Lenvatinib-based treatment regimens in conversion therapy of unresectable hepatocellular carcinoma: A systematic review and meta-analysis

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Abstract. Hepatocellular carcinoma (HCC) is a malignancy associated with high morbidity and mortality rates. Conversion therapy provides patients with unresectable HCC (uHCC) the opportunity to undergo radical treatment and achieve long-term survival. Despite accumulating evidence regarding the efficacy of conversion therapy, the optimal treatment approach for such therapy remains uncertain. Lenvatinib (LEN) has shown efficacy and tolerable rates of adverse events (AEs) when applied in combination with immune checkpoint inhibitors (ICIs) or locoregional therapy (LRT) over the past decade. Therefore, the present meta-analysis was performed to systematically assess the safety and efficacy of LEN-based treatment regimens in conversion therapies for uHCC. Data on outcomes, including the conversion rate, objective response rate (ORR), disease control rate (DCR) and AE incidence in patients with uHCC, were collected. A systematic literature search was performed using MEDLINE, Embase, Web of Science and Cochrane Library databases, up to the date of September 1, 2023. In total, 16 studies, encompassing a total of 1,650 cases of uHCC, were included in the final meta-analysis. The pooled conversion rates for LEN alone, LEN + ICI, LEN + LRT and LEN + ICI + LRT were calculated to be 0.04 (95% CI, 0.00-0.07; I^2=77%), 0.23 (95% CI, 0.16-0.30; I^2=66%), 0.14 (95% CI, 0.10-0.18; I^2=0%) and 0.35 (95% CI, 0.23-0.47; I^2=88%), respectively. The pooled ORRs for LEN alone, LEN + ICI, LEN + LRT and LEN + ICI + LRT were found to be 0.45 (95% CI, 0.23-0.67; I^2=96%), 0.49 (95% CI, 0.39-0.60; I^2=78%), 0.43 (95% CI, 0.24-0.62; I^2=88%) and 0.69 (95% CI, 0.56-0.82; I^2=92%), respectively. The pooled DCRs for LEN alone, LEN + ICI, LEN + LRT and LEN + ICI + LRT were observed to be 0.77 (95% CI, 0.73-0.81; I^2=23%), 0.82 (95% CI, 0.69-0.95; I^2=90%), 0.67 (95% CI, 0.39-0.94; I^2=94%) and 0.87 (95% CI, 0.82-0.93; I^2=67%), respectively. The pooled grade ≥3 AEs for LEN alone, LEN + ICI, LEN + LRT and LEN + ICI + LRT were 0.25 (95% CI, 0.14-0.36; I^2=89%), 0.43 (95% CI, 0.34-0.53; I^2=23%), 0.42 (95% CI, 0.19-0.66; I^2=81%) and 0.35 (95% CI, 0.17-0.54; I^2=94%), respectively. These findings suggested that LEN-based combination strategies may confer efficacy and acceptable tolerability for patients with uHCC. In particular, LEN + ICI, with or without LRT, appears to represent a highly effective conversion regimen, with an acceptable conversion rate and well-characterized safety profile.

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent types of malignancy worldwide (1). To date, the primary therapeutic approach for patients with HCC is surgical resection (2). The majority of patients with early-stage HCC are eligible for a number of radical treatments, such as surgical resection, local ablation and liver transplantation, resulting in a median survival time of >5 years; however, a significant proportion of patients with HCC are initially diagnosed at intermediate or advanced stages, due to the subtle onset of symptoms (3,4). This delayed diagnosis frequently results in these patients being categorized as 'unresectable', precluding them from the benefits of timely radical hepatectomy. Currently available non-surgical treatment options for unresectable HCC (uHCC) include locoregional therapy (LRT) and systemic antitumor therapy, which may improve prognosis (5-8).

The primary aim of conversion therapy is to transform uHCC into resectable HCC, so that patients can receive radical treatment and achieve long-term survival (9). Supporting this, patients with uHCC have previously been reported to experience tumor shrinkage and downstaging following LRT and systemic therapies. Such changes include reductions in primary

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tumor size, decreases in tumor count, regression of portal vein tumor thrombus or even the complete disappearance of metastases, ultimately meeting the 'resectable' criteria (10-13). However, guidelines from the National Comprehensive Cancer Network and the European Association for the Study of Liver suggest that surgical interventions are not sufficient to fulfill a satisfactory role for patients with advanced HCC (14,15). Therefore, it is recommended that non-surgical conversion therapies, such as LRTs and systemic therapy, are considered before surgical resection. LRT options for conversion therapy include hepatic arterial infusion chemotherapy (HAIC), transcatheter arterial radioembolization and transcatheter arterial chemoembolization (TACE) (16-18). Systemic options for conversion therapy typically consist of targeted therapy, chemotherapy and immunotherapy.

Various types of therapeutic agents have been proposed following the outcomes of various in-depth studies into the mechanisms underlying tumor-related immune escape (19-21). Lenvatinib (LEN) is one such agent, which has been recommended as a first-line treatment strategy for the systemic treatment of HCC (22). In a previous phase III, multinational, randomized and non-inferiority trial (REFLECT), LEN was comparable to sorafenib in terms of overall survival (OS), whereas it achieved a higher objective response rate (ORR) and superior progression-free survival (PFS) time (23). In addition, combining LEN with immune checkpoint inhibitors (ICIs) has yielded promising results in enhancing the conversion rate. As a result, explorations into the efficacy of triple therapy involving LEN, ICIs and LRT has intensified, with superior conversion rates being reported (12,24-26). Despite the accumulating evidence on conversion therapy, optimal treatment approaches for uHCC remain elusive (27-30). Therefore, a meta-analysis was performed to systematically assess the safety and efficacy profile of LEN-based treatment regimens in conversion therapy, by specifically measuring the conversion rate, ORR, disease control rate (DCR) and adverse event (AE) incidence in patients with uHCC. The aim of the present study was to provide a basis for guiding clinical decision making for patients with uHCC.

Materials and methods

Logistics. The present systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (31), and have been registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (https://www.crd.york.ac.uk/PROSPERO/) (registration no. CRD42023411289). The present review was conducted by following the methodological guidance outlined in the Cochrane Handbook for Systematic Reviews of Interventions (32). Any amendments made to this protocol during the study were documented and reported in PROSPERO.

Search strategy. Relevant studies were searched for in Medline (via PubMed; https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://clarivate.com.cn/solutions/web-of-science/), EMBASE (https://www.embase.com/) and The Cochrane Library (https://www.cochranelibrary.com/) databases. These aforementioned databases were used to identify suitable studies that were published up until September 1, 2023. In total, three search terms were combined with the Boolean operator 'and' when searching databases. The following search terms were used: 'Lenvatinib', 'Conversion therapy' and 'Hepatocellular Carcinoma'.

Inclusion and exclusion criteria. Studies were included if they fulfilled the following criteria: i) Study participants included patients with uHCC receiving a LEN-based treatment regimen; ii) outcomes assessed included conversion rate or the number of individuals successfully converted, ORR, DCR and grade ≥3 treatment-associated AE rate; and iii) the studies were either a randomized controlled trial (RCT), high-quality case-control study or cohort study.

The exclusion criteria were as follows: i) Incomplete or unavailable outcome data; ii) duplicate reports, case reports, comments and letters to the editors, systematic reviews or meta-analyses; and iii) studies with the same population or multiple publications from the same research series. For iii), if multiple studies were found, then the study with the most direct interventions or the largest sample size was adopted. A total of two reviewers (ZZ and SL) independently assessed the articles according to the inclusion criteria. Any disagreements were resolved through discussions with a third reviewer (ZW).

Data extraction and quality analyses. Data extraction from the included studies was performed independently by two reviewers (ZZ and DL), with any discrepancies resolved by a third reviewer (MS). In cases of unclear or insufficient information, attempts were made to contact the authors of the primary studies by email to obtain the missing data. The extracted data included the first author, publication year, country, study type, sample size, clinical outcomes, conversion rate or the number of individuals successfully converted, ORR, DCR and grade ≥3 AE rate. Tumor response was assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST), which categorizes tumor responses into complete remission (CR), partial remission (PR), stable disease (SD) or progressive disease. ORR was defined as the percentage of patients achieving CR or PR, whereas DCR was defined as the percentage of patients achieving the best tumor response of CR, PR or SD (33).

Literature quality evaluation. Eligible studies underwent assessment by two independent reviewers using the Methodological Index for Non-randomized Studies (MINORS) tool to evaluate the methodological quality of both RCTs and non-RCTs treated as single-arm studies (34). Additionally, the Institute of Health Economics Quality Appraisal (IHEQA) checklist was used to evaluate the methodological quality of cohort and case-control studies, treating them as case series (35).

Statistical analysis. Data analysis was performed using Stata version 17.0 (StataCorp LP). The pooled event rates (conversion rate, ORR, DCR and grade ≥3 AE rate) are expressed as risk ratio and corresponding 95% confidence interval (CI). $P<0.05$ was considered to indicate statistical significance. Forest plots were used to visualize the pooled estimates and the extent of heterogeneity among studies. The I^2 statistic was

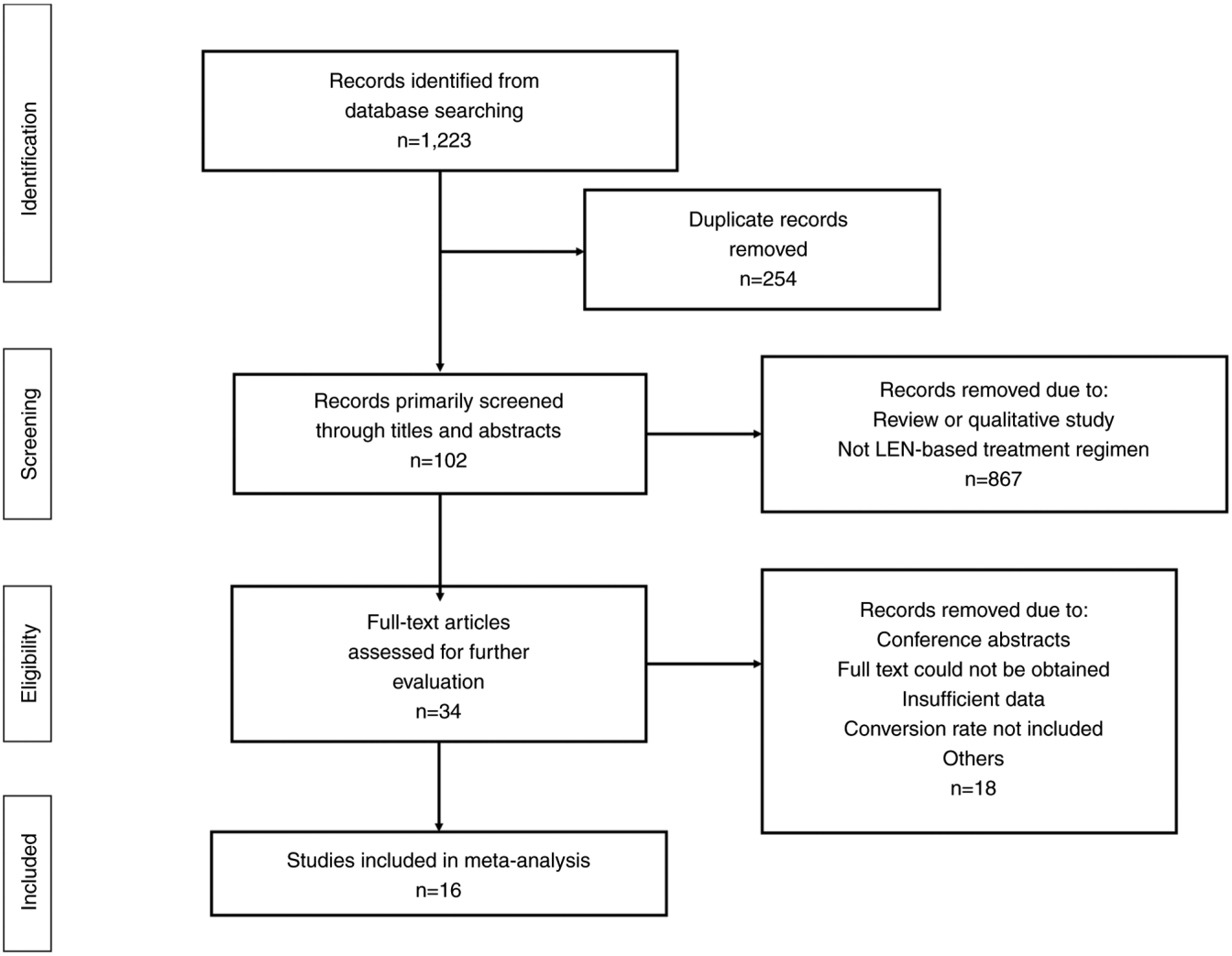

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram of study selection and screening. LEN, lenvatinib.

used to assess statistical heterogeneity among the included studies, with >50% considered to indicate significance, and a random-effects model (the DerSimonian and Laird method) was used to analyze the outcomes (36). Sensitivity analysis was performed to assess the robustness and reliability of the pooled results of the meta-analysis. Funnel plots and Egger's tests were used to assess publication bias (37).

Results

Search results and eligibility. The database searches returned 1,223 results, 254 of which were excluded due to duplication (Fig. 1). Furthermore, 867 studies were excluded due to being reviews, qualitative studies or not being relevant to the topic studied. The remaining articles were then read in full. In total, 16 studies were included in the final meta-analysis (12,24-26,38-49).

Characteristics of the included studies. The characteristics of the included studies are summarized in Table I, all of which were published between 2021 and 2023. The sample size reported by the included studies ranged from 16 to 187, encompassing a total of 1,650 cases with uHCC. According to the IHEQA checklist, 13 studies were deemed to be of acceptable quality (Table SI) (12,24-26,40,42-49), whereas the remaining three studies were deemed to be of high quality by the MINORS tool (Table SII) (38,39,41).

Systemic therapy. In total, seven studies adopted systemic therapy and reported the conversion rate, the ORR and the DCR, and six studies reported grade ≥3 AEs (38-44). The seven studies comprised 944 patients with uHCC (38-44). Among these studies, three studies adopted LEN alone (39,42,44). By contrast, the remaining four adopted LEN + ICI, including various types of anti-programmed cell death protein 1 (PD-1) antibodies (such as sintilimab, toripalimab, tislelizumab and pembrolizumab) (38,40,41,43).

The conversion rate among the included studies varied from 0.02 to 0.31, with a pooled conversion rate of 0.14 (95% CI, 0.08-0.21; I^2=94%) (38-44). Subgroup analysis comparing LEN + ICI treatment with LEN alone revealed a conversion rate of 0.23 (95% CI, 0.16-0.30; I^2=66%) in the group receiving LEN + ICI and 0.04 (95% CI, 0.00-0.07; I^2=77%) in the LEN-alone group. The conversion rate in the LEN + ICI group was found to be significantly higher compared with that in the LEN-alone group (P<0.01; Fig. 2A).

Table I. Characteristics of included studies.

First author, year	Design	Group of interventions	Subgroup of interventions	Sample size	Reasons for unresectability	Definition of successful conversion	(Refs.)
Wang, 2023	Prospective single-arm	ST	LEN + ICI	36	Poor location; inability to perform R0/R1 resection; insufficient FLR	R0/R1 resection; adequate FLR; sufficient physical condition	(38)
Peng, 2023	RCT	ST	LEN	168	Advanced HCC	Downstaging for resection	(39)
Yi, 2022	Retrospective cohort	ST	LEN + ICI	107	Intermediate to advanced HCC; insufficient FLR	R0 resection; adequate FLR	(40)
Zhu, 2022	Prospective single-arm	ST	LEN + ICI	101	Intermediate to advanced HCC; insufficient FLR	Downstaging to resectable; R0 resection	(41)
Shindoh, 2021	Retrospective cohort	ST	LEN	107	Advanced HCC	R0 resection	(42)
Xu, 2022	Retrospective cohort	ST	LEN + ICI	187	Oncological reasons; BCLC stage B/C	R0 resection; adequate FLR	(43)
He, 2021	Retrospective cohort	ST	LEN	86	Advanced HCC; BCLC stage C; extrahepatic spread	Tumor shrinkage to resectable	(24)
Niizeki, 2022	Retrospective cohort	ST	LEN	152	Advanced HCC	Downstaging to resectable	(44)
Peng, 2023	RCT	LRT + ST	LEN + DEB-TACE	170	Advanced HCC	Downstaging for resection	(39)
Qu, 2022	Retrospective cohort	LRT + ST	LEN + TACE	21	Inability to perform R0 resection; insufficient FLR; insufficient resection margin	R0 resection	(12)
Chen, 2022	Retrospective cohort	LRT + ST	LEN + TACE	72	Intermediate to advanced HCC; insufficient FLR	Downstaging for resection	(25)
Mu, 2023	Retrospective cohort	LRT + ST	LEN + ICI + TACE	16	Insufficient FLR; ECOG PS score of 0 or 1	Downstaging for resection	(26)
Wu, 2023	Retrospective cohort	LRT + ST	LEN + ICI + TACE	35	Advanced HCC	Downstaging for resection	(45)
Li, 2023	Retrospective cohort	LRT + ST	LEN + ICI + TACE	97	Inability to perform R0 resection; insufficient FLR; major vascular invasion; intrahepatic metastases; extrahepatic metastases	R0 resection; adequate FLR	(46)
Gan, 2023	Retrospective cohort	LRT + ST	LEN + ICI + HAIC	37	Inability to perform R0 resection; insufficient FLR	Downstaging for resection	(47)
Qu, 2022	Retrospective cohort	LRT + ST	LEN + ICI + TACE	30	Inability to perform R0 resection; insufficient FLR; insufficient resection margin	R0 resection	(12)
Zhang, 2021	Retrospective cohort	LRT + ST	LEN + ICI + HAIC	25	Advanced HCC	R0 resection; adequate FLR	(48)
He, 2021	Retrospective cohort	LRT + ST	LEN + ICI + HAIC	71	Advanced HCC; BCLC stage C; extrahepatic spread	Tumor shrinkage to resectable	(24)
Wu, 2021	Retrospective cohort	LRT + ST	LEN + ICI + DEB-TACE	62	Advanced HCC; major vascular invasion	R0 resection; adequate FLR	(49)
Chen, 2022	Retrospective cohort	LRT + ST	LEN + ICI + TACE	70	Intermediate to advanced HCC; insufficient FLR	Downstaging for resection	(25)

LRT, locoregional therapy; ST, systemic treatment; RCT, randomized controlled trial; TACE, transcatheter arterial chemoembolization; DEB-TACE, drug-eluding beads TACE; HAIC, hepatic arterial infusion chemotherapy; LEN, lenvatinib; ICI, immune checkpoint inhibitor; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; FLR, future liver remnant; ECOG PS, Eastern Cooperative Oncology Group performance status.

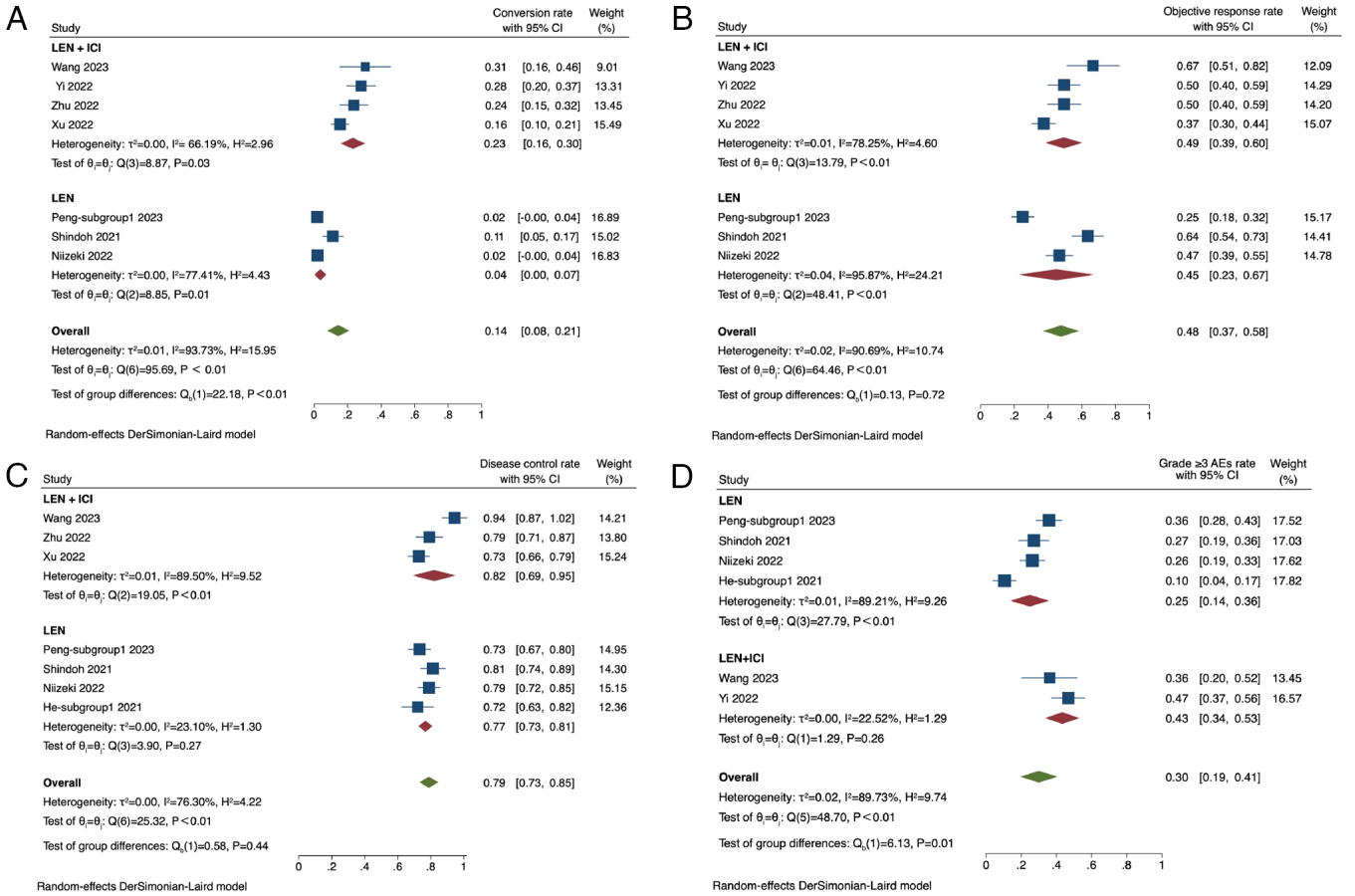

Figure 2. Forest plot for systemic therapy. (A) Pooled conversion rate, (B) pooled objective response rate, (C) pooled disease control rate and (D) pooled grade ≥3 AE rate according to the use of LEN alone or LEN combined with ICIs. AE, adverse event; ICI, immune checkpoint inhibitor; LEN, lenvatinib.

The ORR ranged from 0.25 to 0.67, with a pooled ORR of 0.48 (95% CI, 0.37-0.58; I^2=91%). The ORR was 0.49 (95% CI, 0.39-0.60; I^2=78%) in the group receiving LEN + ICI, whilst the LEN-alone group had an ORR of 0.45 (95% CI, 0.23-0.67; I^2=96%). No significant difference could be found in the ORR between the LEN + ICI group and the LEN-alone group (P=0.72; Fig. 2B).

In terms of DCR, it ranged from 0.72 to 0.94, with a pooled DCR of 0.79 (95% CI, 0.73-0.85; I^2=76%). In the subgroup analysis, the LEN + ICI group exhibited a DCR of 0.82 (95% CI, 0.69-0.95; I^2=90%), whilst the LEN-alone group had a DCR of 0.77 (95% CI, 0.73-0.81; I^2=23%). No significant difference was found in the DCR between the two subgroups (P=0.44; Fig. 2C).

For the grade ≥3 AEs, the rate ranged from 0.10 to 0.47, with a pooled rate of 0.30 (95% CI, 0.19-0.41; I^2=90%). Within the subgroups, the LEN + ICI group had a grade ≥3 AE rate of 0.43 (95% CI, 0.34-0.53; I^2=23%), whereas the LEN-alone group had a rate of 0.25 (95% CI, 0.14-0.36; I^2=89%). The grade ≥3 AE incidence in the LEN-alone group was significantly higher compared with that in the LEN + ICI group (P<0.01; Fig. 2D).

Combined with LRT and systemic therapy. In 10 studies, a total of 706 patients with uHCC were included, 12 subgroups explored the efficacy of adding LRT into the LEN therapy regimen for uHCC. All 12 subgroups of studies reported the conversion rate and ORR, whereas 11 subgroups from nine studies reported the DCR, and eight studies provided data on the incidence of grade ≥3 AEs. Regarding the treatment strategies, three subgroups adopted LEN + LRT (12,25,39) and nine subgroups adopted LEN + ICI + LRT (12,24-26,45-49). Among the nine studies that used TACE, two utilized drug-eluting bead TACE (39,49). In addition, three studies implementing HAIC used the FOLFOX regimen [oxaliplatin 85 mg/m^2; leucovorin 400 mg/m^2; 5-fluorouracil bolus (400 mg/m^2) on day 1 and 5-fluorouracil infusion (2,400 mg/m^2) for 46 h; every 3 weeks] (24,47,48).

The conversion rate across the included studies ranged from 0.06 to 0.60, resulting in a pooled conversion rate of 0.29 (95% CI, 0.20-0.38; I^2=88%). Subgroup analysis based on the combination of treatments revealed a conversion rate of 0.35 (95% CI, 0.23-0.47; I^2=88%) for the LEN + ICI + LRT groups and 0.14 (95% CI, 0.10-0.18; I^2=0%) for the LEN + LRT group. The conversion rate in the LEN + ICI + LRT group was significantly higher compared with that in the LEN + LRT group (P<0.01; Fig. 3A).

The ORR ranged from 0.28 to 0.96, with a pooled ORR of 0.62 (95% CI, 0.49-0.75; I^2=94%). In the subgroup analysis, the group receiving LEN + ICI + LRT achieved an ORR of 0.69 (95% CI, 0.56-0.82; I^2=92%), whereas the LEN + LRT group had an ORR of 0.43 (95% CI, 0.24-0.62; I^2=88%). The ORR in the LEN + ICI + LRT group was significantly higher compared with that in the LEN + LRT group (P=0.03; Fig. 3B).

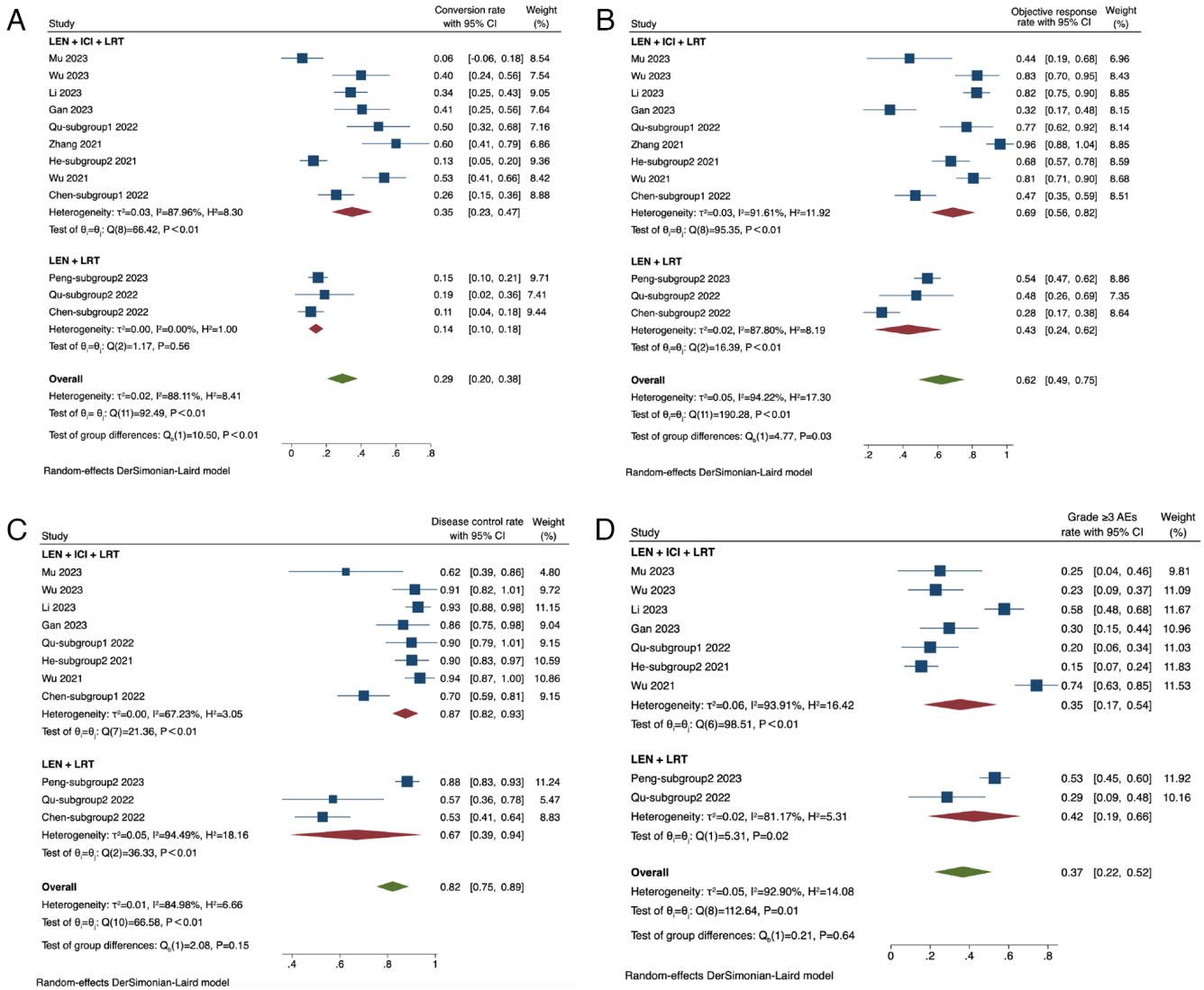

Figure 3. Forest plot for combined LRT-systemic therapy. (A) Pooled conversion rate, (B) pooled objective response rate, (C) pooled disease control rate and (D) pooled grade ≥3 AE rate according to the use of LEN combined with LRT or LEN combined with ICIs and LRT. AE, adverse event; ICI, immune checkpoint inhibitor; LEN, lenvatinib; LRT, locoregional therapy.

For the DCR, the range spanned from 0.53 to 0.94, with a pooled DCR of 0.82 (95% CI, 0.75-0.89; I^2=85%). Subgroup analysis indicated a DCR of 0.87 (95% CI, 0.82-0.93; I^2=67%) for the LEN + ICI + LRT group and 0.67 (95% CI, 0.39-0.94; I^2=94%) for the LEN + LRT group. No significant difference in DCR was observed between the two groups (P=0.15; Fig. 3C).

In terms of grade ≥3 AEs, the rate ranged from 0.15 to 0.74, with a pooled rate of 0.37 (95% CI, 0.22-0.52; I^2=93%). The LEN + ICI + LRT group had a grade ≥3 AEs rate of 0.35 (95% CI, 0.17-0.54; I^2=94%), whereas the LEN + LRT group had a rate of 0.42 (95% CI, 0.19-0.66; I^2=81%). No significant difference in the grade ≥3 AEs rate could be found between the two groups (P=0.64; Fig. 3D).

Publication bias and sensitivity analysis. Egger's test and funnel plots were used to evaluate the publication bias. No indication of publication bias was observed for the conversion rate (Egger's test, P=0.05), ORR (Egger's test, P=0.17), DCR (Egger's test, P=0.38) and grade ≥3 AE rate (Egger's test, P=0.34) of systemic therapy. In addition, no indication of publication bias was observed for the conversion rate (Egger's test, P=0.08), ORR (Egger's test, P=0.19), DCR (Egger's test, P=0.31) and grade ≥3 AE rate (Egger's test, P=0.27) of LEN combined with LRT and/or systemic therapy. Funnel plots were visually examined to assess the symmetry of all outcomes reported, and no publication bias was found (Figs. 4 and 5). Furthermore, sensitivity analysis was performed for conversion rate. The pooled rates did not markedly fluctuate after the removal of any single study that used systemic therapy and LEN combined with LRT and/or systemic therapy (Fig. S1).

Discussion

Conversion therapy holds promise for enhancing the OS and tumor-free survival of patients with uHCC, with advancements in tyrosine kinase inhibitor (TKI) use and immunotherapy (17). LEN has emerged as a cornerstone of HCC treatment since its introduction in 2018. ICIs, such as PD-1 and cytotoxic T-lymphocyte-associated protein 4 antibodies, have also been incorporated into the HCC treatment schedule (29). Combining

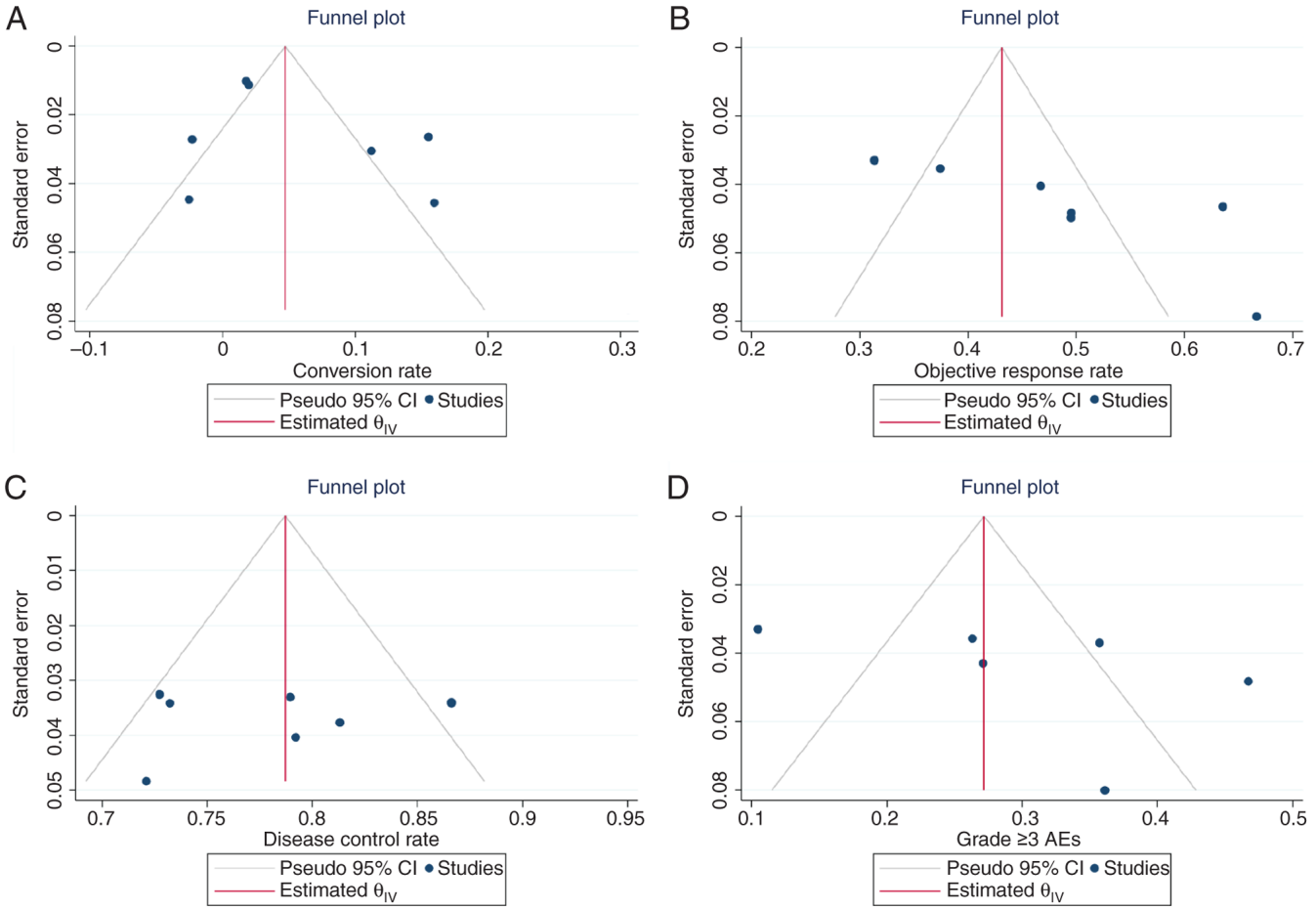

Figure 4. Funnel plots for systemic therapy. (A) Conversion rate, (B) objective response rate, (C) disease control rate and (D) grade ≥3 AE rate. AE, adverse event.

LEN, ICIs and LRT may confer potential synergistic effects, given the distinct reported anti-malignancy mechanisms exhibited by each modality (50). This combination therefore holds promise for achieving efficacy in patients with advanced HCC (51). However, while multiple conversion therapy options do exist, the optimal option remains elusive (52). To the best of our knowledge, the present meta-analysis is the first to assess the safety and efficacy of LEN-based treatment regimens in conversion therapy for uHCC, thus bridging the knowledge gap in the field.

In the present meta-analysis, 16 studies focusing on the safety and efficacy of LEN-based treatment regimens in conversion therapy for uHCC were systematically reviewed. In terms of efficacy, the conversion rate, ORR and DCR between systemic therapy and LEN combined with LRT were compared. In systemic therapy, LEN + ICI yielded a markedly higher conversion rate compared with that in the LEN-alone group, whereas the most favorable outcomes were achieved when LRT was added alongside LEN, surpassing LEN alone or LEN + ICIs. In addition, the conversion rate of LEN + LRT + ICIs was found to reach 35%. Similarly, ORR and DCR could be improved by combining LEN with LRT and ICIs, offering potential surgical opportunities for patients with uHCC. However, LEN + LRT (43%) resulted in comparable ORR compared with LEN alone (45%) and LEN + ICI (49%). Regarding safety, the analysis focused on the incidence of grade ≥3 AEs. It was observed that LEN + ICI had the highest AE rate (43%). However, it is worth noting that this combination also achieved a significantly higher conversion rate (23%) compared with that in the LEN-alone group (4%). Therefore, the decision to opt for combination therapy when systemic therapy alone is also available should be carefully weighed.

The development of conversion therapy for patients with uHCC spans >50 years. In the 1970s, Hermann and Lonsdale (53) reported the use of chemotherapy and radiotherapy for shrinking giant hepatoblastomas, followed by surgical resection. In the subsequent 50 years, various approaches, including TACE, internal radionuclide radiotherapy, external radiotherapy and chemotherapy, have been employed to induce tumor shrinkage and downstaging, ultimately facilitating surgical resection (54-56). The outcomes of conversion therapy have been promising, with reported 5-year survival rates ranging from 50 to 60%, comparable to those achieved through resection in early-stage HCC (57,58). However, the success rate of conversion therapy remains limited, ranging from 1.8 to 34.6% (59,60). Consequently, conversion therapy can benefit only a relatively small subset of patients with uHCC due to the restricted range of available options.

Sorafenib previously held the position as the primary first-line treatment option for uHCC until the approval of LEN in 2018 (19). The pivotal REFLECT study previously

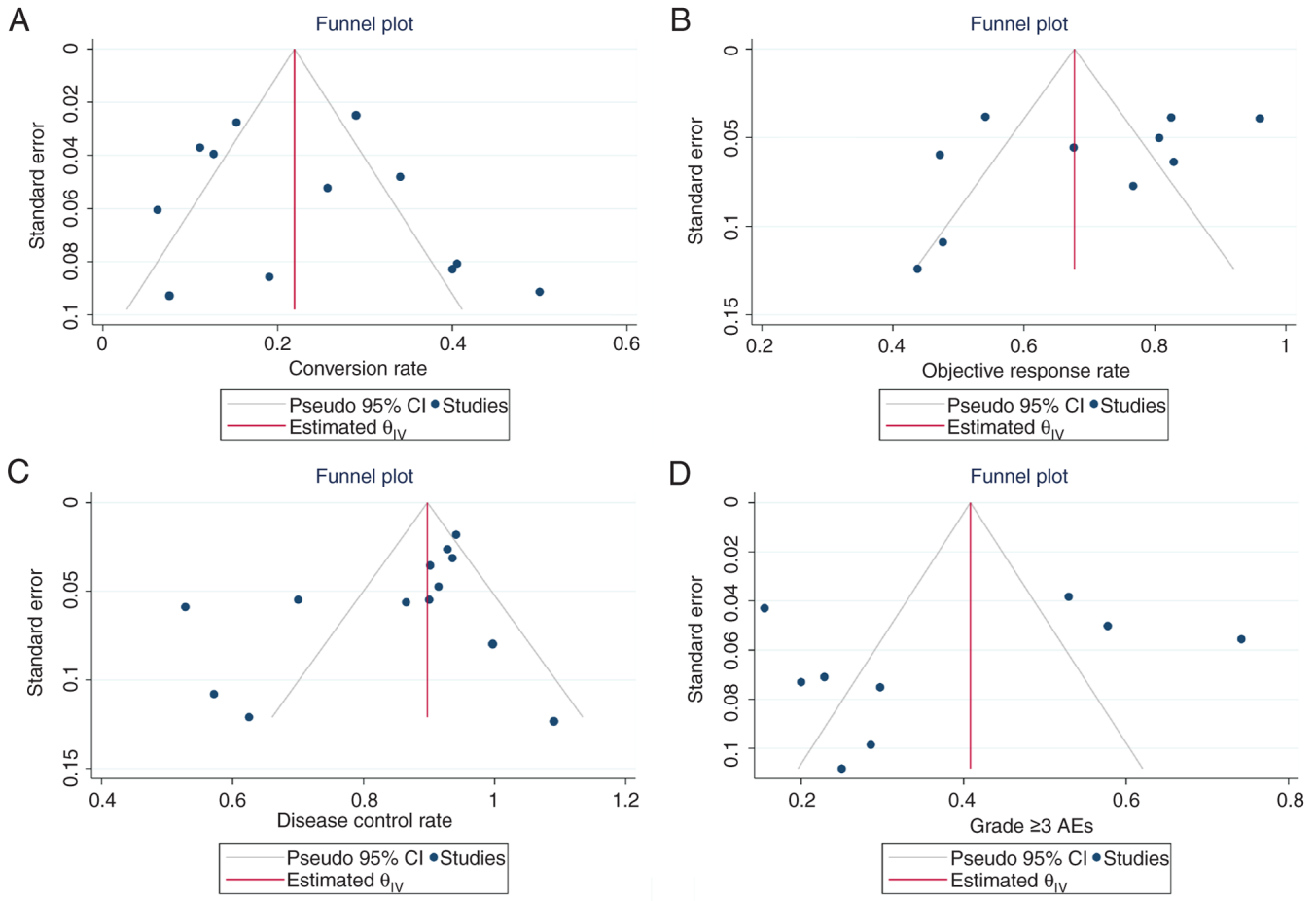

Figure 5. Funnel plots for combined locoregional therapy-systemic therapy. (A) Conversion rate, (B) objective response rate, (C) disease control rate and (D) grade ≥3 AE rate. AE, adverse event.

demonstrated the similar efficacy conferred by LEN to that by sorafenib in terms of OS [13.6 vs. 12.3 months; hazards ratio (HR), 0.92; 95% CI, 0.79-1.06] when used as a first-line treatment for uHCC. LEN also significantly improved various secondary endpoints, including PFS (7.4 vs. 3.7 months; HR, 0.66; 95% CI, 0.57-0.77), time to progression (8.9 vs. 3.7 months; HR, 0.63; 95% CI 0.53-0.73) and ORR (24.1 vs. 9.2%; OR, 3.1; 95% CI, 2.2-4.6), according to the mRECIST. While LEN appeared to confer notable advantages in terms of PFS and ORR compared with sorafenib, it remains unsatisfactory that 75% patients with uHCC do not respond to this treatment. Accumulating evidence supports the combination of ICIs and TKIs for treating this malignancy (30,61,62). In addition, the pooled data from the present meta-analysis provided promising results, suggesting that LEN combined with ICIs can achieve favorable efficacy and conversion rates whilst maintaining acceptable toxicity. However, the selection of which specific ICI remains an issue that requires further study. In real-world clinical practice, LEN combined with various ICIs has demonstrated superior outcomes in terms of OS, PFS and ORR according to the RECIST version 1.1 compared with LEN alone. In particular, subgroup analysis indicated that the type of ICI did not have a notable impact on OS or PFS (24,38-43).

Further research into tumor-related mechanisms has gradually validated the potential for enhanced conversion when drugs with different reported antitumor mechanisms are used in combination (63,64). This rationale has led to the proposal of combining LRT and systemic therapy, which has resulted in higher conversion rates in uHCC (65). In the present study, the assessment of LEN + ICI + LRT demonstrated additional promising outcomes compared with LEN + LRT. Notably, 35% patients receiving triple-therapy compared with 14% of patients receiving double-therapy achieved conversion. These findings suggested that the inclusion of ICIs alongside LEN and LRT may further elevate the rate of successful conversion therapy.

LEN can not only exert a direct antitumor effect, but can also promote vessel normalization and prevent hypoxia in the tumor tissue (66). In addition, accumulating evidence suggested that LEN possesses immunomodulatory effects, impacting the activity and number of infiltrating immune cells, thereby indicating potential synergistic effects with immunotherapy (50,67,68). When combined with an anti-PD-1 antibody, LEN has been reported to enhance antitumor activity in murine HCC models by increasing the levels and cytotoxic activity of $CD8^+$ T cells, activating immune pathways, preventing regulatory T-cell infiltration and downregulating programmed death-ligand 1 and PD-1 expression (69). In addition, such combination therapy may elicit long-term immune memory. LRT for HCC can shape tumor immunity by modifying the composition of the tumor microenvironment (70).

Following thermal treatment using percutaneous techniques or other LRTs, tumor cell necrosis typically results in the release of tumoral neoantigens, facilitating the recruitment and activation of dendritic cells within the microenvironment. This effect can be utilized to shift an immunosuppressive microenvironment, which may not favor checkpoint inhibitor therapy, into an immune-supportive setting where systemic therapies may yield greater efficacy (5,71). However, larger scale RCTs remain of importance to definitively validate and elucidate these findings.

The safety profiles of the combined treatment were also investigated in the present study. In the case of LEN + ICI + LRT, the grade ≥3 AE rate was 35%, which appears acceptable given its substantial 35% conversion rate. AEs of grade ≥3 warrant treatment interruption or discontinuation followed by prompt corticosteroid administration, with escalation to immunosuppressants in cases of the lack of response (72). AEs serve an intriguing role in the assessment of survival benefits. A post hoc analysis performed by the REFLECT study revealed that the presence of diarrhea, hypertension, hypothyroidism and proteinuria was associated with improved OS (73). Furthermore, immune-related AEs induced by ICIs have been reported to be associated with enhanced clinical benefits (74).

There were a number of limitations in the present study. The present meta-analysis focused on conversion rate, leading to the exclusion of studies that solely examined the efficacy and safety of conversion therapy during the screening process. The majority of the included studies did not utilize conversion rate as the primary endpoint since conversion therapy for HCC has only recently garnered attention. It is anticipated that higher quality RCTs will emerge in the near future exploring this aspect more comprehensively. Determining the optimal ICIs and LRT in combination with LEN remains challenging, although several phase II or III studies are currently evaluating the efficacy and safety of LEN in combination with ICIs and LRT (https://clinicaltrials.gov/study/NCT04523493, https://clinicaltrials.gov/study/NCT04194775 and https://clinicaltrials.gov/study/NCT05312216). Whilst these trials may assist clinicians in selecting among various second-line therapeutic options, a comprehensive understanding of this field necessitates additional studies. In addition, only two articles included in the present study were RCTs, and the rest were retrospective studies. This may impact the overall quality of results. A high degree of heterogeneity remains among the included studies in the present meta-analysis. Possible sources of this may have been that the characteristics of patients varied among included studies or that the determination of successful conversion is relatively subjective, even if the criteria for successful conversion are clearly defined.

LEN has transformed the treatment landscape of uHCC. Since preclinical studies have progressively elucidated the antitumor and resistance mechanisms of this drug, patients with uHCC may benefit from LEN-based treatment regimens. To clarify the significance of conversion therapy, it is necessary to compare the long-term results of patients who underwent conversion surgery because of a favorable tumor response to systemic therapy and patients who did not despite a favorable tumor response. The search for reliable prognostic biomarkers to guide the development of targeted treatments or immunotherapy has been another focus of research. However, consistent conclusions have remained elusive, indicating the need for further progress in the screening and validation of biomarkers. Ongoing clinical trials are actively investigating additional combination strategies as options and insights for the treatment of patients with uHCC (https://clinicaltrials.gov/study/NCT05312216 and https://clinicaltrials.gov/study/NCT04740307).

In conclusion, the present meta-analysis provides valuable insight and suggests that LEN-based combination strategies may confer efficacy and acceptable tolerability for patients with uHCC. In particular, LEN + ICI with or without LRT appears to represent a highly effective conversion regimen with an acceptable conversion rate and a well-characterized safety profile.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ZW and KL developed the initial idea for the study. SL and ZW designed the study. SL and ZZ analyzed some of the data and wrote the manuscript. KW, DL and MS contributed to the acquisition, analysis and interpretation of data for the work. ZZ, ZW and KL revised the manuscript. SL, ZZ, ZW, KW, DL, MS and KL confirm the authenticity of all the raw data. SL and ZZ contributed equally to this paper and are co-first authors. All authors read and approved the final 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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