only for palliative systemic treatment (6). However, treatment guidelines have been updated across various regions, including mainland China (7), Hong Kong (8) and Japan (9). Portal vein invasion does not preclude surgical resection, which has been shown to markedly improve the survival of patients with HCC and PVTT (10). Notably, the surgical mortality rate for these cases remains <10% (11). A study from Japan have indicated that the median survival time for patients undergoing surgical removal of PVTT ranges between 8 and 22 months, with 1-year overall survival (OS) rates varying between 21.7 and 69.6% (11).

Neoadjuvant therapies, including radiotherapy (12), chemotherapy (13), immunotherapy (14), targeted therapy (15) and interventional therapy (16), have gained attention for treatment of HCC. Advocates of neoadjuvant therapy argue that it can help manage small metastatic lesions, reduce the preoperative tumor burden, lower recurrence rates and improve OS. Additionally, neoadjuvant therapies for tumor downstaging are often characterized by a relatively short treatment duration and high patient compliance (17). On the other hand, some experts recommend surgical resection as the preferred treatment for HCC with isolated PVTT, due to the fact that surgery typically results in improved preservation of liver function compared with non-surgical approaches (18). In light of the ongoing debate surrounding neoadjuvant therapy, the present study aimed to perform a meta-analysis of the available literature to evaluate the efficacy and safety of neoadjuvant therapy for the treatment of resectable HCC with PVTT.

Materials and methods

Search strategy. The present meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The present study was registered with the International Prospective Register of Systematic Reviews (19) (ID no. CRD42024539943). A comprehensive literature search was performed across multiple databases, including PubMed (pubmed.ncbi.nlm.nih.gov/), Web of Science (webofscience.clarivate.cn/wos/alldb/basic-search), Embase (https://www.embase.com/) and the Cochrane Library (cochranelibrary.com/?contentLanguage=eng), covering studies from inception to September 2024. Additional relevant studies were identified through manual searches of reference lists and Google Scholar (scholar.nq69.top/). The search strategy incorporated a combination of Medical Subject Headings (MeSH) and free-text terms, including 'neoadjuvant chemotherapy' (MeSH), 'neoadjuvant radiation' (MeSH), 'neoadjuvant therapies' (MeSH), 'neoadjuvant chemoradiotherapy' (MeSH), 'interventional therapy', 'targeted therapy', 'immunotherapy', 'hepatocellular carcinoma', 'HCC', 'portal vein thrombosis' and 'PVTT' (Supplementary Search Strategy).

Inclusion and exclusion criteria. The inclusion criteria for studies were as follows: i) Patients were diagnosed with HCC and PVTT; ii) neoadjuvant therapy administered prior to hepatectomy in the experimental group, while the control group underwent hepatectomy as the initial intervention; iii) the primary outcomes assessed were OS and relapse-free survival (RFS); and iv) the study design included randomized controlled trials (RCTs), cohort studies or case-control studies. Studies were excluded based on the following criteria: i) Inability to extract data; ii) unavailability of the full text; iii) duplication of data from the same cohort; in such cases, the most comprehensive or recent study was selected (when article is equally comprehensive and there is no data update and sample size increases, the latest literature is preferred; iv) non-English language publications; and v) no interesting outcomes.

Data extraction and quality evaluation. Data extraction was independently performed by two authors using a standardized form to collect relevant information, including basic details (author names, country, year of recruitment and year of publication) and clinical data (number of patients, age, sex, neoadjuvant therapy regimen, follow-up duration, PVTT classification and complications). Any discrepancies between the authors were resolved through discussion and reevaluation of the literature. The quality of cohort and case-control studies was assessed using the Newcastle-Ottawa Scale (NOS) (20). Studies were classified as high quality (scores 8-9), moderate quality (scores 6-7) or low quality (scores <6). Only studies with a score of ≥6 were included in the analysis. For RCTs, the risk of bias was evaluated using the Cochrane Handbook's criteria (21) and the Cochrane Collaboration tool (RoB2).Factors such as random sequence generation, allocation concealment, subject and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting and other potential bias were assessed.

Statistical analysis. Statistical analyses were conducted using Stata version 12.0 (StataCorp LLC). The association between neoadjuvant therapy and long-term prognosis in HCC with PVTT was evaluated using hazard ratios (HRs) and 95% CIs. A HR <1 indicated a benefit for the experimental group, while a HR >1 favored the control group. Postoperative complications were analyzed using odds ratios (ORs) for dichotomous variables and mean differences (MDs) in the case of continuous variables, both with corresponding 95% CIs. Heterogeneity among the studies was assessed using the χ^2 test and expressed as I^2. An I^2 value >50% was indicative of substantial heterogeneity, whereas an I^2 value of <50% indicated low heterogeneity. A random-effects model was applied to account for variability in treatment regimens, inclusion criteria and study designs. If the number of included articles was insufficient, the test's efficiency was considered low, in accordance with previous meta-analyses (22-24). All statistical tests were two-sided. P<0.05 was considered to indicate a statistically significant difference.

Results

Study selection. A total of 2,016 related literatures were generated in the initial electronic database and manual retrieval. The titles and abstracts of 1567 non-duplicate articles were screened, and 1541 records were further excluded. The including 26 articles were read in full text, and 20 were excluded due to no interesting outcomes (n=9), unavailability

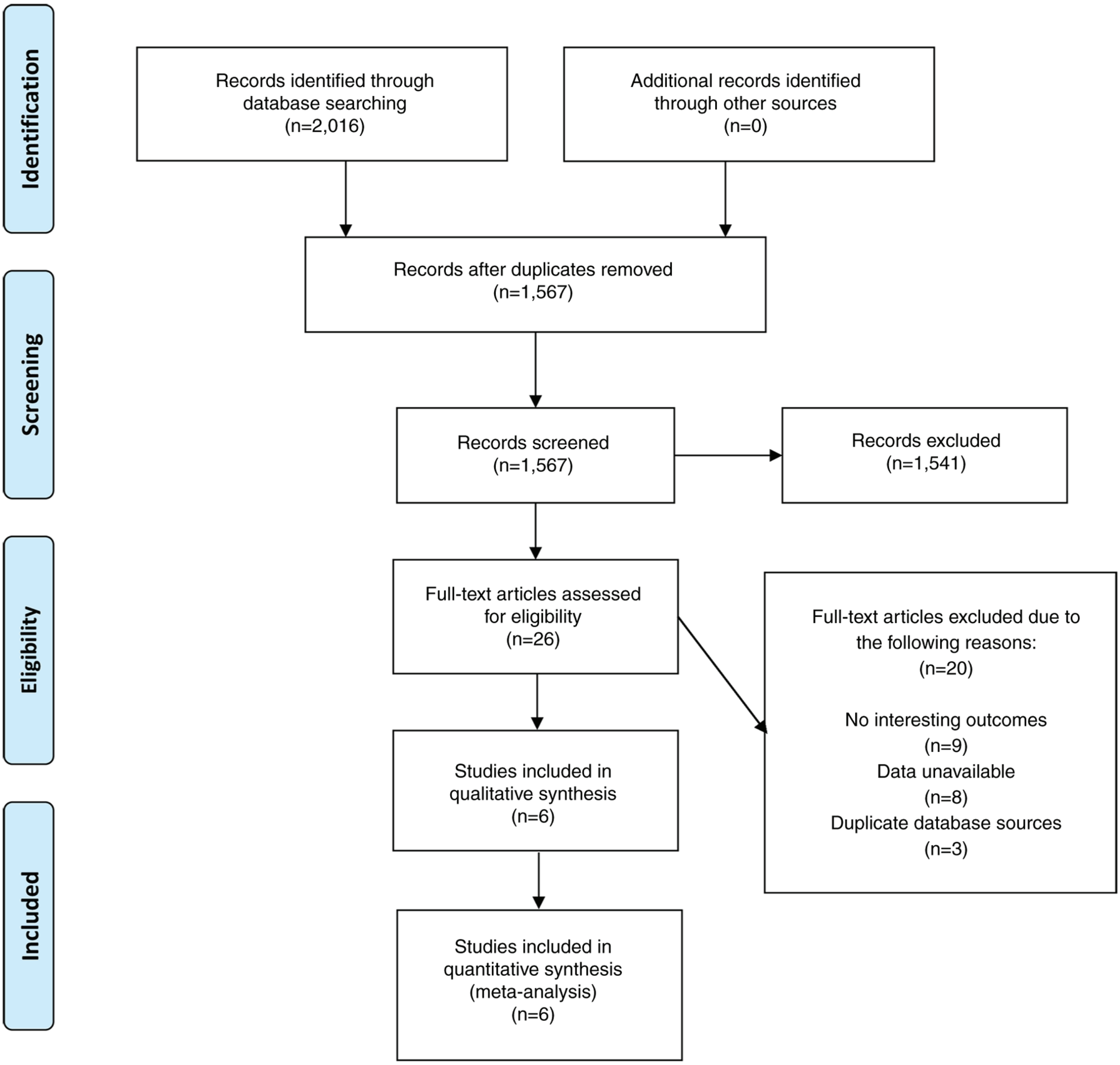

Figure 1. Flow diagram containing details of study selection.

of data (n=8), and data source duplication (n=3). Ultimately, six studies (25-30) were selected for inclusion in the meta-analysis. A detailed PRISMA flowchart illustrating the study selection process is shown in Fig. 1.

Study characteristics. The six selected studies, published between 2007 and 2023, included one RCT (25), one case-control study (26) and four cohort studies (27-30), encompassing a total of 750 patients with HCC and PVTT. Of these, 312 patients received neoadjuvant therapy, while 438 patients were included in the control group, undergoing various treatments such as radiotherapy, chemotherapy and interventional therapy. The majority of patients (84-100%) had preserved liver function and were classified as Child-Pugh grade A (Table SI) (31). Detailed characteristics of the included studies are presented in Tables I and SI.

Methodological quality of the included studies. The quality of the RCT was evaluated using the Cochrane Collaboration tool (RoB2) (21), which identified a high risk of bias due to the absence of blinding, given the nature of the interventions (Table SII). In addition, one study (25) also excluded patients with hepatitis C virus-related HCC, potentially introducing biases related to differing surgical indications across centers. The observational studies were assessed using the NOS (20), with all studies rated as moderate to high quality, scoring at least 6 out of 9 points. Propensity score matching (PSM) is applied in a case-control study (26) to eliminate bias from gender, age, body mass index. The appropriate design of the experimental and control groups provides better comparisons. Scoring of outcomes is according to the sufficient description. For cohort studies, the differences in sample size, surgeons, and operative procedures decrease comparability. To address

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

First author/s, year	Country	Cohort years	Patient numbers		Neoadjuvant therapy regimen	PVTT classification	Mean follow-up period, months		Study design	(Refs.)
			EG	CG			EG	CG		
Kamiyama *et al*, 2007	Japan	1990-2006	15	28	RT	NA	83		Cohort study	(27)
Li *et al*, 2016	China	2010-2013	39	50	3D-CRT	Type III	8.4		Cohort study	(28)
Zhang *et al*, 2016	China	2006-2011	85	205	TACE	Mixed-type	NA		Cohort study	(29)
Chong *et al*, 2018	South Korea	2005-2014	26	18	CCRT + HAIC	Type II/type III	13		Cohort study	(30)
Wei *et al*, 2019	China	2016-2017	82	82	RT	Type II/type III	15.2	10.8	RCT	(25)
Hu *et al*, 2023	China	2017-2021	65	55	HAIC	Mixed-type	33.8	38.7	Case-control study	(26)

RT, radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; TACE, transcatheter arterial chemoembolization; CCRT, concurrent chemoradiotherapy; HAIC, hepatic artery infusion chemotherapy; PVTT, portal vein tumor thrombus; EG, experimental group; CG, control group; NA, not available; RCT, randomized controlled study.

this issue, some studies have used methods such as using the same surgical protocol for patients (28). Absence of a statement describing the follow-up results in a score of 0 for the section. Further details are provided in Tables SII and SIII.

RFS and OS. RFS data were reported in four studies (25,26,28,30), involving 417 patients. The neoadjuvant therapy group demonstrated significantly higher RFS compared with the control group (HR, 0.31; 95% CI, 0.17-0.55; P<0.001; Fig. 2), although the heterogeneity was substantial (I^2=72.6%). The OS data from six studies (25-30) indicated that the neoadjuvant therapy group had a markedly improved OS compared with the control group (HR, 0.39; 95% CI, 0.30-0.50; P<0.001; I^2=18.0%; Fig. 3).

Subgroup analysis. In the subgroup analysis, patients receiving neoadjuvant radiotherapy exhibited improved RFS compared with control group (HR, 0.24; P=0.004; Fig. 4A). However, no significant difference in RFS was observed in the broader neoadjuvant intervention group (HR, 0.11; P=0.095; Fig. 4B). In the Chinese subgroup, neoadjuvant therapy significantly improved RFS (HR, 0.41; P<0.001; Fig. 5). Regarding OS, both the neoadjuvant radiotherapy group (HR, 0.34; P<0.001; Fig. 6A) and the neoadjuvant intervention group (HR, 0.37; P=0.001; Fig. 6B) outperformed the control group. Neoadjuvant therapy in the Chinese subgroup also showed a significant OS advantage compared with the control group (HR, 0.41; P<0.001; Fig. 7A). In other regions such as Japan and South Korea, there was no significant difference in OS between the neoadjuvant group and the control group (HR, 0.25; P=0.057; Fig. 7B).

Analysis of postoperative complications. A comparative analysis of perioperative complications, including intraoperative blood transfusion, blood loss, operative time, bile leakage, ascites, peritoneal infection, postoperative hemorrhage, complications and mortality, revealed no significant differences between the neoadjuvant therapy and control groups (all P>0.05; Table II).

Sensitivity analysis and publication bias. Sensitivity analysis and Begg's weighted regression test for detecting potential publication bias are typically suitable for meta-analyses including >10 studies (23). Given the limited number of studies in the present analysis, these tests were not performed.

Discussion

HCC is classified using various staging systems, with the BCLC staging system (32) being the most widely adopted. Under this system, patients with HCC and PVTT are categorized as stage C (33). In a number of Western medical systems, including the United States, any degree of vascular invasion has traditionally been considered a contraindication for surgical intervention (34). However, the 2022 updated BCLC guidelines recommend atezolizumab-bevacizumab as the first-line treatment for these patients (35).

In contrast to Western practices, vascular invasion, whether in the portal vein, hepatic vein or with extrahepatic metastasis, does not universally preclude surgical resection

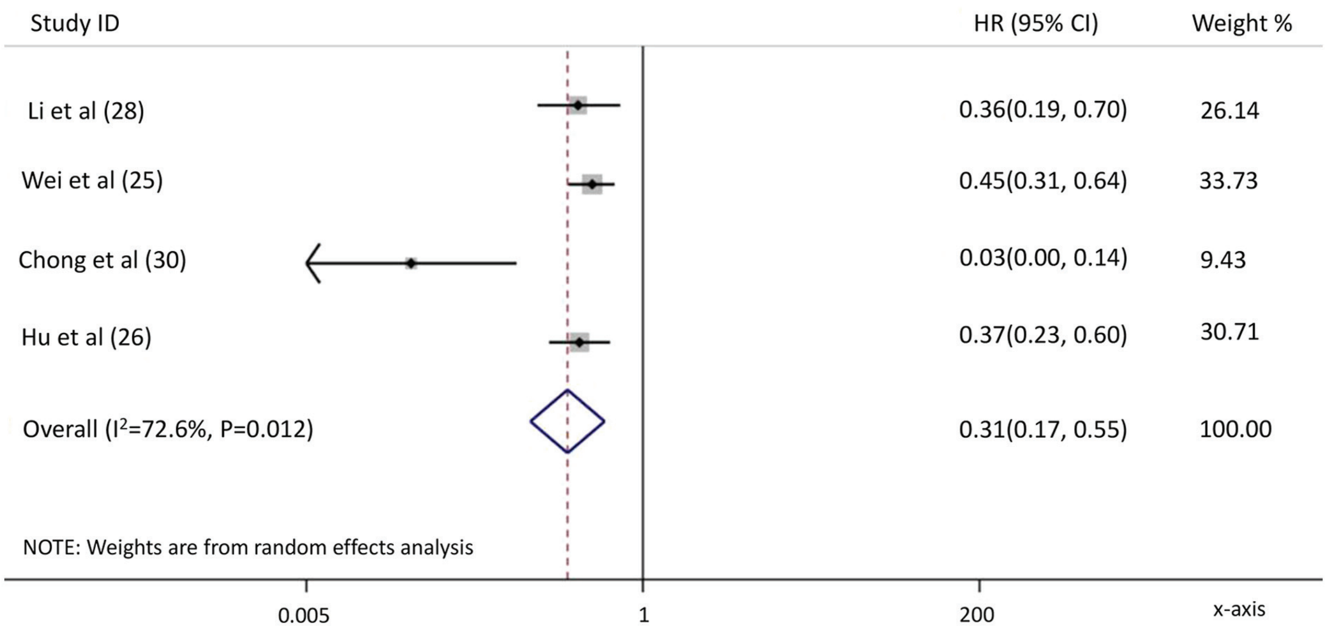

Figure 2. Forest plot of the effect of neoadjuvant therapy on relapse-free survival in patients with hepatocellular carcinoma and portal vein tumor thrombus (P<0.001). HR, hazard ratio.

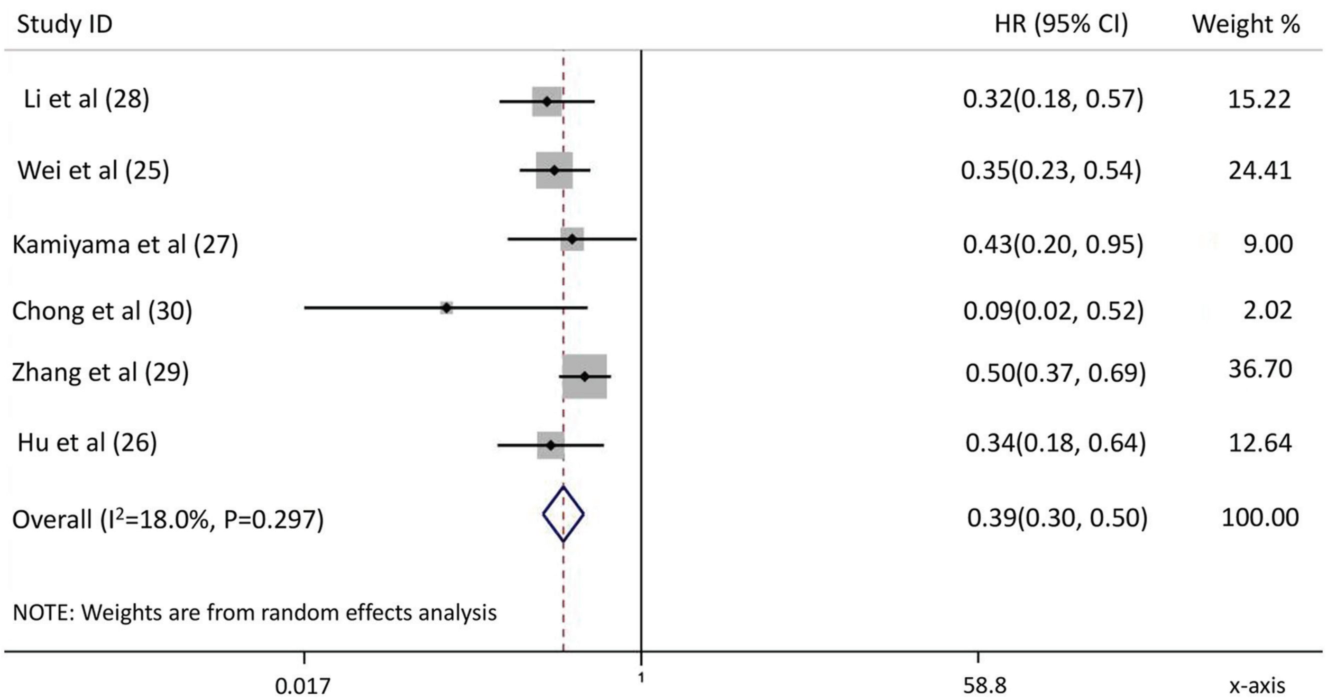

Figure 3. Effect of neoadjuvant therapy on overall survival in patients with hepatocellular carcinoma and portal vein tumor thrombus (P<0.001). HR, hazard ratio.

in HCC management (36). Several surgical centers in Asia have reported favorable clinical outcomes for patients with technically resectable BCLC stage C HCC (36,37). For instance, a national multicenter study in Japan conducted by Kokudo *et al* (38) revealed that hepatectomy in patients with PVTT confined to the primary or peripheral branches markedly extended the median survival by 1.77 years compared with non-surgical management. These findings suggest that hepatectomy may be a viable option for treating HCC with PVTT in carefully selected cases.

While surgical resection offers a potentially curative approach for HCC with PVTT, its effectiveness is limited by several critical factors. Surgical resection is primarily feasible for patients with type I/II PVTT, where prognosis is comparatively more favorable, with 5-year OS rates ranging between 10 and 59% (39). By contrast, for patients with type III/IV PVTT, the prognosis is worse, with survival rates dropping to 0-26% (39). Additionally, hepatic resection is only possible under specific conditions, such as a performance status grade of 0-2, Child-Pugh grade A or sufficient liver reserve, which

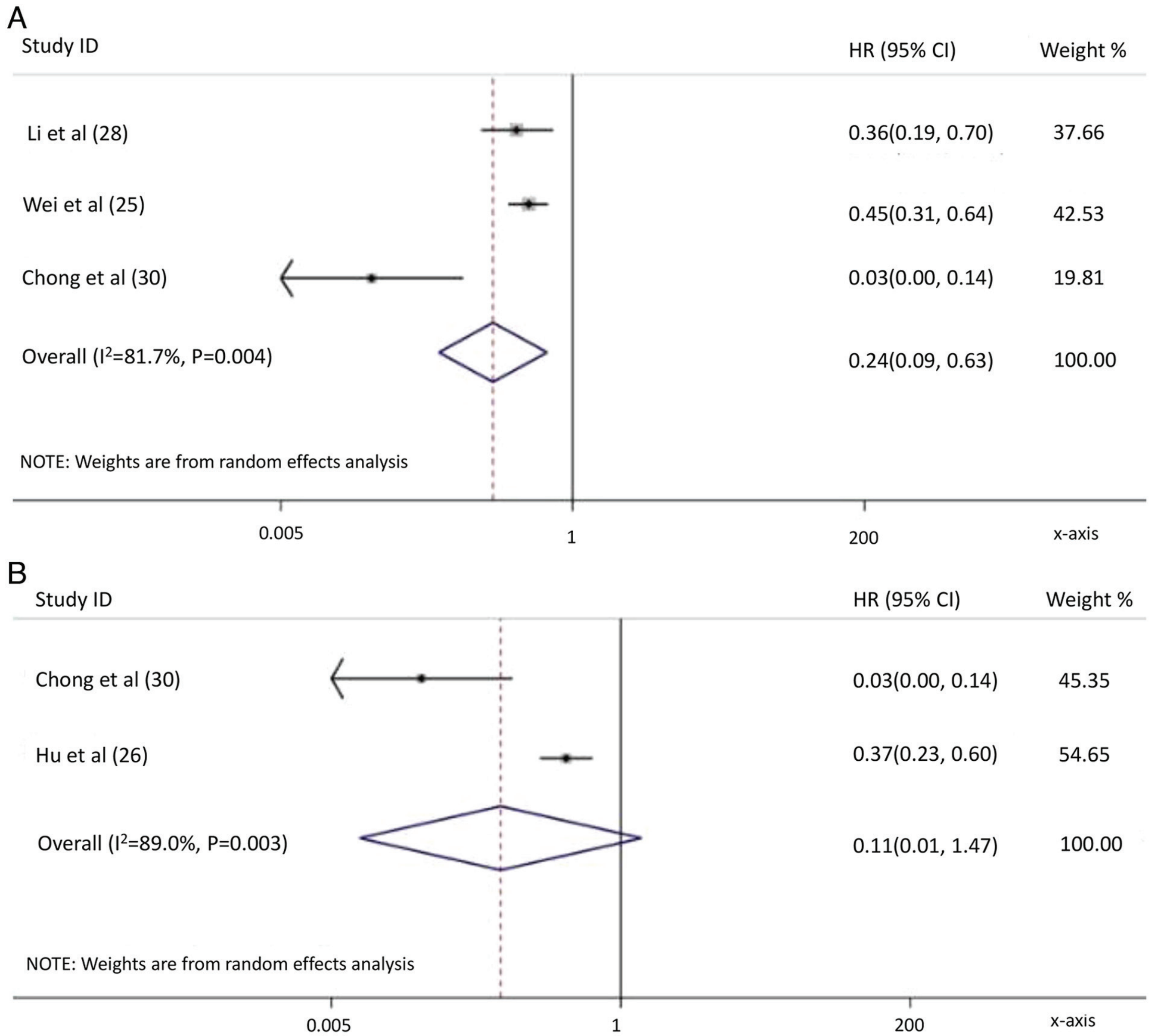

Figure 4. Forest plot of relapse-free survival subgroup analysis in patients with hepatocellular carcinoma and portal vein tumor thrombus treated with (A) neoadjuvant radiotherapy (P=0.004) and (B) neoadjuvant interventional therapy (P=0.095). HR, hazard ratio.

restricts the number of eligible patients (40,41). Furthermore, hepatectomy is associated with considerable trauma and carries the risk of severe complications, particularly in cases of advanced HCC with metastasis. In such cases, resecting the primary tumor often does little to improve survival due to the high likelihood of recurrence (42). A clinical trial involving 47 patients with advanced HCC underscored this issue, reporting 40 fatalities, 37 of which were due to tumor recurrence (43). Furthermore, when PVTT extends to the main, left or right branches of the portal vein, the complexity of the surgery increases substantially, leading to worse postoperative survival outcomes (44).

Due to these limitations, there is a growing emphasis on multimodal combination therapies to improve long-term survival in these patients, including neoadjuvant/adjuvant/downstaging therapy for surgery and the combined modality of non-operative therapies (45). The present literature analysis aimed to evaluate whether combining neoadjuvant therapy with hepatectomy is associated with improved prognostic outcomes compared with priority surgery. Data from Eastern countries indicated that integrating neoadjuvant therapy with surgery offers a survival advantage over prioritizing surgery as the sole treatment.

Neoadjuvant therapy, including radiotherapy and interventional therapy, improves the prognosis of patients with HCC and PVTT when combined with hepatectomy. Neoadjuvant radiotherapy can effectively downstage PVTT, expanding the pool of patients eligible for surgical intervention and increasing the success rate of surgeries (25-30). A pivotal study (46) reported a 5-year survival rate of 57% for patients who underwent salvage surgery following the downstaging of initially unresectable HCC, which compares favorably to that in patients who underwent liver resection when they first presented with resectable tumors, demonstrating notable improvement in long-term outcomes.

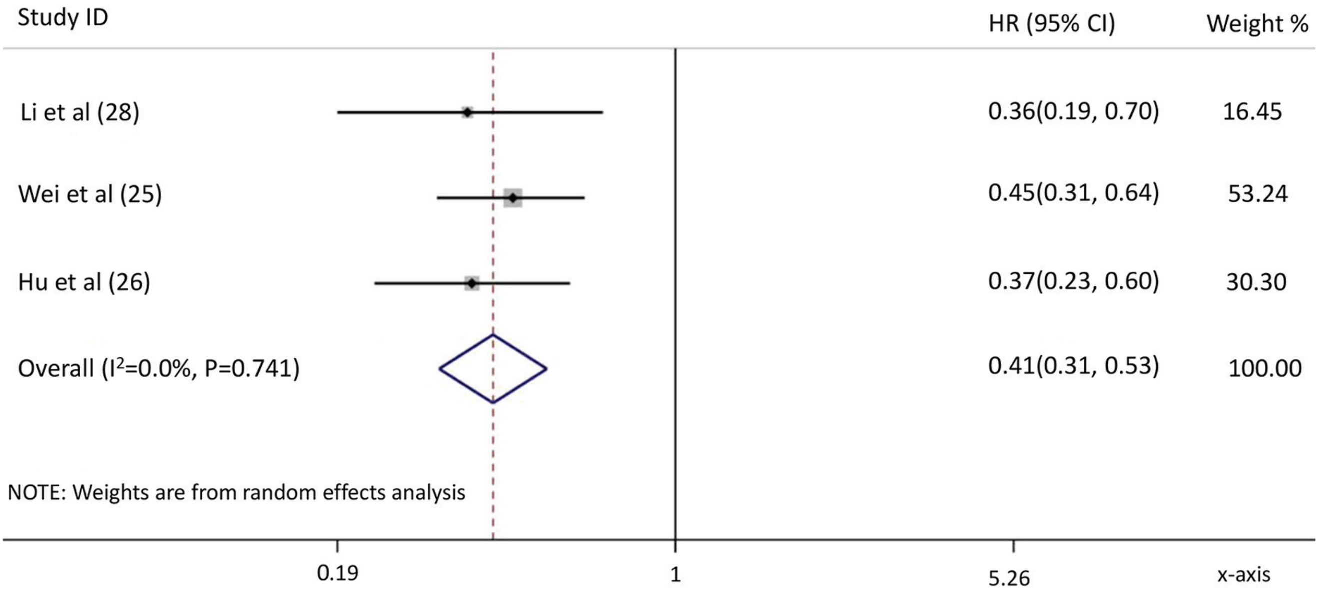

Figure 5. Forest plot of the effect of neoadjuvant therapy on relapse-free survival in patients with hepatocellular carcinoma and portal vein tumor thrombus in the Chinese subgroup (P<0.001). HR, hazard ratio.

By alleviating the adverse effects of PVTT on the blood supply of the hepatic portal vein, which is crucial for maintaining liver function, neoadjuvant radiotherapy prevents tumor cell dissemination into surrounding liver tissues, thereby reducing the risk of intrahepatic and extrahepatic metastases (47-51). This approach utilizes a targeted radiation dose that is markedly lower than that used in adjuvant therapies, minimizing damage to the liver while focusing primarily on the tumor thrombus (52). Furthermore, the use of low-dose radiation, critical for ensuring both surgical safety and efficacy, is effective in lowering HCC-related mortality and recurrence rates, while concurrently preserving liver function and capacity (25).

By reducing the size and extent of PVTT, neoadjuvant therapy decreases the risk of tumor dissemination during hepatectomy (25). This is especially crucial when the thrombus extends into major portal branches, facilitating a more comprehensive resection of cancerous tissue and lowering the risk of postoperative recurrence (12). Neoadjuvant radiotherapy can markedly increase surgical margins. For instance, one study demonstrated that the median surgical margin increased from 0 to 1 cm, with the addition of neoadjuvant intensity modulated radiation therapy (IMRT), making nearly half of previously unresectable lesions suitable for surgery (53). This suggests neoadjuvant IMRT may be associated with improved OS by increasing the R0 resection rate. This improvement not only enhances the likelihood of achieving a complete resection but also reduces the incidence of positive surgical margins, thereby improving OS outcomes for patients (12).

In addition to neoadjuvant radiotherapy, interventional therapies such as transcatheter arterial chemoembolization (TACE) serve a pivotal role in the management of liver cancer, particularly in intermediate to advanced stages of HCC (54). TACE, including its variants conventional TACE and drug-eluting beads TACE, targets the hepatic artery, the primary vascular supply for both HCC and PVTT.TACE refers to injection of selective vascular embolization with chemotherapy drugs into the tumor-feeding arteries to prevent its nutrition and blood supplying, thereby leading to ischemic necrosis of the targeted tumor (55). TACE improves survival rates in patients with all types of PVTT compared with those of patients receiving conservative treatment (56).

Another advanced interventional option, hepatic arterial infusion chemotherapy (HAIC), offers a more consistent and targeted delivery of chemotherapeutic agents directly to the tumor. HAIC is particularly beneficial for patients with significant arterial-portal shunts or complete portal vein obstruction, maximizing therapeutic efficacy while minimizing systemic side effects (57). A study performed by Hatooka *et al* (58) demonstrated that HAIC achieved notable disease control and objective response rates of 79.9 and 25.4%, respectively. These interventional strategies underscore the evolving landscape of neoadjuvant therapies, affirming their role in improving the long-term prognosis of patients with advanced HCC.

In the present study, compared with the control group (priority hepatectomy group), neoadjuvant therapy was associated with a survival advantage across the Chinese, Japanese and Korean subgroups; however, the survival benefits did not reach statistical significance in the Japanese and Korean groups. The pronounced effects observed in the Chinese subgroup can be attributed to the substantial representation of Chinese cases, reflecting the broader epidemiological reality, as China accounts for ~50% of the global HCC incidence (59), with PVTT prevalence rates between 44 and 62% (5). Since 1995, Chinese medical institutions have increasingly adopted the associating liver partition and portal vein ligation for staged hepatectomy procedure for managing large HCCs, leading to improvements in 1-, 3- and 5-year OS rates compared with earlier decades (60). This surgical approach has transitioned numerous patients from being considered inoperable to operable, enhancing treatment outcomes beyond palliative care (46,60). Additionally, experienced surgical teams in

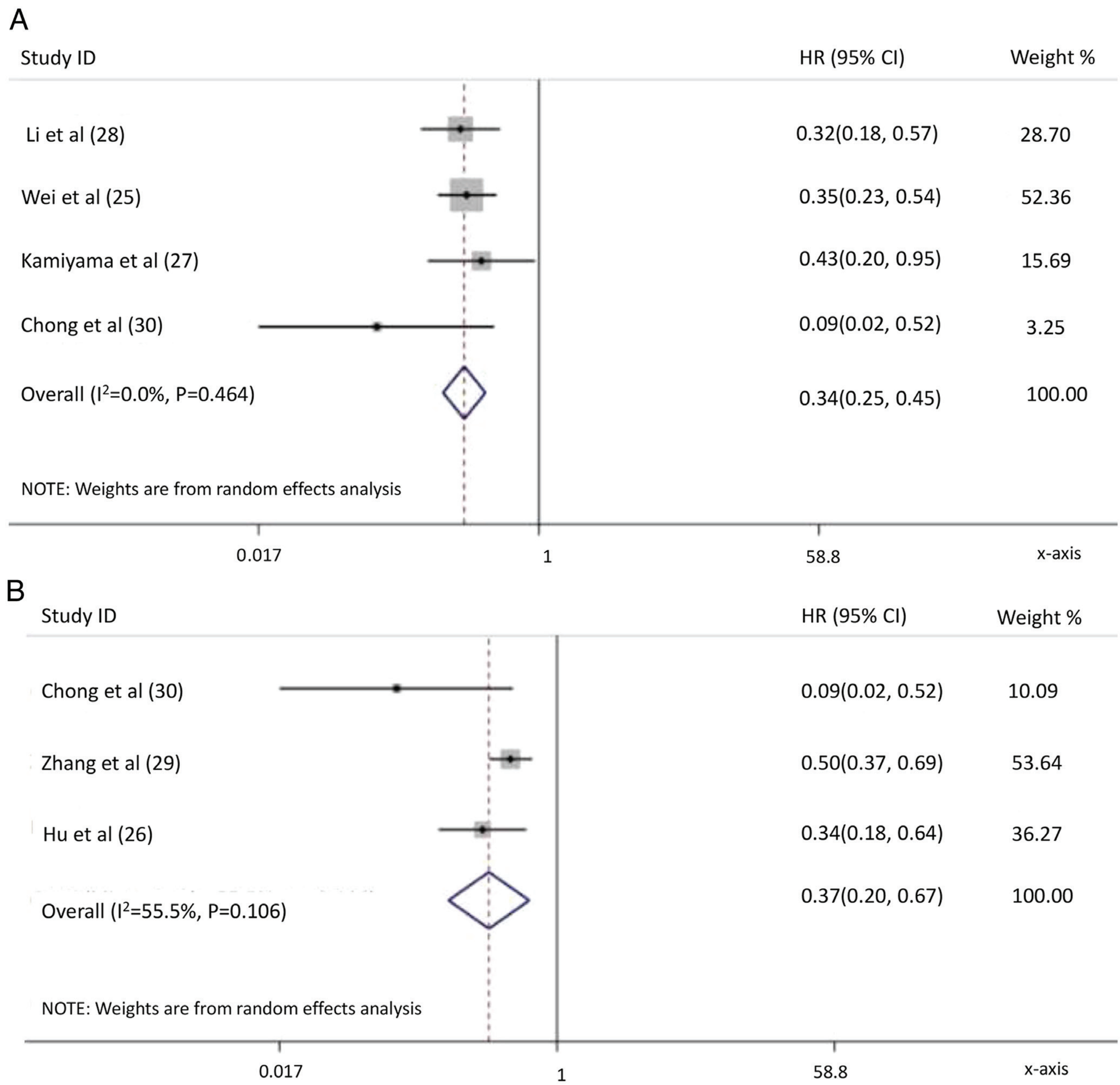

Figure 6. Forest plot of overall survival subgroup analysis in patients with hepatocellular carcinoma and portal vein tumor thrombus treated with (A) neoadjuvant radiotherapy (P<0.001) and (B) neoadjuvant interventional therapy (P=0.001). HR, hazard ratio.

China have managed to reduce 30-day mortality rates to 2.7%, notably below the global average of 5-10% (61), highlighting the critical role of surgical expertise in improving these outcomes. In the present study, the efficacy of interventional therapies, particularly regarding RFS, remains inconclusive, potentially due to the limited sample size.

Another concern is the impact of neoadjuvant therapy on liver function and the associated risks. Preoperative interventions, including TACE, have been scrutinized for potential adverse effects, including hepatic artery injury, on-target embolization, fever and decreased immune function, all of which could compromise postoperative recovery (62). For example, an RCT by Zhou *et al* (63) indicated that while preoperative TACE did not improve mortality or tumor recurrence rates, it increased the complexity and duration of surgical procedures and elevated the risk of postoperative liver failure. Similarly, another study highlighted that preoperative targeted immunotherapy raised the risk of severe biliary complications (64). However, data from other studies, including those by Hu *et al* (26) and Zhang *et al* (29), suggest that neoadjuvant TACE did not exacerbate postoperative complications, affirming its safety when performed in experienced clinical settings. The present comprehensive statistical analysis supports these findings, showing no significant increase in complications such as bile leakage or ascites, thereby confirming the overall safety profile of neoadjuvant therapy in the surgical management of HCC with PVTT.

The present meta-analysis systematically and comprehensively evaluated the efficacy and safety of neoadjuvant therapy in patients with HCC complicated by PVTT, suggesting that

Table II. Subgroup analysis of postoperative complications.

Complication	No. of studies	OR/MD (95% CI)	P-value	I^2, %
No. of blood transfusions	4	1.44 (0.85, 2.43)[a]	0.18	28
Operative blood loss, ml	4	83.60 (-149.43, 316.62)[b]	0.48	53
Operation time, min	3	14.76 (-7.14, 36.66)[b]	0.19	82
Bile leakage	2	1.11 (0.27, 4.48)[a]	0.89	0
Ascites pleural effusion	2	0.91 (0.19, 4.35)[a]	0.91	50
Intra-abdominal infection	2	0.43 (0.12, 1.60)[a]	0.21	0
Postoperative hemorrhage	2	1.90 (0.64, 5.64)[a]	0.25	0
Postoperative complications	4	1.72 (0.90, 3.28)[a]	0.10	55
Mortality	3	0.74 (0.20, 2.82)[a]	0.66	0

[a]OR (95% CI). [b]MD2 (95% CI). OR, odds ratio; MD, mean difference.

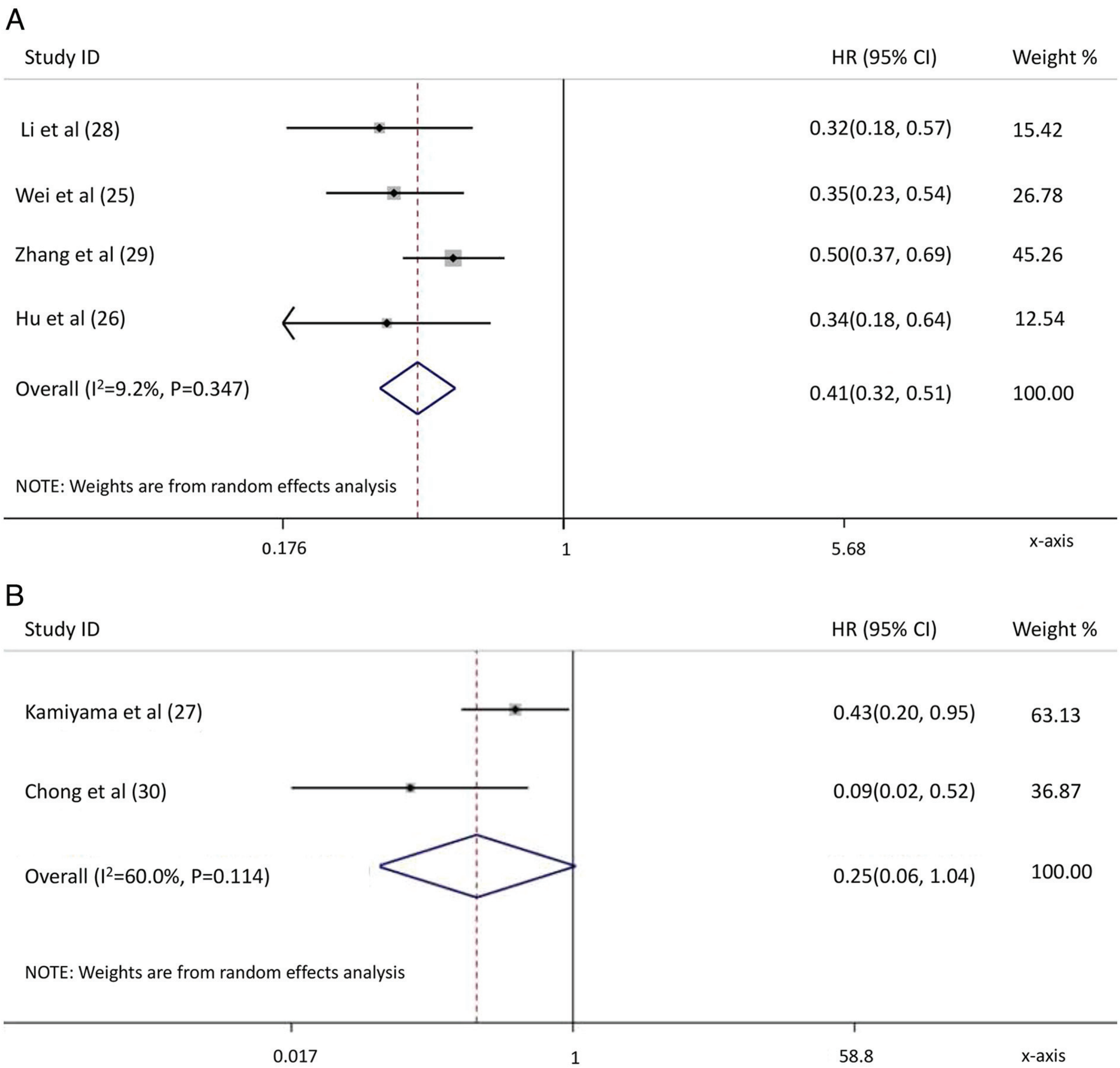

Figure 7. Forest plot of overall survival subgroup analysis of neoadjuvant therapy for patients with hepatocellular carcinoma and portal vein tumor thrombus in different regional subgroups. (A) China (P<0.001). (B) Japan and Korea (P=0.057). HR, hazard ratio.

neoadjuvant therapy represents a viable alternative treatment modality. A total of four previous meta-analyses (65-68) have assessed the efficacy of adjuvant therapies (in single or combined modalities) in patients with HCC and PVTT. A key distinction between these studies and the present study lies in the inclusion criteria. In three network meta-analyses (65-67), the experimental groups consisted of patients receiving adjuvant therapy (single or combined), and these studies comprehensively compared the benefits and safety of various treatment methods for patients with HCC and PVTT. In another study (68), only seven of the included articles focused on comparative studies of adjuvant therapy, which was administered either before or after surgery.

By contrast, the present study strictly limited the experimental and control groups to neoadjuvant therapy plus surgery vs. priority surgery, providing novel insights into the comparative prognosis and safety of these two approaches, an aspect not addressed in previous studies. For patients with HCC and PVTT, only a select few undergo radical surgery; however, the findings of the present study suggested that surgery following neoadjuvant therapy yielded superior outcomes compared with priority surgery. This expands the candidate pool for radical surgery, representing a significant and core contribution of the present research. Neoadjuvant therapy combined with surgery not only improved patient survival rates and reduced recurrence but was also safe. Additionally, the present study conducted a subgroup analysis based on the type of neoadjuvant therapy, which has not been performed in similar studies.

The classification of PVTT influences the outcomes of neoadjuvant therapy (69), and future studies should take this into consideration. However, several limitations of the present study warrant emphasis. Firstly, the number of included studies was limited, which may affect the robustness of the conclusions and precluded the use of a suitable network meta-analysis. Secondly, while the classification of PVTT is crucial in determining treatment strategies and outcomes, the lack of original data hindered the ability to perform subgroup analyses based on PVTT classifications. Thirdly, most of the included studies were observational, and there were substantial differences in treatment methods, contributing to the heterogeneity in statistical results and potentially weakening the reliability of the findings. Beyond treatment heterogeneity, variations in patient populations also introduce unavoidable heterogeneity. The disease characteristics of HCC differ between patients in Asia and Western regions (70), and since the present study population predominantly comprised East Asian individuals, the generalizability of these findings to a global context is limited. The development of neoadjuvant therapies in HCC is progressing rapidly, and the present study will be updated as new relevant literature is published.

The present meta-analysis evaluated the long-term prognosis and safety of neoadjuvant therapy in patients with HCC complicated by PVTT. The findings suggested that neoadjuvant therapy not only offered superior efficacy compared with priority surgery, but also demonstrated a favorable safety profile. However, these preliminary conclusions require further validation through larger, multicenter RCTs to improve their reliability and generalizability across diverse patient populations.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

WX, XiaZ, YF, YZ, ZX, YY, QW and XinZ contributed to the conception and development of the paper. WX and XiaZ confirm the authenticity of all the raw data. WX and XiaZ designed the research process. YF and YZ conducted the database search and extracted relevant data from the articles. ZX and YY performed the statistical analysis. QW and XinZ drafted the meta-analysis. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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