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Neoadjuvant immunotherapy for resectable hepatocellular carcinoma: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Immune checkpoint inhibitors have initiated a new era in hepatocellular carcinoma (HCC) treatment. For improving the prognosis of patients with resectable HCC and reducing postoperative recurrence, immunotherapy is being developed in the neoadjuvant setting. However, the efficacy and safety of neoadjuvant immunotherapy remain unclear.

MATERIALS AND METHODS: PubMed, Embase, Medline, and Cochrane Library databases were systematically searched for the clinical trials of neoadjuvant immunotherapy for resectable HCC. A single-arm meta-analysis was conducted to calculate the odds ratio and 95% confidence interval (CI), and statistical transformation was performed to obtain the pooled rate P(t) and its CI. Subgroup analyses were performed according to the type of combination therapy.

RESULTS: 81 patients from four studies were included in this meta-analysis. In patients with resectable HCC, the pooled major pathological response (MPR) rate and pathological complete response (pCR) rate for neoadjuvant immunotherapy were 0.23 (95% CI, 0.14-0.36) and 0.19 (95% CI, 0.10-0.30), respectively. The pooled objective response rate (ORR) was 0.18 (95% CI, 0.10-0.28), comparable to the results of immunotherapy for advanced HCC. The overall treatment-related adverse events (TRAE) rate was 0.80 (95% CI, 0.68-0.89), but the grade ≥3 TRAE rate was low at 0.21 (95% CI, 0.13-0.33). The pooled surgical resection rate and surgical delay rate were 0.95 (95% CI, 0.85-0.98) and 0.05 (95% CI, 0.02-0.16), respectively. Subgroup analyses revealed no significant differences in clinical outcomes between immunotherapy combinations.

CONCLUSIONS: This meta-analysis provides preliminary evidence of the efficacy and safety of neoadjuvant immunotherapy for HCC, suggesting that it is a promising perioperative treatment option. Conclusive evidence supporting its use requires additional data from large-scale clinical trials.

Key Words:
Neoadjuvant immunotherapy, HCC, Hepatocellular carcinoma, Resectable, Systematic review, Meta-analysis.

Introduction

Hepatocellular carcinoma (HCC) is a major threat to humans. Hepatectomy is a crucial radical treatment option for HCC. However, HCC has a high postoperative recurrence rate and a lack of effective prognostic biomarkers, leading to poor survival outcomes[1]. These concerns have prompted researchers to assess the advantages of neoadjuvant and adjuvant techniques used for improving resectability and reducing recurrence rates[2]. Treatments such as transarterial chemoembolization and transarterial radioembolization have been evaluated as neoadjuvant options, and systemic therapies [chemotherapy, tyrosine kinase inhibitors (TKIs)] were tested as adjuvant options. However, whether these therapies significantly improve the overall survival (OS) of patients remains unknown[3-6].

Exciting developments in immunotherapy for advanced HCC have been made in the past 10 years, with atezolizumab plus bevacizumab receiving FDA approval as the first-line therapy for HCC. Moreover, nivolumab and pembrolizumab were approved by multiple regulatory agencies as second-line therapies, thus offering significant survival benefits for HCC patients[7,8]. In the encouraging immunotherapy landscape, neoadjuvant immunotherapy for HCC is evolving. Several clinical trials[9,10] on neoadjuvant immunotherapy have offered promising preliminary results, and more such trials are underway. Introducing

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systemic therapy at the preoperative stage may be a new approach for improving prognosis.

By removing invisible micro-metastatic lesions, neoadjuvant immunotherapy may lower the recurrence risk and transform unresectable diseases into resectable diseases. In addition, the efficacy of the neoadjuvant immunotherapy can be used as a prognostic and predictive sign for facilitating clinicians in making neoadjuvant therapy-related decisions[10]. The efficacy of neoadjuvant immunotherapy has been evaluated in non-small cell lung cancer, resectable head and neck cancer, melanoma, early triple-negative breast cancer, and resectable esophageal cancer[11-15]. However, relatively few studies[10,16] have supported the use of neoadjuvant immunotherapy for HCC, and its efficacy and safety remain unclear.

This meta-analysis attempts to gather the findings of existing clinical studies and assess the effectiveness and safety of neoadjuvant immunotherapy for resectable HCC to provide additional options for clinical treatment.

Materials and Methods

The Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines were followed while reporting this study[17]. The meta-analysis was registered in PROSPERO, identifier CRD42023439852.

Search Strategy

We systematically searched PubMed, Embase, Medline, and Cochrane Library for clinical trials on neoadjuvant immunotherapy for resectable HCC since their inception until August 1, 2022. In order to obtain as much unpublished and up-to-date data as possible, we searched the abstracts and reports of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) congresses up to August 1, 2022. No language restrictions were placed. The search terms used included "hepatocellular carcinoma" or "liver cell carcinoma" in combination with "neoadjuvant therapy", "immunotherapy" or "immune checkpoint inhibitors" and their related variants. We also conducted manual searches to identify other relevant studies by reviewing the reference lists of the key articles.

Selection Criteria

We developed the inclusion and exclusion criteria based on the patient, intervention, comparison, outcomes (PICOs) principles of evidence-based medicine (EBM). The following criteria were used to select studies for inclusion: (1) trials that enrolled patients with resectable HCC (stages I-III) who had never received any prior immunotherapy; (2) patients who had received immune checkpoint inhibitors (ICIs) before surgery with single ICI, dual ICI combination or immunotherapy combined with targeted therapy; (3) neoadjuvant therapy's effectiveness and safety were assessed by at least one metric, such as major pathological response (MPR), pathological complete response (pCR), objective response rate (ORR), treatment-related adverse events (TRAE), resection rate, and the delay rate of surgery; (4) the type of study was set to prospective randomized clinical trial. Reviews, case reports, and retrospective studies were excluded. Past studies that reported only protocols and did not include any primary observational endpoints were also excluded. When the same patient cohort was repeatedly published in different publications (for example, congress abstracts and full text), the most recent and relevant one was included for assessment.

Data Collection

After reviewing the full text, two authors (YH and JB) independently extracted information from each study and negotiated with the third author in case of disagreement. The following data were extracted whenever possible: basic information (first author, year of publication, number of clinical trials), study design (study phase, intervention model, masking, the number of patients enrolled), treatment regimen (drug, dose, time of administration), and the primary clinical outcomes (MPR, pCR, ORR, incidence of TRAE, surgical resection rate, the surgical delay rate).

Quality Assessment

As the included studies did not include any control group using conventional chemotherapy drugs, we assessed the study quality in accordance with the Methodological Index for Non-randomized Studies (MINORS)[18]. Two assessors (YH and JB) conducted the assessment independently and resolved any differences through discussion with the third assessor.

Statistical Analysis

The proportions of patients who achieved MPR, pCR, and objective response, as well as the TRAE frequency, resection rate, and delay rate were calculated and statistically transformed.

Using the following formula, the values of P and standard error [SE (P)] were determined:

$P = \ln(odds) = \ln(x/(n-x))$ $SE(P) = SE(\ln(odds)) = \sqrt{(1/x + 1(n-x))}$.

Statistical analysis was performed with the RevMan 5.3 software version (Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark) to calculate the odds ratio (OR) and 95% confidence interval (CI), and the forest plots were plotted. OR and 95% CI were converted to obtain P(t) and its 95% CI served as the pooled rate. The formula used was as follows:

$P(t) = OR/(1+OR)$, $LL(t) = LL/(1+LL)$, $UL(t) = UL/(1+UL)$.

Heterogeneity between the studies was measured by the χ^2 test and the I^2 test, while the choice of using a fixed-effects model or a random-effects model was made based on the level of heterogeneity. Statistics were deemed significant at $p<0.05$. We also conducted exploratory analyses to compare whether there were differences in the proportion of patients with each clinical outcome across the treatment regimens. The number of included studies was small and most of them were single-arm trials. The results were descriptive rather than comparative. There were no "positive" results or statistically significant outcomes, and all results were stable. As a result, we did not perform any sensitivity analysis or publication bias tests.

Results

Retrieval Results and Study Characteristics

Applying the search strategy, 1,372 studies were retrieved. After removing duplicate articles and reading the titles and abstracts, the remaining 14 articles were reviewed in full detail. Four studies were ongoing clinical trials that had not yet reported results, three studies did not meet the inclusion criteria for resectable HCC, and four were duplicate published studies. Ultimately, 81 patients from four studies[19-22] were included in the meta-analysis. Figure 1 presents the overall selection process. One[19] of the four publications was a conference abstract presented at the 2022 ASCO Congress, and the remaining three[20-22] were full-text publications. Three articles[20-22] were on phase II trials and one article19 was on a phase Ib trial. One[20] was a randomized, dual-arm, open-label experiment, and the other three[19,21,22] were single-arm, open-label trials. In this dual-arm trial, patients were randomly allocated (1:1) to receive nivolumab (group A) or nivolumab plus ipilimumab (group B)[20]. In subsequent analyses, we included this dual-arm trial as two cohorts in the meta-analysis. Of the 81 patients, 34 patients received ICI monotherapy, 29 received dual ICI therapy, and 18 in one[22] trial received immunotherapy combined with targeted therapy. The ICIs used in the studies were nivolumab, cemiplimab, camrelizumab, and ipilimumab, which are PD-1 and CTLA-4 monoclonal antibodies. Table I summarizes the important details of the four studies.

Treatment Response

Surrogate endpoints commonly used in the clinical trials of antineoplastic agents included pathological and imaging assessments. MPR was defined according to the degree of tumor necrosis. Considering that a validated cut-off value for tumor necrosis in HCC is lacking, MPR was defined differently among the original studies. To incorporate as much literature as possible, we finally included literature reporting tumor necrosis of ≥70% or 90%. Four trials[20-22] (the study by Kaseb 2022[20] including two trials: group A and group B) reporting MPR were included in the meta-analysis. The pooled OR of MPR was 0.30 (95% CI, 0.16-0.57) and $p=0.0002$ (Figure 2A). After conversion, the pooled MPR rate was 0.23 (95% CI, 0.14-0.36). The post-treatment lack of remaining tumor cells was used to define pCR. pCR was reported in all five trials[19-22] with a pooled OR of 0.23 (95% CI, 0.12-0.44) and $p<0.0001$ (Figure 2B), and the pooled pCR rate after transformation was 0.19 (95% CI, 0.10-0.30). ORR is an imaging assessment endpoint for clinical trials of antineoplastic agents and is evaluated using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. ORR was reported in all five trials[19-22] with a pooled OR of 0.22 (95% CI, 0.12-0.40) and $p<0.00001$ (Figure 2C), and after conversion, pooled ORR was 0.18 (95% CI, 0.10-0.28).

Progression-Free Survival

Only one study[20] reported progression-free survival (PFS), and a meta-analysis could not be performed. Kaseb et al[20] found that after a mean follow-up of 24.6 months, PFS with nivolumab was 9.4 months [95% CI, 1.47-not estimable (NE)] and with nivolumab plus ipilimumab was 19.53 months (95% CI, 2.33-NE). Nivolumab plus

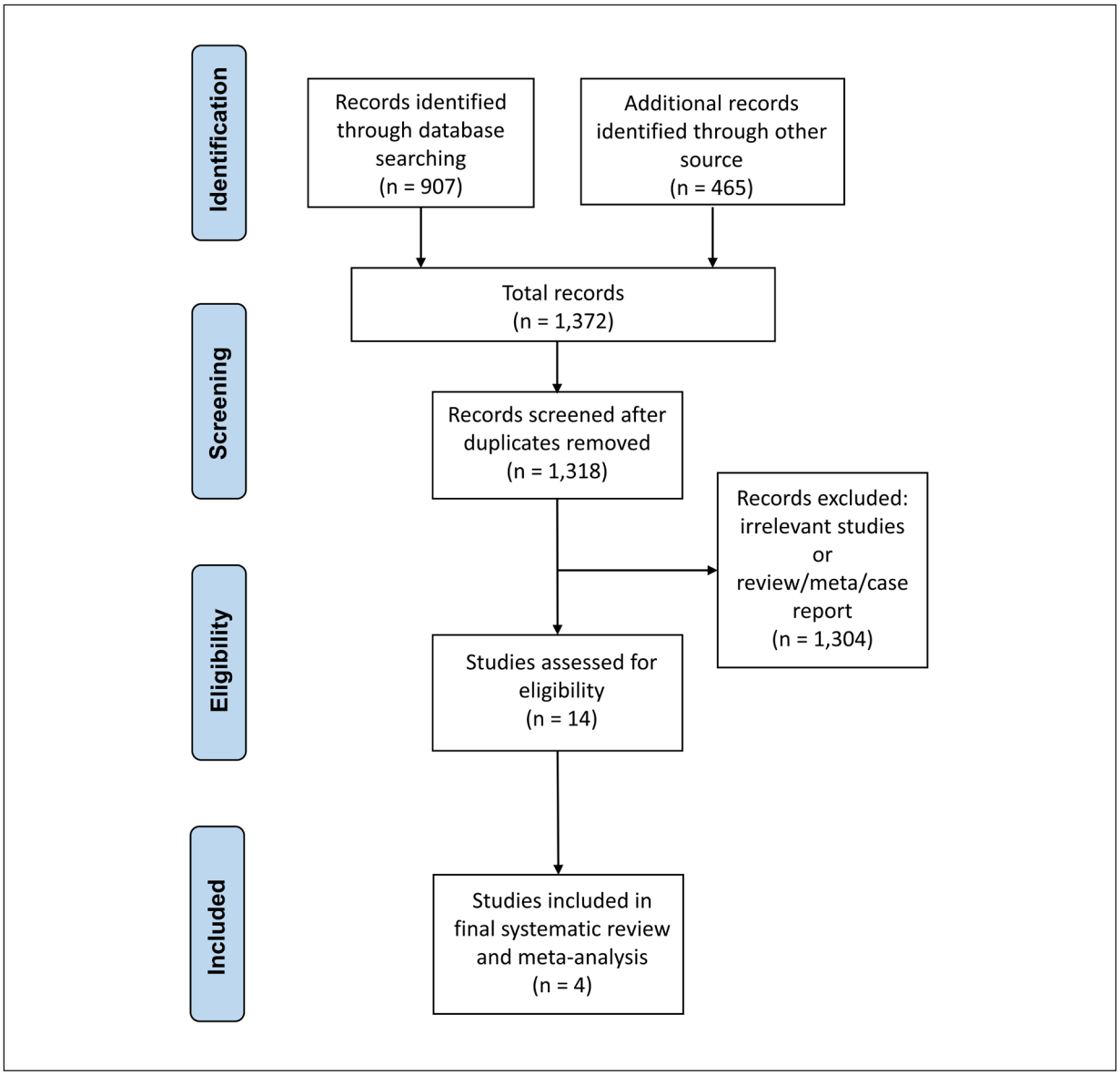

Figure 1. The PRISMA flow diagram outlining the selection of eligible research.

ipilimumab had a greater PFS than nivolumab alone, although the difference was nonsignificant.

Recurrence-Free Survival

Two studies evaluated the recurrence-free survival (RFS) of patients who received surgery. In one study[20], patients who achieved MPR had significantly better RFS than those who did not (p=0.049). In another study[22], the 1-year RFS rate with camrelizumab plus apatinib was 53.85% (95% CI, 24.77%-75.99%), and the 1-year recurrence rate was lower than previously reported. Similarly, RFS was greater in the MPR/pCR group than in the non-MPR/pCR group, but the difference was nonsignificant.

Treatment-Related Adverse Events

The frequency of TRAE and the incidence of serious TRAE (grade ≥3) are among the most crucial indicators of the safety of neoadjuvant immunotherapy. Five trials[19-22] reported TRAE with pooled OR=2.64 (95% CI, 0.86-8.15), I^2=76%, significant heterogeneity, the random-effects model adopted, and p=0.09 (Figure 3A). The pooled TRAE rate after conversion was 0.72 (95% CI, 0.46-0.89).

We speculated Marron et al's[21] study as the main source of heterogeneity. Marron et al[21] reported TRAE and AE (adverse events), whereas no other study reported AE, and we, therefore, inferred that the different definitions of TRAE and AE in

Table I. Summary of characteristics of included studies.

Study	Registration number and date	Study phase	Intervention model	Masking	Number of patients	ICI	Dose of ICI	MPR	pCR	ORR	TRAE	Grade 3 or greater TRAE	Resection rate	Delay rate
Alessio 2022[19]	NCT03682276 24/09/2018	Ib	Single-arm	Open-label	15	Nivolumab plus ipilimumab	**Nivolumab** (3 mg/kg, day 1, 22) plus **ipilimumab** (1 mg/kg, day 1 only)	Not reported	22.2% (2/9)	23.1% (3/13)	73.3% (11/15)	6.7% (1/15)	Not reported	0
Kaseb 2022[20]	NCT03222076 19/07/2017	II	Dual-arm	Open-label	13 (group A)	Nivolumab (group A)	**Nivolumab** (250 mg, every 2 weeks up to three doses)	33.3% (3/9)	22.2% (2/9)	23.1% (3/13)	76.9% (10/13)	23.1% (3/13)	100% (9/9)	0
					14 (group B)	Nivolumab plus ipilimumab (group B)	**Nivolumab** (250 mg, every 2 weeks up to three doses) plus **ipilimumab** (1 mg/kg, one dose)	27.3% (3/11)	27.3% (3/11)	0	85.7% (12/14)	42.9% (6/14)	100% (11/11)	0
Marron 2022[21]	NCT03916627 16/04/2019	II	Single-arm	Open-label	21	Cemiplimab	**Cemiplimab** (350 mg, every 3 weeks up to two doses)	20.0% (4/20)	15.0% (3/20)	15.0% (3/20)	30.0% (6/20)	10.0% (2/20)	95.2% (20/21)	5.0% (1/20)
Xia 2022[22]	NCT04297202 05/03/2020	II	Single-arm	Open-label	18	Camrelizumab plus apatinib	**Camrelizumab** (200 mg, every 2 weeks up to three doses) plus **apatinib** (250 mg, day 1 to day 21)	17.6% (3/17)	5.9% (1/17)	16.7% (3/18)	88.9% (16/18)	16.7% (3/18)	94.4% (17/18)	Not reported

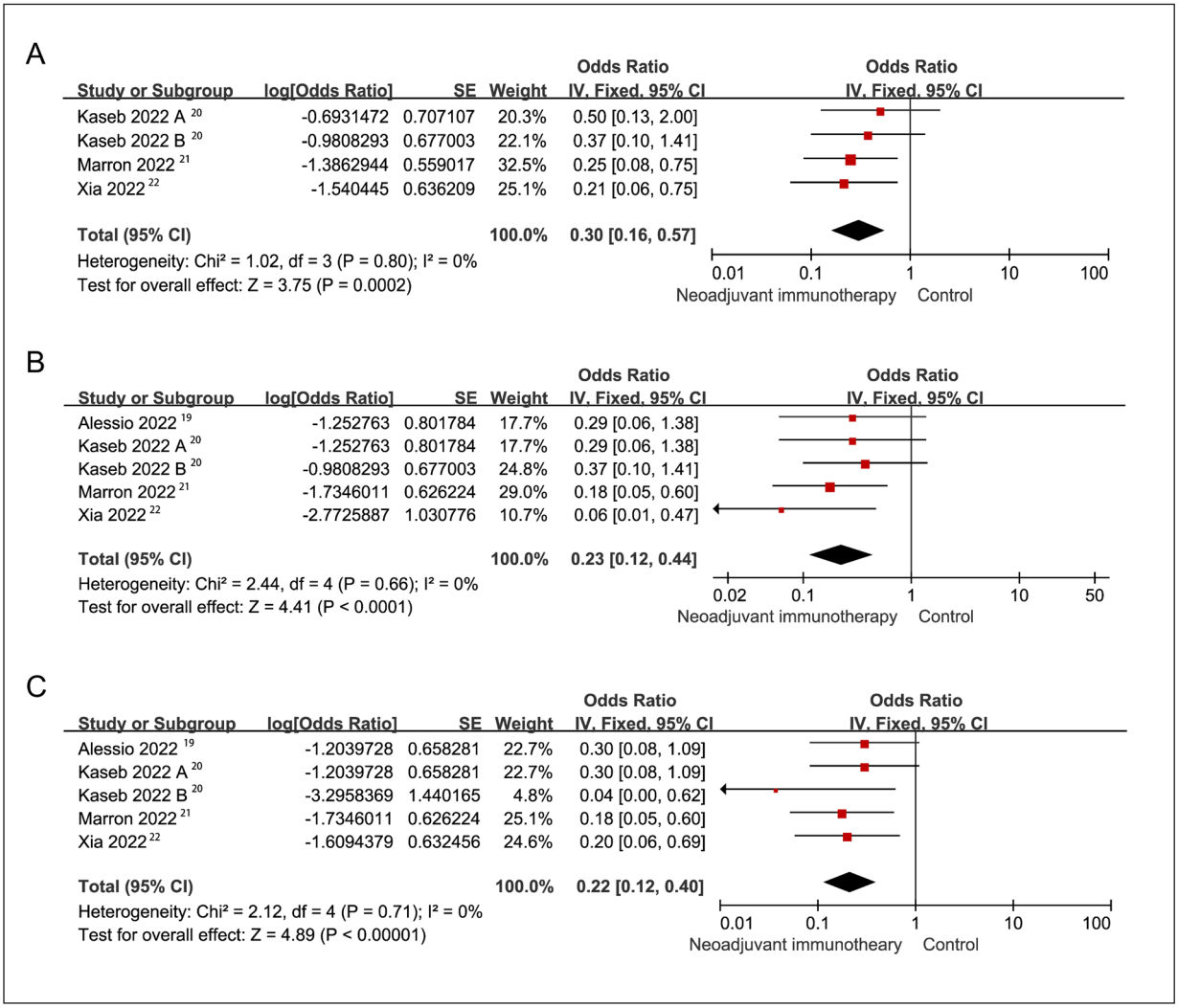

Figure 2. Forest plots of the efficacy outcomes. **A**, MPR, (**B**) pCR, (**C**) ORR.

each study could be the source of heterogeneity. Once that study was excluded, heterogeneity was significantly lower with pooled OR=4.19 (95% CI, 2.16-8.14), I^2 =0%, p<0.0001 (Figure 3B), and converted TRAE rate=0.80 (95% CI, 0.68-0.89). Five trials[19-22] reported grade ≥3 TRAE with pooled OR=0.27 (95% CI, 0.15-0.49), p<0.0001 (Figure 3C), and the rate of grade ≥3 TRAE=0.21 (95% CI, 0.13-0.33) after transformation. The reported TRAE included nausea, diarrhea, fatigue, fever, constipation, abdominal pain, pruritis, maculopapular rash, anemia, decreased platelet count, drug-induced liver injury, hypothyroidism, increased blood creatine phosphokinase, hypoalbuminemia, elevated lipase levels, and elevated lactate dehydrogenase levels. Grade ≥3 TRAE included grade 3 maculopapular rash, grade 3 pneumonitis, and grade 3 ALT/AST elevation.

Resection Rate and Delay Rate

Surgical resection was reported in four trials[20-22]. Only two patients who were expected to undergo surgery were unsuccessful because one patient developed metastatic lymph nodes in the porta hepatis and another patient exhibited disease progression, with no specific progression mentioned. The pooled OR of the resection rate =18.60 (95% CI, 5.82-59.43) and p<0.00001 (Figure 4A), and the resection rate after conversion was 0.95 (95% CI, 0.85-0.98). Neoadjuvant immunotherapy-related side effects can cause surgical delays. Four trials[19-21] reported surgical delays. The delay in one patient was due to the deteriorating liver function (unrelated to ICI) and in another patient (delay of 2 weeks) due to drug-induced pneumonia requiring steroids. The pooled OR of surgical delay was 0.05 (95% CI, 0.02-0.19) and p<0.00001

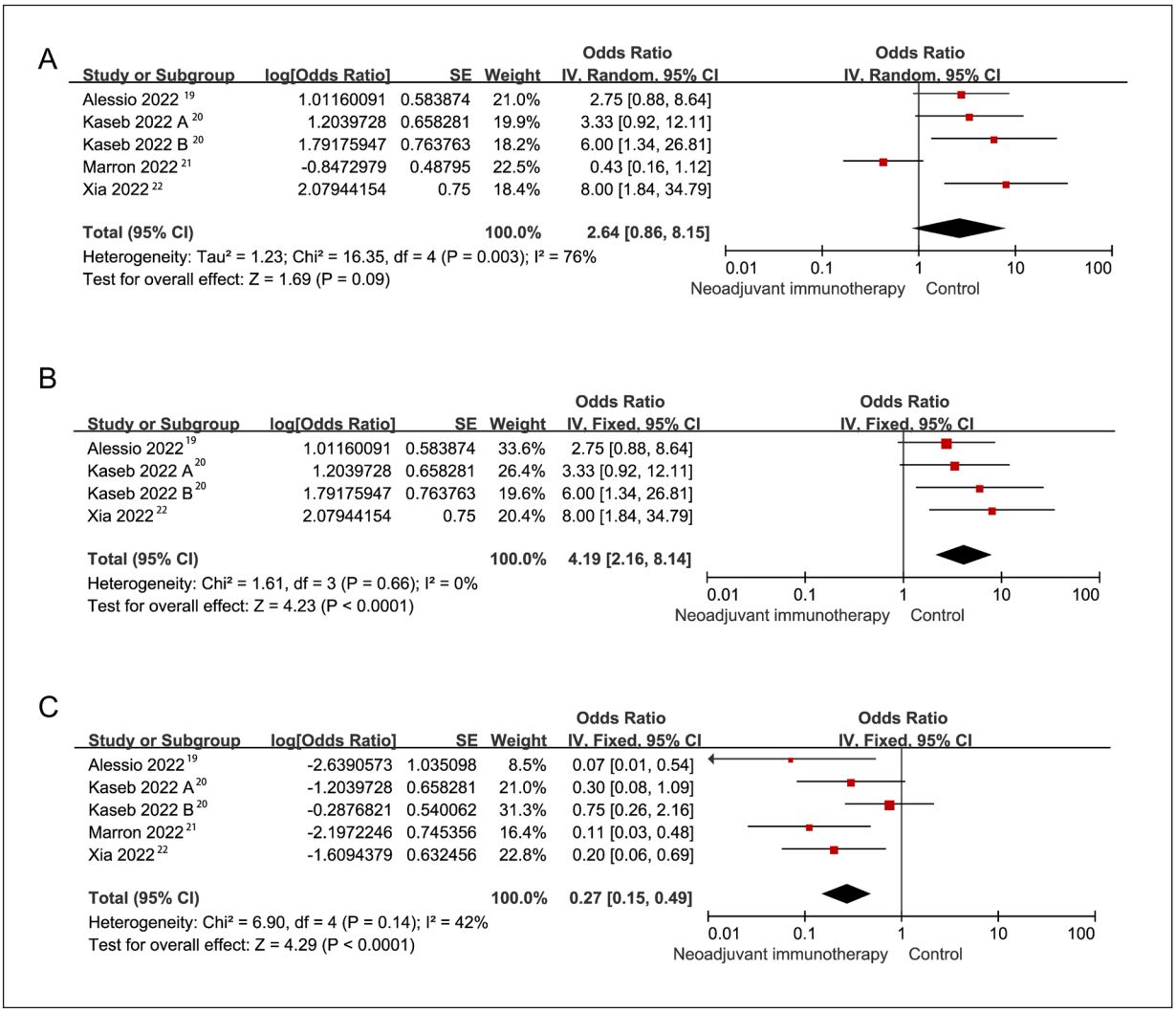

Figure 3. Forest plots of the TRAE. **A**, Pooled OR of TRAE of all five studies. **B**, Pooled OR of TRAE after removing the heterogeneous study. **C**, Pooled OR of grade ≥3 TRAE.

(Figure 4B), and the delay rate after conversion was 0.05 (95% CI, 0.02-0.16).

Exploratory Subgroup Analysis

Currently, three main regimens of neoadjuvant immunotherapy are available for resectable HCC: monotherapy, dual ICI combination, and immunotherapy combined with targeted therapy. Through an exploratory subgroup analysis, we investigated whether different regimens have different effects on the clinical outcomes of the treatment. Two trials (the group A of Kaseb 2022[20] and the Marron 2022[21]) reported nivolumab and cemiplimab as monotherapy, two trials (the Alessio 202219 and the group B of Kaseb 202220) reported ipilimumab plus nivolumab as combination therapy, and one trial[22] reported camrelizumab plus apatinib. Finally, the exploratory analysis included four trials[19-21] based on single-agent or dual ICI therapy and examined clinical outcomes such as pCR, ORR, TRAE, and surgical delay rates. The subgroup analysis results revealed that the pooled OR of pCR (Figure 5A) for dual ICI therapy was higher than that for monotherapy, and the pooled OR of ORR (Figure 5B) for dual ICI therapy was lower than that for monotherapy. The pooled ORs of TRAE (Figure 6A) and grade ≥3 TRAE (Figure 6B) for dual ICI therapy were higher than those for monotherapy, and the pooled OR of surgical delay rate (Figure 6C) for dual ICI therapy was lower than that for monotherapy. However, no difference between the groups was statistically significant. Therefore, judging differences in efficacy or safety between single-drug or dual ICI therapy based on the present results are not possible.

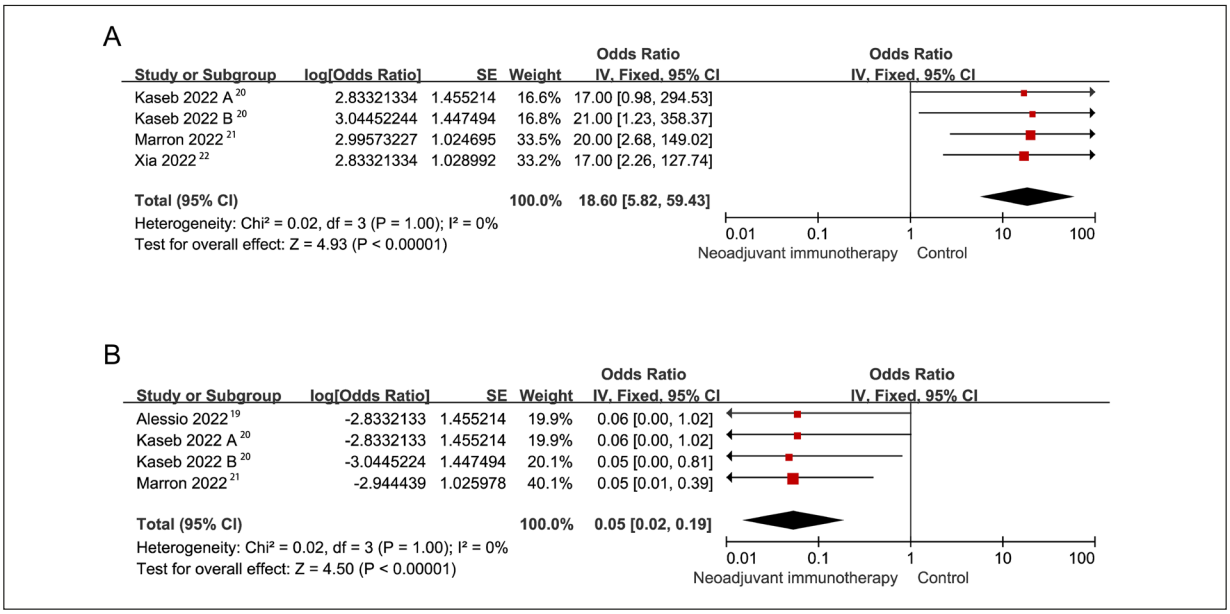

Figure 4. Forest plots of the resection rate and the delay rate. **A**, Resection rate. **B**, Delay rate.

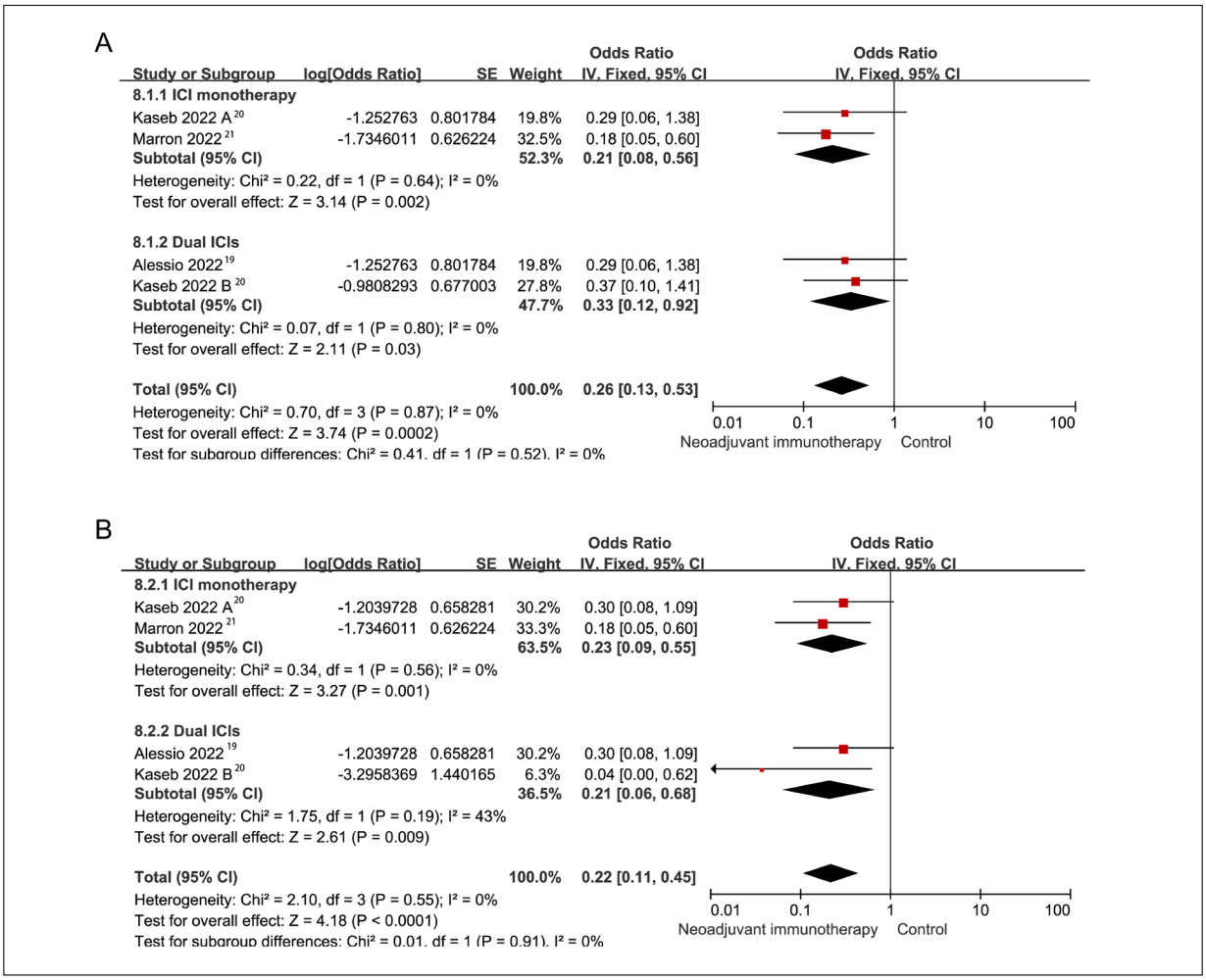

Figure 5. Subgroup analysis based on monotherapy or double ICIs combination for (**A**) pCR and (**B**) ORR.

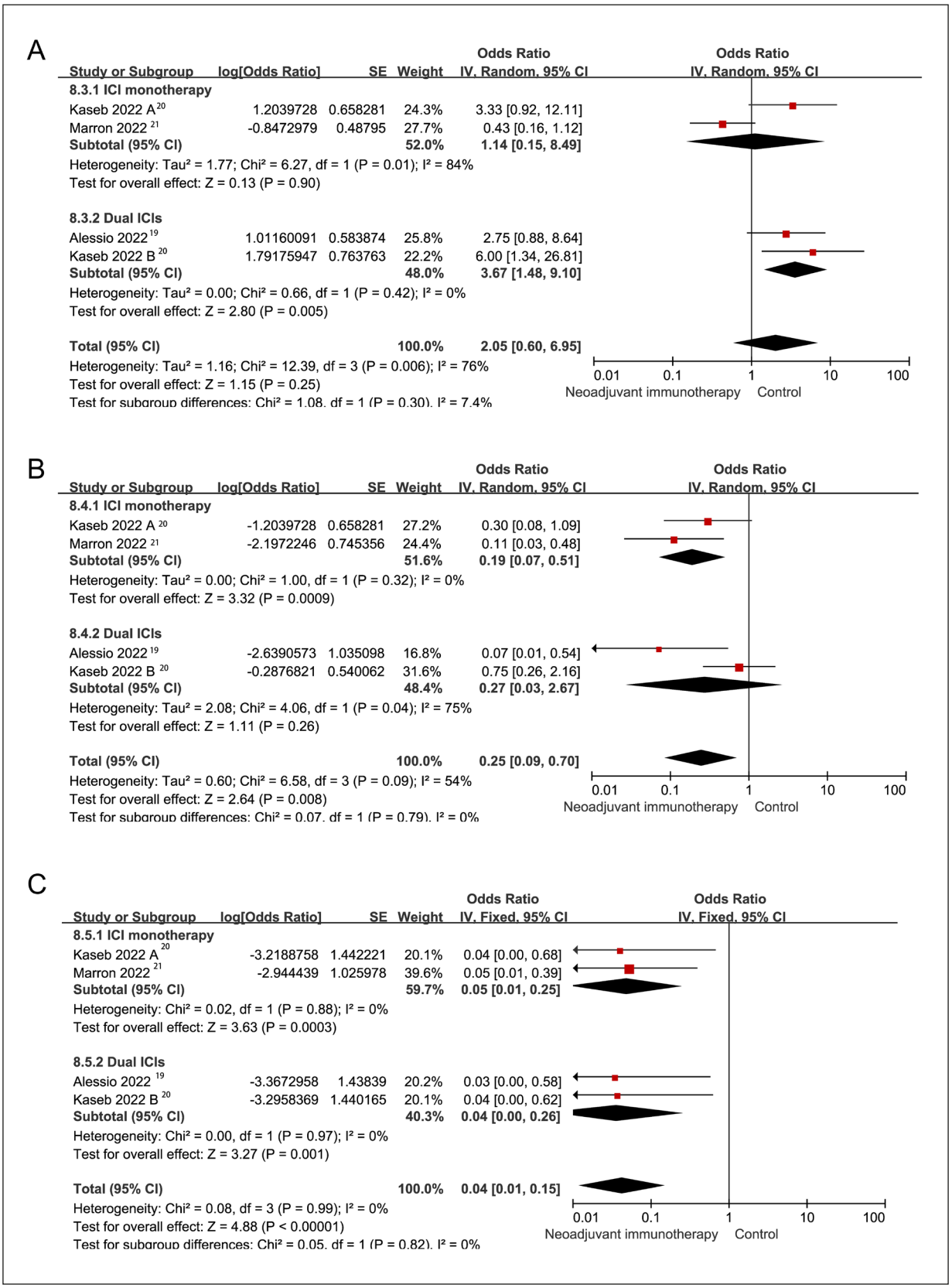

Figure 6. Subgroup analysis based on monotherapy or double ICIs combination for (**A**) TRAE, (**B**) grade ≥ 3 TRAE, and (**C**) surgical delay rate.

Discussion

The role of neoadjuvant immunotherapy in resectable HCC management is currently unclear, and to our knowledge, this is the first systematic review and meta-analysis evaluating immunotherapy for resectable HCC. Overall, our findings support the effectiveness and safety of neoadjuvant immunotherapy for resectable HCC as well as the exploration of this approach in larger registry studies. The present meta-analysis revealed that the pooled MPR, pCR, and objective response rates were 23%, 19%, and 18%, respectively, similar to the efficacy of neoadjuvant ICI therapy against other cancers[23]. This encouraging finding promises the anti-tumor efficacy of ICIs in terms of the pathological response and radiology. Further, we searched for other studies reporting the efficacy of ICIs in advanced HCC for comparison with our study. A meta-analysis[24] reported an overall ORR of 0.20 (95% CI, 0.16-0.24) for PD-1/PD-L1 inhibitors in advanced HCC, comparable to our results. Another meta-analysis[25] reported that ICI treatment is associated with a better ORR than treatment with sorafenib, the standard first-line treatment for advanced HCC. Although the lack of standard neoadjuvant therapies precludes further comparative analysis of the efficacy of ICIs in resectable HCC, through comparison with the ORR of advanced HCC patients who received ICIs, we conclude that neoadjuvant immunotherapy offers satisfactory objective remission in resectable HCC.

Complete survival data from most neoadjuvant immunotherapy trials are not yet available and quantifying the benefit of neoadjuvant immunotherapy for increased survival is difficult. However, post-surgery follow-up revealed that the achievement of MPR or pCR was associated with RFS[20,22]. Kaseb et al[20] immunologically analyzed tumor samples from HCC patients after treatment. They found that patients who achieved MPR after ICI therapy had a favorable tumor microenvironment, whereas those who did not have an immunosuppressed myeloid-rich tumor microenvironment[20]. In addition, according to Marron et al[21], significant immune infiltration was noted in responders compared with non-responders. Moreover, this increased immune infiltration was also observed in the responders at baseline, suggesting that pre-existing immune infiltration predisposes a patient to an aggressive immunotherapy response[21]. These results indicate that an individual's response to neoadjuvant immunotherapy depends on the state of tumor immune infiltration, which may influence the long-term survival benefit. This has also been noted in melanoma[26]. Thus, MPR or pCR could be used as a predefined primary or secondary endpoint in future neoadjuvant immunotherapy studies for HCC.

Regarding the safety of neoadjuvant immunotherapy, the meta-analysis revealed a pooled TRAE rate of 0.72 (95% CI, 0.46-0.89); however, heterogeneity was high due to the different reporting of AE and TRAE. We obtained a pooled TRAE rate of 0.80 (95% CI, 0.68-0.89) with little heterogeneity after the study[21] reporting AE was excluded. Despite the high overall TRAE rate, the pooled TRAE rate of grade ≥3 was 0.21 (95% CI, 0.13-0.33) and did not result in serious adverse outcomes. Moreover, a meta-analysis[27] of the toxicity of systemic therapies for advanced HCC revealed that ICIs are associated with fewer serious AE than TKIs, demonstrating that their use is safe. Most immune-related toxicities are manageable; however, they can interfere with the treatment course, and in severe cases, even threaten the patient's life. Accurate prognosis, prompt diagnosis, and early intervention are crucial for enhancing the effectiveness of immunotherapy[28,29]. On the other hand, the overall surgical resection rate after neoadjuvant immunotherapy reached 95%, with a surgical delay rate of only 5%. However, two patients who were expected to undergo surgery were unsuccessful due to disease progression. In one patient, surgery was postponed as steroids were used for drug-induced pneumonia. And no treatment-related deaths were reported. Preoperative neoadjuvant therapy may deprive patients otherwise eligible for surgery or result in delayed surgery and the length of perioperative drug induction or high doses may increase the potential for toxicity. Therefore, developing a standard perioperative regimen with the shortest possible duration and dose reduction for maximizing patient benefit while improving treatment safety are the next challenges.

Several studies[10,16] have currently demonstrated the versatility of perioperative treatment options. Combinations of two ICIs (anti-PD-1/PD-L1 and anti-CTLA-4) and those of ICIs with angiogenesis inhibitors have been used in several clinical trials[20,22,30]. However, the effect of the combination remains inconclusive. Theoretically, dual immune combination therapy may improve the efficacy of immunotherapy[31]. However, our exploratory subgroup analysis exhibited

no differences in efficacy and safety between dual immune combination and monotherapy (test for subgroup differences: $p>0.05$). Kaseb et al[20] found no significant differences in MPR, pCR, ORR, and TRAE between the nivolumab and nivolumab plus ipilimumab groups. These results may be obtained due to the small sample size. A dual ICI combination has been confirmed to be efficacious in advanced HCC. In patients already treated with sorafenib, the ORR of the nivolumab plus ipilimumab treatment was 31% (95% CI, 18%-45%) compared with that of the nivolumab monotherapy (15%; 95% CI, 6%-28%). Combination therapy resulted in a better ORR than monotherapy[32]. However, the incidence of grade ≥3 TRAE was also higher with dual immune combination therapy[33].

We could not perform a subgroup analysis of ICI combined anti-VEGF because only one trial22 was included. However, a meta-analysis[34] of ICI efficacy in advanced HCC revealed that the combination of ICI and anti-vascular endothlial growth factor (anti-VEGF) therapy resulted in better outcomes in terms of disease control rate (DCR), ORR, PFS, and OS than ICI monotherapy. ICI and VEGF inhibitors in combination produced synergistic antitumor effects, with VEGF inhibition reducing immunosuppression, promoting normalization of the tumor vascular system, and enhancing cytotoxic T lymphocyte infiltration and effector functions in the microenvironment[35,36]. Moreover, approval of atezolizumab (anti-PD-L1) plus bevacizumab (anti-VEGF) as the first-line treatment for advanced HCC indicates that immunotherapy combined with targeted therapy may become the future direction[37].

Neoadjuvant immunotherapy is a new strategy for reducing the postoperative recurrence rate and improving the survival of HCC patients. It is theoretically more effective than postoperative adjuvant immunotherapy[38]. Mechanistically, when tumors are larger, antigen-presenting cells take on a larger antigen load and thus generate a stronger antitumor T-cell response[39]. Moreover, neoadjuvant trials allow the presentation of the dynamic effects of immunotherapy *in vivo*. In-depth analysis of pre-and post-treatment blood and tissue specimens can help analyze the immune microenvironment at baseline and post-treatment, thus facilitating the characterization of intervention effects. Therefore, neoadjuvant immunotherapy helps address the current challenges of clinical response heterogeneity and lack of validated biomarkers for immunotherapy[10].

Neoadjuvant immunotherapy may offer a wide treatment option. In addition to the currently explored perioperative treatment of resectable HCC with neoadjuvant immunotherapy, some studies[40-42] have suggested the advantages of this treatment option in downstaging and conversion of advanced HCC. Moreover, some studies[43,44] have reported the efficacy and safety of neoadjuvant ICI in the liver transplantation field.

Limitations

This meta-analysis has certain limitations. First, this analysis included a small number of clinical trials, which resulted in the inclusion of a relatively modest number of patients. Second, uniform criteria defining pathological and imaging responses in neoadjuvant therapy for HCC are lacking, and most trials did not meet the expected OS or PFS endpoints, which have not yet suggested a long-term benefit of neoadjuvant therapy for patients. Moreover, treatment safety assessment should also include surgical difficulty and postoperative complications. We could not perform a comprehensive analysis because these data were lacking.

Conclusions

This meta-analysis provides preliminary evidence of the efficacy and safety of neoadjuvant immunotherapy for HCC, thereby offering confidence for future clinical trials. Regarding efficacy, neoadjuvant immunotherapy resulted in pathological or imaging remission in some patients and may have therapeutic benefits for long-term survival as implied by the histopathological response. Regarding safety, although the overall TRAE rate was high for neoadjuvant immunotherapy, most reactions were mild and did not result in serious adverse outcomes. Furthermore, we indicate the need to identify more biomarkers for predicting the response to immunotherapy for maximizing the therapeutic benefits. Conclusively, neoadjuvant immunotherapy is a promising perioperative treatment option for resectable HCC. Conclusive evidence of its use needs to be verified through additional large-scale clinical trials.

Data Availability

All data were sourced from published studies and are accessible to anyone interested.

Informed Consent
Not applicable.

Ethics Approval
Not applicable.

Conflict of Interests
The authors declare no conflict of interests in this study.

Authors' Contributions
YH conceived and designed the study. YH and JB performed the studies search and analyzed the data. YH wrote the manuscript. LL edited the article and provided the necessary guidance. The article's submission and publishing were approved by all authors.

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