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Systemic conversion therapies for initially unresectable hepatocellular carcinoma: a systematic review and meta-analysis

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Abstract

Background Systemic conversion therapy provides patients with initially unresectable hepatocellular carcinoma (HCC) the chance to salvage radical liver resection and superior survival outcomes, but the optimal conversion strategy is unclear.

Methods A systematic literature search was conducted on PubMed, EMBASE, Web of Science, Scopus, and the Cochrane Library between 2007 and 2024 focusing on studies reporting conversion therapy for HCC. The treatment groups were divided into Tyrosine kinase inhibitors (TKI), TKI plus loco-regional therapy (LRT), TKI plus anti-PD-1 therapy (TKI + PD-1), TKI + PD-1 + LRT, immune checkpoint inhibitors (ICI) plus LRT, and Atezolizumab plus bevacizumab (A + T) groups. The conversion to surgery rate (CSR), objective response rate (ORR), grade ≥ 3 treatment-related adverse events (AEs), overall survival (OS) and progression-free survival (PFS) were analyzed.

Results 38 studies and 4,042 patients were included. The pooled CSR were 8% (95% CI, 5-12%) in TKI group, 13% (95% CI, 8-19%) in TKI + LRT group, 28% (95% CI, 19-37%) in TKI + PD-1 group, 33% (95% CI, 25-41%) in TKI + PD-1 + LRT group, 23% (95% CI, 1-46%) in ICI + LRT group, and 5% (95% CI, 3-8%) in A + T group, respectively. The pooled HR for OS (0.45, 95% CI, 0.35–0.60) and PFS (0.49, 95% CI, 0.35–0.70) favored survival benefit of conversion surgery. Subgroup analysis revealed that lenvatinib + PD-1 + LRT conferred higher CSR of 35% (95% CI, 26-44%) and increased ORR of 70% (95% CI, 56-83%).

Conclusions The current study indicates that TKI + PD-1 + LRT, especially lenvatinib + PD-1 + LRT, may be the superior conversion therapy with a manageable safety profile for patients with initially unresectable HCC. The successful conversion therapy favors the superior OS and PFS compared with systemic treatment alone.

Trial registration International prospective register of systematic reviews (PROSPERO) (registration code: CRD 42024495289).

Keywords Hepatocellular carcinoma, Immunotherapy, Targeted therapy, Tyrosine kinase inhibitors, Conversion therapy, Meta-analysis

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Introduction

Hepatocellular carcinoma (HCC) ranks the sixth most common malignancy and the third leading cause of cancer-related death worldwide [1]. Liver resection and liver transplantation offer the potential curative chance for HCC patients with a better long-term survival [2]. Unfortunately, more than 70% of the HCC patients are diagnosed in an intermediate or advanced stage, which may often miss the opportunity for radical surgery due to insufficient functional liver reservation, macrovascular invasion, multiple lesions around the liver, or comorbidities [3]. Currently, the standard of care for unresectable HCC includes tyrosine kinase inhibitors (TKI) and/or immune checkpoint inhibitors (ICI), such as Sorafenib, Lenvatinib, Atezolizumab plus bevacizumab, Sintilimab plus IBI305, Camrelizumab plus apatinib, Durvalumab plus tremelimumab, etc., offering the prolonged survival compared with placebo [4–6].

In most recent, studies have showed that parts of the initially unresectable HCC could regain the opportunity for curative surgery after the successful downstaging systemic treatment, namely the conversion therapy for advanced HCC [7]. Compared with systemic therapy alone, the successful conversion therapy significantly improved the long-term outcome of HCC, reaching the 80% of 3-year overall survival (OS) and 50% of 3-year recurrence-free survival (RFS) [8]. Of which, some of the patients could achieve the complete pathologic response (CPR) and get the enhanced long-term survival similar to those initially resectable HCC [9, 10]. However, the successful conversion rate ranges from 0.7 to 70% due to different conversion regimen applied as well as the variation in patients status [11, 12]. Given that several prospective clinical trials are ongoing, no consensus on the optimal conversion protocol has been reached to date, the treatment for unresectable HCC remains controversial. Therefore, we here systematically summarized the current published evidence on systemic conversion therapy for initially unresectable HCC and conducted meta-analysis on evaluating the efficacy and safety of representative treatment strategies in order to provide theoretical basis for clinical practice.

Patients and methods

This systematic review and meta-analysis were reported following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement and registered in the International prospective register of systematic reviews (PROSPERO) (registration code: CRD 42024495289).

Search strategy and selection criteria

This systematic review and meta-analysis were performed to identify studies regarding the systemic conversion therapy for initially unresectable HCC in patients without prior treatment history. It was reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [13] and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines [14]. Literature search was conducted on PubMed (https://pubmed.ncbi.nlm.nih.gov), EMBASE (https://www.embase.com), the Cochrane library (https://www.cochranelibrary.com), Web of Science (https://www.webofscience.com), and Scopus (https://www.scopus.com) between 1 January 2007 and 5 January 2024. All studies were restricted to published in English only. If multiple publications of the same or overlapped population were identified, the most recent publication was retrieved. The detailed search strategy was showed in Supplementary Table S1.

Studies regarding the systemic conversion therapy for initially unresectable HCC were selected. The inclusion criteria were as follows: (1) Studies reported systemic therapy as neoadjuvant treatment modalities in initially unresectable HCC; (2) Studies reported at least one of the following outcomes of interest: the conversion rate or the number of people successfully converted to surgery, the objective response rate (ORR), the grade≥3 treatment-related adverse events (AEs), or the survival outcomes (OS and/or PFS); (3) Studies reported as least 9 cases of eligible participants; (4) Study participants with mean age≥18 years. The exclusion criteria were as follows: (1) Studies including protocol, conference abstracts, editorial, case report, reviews, meta-analyses, or animal experiments; (2) Studies reported only locoregional therapy (LRT) as conversion strategy; (3) Studies reported conversion therapy for liver transplantation or radiofrequency ablation.

Two independent authors (X.H.W and Z.H.L) screened the records by title/abstract and full-text review afterwards. If discrepancies generated during the screening progress, evaluation by a third author (W.Y.G) was required and conflicts were discussed and resolved among all authors.

Data extraction

Two independent authors (X.H.W and Z.H.L) identified and extracted data by full-text review for further analysis. Any discrepancies were resolved by discussion with a third author (W.Y.G). For each eligible study, the recorded data included: first author, year of publication, study type, treatment strategy, inclusion and exclusion criteria, sample size, tumor marker, tumor stage, etiology, conversion to surgery rate (CSR), ORR, disease control rate (DCR), AEs, grade≥3 AEs, mOS, and mPFS. ORR was identified as the percentage of patients achieving either complete response (CR) or partial response (PR). DCR was calculated as the percentage of patients

achieving either CR, PR, or stable disease (SD) according to mRECIST criteria. The primary outcome of this meta-analysis was the CSR, and the secondary outcomes were the ORR, grade≥3 AE rate, and the survival outcomes.

Quality assessment

The quality assessment for selected studies was performed using the Modified Methodological Index for Non-Randomized Studies (MINORS) and Newcastle-Ottawa Scale (NOS), which including the following: (1) Consecutive patients; (2) Prospective data collection; (3) Reported primary endpoints; (4) Unbiased peri-procedural evaluation; (5) Appropriate control intervention; (6) Contemporary groups; (7) Group equivalent; and (8) Sample size. Two authors (L.B and C.K.F) independently assessed the quality of studies, and discrepancies were resolved after discussion with the third author (W.Y.G).

Statistical analysis

For CSR, ORR, CR, and AEs, the pooled event rate and 95% confidence interval (95% CI) were calculated. For OS and PFS, the hazard ratios (HR) and 95% CI were estimated. Heterogeneity was assessed by I^2 statistics and *P* value. The random-effects model was applied if $I^2 > 50\%$ or $P<0.1$, otherwise a fixed-effects model was used. The publication bias was assessed by funnel plots. Subgroup analyses were conducted based on the type of TKI involved, as the most popular TKI used in recent years was lenvatinib compared with other TKIs. All data analysis was performed using Revman version 5.3 and R software version 4.1.2. *P* values<0.05 were indicated statistically significant.

Results

Study selection

The initial search strategy retrieved 4191 records from the abovementioned five databases. After removing of duplicates, 3376 records were left for title and abstract screening. Subsequently, 99 studies underwent full-text review according to the inclusion and exclusion criteria. Of which, 60 records were further removed for reasons detailed in Fig. 1. Finally, 38 studies compromising 4,042 patients were selected for further analyses [8–12, 15–47].

Study characteristics

The characteristics of the included studies are summarized in Supplementary Table S2 and S3. In total, 7 studies [11, 20–22, 34–36] reported single TKIs treatment (TKI group), 5 studies [15, 17, 27, 31, 46] reported TKIs combined with LRT (TKI+LRT group), 8 studies [8, 9, 16, 37, 40, 41, 44, 47] reported TKIs combined with anti-PD-1immunotherapy (TKI+PD-1 group), 16 studies [10, 17, 19, 24–26, 28–31, 38, 39, 42, 43, 45, 46] reported TKIs combined with anti-PD-1immunotherapy and LRT (TKI+PD-1+LRT group), 3 studies [12, 18, 32] reported ICIs combined with LRT (ICI+LRT group), and 3 studies [23, 33, 36] reported Atezolizumab plus Bevacizumab treatment (A+T group) were identified.

The TKIs used in all studies included Sorafenib, Lenvatinib, Apatinib, and Donafenib. The ICIs used in all studies included Pembrolizumab, Sintilimab, and Nivolumab, Camrelizumab, Toripalimab, Tislelizumab. The LRT treatments included TACE, HAIC, and/or SBRT. The median age of all enrolled patients was 50 to 76.3 years old, and the majority of them were male patients (52.8-97.0%). The general liver function of patients was Child Pugh A (78-100%), except for one study that focused on ICI+LRT conversion therapy covered 36.4% patients of Child A classification. Of the total 4042 cases, 3629 cases reported the tumor stage according to BCLC classification, and the proportion of BCLC B/C stage was 42.2%/57.8%. The year of publication in all studies ranged from 2021 to 2024. All studies included for analysis were considered as moderate to high quality according to MINORS score and NOS score (Supplementary Table S4a, S4b&S4c).

Conversion to surgery rate

A total of 36 studies [8–10, 12, 20–25, 27, 29–47], including 41 subgroups reported the CSR or the number of patients successfully converted to surgical resection. The total number of cases enrolled in these studies were 3880, and the CSR ranged from 1 to 89%. The pooled CSRs were 8% (95% CI, 5-12%; I^2 = 93%) in TKI group, 13% (95% CI, 8-19%; I^2 = 0%) in TKI+LRT group, 28% (95% CI, 19-37%; I^2 = 87%) in TKI+PD-1 group, 33% (95% CI, 25-41%; I^2 = 89%) in TKI+PD-1+LRT group, 23% (95% CI, 1-46%; I^2 = 95%) in ICI+LRT group, and 5% (95% CI, 3-8%; I^2 = 0%) in A+T group, respectively (Fig. 2).

Objective response rate

The ORR was reported in 32 studies [8–10, 12, 15–17, 19–21, 23–31, 33–37, 39, 41–47]. Of which, 37 subgroups containing 2759 cases were selected for further analysis. The ORR ranged from 29 to 65% in all groups. The pooled ORRs were 35% (95% CI, 15-56%; I^2 = 94%) in TKI group, 40% (95% CI, 26-53%; I^2 = 70%) in TKI+LRT group, 44% (95% CI, 35-54%; I^2 = 79%) in TKI+PD-1 group, 69% (95% CI, 59-78%; I^2 = 94%) in TKI+PD-1+LRT group, and 29% (95% CI, 20-39%; I^2 = 76%) in A+T group, respectively. The detailed data of therapeutic response were showed in Fig. 3 and Supplementary Figure S1.

Adverse events

There were 21 studies [9, 10, 12, 16, 18, 19, 24, 27, 29–34, 37, 39, 41, 43–46] reported AEs, and among them the grade≥3 AE rates were evaluated and recorded in 1383 cases of 20 subgroups. The pooled grade≥3 AE rates

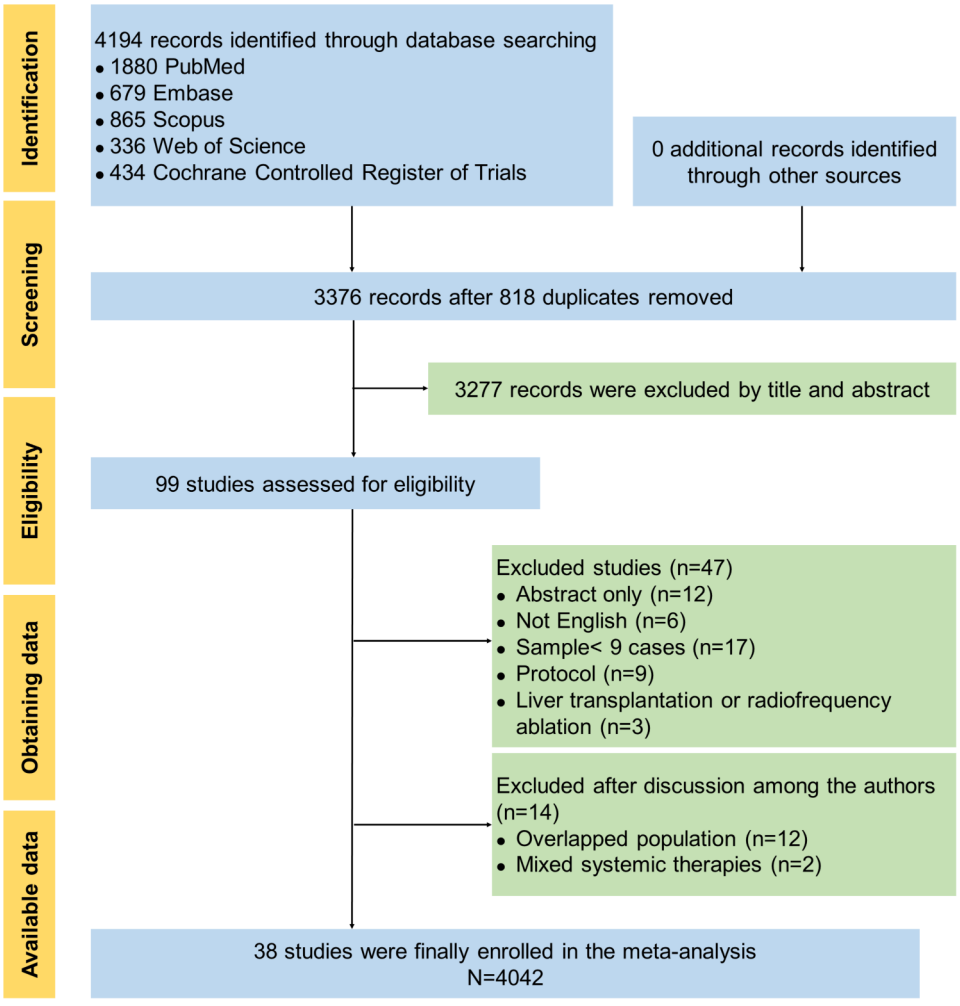

Fig. 1 PRISMA flowchart of included studies

were 18% (95% CI, 1-36%; I^2 = 70%) in TKI+LRT group, 45% (95% CI, 25-65%; I^2 = 91%) in TKI+PD-1 group, and 37% (95% CI, 20-53%; I^2 = 96%) in TKI+PD-1+LRT group, respectively (Fig. 4). One study reported 27%(19-36%) in TKI treatment and one study reported 33%(17-49%) in ICI+LRT group [18], respectively.

Survival outcomes

For patients successfully converted to resectable HCC, the survival outcomes were compared to those failed to receiving conversion surgery in 11 studies [8, 21, 22, 24, 34, 36, 37, 44–47]. The data showed that conversion surgery reduced the risk of death by 55%, indicated by the pooled HR for OS (0.45, 95% CI, 0.35–0.60; I^2 = 63%). Similarly, the conversion surgery could reduce the risk of progression by 51% compared to those without conversion resection, as presented in Fig. 5 showing the pooled HR for PFS (0.49, 95% CI, 0.35–0.70; I^2 = 12%). Different systemic therapy regimens also showed survival benefits after conversion resection both in OS (Supplementary Figure S2) and PFS (Supplementary Figure S3).

Subgroup analysis of lenvatinib-based therapy

Given the TKIs used in different studies varied from each other, and the most often used was lenvatinib in clinical practice, we next performed subgroup analysis specifically focusing on lenvatinib-based conversion therapy. Of which, 20 studies reported lenvatinib as the main treatment strategy were enrolled for further analysis [8–11, 17, 19–22, 24, 25, 31, 34, 36–41, 44]. The pooled CSRs were 14% (95% CI, 6-21%; I^2 = 95%) in Lenvatinib group, 12% (95% CI, 6-19%; I^2 = 0%) in Lenvatinib+LRT group, 28% (95% CI, 16-39%; I^2 = 89%) in Lenvatinib+PD-1 group, and 35% (95% CI, 26-44%; I^2 = 83%) in Lenvatinib+PD-1+LRT group, respectively (Fig. 6). The pooled ORRs were 42% (95% CI, 20-63%; I^2 = 93%) in Lenvatinib group, 51% (95% CI, 37-65%; I^2 = 79%) in Lenvatinib+PD-1 group, and 70% (95% CI, 56-83%; I^2 = 91%) in Lenvatinib+PD-1+LRT group, respectively

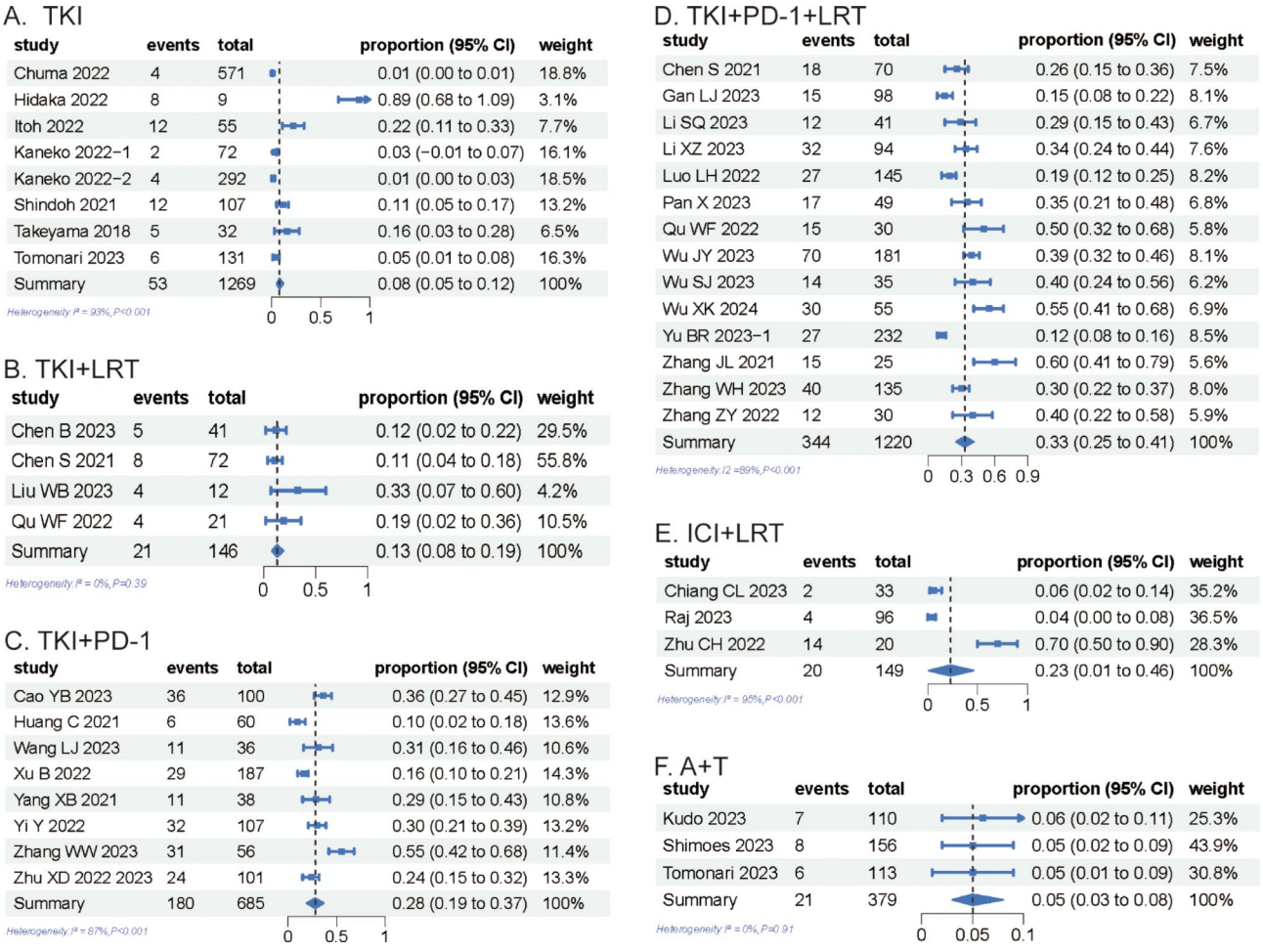

Fig. 2 The pooled CSRs in (**A**) TKI group, (**B**) TKI + LRT group, (**C**) TKI + PD-1 group, (**D**) TKI + PD-1 + LRT group, (**E**) ICI + LRT group, and (**F**) A + T group

(Supplementary Figure S4). The pooled grade ≥ 3 AE rates were 50% (95% CI, 27-72%; $I^2 = 91\%$) in Lenvatinib + PD-1 group, and 35% (95% CI, 16-54%; $I^2 = 93\%$) in Lenvatinib + PD-1 + LRT group, respectively (Supplementary Figure S5).

Integrative analysis of targeted therapy with immunotherapy

Given that the reported evidence on A + T group as conversion therapy was relatively scarce, we next merged the A + T group with TKI + PD-1 group as one group for further analysis (Targeted therapy + ICIs group). The results showed that the pooled CSR was 21% (95% CI, 14-28%; $I^2 = 93\%$), ORR was 39% (95% CI, 32-47%; $I^2 = 83\%$), respectively (Supplementary Figure S6).

Publication bias

The funnel plots of the CSRs in different groups was used to assess the publication bias (Supplementary Figure S7). The funnel plot was basically inverted and funnel-shaped with no presence of obvious asymmetry.

Discussion

In this meta-analysis, we systematically summarized the conversion therapy for initially unresectable HCC, and we found that TKI + PD-1 + LRT strategy was associated with the highest potential to successful conversion to surgical resection along with acceptable AEs rates. For patients finally received the conversion liver resection, long-term survival outcomes were better than those without conversion surgery. Subgroup analysis revealed that Lenvatinib + PD-1 + LRT regimen conferred the most effective and safe strategy among TKIs-based conversion therapies.

In terms of treatment strategies, the conversion regimens across various centers included monotherapy TKI, combined TKI + LRT, TKI + PD-1, TKI + PD-1 + LRT, and the A + T based on IMbrave150. As mentioned above, among these combination strategies, the TKI + PD-1 + LRT regimen exhibited the highest conversion rate, followed by TKI + PD-1. Theoretically, the combination of systemic and local treatments, due to their distinct anti-tumor mechanisms, may demonstrate

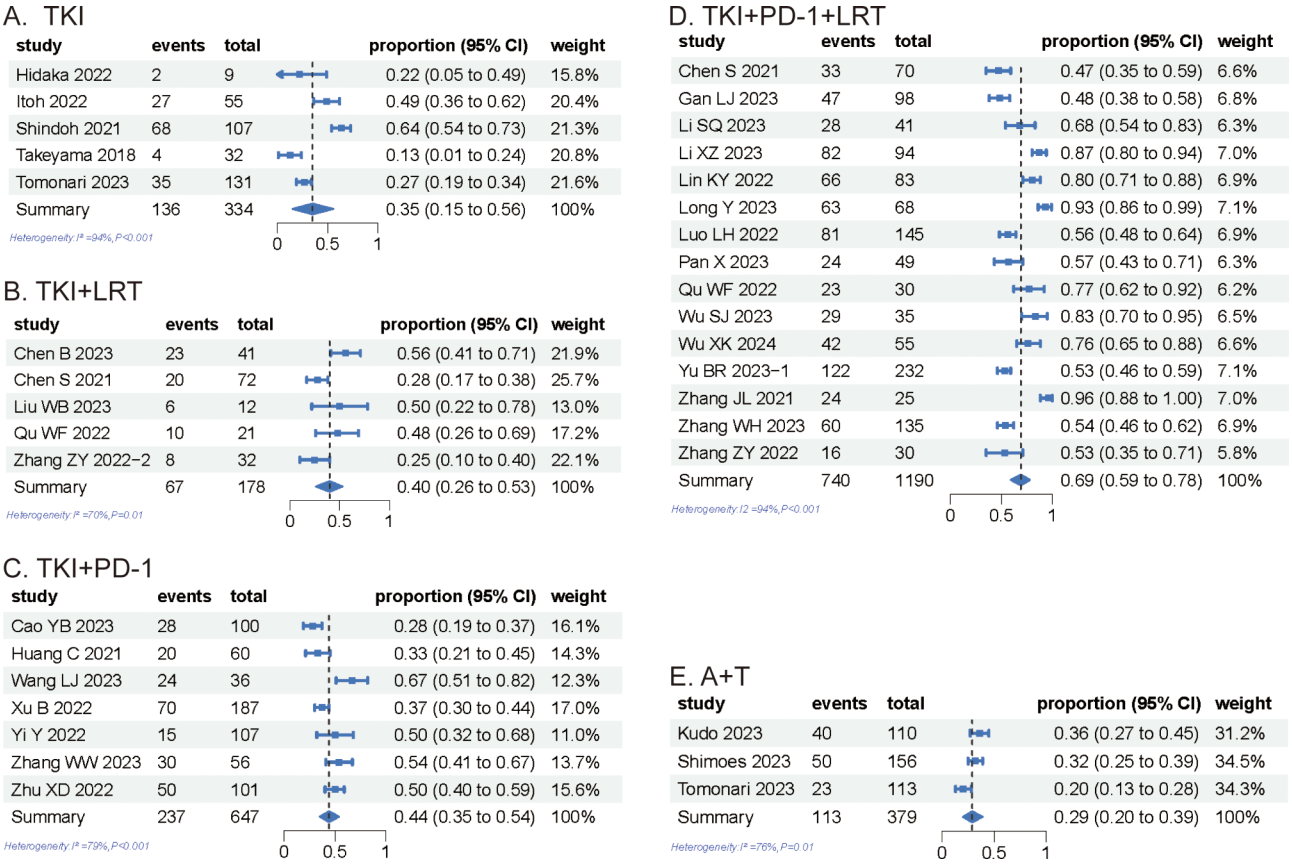

Fig. 3 The pooled ORR in (**A**) TKI group, (**B**) TKI + LRT group, (**C**) TKI + PD-1 group, (**D**) TKI + PD-1 + LRT group, (**E**) ICI + LRT group, and (**F**) A + T group

a synergistic effect. Currently, the most commonly used LRT in clinical practice include TACE, HAIC, and local radiotherapy. Although single LRT treatments generally have fewer side effects, their conversion rates alone are also comparatively lower [48]. Through the combination the LRT and systemic targeted and immunotherapies, we found that TKI+PD-1+LRT, compared with TKI+PD-1, did not significantly increase the incidence of adverse reactions but achieved higher conversion rates, thereby further confirming the safety and efficacy of this combination.

When the primary endpoint of a certain study is not focusing on conversion resection, data on ORRs more effectively reflect the efficacy of different treatment combinations. In this study, we found that TKI+PD-1+LRT exhibited the highest ORR, further suggesting a higher likelihood of successful conversion. Single use of TKI or combined with systemic immunotherapy showed comparable ORRs, but the addition of LRT significantly increased the treatment response rate. Notably, the ORR for the A+T regimen was not superior in this study, which is inconsistent with previous reports [49, 50]. This discrepancy may be attributed to the inclusion criteria of the current study, we solely focused on studies with conversion intent or cases reporting successful conversion surgeries. Studies aiming at comparing long-term survival of the certain treatment strategies regardless of conversion surgery were not included, which may contribute to the current different result. Despite this, the study indicated that, similar to the conversion rate, TKI+PD-1+LRT demonstrated favorable performance in therapeutic responsiveness.

When evaluating the safety profile of all treatment regimens, it was evident that the combination of systemic and local treatments did not significantly increase the incidence of AEs, confirming the safety of TKI+PD-1+LRT as the optimal conversion therapy in selected patients. However, it is noteworthy that the AEs rate for the TKI+PD-1 group was relatively higher. Reasons behind this may be the potential selection bias due to the limited literature reporting AEs in enrolled studies, thus necessitating a cautious interpretation of the results. On the other hand, in terms of long-term survival, patients successfully received conversion surgeries benefited more in both OS and PFS, suggesting that a safe and effective conversion regimen along with successful implementation of surgery may emerge as a promising direction for HCC management in the future.

Apart from sorafenib, various TKIs have also been explored in the realm of targeted therapy for liver

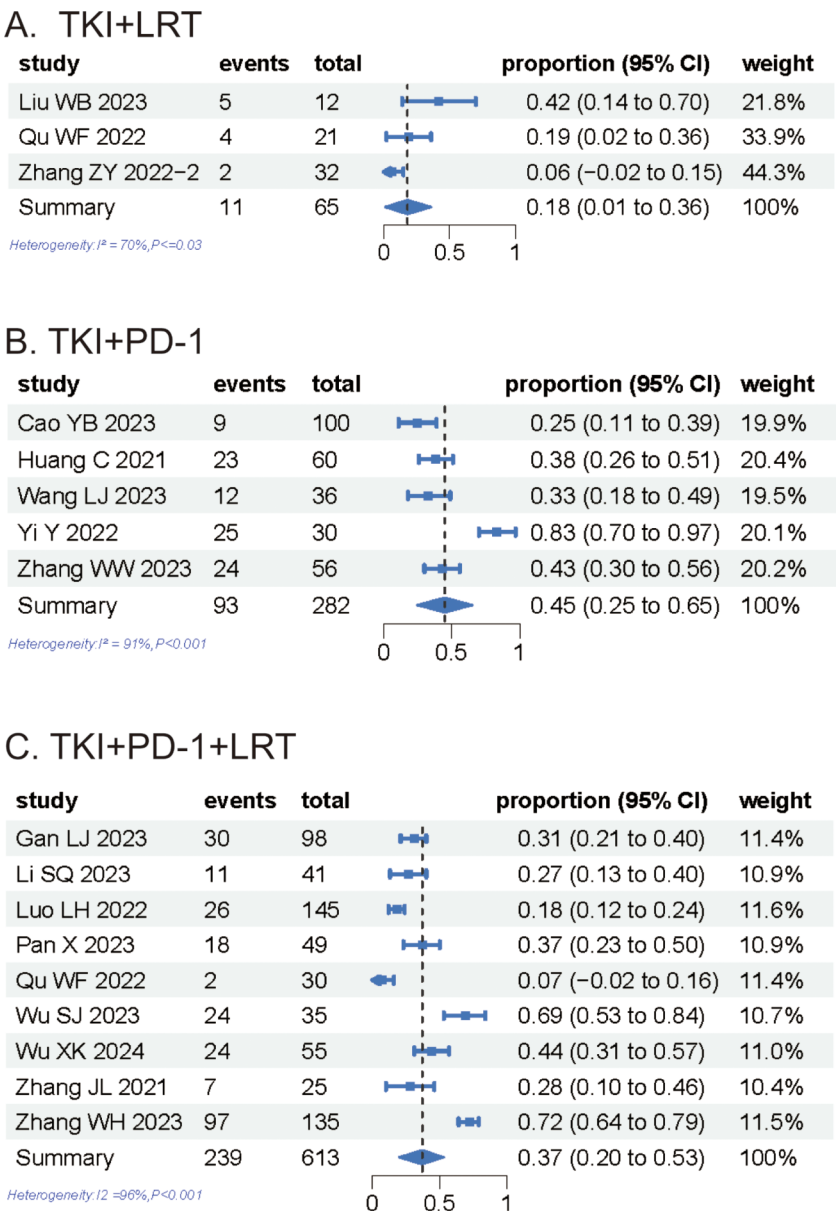

Fig. 4 The pooled AE ≥ 3 grades in (**A**) TKI + LRT group, (**B**) TKI + PD-1 group, (**C**) TKI + PD-1 + LRT group

cancer. However, the optimal TKI+PD-1+LRT combination regimen that yields superior conversion outcomes remains unclear. In fact, not all studies included in this research elaborated on the details of the specific drugs used in the TKI groups, but the majority of these studies demonstrated the use of lenvatinib as the TKI reagent. Moreover, since the publication of the REFLECT study in 2018, lenvatinib had rapidly become popular in first-line HCC treatment. Therefore, we next conducted further subgroup analysis based on lenvatinib treatment. It was pleasantly surprising to observe that the lenvatinib+PD-1+LRT combination exhibited even higher conversion rates, enhanced ORRs, and did not significantly elevate the incidence of AEs in the meanwhile. Given the superior efficacy of lenvatinib as a monotherapy compared to sorafenib, combining it with additional treatments would theoretically further enhance therapeutic outcomes. On the contrary, there is insufficient evidence to establish the superiority of apatinib monotherapy over sorafenib or lenvatinib and apatinib has not yet been approved in clinical practice as a first-line monotherapy, so the application of apatinib in TKI-based regimen remains to be explored. Therefore, TKI+PD-1+LRT conversion regimens, with lenvatinib as a representative, appear to be a rational and effective choice for conversion therapy.

This study is certainly associated with many limitations. Firstly, the majority of studies included are in the

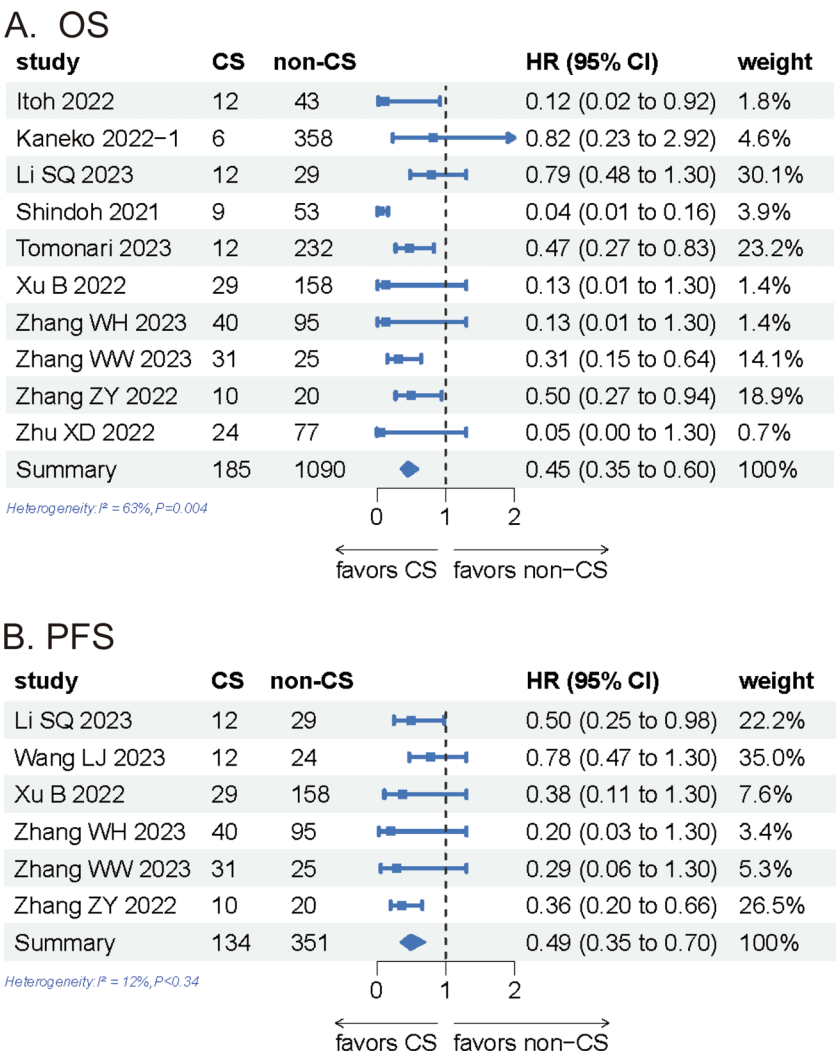

Fig. 5 The pooled HR for (**A**) OS and (**B**) PFS in CSR and NCSR group

retrospective nature with unavoidable inherent biases in case selection. Secondly, in the real-world clinical scenarios, conversion therapy could be categorized into intentional and unintentional conversions. The intentional conversion therapy might involve patients with better overall status and liver function, but this aspect is not thoroughly elucidated in each specific study, contributing to potential biases in this research. Furthermore, each study may emphasize different aspects of their interest, and the inclusion of fewer studies for AEs and survival outcomes might also introduce some publication bias. In addition, the LRT treatments differ among centers, the specific modality, such as c-TACE or DEB-TACE, used in each study may have inherent influence on survival outcomes. Despite these, the current study systematically analyzed the commonly used conversion regimens in clinical practice, providing a preliminary identification of optimal conversion treatment strategies, which may offer a basis for clinical treatment decisions. Future researches with larger sample sizes and multi-center randomized controlled trials for a more rigorous and comparable design are warranted.

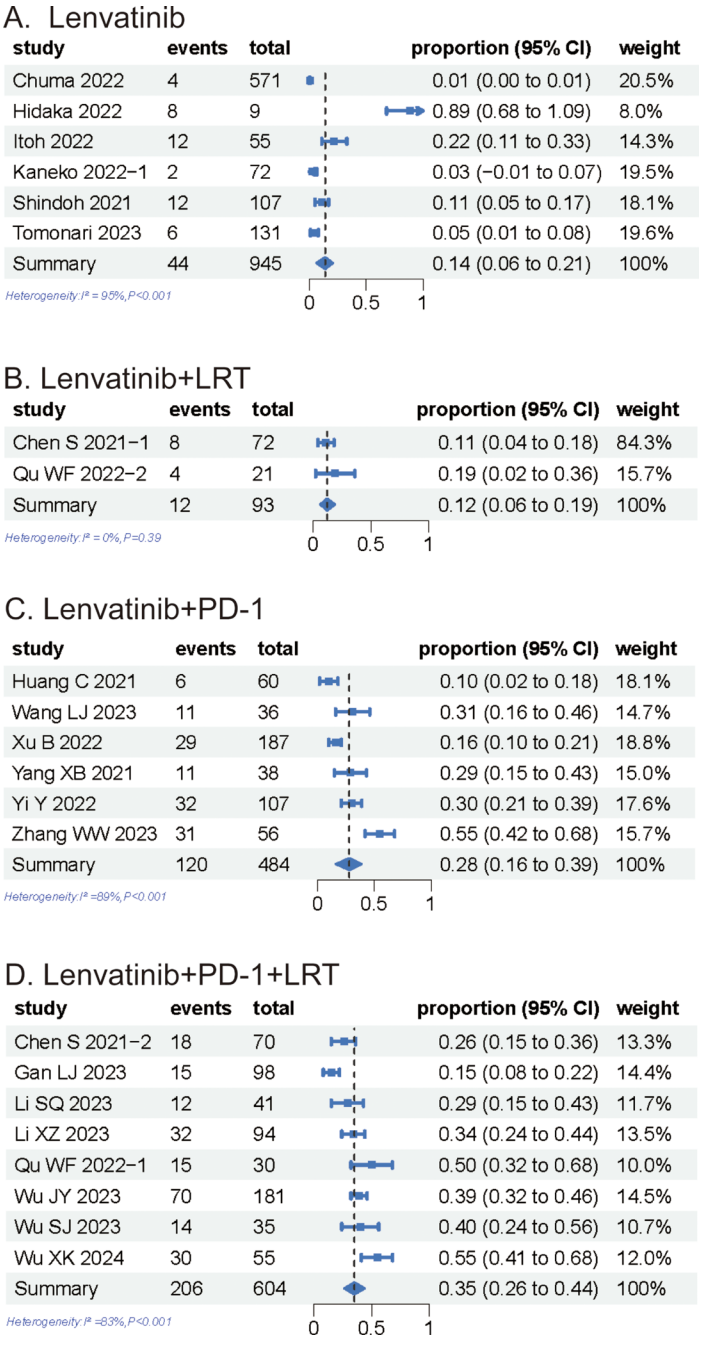

Fig. 6 The pooled CSRs in (**A**) Lenvatinib group, (**B**) Lenvatinib + LRT group, (**C**) Lenvatinib + PD-1 group, (**D**) Lenvatinib + PD-1 + LRT group

Conclusion

The results of the current study indicate that TKI + PD-1 + LRT, especially lenvatinib + PD-1 + LRT, as the conversion therapy is associated with higher conversion rate together with a manageable safety profile for patients with initially unresectable HCC. The successful conversion therapy favors the superior OS and PFS compared with systemic treatment alone.

Abbreviations

HCC	Hepatocellular carcinoma
TKI	Tyrosine kinase inhibitors
LRT	Loco-regional therapy
ICI	Immune checkpoint inhibitors
A + T	Atezolizumab plus bevacizumab
CSR	Conversion to surgery rate
ORR	Objective response rate
AEs	Adverse events
OS	Overall survival
PFS	Progression-free survival

CPR	Complete pathologic response
DCR	Disease control rate
CR	Complete response
PR	Partial response
SD	Stable disease
95% CI	Confidence interval
HR	Hazard ratios

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-12772-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

Supplementary Material 11

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Not applicable.

Author contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Xu Hongwei, Zhang Haili and Wei Yonggang. The first draft of the manuscript was written by Xu Hongwei and Zhang Haili. Li Bo, Chen Kefei and Wei Yonggang perform the analysis with constructive discussions. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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