

Jianpi Rougan Method in Support of Lenvatinib Therapy: A Real-World Study on Maintaining Relative Dose Intensity and Mitigating Toxicity–Driven Discontinuation in Intermediate-to-Advanced HCC

Tianbin Zhang¹, Peng Kuang² 

¹Department of Oncology, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310005, People's Republic of China; ²Department of Traditional Chinese Medicine, Ji'an Central People's Hospital, Ji'an, Jiangxi, 343000, People's Republic of China

Correspondence: Peng Kuang, Department of Traditional Chinese Medicine, Ji'an Central People's Hospital, No. 106 Jinggangshan Avenue, Ji'an, Jiangxi, 343000, People's Republic of China, Email 17776489427@163.com

Purpose: To investigate the effects of Jianpi Rougan method on lenvatinib (LEN) relative dose intensity (RDI), toxicity-related treatment discontinuation, and treatment tolerability in intermediate-to-advanced hepatocellular carcinoma (HCC).

Methods: A real-world, retrospective study was conducted on 152 intermediate-to-advanced HCC patients receiving LEN. Patients were grouped based on concurrent use of Jianpi Rougan decoction (combined, $n = 73$) or not (monotherapy, $n = 79$). Primary endpoints were RDI at weeks 8, 12, and overall, and the proportion of $\text{RDI} \geq 80\%$. Secondary endpoints included toxicity-related discontinuation, adverse events, and short-term efficacy (objective response rate, ORR; disease control rate, DCR). Propensity score matching (PSM, 1:1) was employed to balance baseline confounders.

Results: After PSM (65 pairs, $n = 130$), baseline characteristics were balanced. The combined group showed significantly higher RDI at week 12 ($P = 0.001$) and overall ($P = 0.003$), increased proportion of $\text{RDI} \geq 80\%$ ($P = 0.029$), fewer dose reductions ($P = 0.022$) and interruptions ($P = 0.045$), reduced toxicity-related permanent discontinuation ($P = 0.021$), decreased overall discontinuation ($P = 0.034$), and longer treatment duration ($P = 0.042$). Decreased appetite was less frequent in the combined group ($P = 0.036$), with trends towards less diarrhea and transaminase elevation. ORR and DCR were higher in the combined group, but the differences were not statistically significant ($P > 0.05$).

Conclusion: Jianpi Rougan method combined with LEN was associated with improved RDI, lower rates of toxicity-related treatment discontinuation, and enhanced treatment persistence in real-world practice, supporting its role as a feasible integrative strategy to maintain targeted therapy intensity.

Keywords: intermediate-to-advanced hepatocellular carcinoma, lenvatinib, relative dose intensity, Jianpi Rougan method, integrative Chinese and western medicine, real-world study, treatment tolerability, toxicity-related discontinuation

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and remains one of the leading causes of cancer-related mortality worldwide. Recent epidemiological data indicate that liver cancer continues to impose a substantial global health burden, particularly in East Asia, where chronic hepatitis B virus infection remains a major etiological factor. Despite advances in surveillance and diagnostic techniques, a substantial proportion of patients are still diagnosed at an intermediate or advanced stage, thereby losing the opportunity for potentially curative treatments such as surgical resection, liver transplantation, or local ablation.^{1,2} Consequently, systemic therapy has become the cornerstone of treatment for these patients. Recent advances in molecular oncology and translational research have substantially improved the understanding of HCC pathogenesis, therapeutic targets, and the tumor immune microenvironment, providing new opportunities for precision medicine and individualized treatment strategies.^{3–5} In parallel, molecular targeted therapy, immunotherapy, and combination treatment strategies have significantly improved clinical outcomes in patients with unresectable HCC, although treatment-related toxicities and treatment sustainability remain important

challenges in real-world practice.^{6–8} Among these agents, lenvatinib (LEN), a multikinase inhibitor, has demonstrated favorable antitumor activity and has been established as an important first-line treatment option for unresectable HCC.⁹

However, LEN treatment is often accompanied by adverse events (AEs) such as hypertension, diarrhea, fatigue, and hand-foot syndrome, whose frequency and severity are more pronounced in real-world populations.¹⁰ Previous studies indicate that the efficacy of LEN is somewhat dose-intensity dependent. In clinical practice, AEs frequently lead to dose reductions or premature treatment discontinuation, creating a vicious cycle of toxicity–dose reduction–discontinuation–compromised efficacy, which becomes a key issue affecting long-term patient benefit.^{11,12}

Relative dose intensity (RDI) reflects the ratio of the actual cumulative drug dose received by the patient over a planned period to the standard planned dose, providing a comprehensive evaluation of treatment persistence and accessibility.¹³ Studies have suggested that in various anti-cancer treatments, a higher RDI is associated with better progression-free survival (PFS) and overall survival (OS).¹⁴ Compared to pure efficacy endpoints, RDI more closely reflects real-world clinical practice by indicating a patient's overall tolerance to the treatment regimen and treatment continuity. Therefore, RDI is considered an important surrogate marker for assessing the real-world benefit of targeted therapy, particularly suitable for retrospective and real-world studies.

In traditional Chinese medicine (TCM) theory, HCC is often categorized as a deficiency in origin and excess in manifestation syndrome, with liver stagnation and spleen deficiency as the root cause, and blood stasis and toxin accumulation as the manifestations.¹⁵ Patients with intermediate-to-advanced disease often present with symptoms such as poor appetite, fatigue, abdominal distension, loose stools, and emotional depression, which highly overlap with the clinical manifestations of targeted therapy-related AEs. The Jianpi Rougan method, centered on harmonizing the liver and spleen and supporting healthy Qi, is commonly used in clinical practice to improve digestive function, alleviate fatigue, and address mood disorders.

Previous research suggests that TCM as supportive therapy can improve the quality of life and treatment tolerance in cancer patients to some extent.¹⁶ However, systematic evaluation at the real-world level regarding its potential to help patients maintain the dose intensity of targeted agents and reduce toxicity-related dose reductions or discontinuations is still lacking. Given these considerations, we conducted a real-world retrospective cohort study to evaluate whether Jianpi Rougan therapy was associated with improved maintenance of lenvatinib dose intensity, reduced toxicity-related discontinuation, and better treatment tolerability in patients with intermediate-to-advanced HCC.

Materials and Methods

Study Population

This single-center, retrospective cohort study enrolled patients with intermediate-to-advanced HCC treated at our hospital between January 2024 and June 2025. The Ethics Committee reviewed the study protocol and specifically approved the waiver of informed consent prior to study initiation because only anonymized retrospective clinical data were analyzed and no additional patient intervention was involved.

Inclusion criteria were: 1) Pathologically or clinically diagnosed HCC according to the American Association for the Study of Liver Diseases/European Association for the Study of the Liver guidelines;¹⁷ 2) Initially diagnosed as Barcelona Clinic Liver Cancer (BCLC) stage B or C; 3) Receiving first-line systemic therapy with LEN; 4) Having received at least one cycle of LEN with at least one post-baseline safety or efficacy assessment record; 5) Aged 18–80 years with complete clinical data. Exclusion criteria were: 1) Previous receipt of other systemic anti-cancer therapies (eg, chemotherapy, immunotherapy); 2) Concurrent other malignancies or severe psychiatric disorders; 3) Poor treatment adherence preventing accurate assessment of actual drug intake; 4) No follow-up data despite receiving treatment.

Based on treatment regimen, patients were divided into two groups: combined group (received standard LEN treatment combined with TCM decoction based on the Jianpi Rougan method) and monotherapy group (received standard LEN treatment alone without TCM). Basic clinical information, including demographics, liver function, tumor burden, and prior treatment history, was collected via the hospital information system (HIS), picture archiving and communication system (PACS), and laboratory information system (LIS). The study protocol was approved by The Second Affiliated Hospital of Zhejiang Chinese Medical University (Approval No. 2025–021-01) Ethics Committee,



complying with the ethical principles of the *Declaration of Helsinki*. Due to the retrospective nature and absence of privacy disclosure risks, informed consent was waived. All data were anonymized before analysis.

The sample size calculation was based on the primary endpoint, LEN RDI. Referring to previous real-world data, the average RDI for patients with intermediate-to-advanced HCC on LEN monotherapy was approximately 65–70%, with a standard deviation (SD) of 20–25%.¹⁸ We hypothesized that the Jianpi Rougan decoction could improve tolerability, thereby increasing RDI. It was assumed that the mean RDI would be 70% in the monotherapy group and 80% in the combined group, with an overall SD of 20% for both groups. With a two-sided $\alpha = 0.05$ and power $(1-\beta) = 0.80$, using PASS 15.0 software (NCSS, LLC, Kaysville, Utah, USA) for a two-sample *t*-test, the minimum required sample size was 64 per group. Considering the retrospective design and the planned use of propensity score matching (PSM, 1:1 matching, caliper = 0.02) to control for confounding baseline characteristics (eg, age, Child-Pugh grade, tumor burden), an estimated 10–15% sample loss was anticipated. To ensure sufficient statistical power post-matching and account for potential data loss, the target sample size was set at 152 patients. This sample size provides adequate power for the primary RDI analysis and allows exploratory analysis for secondary endpoints including toxicity-related discontinuation (assuming 25% in monotherapy group vs. < 10% in combined group).

Grouping and Treatment Regimens

Combined group (Jianpi Rougan method + LEN): Patients received standard LEN alongside a standardized TCM decoction based on the Jianpi Rougan method. The core formula was fixed: *Atractylodes macrocephala* (Baizhu) 15 g, *Poria cocos* (Fuling) 15 g, *Paeonia lactiflora* (Baishao) 12 g, *Bupleurum chinense* (Chaihu) 10 g, *Angelica sinensis* (Danggui) 10 g, and *Curcuma aromatica* (Yujin) 10 g. Limited, predefined modifications were allowed: For significant fatigue/poor appetite, *Astragalus membranaceus* (Huangqi) 15 g and *Codonopsis pilosula* (Dangshen) 15 g were added. For marked emotional depression/liver stagnation, *Cyperus rotundus* (Xiangfu) 10 g and *Albizia julibrissin* (Hehuanpi) 15 g were added. For damp-heat or elevated transaminases, *Artemisia capillaris* (Yinchen) 15 g and *Gardenia jasminoides* (Zhizi) 10 g were added. For pain or blood stasis signs, *Salvia miltiorrhiza* (Danshen) 15 g and *Ligusticum chuanxiong* (Chuanxiong) 10 g were added. A maximum of 1–2 modification categories were allowed per prescription. All decoctions were prepared uniformly by the hospital pharmacy: one dose daily, decocted to 200 mL, and taken twice daily. The TCM treatment duration required a minimum of 3 months or coverage of $\geq 50\%$ of the LEN treatment period if < 3 months. Unplanned interruption exceeding 14 days led to exclusion from the combined group analysis.

Monotherapy group (LEN): Patients received standard-dose LEN only. The standard dose was 12 mg/day for body weight ≥ 60 kg and 8 mg/day for weight < 60 kg. Dose adjustments were permitted based on clinical response and AEs per physician's judgment.

Data Collection and Variable Definitions

Data were collected retrospectively using a standardized case report form from HIS, LIS, and PACS. The variables included: 1) Demographics: age, gender, weight, body mass index (BMI), smoking/drinking history, and Eastern Cooperative Oncology Group (ECOG) performance status (PS; 0 = fully active to 5 = fully bedridden); 2) Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), albumin (ALB), and Child-Pugh grade; 3) Tumor characteristics: maximum tumor diameter, tumor number, presence of portal vein tumor thrombus (PVTT), alpha-fetoprotein (AFP) level, and BCLC stage; 4) Prior treatment history: transarterial chemoembolization (TACE), ablation, or resection; 5) Treatment details: starting dose of LEN, treatment dates, dose adjustments, TCM usage (for combined group); 6) Safety: treatment-emergent AEs graded per the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) version 5.0; 7) Short-term efficacy: objective response rate (ORR) and disease control rate (DCR) assessed radiologically per the modified Response Evaluation Criteria in Solid Tumors (mRECIST).

RDI

RDI was calculated as: $\text{RDI (\%)} = (\text{actual cumulative dose received} / \text{planned cumulative dose}) \times 100\%$.¹⁹ The planned dose was 12 mg/day (≥ 60 kg) or 8 mg/day (< 60 kg). RDI was calculated for the first 8 weeks (early RDI), first 12 weeks, and the entire treatment period. Patients were categorized into high-intensity ($\text{RDI} \geq 80\%$) and low-intensity ($\text{RDI} < 80\%$) groups. The threshold of $\text{RDI} \geq 80\%$ was selected because maintenance of this level of dose intensity has been associated with improved clinical outcomes in patients receiving lenvatinib therapy. The 8-week and 12-week time points were chosen because early dose intensity during the first 2–3 months of treatment has been reported to be predictive of subsequent treatment response and treatment continuation.²⁰

Toxicity-Related Treatment Discontinuation Rate

Toxicity-related treatment discontinuation rate was defined as the proportion of patients permanently discontinuing LEN due to treatment-related AEs.²¹ The focus was on discontinuations due to severe AEs (eg, hypertension, diarrhea).

Safety and Tolerability

All AEs were recorded and graded per the NCI-CTCAE v5.0.²² The incidence of grade ≥ 3 AEs (eg, severe hypertension, diarrhea, hand-foot syndrome) was analyzed to assess tolerability differences.

Short-Term Efficacy Evaluation

Efficacy was assessed by imaging at 3–6 months post-treatment using the mRECIST.²³ Responses were categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). ORR (CR + PR) and DCR (CR + PR + SD) were calculated.

Statistical Analysis

All statistical analyses were performed using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). Propensity score matching was conducted using the MatchIt package (version 4.7.0), and covariate balance was assessed using the cobalt package (version 4.6.0). Continuous variables were presented as mean $\pm$ standard deviation or median (interquartile range) based on distribution. Categorical variables were presented as number (percentage). Group comparisons used appropriate parametric or non-parametric tests. To reduce confounding bias from baseline differences inherent to real-world studies, PSM was employed. A multivariate logistic regression model calculated PS, followed by 1:1 nearest neighbor matching. The standardized mean difference (SMD) was used to evaluate covariate balance, and $\text{SMD} < 0.10$ indicated good balance post-matching, visualized via Love plots. In the matched cohort, continuous outcomes were compared using paired tests, binary outcomes were compared with paired contingency analyses, and time-to-event outcomes were estimated via the Kaplan-Meier method. All tests were two-sided, with $P < 0.05$ considered statistically significant.

Results

Patient Disposition and Baseline Characteristics

A total of 172 patients were screened, and 20 were excluded (10 failed the inclusion/exclusion criteria, 6 had missing key data, 4 other reasons). The original cohort comprised 152 patients (combined group: $n = 73$; monotherapy group: $n = 79$). After PSM [1:1 nearest neighbor matching on logit(PS) with caliper restriction] balancing age, gender, BMI, smoking/drinking history, ALT, AST, TBIL, ALB, Child-Pugh grade, maximum tumor diameter, tumor number, PVT, AFP, BCLC stage, and prior treatments (TACE, ablation, surgery), 65 matched pairs ($n = 130$) were obtained. Post-matching, covariate balance improved markedly, with most SMDs below 0.10 (Love plot, Figure 1), indicating good comparability. Baseline characteristics before and after PSM are shown in Tables 1 and 2.

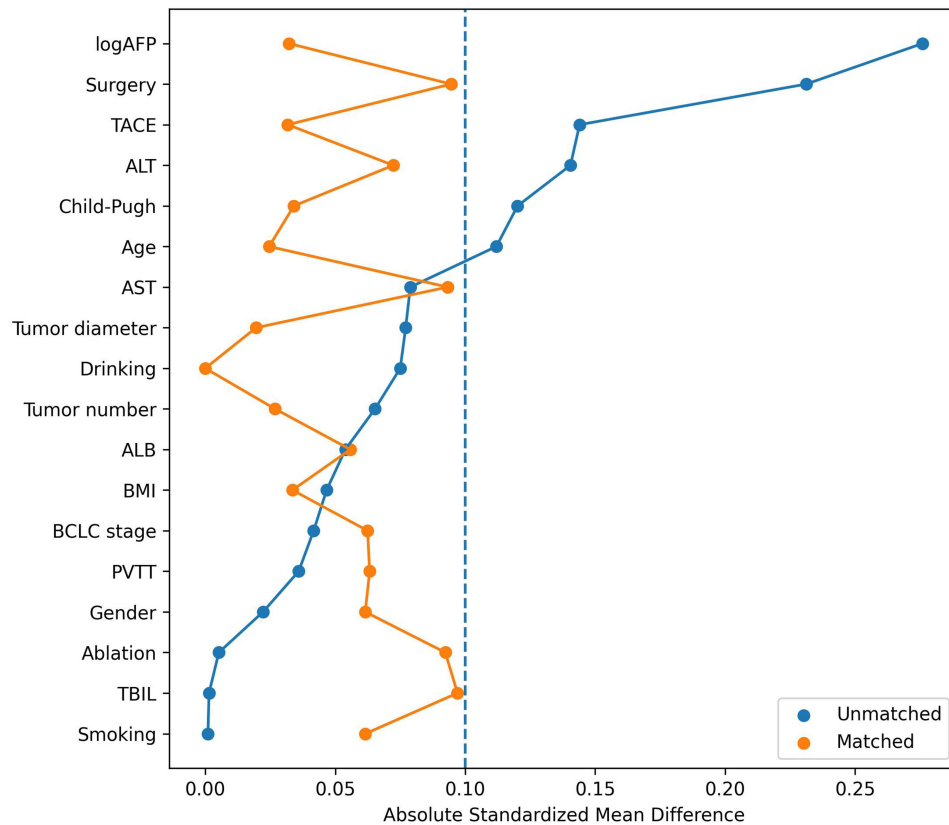


Figure 1 Love plot showing covariate balance before and after PSM.

Abbreviation: PSM, propensity score matching.

Comparison of LEN RDI

In the matched cohort, the combined group demonstrated significantly better dose maintenance capability (Figure 2 and Table 3). Both early (8-week) and 12-week RDI were significantly higher in the combined group, as was the overall RDI. The rate of achieving RDI $\geq 80\%$ within 12 weeks was significantly higher in the combined group ($P = 0.029$).

Table 1 Baseline Characteristics Before PSM

Variable	Combined Group (n = 73)	Monotherapy Group (n = 79)	P	SMD
Age (years)	52.31 $\pm$ 13.84	49.67 $\pm$ 14.52	0.213	0.186
Male [n (%)]	42 (57.53)	39 (49.37)	0.321	0.165
BMI (kg/m ²)	24.38 $\pm$ 3.41	25.12 $\pm$ 3.56	0.172	-0.212
Smoking history [n (%)]	31 (42.47)	38 (48.10)	0.498	-0.113
Drinking history [n (%)]	34 (46.58)	41 (51.90)	0.528	-0.106
ALT (U/L)	78.42 $\pm$ 34.15	83.96 $\pm$ 36.28	0.352	-0.156
AST (U/L)	71.63 $\pm$ 32.47	76.94 $\pm$ 34.01	0.319	-0.159
TBIL (μ mol/L)	16.12 $\pm$ 6.01	17.03 $\pm$ 6.28	0.354	-0.149
ALB (g/L)	39.84 $\pm$ 4.72	38.93 $\pm$ 4.88	0.238	0.188
Child-Pugh grade [n (%)]			0.122	0.254
A	32 (43.84)	25 (31.65)		
B	21 (28.77)	24 (30.38)		
C	20 (27.39)	30 (37.97)		

(Continued)

Table 1 (Continued).

Variable	Combined Group (n = 73)	Monotherapy Group (n = 79)	P	SMD
Maximum tumor diameter (cm)	6.34 ± 2.11	6.71 ± 2.24	0.287	-0.170
Tumor number	2.68 ± 1.21	3.12 ± 1.34	0.036	-0.344
PVTT [n (%)]	27 (36.99)	35 (44.30)	0.365	-0.149
AFP (ng/mL)	462.18 ± 286.47	498.32 ± 301.15	0.457	-0.122
BCLC stage [n (%)]			0.362	0.15
Stage B	35 (47.95)	32 (40.51)		
Stage C	38 (52.05)	47 (59.49)		
Prior TACE [n (%)]	37 (50.68)	43 (54.43)	0.658	-0.075
Prior ablation [n (%)]	29 (39.73)	36 (45.57)	0.469	-0.117
Prior surgery [n (%)]	26 (35.62)	30 (37.97)	0.767	-0.049

Abbreviations: PSM, propensity score matching; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; PVTT, portal vein tumor thrombus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; SMD, standardized mean difference.

Table 2 Baseline Characteristics After PSM

Variable	Combined Group (n = 65)	Monotherapy Group (n = 65)	P	SMD
Age (years)	50.87 ± 13.26	50.12 ± 13.71	0.764	0.055
Male [n (%)]	36 (55.38)	35 (53.85)	0.858	0.031
BMI (kg/m ²)	24.61 ± 3.35	24.78 ± 3.42	0.781	-0.049
Smoking history [n (%)]	28 (43.08)	27 (41.54)	0.857	0.031
Drinking history [n (%)]	30 (46.15)	29 (44.62)	0.862	0.031
ALT (U/L)	80.11 ± 33.48	81.07 ± 34.12	0.873	-0.028
AST (U/L)	73.02 ± 31.87	74.55 ± 32.64	0.796	-0.048
TBIL (μmol/L)	16.54 ± 5.83	16.71 ± 5.94	0.868	-0.028
ALB (g/L)	39.62 ± 4.65	39.47 ± 4.71	0.861	0.032
Child-Pugh grade [n (%)]			0.857	0.031
A	28 (43.08)	27 (41.54)		
B	19 (29.23)	20 (30.77)		
C	18 (27.69)	18 (27.69)		
Maximum tumor diameter (cm)	6.42 ± 2.08	6.38 ± 2.05	0.918	0.019
Tumor number	2.89 ± 1.25	2.93 ± 1.27	0.856	-0.031
PVTT [n (%)]	25 (38.46)	26 (40.00)	0.859	-0.031
AFP (ng/mL)	481.25 ± 295.63	489.47 ± 292.18	0.879	-0.028
BCLC stage [n (%)]			0.859	0.031
Stage B	31 (47.69)	30 (46.15)		
Stage C	34 (52.31)	35 (53.85)		
Prior TACE [n (%)]	33 (50.77)	32 (49.23)	0.862	0.031
Prior ablation [n (%)]	27 (41.54)	26 (40.00)	0.859	0.031
Prior surgery [n (%)]	25 (38.46)	24 (36.92)	0.859	0.031

Notes: SMD is used to evaluate covariate balance after matching, and SMD < 0.10 indicates good balance.

Abbreviations: PSM, propensity score matching; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; PVTT, portal vein tumor thrombus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; SMD, standardized mean difference.

Regarding dose adjustments, the combined group had lower rates of both dose reductions and dose interruptions ($P = 0.022$ and $P = 0.045$, respectively), suggesting a potential association between Jianpi Rougan therapy and improved treatment sustainability.

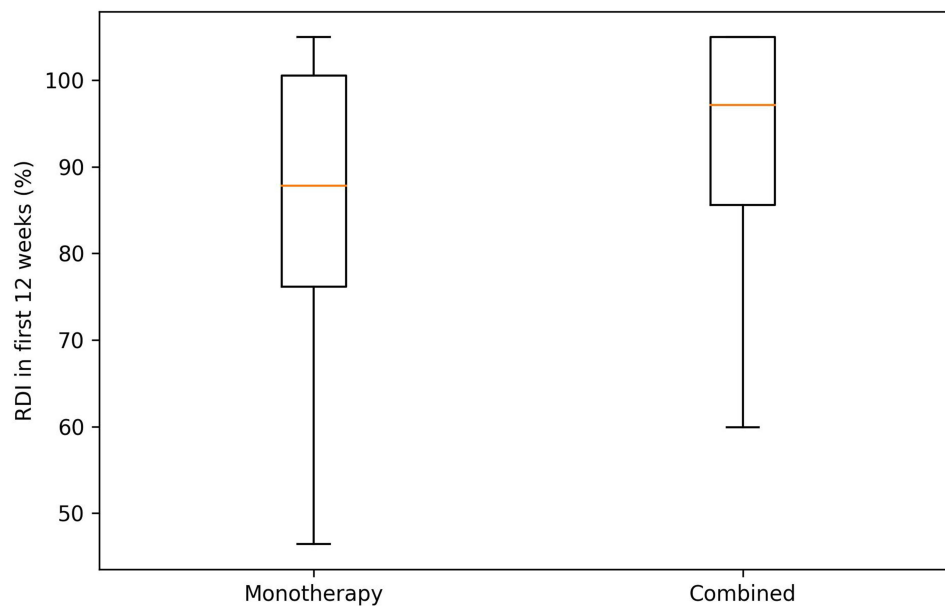


Figure 2 Comparison of LEN RDI distribution in first 12 weeks between groups after PSM.

Abbreviations: LEN, lenvatinib; RDI, relative dose intensity; PSM, propensity score matching.

Treatment Discontinuation and Time to Treatment Failure (TTF)

Permanent discontinuation rate due to AEs was significantly lower in the combined group ($P = 0.021$). Discontinuation rate due to disease progression was also lower ($P = 0.044$). The overall discontinuation rate was significantly reduced in the combined group ($P = 0.034$) (Table 4). TTF was longer in the combined group (5.33 ± 2.14 months vs. 4.58 ± 2.08 months, $P = 0.042$). Kaplan-Meier curves showed a higher probability of remaining on treatment in the combined group (Figure 3).

Table 3 Comparison of RDI and Dose Adjustments (Post-PSM)

Indicator	Combined Group (n = 65)	Monotherapy Group (n = 65)	t	χ^2	P
RDI at week 8 (%)	89.74 ± 9.51	84.21 ± 10.63	3.244		0.002
RDI at week 12 (%)	88.63 ± 9.12	83.11 ± 10.42	3.553		0.001
Overall RDI (%)	87.92 ± 10.02	82.07 ± 11.38	3.086		0.003
RDI ≥ 80% (at week 12)	61 (93.85%)	50 (76.92%)		4.783	0.029
Dose reduction	21 (32.31%)	33 (50.77%)		5.231	0.022
Dose interruption	18 (27.69%)	29 (44.62%)		4.024	0.045

Abbreviations: RDI, relative dose intensity; PSM, propensity score matching.

Table 4 Treatment Discontinuation and Duration (Post-PSM)

Indicator	Combined Group (n = 65)	Monotherapy Group (n = 65)	t	χ^2	P
Permanent discontinuation due to toxicity	8 (12.31%)	18 (27.69%)		5.357	0.021
Discontinuation due to disease progression	14 (21.54%)	24 (36.92%)		4.074	0.044
Discontinuation for any reason	22 (33.85%)	34 (52.31%)		4.487	0.034
TTF (months)	5.33 ± 2.14	4.58 ± 2.08	2.059		0.042

Abbreviations: PSM, propensity score matching; TTF, time to treatment failure.

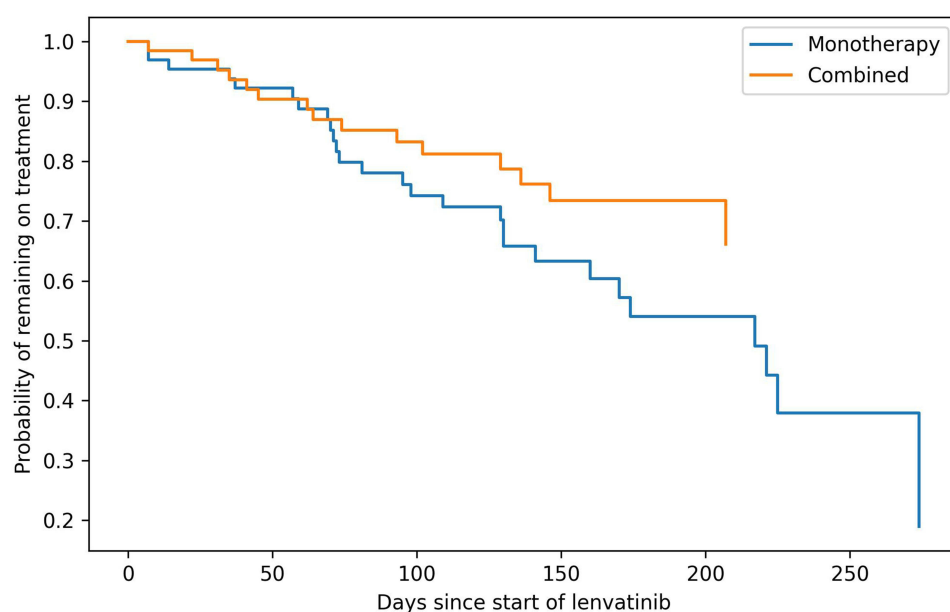


Figure 3 Kaplan-Meier curves for treatment continuation in the matched cohorts.

Safety and AEs

The overall incidence of AEs of any grade did not differ significantly between the groups. Regarding symptoms more relevant to the Jianpi Rougan theory, the incidence of decreased appetite was significantly lower in the combined group ($P = 0.036$), with trends towards lower rates of diarrhea and elevated transaminases. No significant difference was observed in grade ≥ 3 AEs (Table 5). Typical AEs for targeted therapy (eg, hypertension, hand-foot syndrome) showed no significant inter-group differences.

Tumor Response and Radiological Changes

In the matched cohort, both ORR and DCR were numerically higher in the combined group, but the differences were not statistically significant ($P > 0.05$). The distribution of best response (CR/PR/SD/PD) is shown in Table 6, with no significant overall distribution difference ($P > 0.05$). A waterfall plot suggested a greater overall magnitude of tumor shrinkage in the combined group (Figure 4).

Table 5 Comparison of AEs (Post-PSM)

AE	Combined Group (n = 65)	Monotherapy Group (n = 65)	χ^2	P
Any AE	45 (69.23%)	49 (75.38%)	0.615	0.433
$\geq$ Grade 3 AE	12 (18.46%)	14 (21.54%)	0.186	0.666
Fatigue	19 (29.23%)	30 (46.15%)	3.402	0.065
Decreased appetite	21 (32.31%)	33 (50.77%)	4.417	0.036
Diarrhea	18 (27.69%)	27 (41.54%)	2.706	0.1
Transaminase elevation	16 (24.62%)	26 (40.00%)	3.582	0.058
Hypertension	20 (30.77%)	22 (33.85%)	0.145	0.703
Hand-foot syndrome	14 (21.54%)	16 (24.62%)	0.184	0.668

Abbreviations: AE, adverse event; PSM, propensity score matching.

Table 6 Tumor Response and Short-Term Efficacy in the Matched Cohort

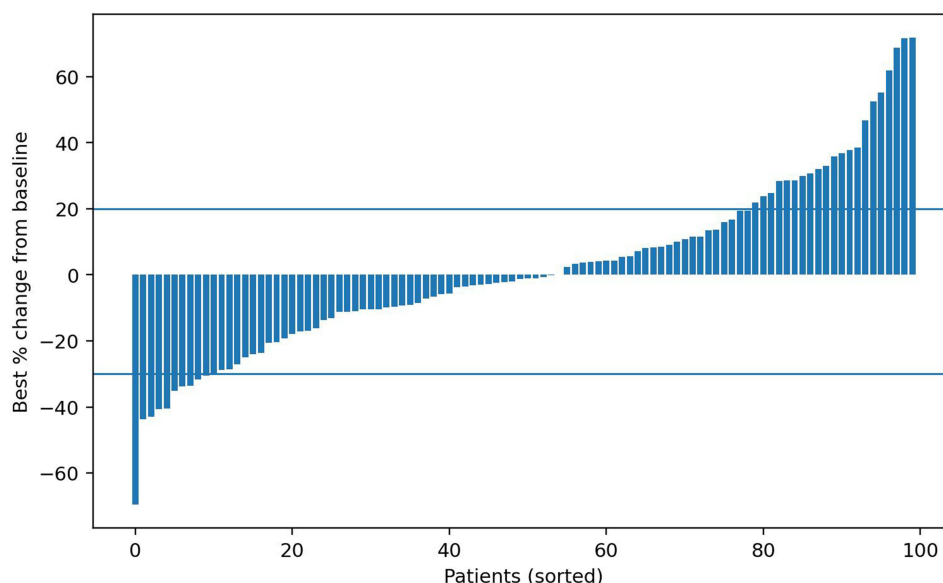
Outcome	Combined Group (n = 65)	Monotherapy Group (n = 65)	χ^2	P
CR	0 (0.00%)	0 (0.00%)	–	–
PR	38 (58.46%)	28 (43.08%)	–	–
SD	19 (29.23%)	21 (32.31%)	–	–
PD	8 (12.31%)	16 (24.62%)	–	–
Response distribution (CR/PR/SD/PD)	–	–	1.482	0.686
ORR (CR + PR)	38 (58.46%)	28 (43.08%)	3.079	0.079
DCR (CR + PR + SD)	57 (87.69%)	49 (75.38%)	2.981	0.084

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Discussion

With targeted therapy becoming a cornerstone of systemic treatment for intermediate-to-advanced HCC, maintaining treatment continuity and adequate dose intensity in real-world practice has emerged as a critical determinant of therapeutic benefit. This real-world retrospective cohort study systematically evaluated the impact of the Jianpi Rougan method combined with LEN on treatment sustainability. After PSM balancing key baseline characteristics, the results showed the combined group had significantly higher RDI at weeks 8, 12, and overall, along with a higher proportion achieving $\text{RDI} \geq 80\%$. Concurrently, the combined group had a significantly lower rate of permanent discontinuation due to toxicity and exhibited longer treatment duration. These findings provide direct evidence of the real-world value of the Jianpi Rougan method in supporting targeted therapy from two dimensions: receiving adequate dose and remaining on treatment longer.

Previous studies have confirmed the correlation between LEN efficacy and dose intensity. The REFLECT trial and subsequent real-world analyses indicate that early RDI decline is associated with shorter PFS and OS.²⁴ Some cohort studies further found that patients maintaining $\text{RDI} \geq 80\%$ during the first 8–12 weeks achieved more durable disease control and better survival outcomes.²⁵ Notably, our study showed that the combined group maintained higher RDI without increasing severe AE rates; instead, it significantly reduced symptoms including fatigue, appetite loss, and

**Figure 4** Waterfall plot showing changes in maximum tumor diameter for patients in the matched cohort after PSM.

Abbreviation: PSM, propensity score matching.

transaminase elevation. These findings suggest a potential association between Jianpi Rougan therapy and improved dose maintenance capacity without an apparent increase in severe adverse events, aligning with existing evidence that RDI is a key determinant of real-world benefit from targeted therapy.²⁶

From a TCM theoretical perspective, HCC patients often present with a pattern of deficiency in origin and excess in manifestation, with liver stagnation and spleen deficiency. Tumor burden, impaired liver function, and long-term targeted therapy further weaken spleen transportation and liver dispersion. The Jianpi Rougan formula, with core herbs such as *Atractylodes macrocephala*, *Poria cocos*, *Paeonia lactiflora*, and *Bupleurum chinense*, addresses both strengthening healthy Qi and relieving stagnation. It may improve spleen deficiency symptoms including poor appetite and fatigue, while alleviating emotional depression and liver Qi stagnation. Previous integrative medicine studies suggest spleen-fortifying formulas may mitigate gastrointestinal toxicity from chemotherapy or targeted therapy by improving gastrointestinal motility, enhancing nutrient absorption, modulating gut microbiota, and reducing inflammation.²⁷ Liver-soothing and dispersion-regulating herbs might alleviate hepatocyte injury and transaminase elevation by modulating the hypothalamic-pituitary-adrenal axis, improving stress response, and enhancing hepatic microcirculation.²⁸ Compared to monotherapy, the combination with TCM intervention showed more significant benefits for AEs closely related to spleen deficiency and liver stagnation (fatigue, appetite loss, liver enzyme abnormalities), while its impact on specific targeted therapy toxicities like hypertension and hand-foot syndrome was relatively limited. This pattern of selective improvement aligns with the core feature of TCM syndrome differentiation and treatment. Rather than directly counter-acting drug toxicity, TCM focuses on supporting healthy Qi, restoring balance, and improving the internal milieu,²⁹ which lends theoretical plausibility to its potential mechanism.

Regarding short-term efficacy, although ORR and DCR showed upward trends in the combined group, they did not reach statistical significance. This finding is consistent with some integrative medicine studies reporting limited differences in short-term radiological response, with potential benefits for long-term outcomes.³⁰ Considering the limited sample size, short follow-up, and primary focus on treatment sustainability rather than survival endpoints in this study, these trends may indicate that the dose maintenance advantage has not yet fully translated into measurable radiological benefit. Notably, the waterfall plot suggested a greater overall magnitude of tumor shrinkage in the combined group, implying that with longer follow-up or larger samples, higher RDI might translate into clearer efficacy and survival advantages, consistent with the established chain of RDI-efficacy-survival relationships.²⁰

This study still has several limitations. First, the retrospective design inherently carries selection bias and unmeasured confounding factors. Although PSM was used, it cannot fully replace prospective randomized controlled trials. Second, sample size and follow-up duration limited the assessment of hard endpoints such as OS and PFS. Third, the allowance for herbal prescription modifications based on syndrome differentiation, while reflecting real-world practice, introduced intervention heterogeneity, making it difficult to quantify the independent effect of individual components precisely. Furthermore, mechanistic investigations, including pharmacological experiments and biomarker-based studies, were beyond the scope of the present study and warrant further exploration in future research. Therefore, future multicenter prospective randomized controlled trials involving larger and more diverse populations are warranted to further validate these findings and improve their generalizability. Although predefined modification rules were applied, the individualized adjustment of herbal prescriptions may still have introduced a degree of intervention heterogeneity.

Conclusion

The combination of the Jianpi Rougan method with LEN was associated with higher dose maintenance capacity and lower rates of toxicity-related treatment discontinuation in this real-world cohort. Its effects align closely with previous research evidence indicating that RDI determines the real-world benefit of targeted therapy. The observed association between Jianpi Rougan therapy and improved treatment sustainability may be partly attributable to its potential effects on spleen/stomach function, hepatic stress adaptation, and systemic tolerability. It offers a biologically plausible and clinically feasible integrative Chinese and Western medicine approach for systemic treatment of intermediate-to-advanced HCC. Future prospective, multicenter randomized studies are warranted to further validate its impact on survival outcomes and define the optimal intervention model.



Data Sharing Statement

The data used and/or analyzed during the current study are available from the corresponding author.

Ethics Approval

This study was approved by the Ethics Committee of The Second Affiliated Hospital of Zhejiang Chinese Medical University (Approval No. 2025-021-01) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. The Ethics Committee reviewed and approved the waiver of informed consent. Owing to the retrospective nature of the study, minimal risk to participants, and the use of anonymized clinical data, written informed consent was waived.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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