Real-World Evidence of the Effectiveness and Safety of First-Line Therapies of Hepatocellular Carcinoma: Systematic Review and Network Meta-Analysis

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and the third leading cause of cancer deaths worldwide (Forner et al., 2018). As chemotherapy and surgical options are often not feasible (known as unresectable HCC, i.e., uHCC), new generation first-line therapies- targeted therapies and immunologic drugs- were sought, and widely recommended by HCC guidelines.

Extrapolating RCT findings to real-world healthcare settings requires real-world studies and meta-analysis for validation. However, up to now, few of these works have focused on the first-line therapies for treating uHCC.

OBJECTIVE

- Synthesize real-world evidence and evaluate the effectiveness and safety of first-line therapies for advanced HCC in real-world settings.
- Comparing the real-world NMA results with previous RCT results, identifying the common supportive evidence and highlighting discrepancies.

METHODS

A systematic search was performed across seven well-known databases, with a time horizon from inception through December 2024. Real-world studies were included, and treatments were selected in one of the five first-line therapies: Atezolizumab-Bevacizumab, Sintilimab-Bevacizumab biosimilar, Lenvatinib, Donafenib, and Sorafenib. Outcomes included overall survival and progression-free survival, objective response rate, and disease control rate (Cumpston et al., 2019). Adverse effects were included for safety evaluation. The Newcastle-Ottawa scale was used for quality assessment, and R 4.5.0 was used to implement the Bayesian model network meta-analysis.

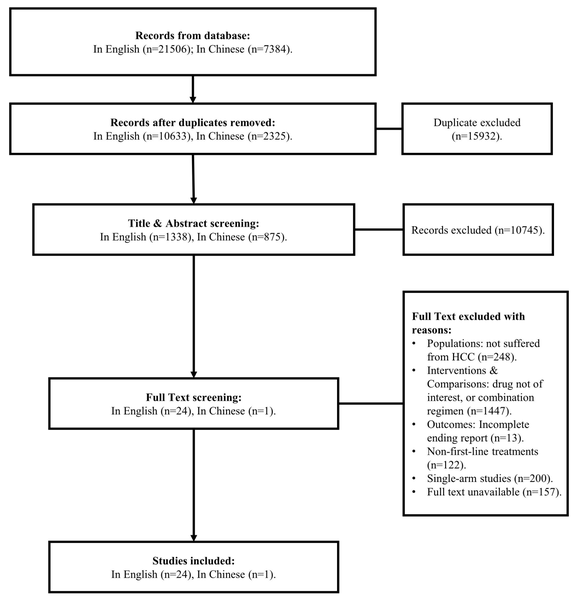
RESULTS*

25 studies, involving 9857 patients, met the inclusion criteria, which included 4 treatments: Atezolizumab-Bevacizumab, Sintilimab-Bevacizumab biosimilar, Lenvatinib, and Sorafenib. Compared with Sorafenib, Lenvatinib demonstrated significant advantages in progression-free survival (HR 0.62, 95%CrI 0.49-0.78), objective remission rate (OR 5.00, 95%CrI 3.40-7.50), and disease control rate (OR 2.20, 95%CrI 1.70-2.90). Atezolizumab-Bevacizumab showed improvement in objective remission rate (OR 3.90, 95%CrI 2.40-6.60) and disease control rate (OR 2.20, 95%CrI 1.50-3.10). Safety analysis revealed no significant results across all therapies.

Both RCTs and real-world studies demonstrated the at least non-inferior effectiveness of Lenvatinib, Atezolizumab plus Bevacizumab, and Sintilimab plus Bevacizumab biosimilar. However, Atezolizumab-Bevacizumab showed a significant advantage in progression-free survival and overall survival observed in the RCT rather than in real-world settings.

*This Bayesian model network meta-analysis result was updated in Jul 2025.

*We also made a systematic review that included Tislelizumab, Apatinib plus Camrelizumab, and FOLFOX4 programs, recommended by the 2024 guideline update. However, no research met our PICOS criteria was found.

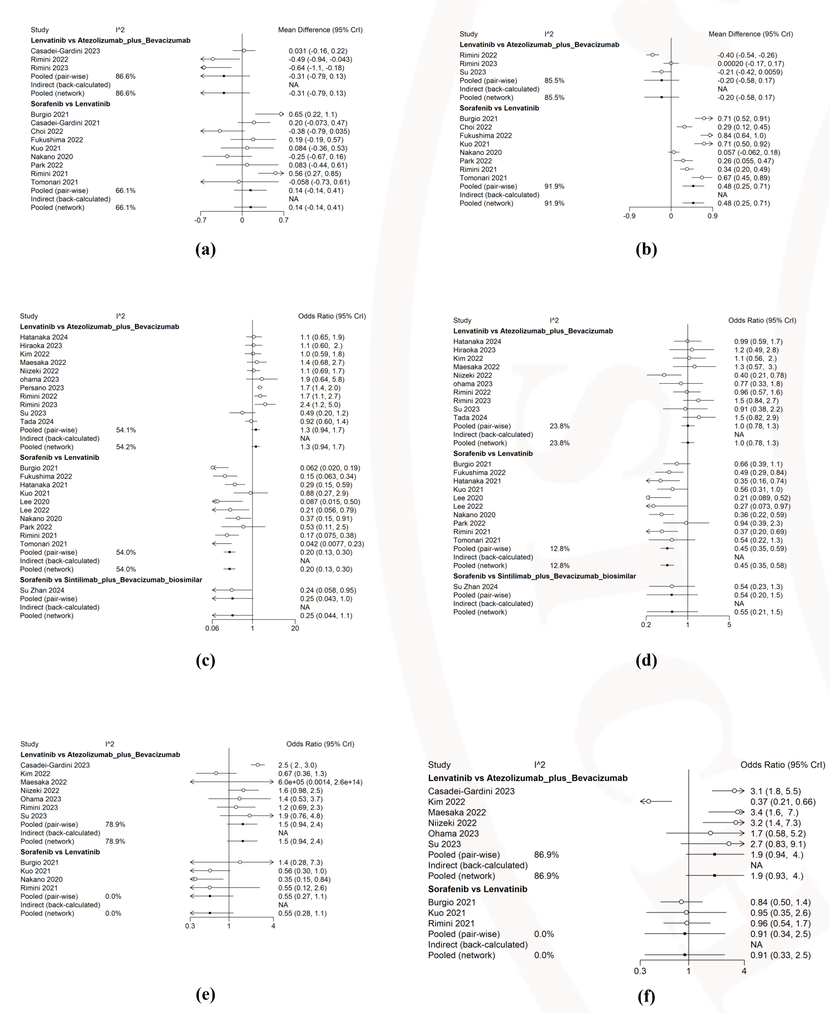


PRISMA diagram for the systematic review

NMA results (Sorafenib as comparison group)

Group	LEN	ATE_BEV	SIN_BEV$
OS	0.87 (0.67-1.10)	1.20 (0.71-2.10)	NA
PFS	0.62 (0.49-0.78)	0.76 (0.49-1.20)	NA
ORR	5.00 (3.40-7.50)	3.90 (2.40-6.50)	4.00 (0.94-22.0)
DCR	2.20 (1.70-2.80)	2.20 (1.50-3.20)	1.80 (0.67-5.00)
AE (ANY GRADE)	1.20 (0.50-2.80)	1.80 (0.87-3.60)	NA
AE (GRADE 3+)	1.10 (0.41-3.00)	0.58 (0.17-1.90)	NA

$Only one study included reported information about Sintilimab plus Bevacizumab biosimilar program compared with Sorafenib, lead to an unreliable result.



Heterogeneity plot: (a) HR for OS in 12 studies; (b) HR for PFS in 10 studies; (c) ORR in 22 studies; (d) DCR in 21 studies; (e) Adverse Effects rate (any grade) in 11 studies; (f) Adverse Effects rate (grade 3 or more) in 9 studies.

Abbreviation: RCT Randomized Controlled Trial, HR Hazard Ratio, OS Overall Survival, PFS progress free survival, ORR Objective Remission Rate, DCR Disease Control Rate, LEN Lenvatinib program, ATE_BEV Atezolizumab plus Bevacizumab program, SIN_BEV Sintilimab plus Bevacizumab biosimilar program, SOR Sorafenib program.

CONCLUSION

This systematic review and network meta-analysis synthesize real-world evidence, finding both real-world and RCT evidence of ORR and DCR support the advantages of Atezolizumab plus Bevacizumab and Lenvatinib compared with Sorafenib. Lenvatinib additionally shows a surprisingly significant PFS advantage, which is different from the RCT. Other indicators, however, show limited evidence in clinical effectiveness or safety.

REFERENCES

Cumpston, M., Li, T., Page, M. J., Chandler, J., Welch, V. A., Higgins, J. P., and Thomas, J. (2019). Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 10(10), ED000142.

Forner, A., Reig, M., and Bruix, J. (2018). Hepatocellular carcinoma. Lancet. 391(10127), 1301-1314.

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