Article

Discovery Medicine 2025; 37(202): 2712–2730
https://doi.org/10.24976/Discov.Med.202537202.227

Symptom Clusters and Quality of Life in Liver Cancer Patients Undergoing Targeted Immunotherapy: A Prospective Longitudinal Cohort Study

Bing Han[1,†], Mengxia Qi[2,†], Lin Huang[1], Wen Wang[3], Shumin Cai[4], Meiying Huang[5], Dan Mou[6], Chunju Cao[1,*]

[1]Nursing Department, The Affiliated Qingyuan Hospital (Qingyuan People's Hospital), Guangzhou Medical University, 511500 Qingyuan, Guangdong, China
[2]School of Nursing, Zhejiang Chinese Medical University, 310053 Hangzhou, Zhejiang, China
[3]General Surgery Ward 6, The Affiliated Qingyuan Hospital (Qingyuan People's Hospital), Guangzhou Medical University, 511500 Qingyuan, Guangdong, China
[4]Endocrinology Department, The Affiliated Qingyuan Hospital (Qingyuan People's Hospital), Guangzhou Medical University, 511500 Qingyuan, Guangdong, China
[5]General Surgery Unit 1, The Affiliated Qingyuan Hospital (Qingyuan People's Hospital), Guangzhou Medical University, 511500 Qingyuan, Guangdong, China
[6]Intensive Care Unit 2, The Affiliated Qingyuan Hospital (Qingyuan People's Hospital), Guangzhou Medical University, 511500 Qingyuan, Guangdong, China
*Correspondence: Chunjucao0812@outlook.com (Chunju Cao)
[†]These authors contributed equally.
Submitted: 27 August 2025 Revised: 12 September 2025 Accepted: 10 October 2025 Published: 20 November 2025

Background: Liver cancer represents a major global health burden, and targeted therapy combined with immune checkpoint inhibitors (ICIs) has become an essential systemic treatment. However, treatment-related symptom clusters may markedly impair quality of life (QOL). This study aimed to examine the longitudinal evolution of symptom clusters and their impact on QOL in patients with malignant liver tumors across the first to fourth treatment phases.

Methods: A prospective cohort of 150 patients receiving combined targeted-ICI therapy was recruited at a tertiary hospital in Qingyuan, China, between January and August 2025. The Chinese version of the Memorial Symptom Assessment Scale (MSAS-C) and the Quality of Life–Liver Cancer (QOL-LC) V2.0 questionnaire were distributed and collected on Day 7 of each treatment phase. The symptom-onset timeline was provided to patients at the initiation of therapy and retrieved on Day 7 of the first phase. Factor analysis, Apriori association rule mining, repeated-measures analysis of variance (ANOVA), correlation analysis, and stepwise multiple regression were applied to identify the dynamic structure of symptom clusters and their associations with QOL outcomes.

Results: The final cohort comprised 150 patients with a mean age of 53.62 years; 67.33% were diagnosed with hepatocellular carcinoma (HCC), and most were in advanced stages. Symptom burden increased progressively during treatment, with high-frequency symptoms, such as fatigue, dry mouth, weight loss, and sleep disturbance, affecting more than 70% of patients by Phase 4. Factor analysis identified 5, 4, 4, and 5 significant symptom clusters at T1–T4, respectively, while Apriori analysis further revealed key antecedent symptoms such as nausea, pain, and nervousness. All five symptom clusters demonstrated significant increases in severity over time ($p < 0.001$), especially those involving emotional-psychological and gastrointestinal symptoms. QOL scores declined markedly during Phases 3 and 4, with significant impairments in physical, psychological, and social functioning (all $p < 0.01$), and an overall score reduction exceeding 20 points ($p < 0.001$). Self-reported evaluations also revealed a substantial decline. The symptom clusters exhibited moderate to strong negative correlations with QOL, with the psychiatric symptom cluster showing a progressively stronger negative association with overall QOL scores from T1 to T4 (r = –0.51 to –0.64). Regression analyses identified psychiatric and emotional–psychological clusters as the strongest predictors of reduced QOL across all treatment stages ($p < 0.001$). In later phases, liver function-metabolic and gastrointestinal clusters also emerged as significant contributors. Demographic variables, including gender and treatment phase, exerted additional effects. The regression model demonstrated a good fit and stable residuals.

Conclusions: Combined targeted-ICI therapy is associated with a progressive increase in symptom cluster burden among patients with liver cancer, leading to a significant decline in QOL. Emotional and psychological symptom clusters exert the most persistent and profound effects, while liver function–metabolic and gastrointestinal symptom clusters become increasingly prominent in later stages.

Keywords: liver malignancy; targeted therapy; immune checkpoint inhibitors; symptom clusters; quality of life; sentinel symptoms

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent and lethal malignancies worldwide. In 2020, liver cancer ranked sixth in global cancer incidence and third in cancer-related mortality, with an estimated 906,000 new cases and 830,000 deaths annually. China alone accounts for nearly half of these global figures, underscoring the substantial and rising national disease burden [1,2]. Despite advances in early detection, the 5-year survival rate for Chinese HCC patients remains below 13% [3]. Most patients are diagnosed at intermediate or advanced stages, rendering them ineligible for curative therapy and resulting in poor prognosis [4].

In recent years, systemic therapies for HCC have advanced considerably. Multi-target tyrosine kinase inhibitors (TKIs), such as sorafenib and lenvatinib, are now widely applied in advanced-stage disease. However, their efficacy as monotherapies is limited, with median overall survival ranging from 6 to 11 months [5]. The advent of immune checkpoint inhibitors (ICIs) has reshaped the therapeutic landscape, particularly with the atezolizumab-bevacizumab combination, which demonstrated significant improvements in overall and progression-free survival in the IMbrave150 trial, thereby establishing it as a first-line standard of care [3]. Ongoing clinical trials are investigating the synergistic potential of combining ICIs with TKIs to further optimize clinical outcomes [6,7].

Despite these therapeutic advances, patients undergoing combined targeted-ICI therapy often experience multiple treatment-related symptoms that adversely affect their quality of life (QOL). Previous studies report a high symptom burden among patients with hepatocellular carcinoma during therapy, commonly including fatigue, sleep disturbance (insomnia), pain, and gastrointestinal symptoms; symptom severity and composition often fluctuate across treatment phases [8]. In a recent cross-sectional study by Chen *et al*. (2024) [9], conducted at a tertiary hospital in Shanghai, network analysis with the Memorial Symptom Assessment Scale (MSAS) identified five symptom clusters: oral, gastrointestinal, fatigue, body image, and pain-sleep. Core symptoms such as pain, “feeling unlike oneself”, and nausea, as well as bridging symptoms including pruritus and abdominal distension, were found to play central roles in cluster interactions [9]. These findings highlight the clinical significance of identifying core and bridging symptoms to guide interventions, disrupt symptom cascade pathways, and preserve QOL.

However, most existing studies have primarily employed cross-sectional designs or restricted assessment to a single treatment phase, thereby lacking longitudinal insights into the evolution of symptom clusters and their relationship with QOL over time. To address this gap, the present study prospectively enrolled patients receiving combined targeted-ICI therapy at a tertiary hospital in Qingyuan, China. Comprehensive data on symptoms and QOL were collected across four consecutive treatment phases using the Chinese versions of MSAS and QOL-LC V2.0. Factor analysis, association rule mining, and multivariate regression were performed to identify key symptom clusters and sentinel symptoms, evaluate their dynamic evolution, and examine their cumulative effects on QOL. The findings aim to inform precision symptom-management strategies during combination immunotherapy for liver cancer.

Methods

Study Design and Participants

This study was conducted as a prospective longitudinal cohort investigation. Based on a preliminary literature review and clinical observations, data were collected at four predefined time points corresponding to Day 7 of each treatment phase (Phase 1 through Phase 4), with Day 1 marking the initiation of each targeted-immune combination therapy phase. Eligible participants were consecutively recruited between January and August 2025 at Qingyuan Affiliated Hospital of Guangzhou Medical University, a tertiary care center in southern China. Written informed consent was obtained from all participants. The study was approved by the institutional ethics committee (IRB No. IRB-2025-025), and was conducted following the guidelines outlined in the Declaration of Helsinki.

Inclusion Criteria

(1) Histologically or cytologically confirmed diagnosis of primary malignant liver tumor;

(2) Age $\geq$18 years;

(3) Willingness to participate and provide written informed consent;

(4) Receiving a treatment regimen including both targeted therapy and immune checkpoint inhibitors.

Exclusion Criteria

(1) History of psychiatric illness or consciousness disturbance;

(2) Communication or cognitive impairment that precluded valid questionnaire completion;

(3) Diagnosis of another concurrent malignancy;

(4) Presence of other severe life-threatening comorbidities.

Sample Size Estimation

Sample size was estimated primarily for exploratory factor analysis, following commonly used recommendations of 5–10 participants per item. In this study, a total of 23 variables were included in the analysis, yielding a required sample size of 115–230 participants. Considering an anticipated attrition rate of 10%–15% during follow-up, a minimum of 127 participants was necessary. To ensure sufficient statistical power and allow for attrition, a total of 150 patients were targeted for enrollment.

Study Measures and Data Collection

Demographic and Clinical Characteristics

A structured questionnaire was used to collect baseline demographic and clinical data. Demographic variables included age, sex, place of residence (rural, town, or urban), marital status (married, unmarried, widowed), education level (primary or below, junior high school, senior high school/vocational, college or above), parental status (with/without children), employment status (employed, retired/unemployed), type of medical coverage (insured, self-paying), and monthly household income ($<$3000 RMB, 3000–5000 RMB, $>$5000 RMB; Exchange rate: 1 USD $\approx$ 7.12 RMB). Clinical variables included tumor histology (intrahepatic cholangiocarcinoma, hepatocellular carcinoma, or mixed type), tumor staging (Ia, Ib, IIa, IIb, IIIa, IIIb, IV), and current treatment phase (Phase 1–4).

Chinese Version of the Memorial Symptom Assessment Scale (MSAS-C)

Symptom burden was assessed using the validated Chinese version of the Memorial Symptom Assessment Scale (MSAS), originally developed by Memorial Sloan Kettering Cancer Center [10,11]. The scale measures 32 common cancer-related symptoms experienced over the past week across three dimensions: frequency, severity, and distress. For the first 24 symptoms, all three dimensions were rated on a Likert scale (4 or 5 points), and a composite score was calculated as their mean. For the remaining 8 symptoms, only severity and distress were assessed. MSAS-C generates scores across four subscales: physical symptoms, psychological symptoms, global distress index, and total symptom burden. The Chinese version has demonstrated strong psychometric properties, with a content validity index of 0.94 and Cronbach's α ranging from 0.79 to 0.89. The questionnaire was administered on Day 7 of each treatment phase and completed by the patient, or, when necessary, with assistance from a trained investigator using standardized, non-leading prompts.

Symptom Onset Log

A custom-designed "Symptom Onset Log" was used to record the initial appearance of each of the 32 MSAS symptoms. Patients were asked to report the number of hours from initiation of combination therapy to first recognition of each symptom. This log was distributed prior to each treatment phase and collected on Day 7. Data were primarily self-reported, or, when required, collected with interviewer assistance either in person or via telephone.

Quality of Life Assessment: QOL-LC V2.0

Health-related quality of life (HRQOL) was evaluated using the QOL-LC V2.0 scale, specifically developed for patients with primary liver cancer by Wan *et al*. [12] and Zhu *et al*. [13]. The instrument comprises 22 items across four domains: physical function, psychological function, treatment-related symptoms and side effects, and social function. The total score ranges from 0 to 220, with higher scores indicating better perceived quality of life. An additional single-item self-evaluation scale (0–100) is included but not incorporated in the overall score. Each item is rated on a 0–10 numerical scale. The QOL-LC V2.0 has demonstrated good cultural adaptability and psychometric reliability in Chinese populations, with Cronbach's α ranging from 0.68 to 0.81. The scale was administered on Day 7 of each treatment phase and completed by patients independently or, when necessary, with assistance from a trained interviewer. Notably, higher scores in the "symptom/adverse effects" domain reflect more severe treatment-related symptoms.

Quality Control Procedures

Prior to data collection, all participants received a standardized explanation of the study objectives, significance, and confidentiality measures. Rapport was established to enhance compliance and minimize attrition. After informed consent was obtained, trained personnel delivered standardized and non-suggestive instructions for questionnaire completion. Surveys were completed independently by patients whenever possible; in cases of illiteracy or physical impairment, neutral assistance was offered by qualified investigators. All questionnaires were reviewed immediately upon submission to check for completeness, and any missing responses were clarified on site.

For telephone-administered surveys, audio recordings were monitored in real time to prevent protocol deviations, such as skipped questions or proxy responses. A subset of participants was randomly selected for follow-up verification to confirm data integrity. To further ensure accuracy, all data were double-entered independently by two trained research assistants, with discrepancies reconciled through cross-checking.

Statistical Analysis

All statistical analyses were conducted using SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA) and SPSS Modeler version 18.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized using frequencies and proportions. Normality of continuous variables was assessed using the Shapiro-Wilk test. Normally

distributed data were reported as means with standard deviations, while non-normally distributed data were presented as medians with interquartile ranges (M [P25, P75]).

1. Exploratory factor analysis (EFA) was applied to identify symptom clusters based on severity scores. Symptoms with prevalence ≥15% were included. Principal component extraction with varimax rotation was employed. Association rule mining using the Apriori algorithm was employed to identify leading (sentinel) symptoms within each symptom cluster, using data from the Symptom Onset Log. Sentinel symptoms appeared earliest in a cluster and met thresholds of support >40%, confidence >60%, and lift >1.0.
2. Longitudinal trends in symptom prevalence and symptom-related distress across four time points were analyzed using Cochran's Q test for categorical variables and the Friedman test for ordinal or non-parametric data.
3. Repeated measures analysis of variance (RM-ANOVA) was used to examine changes in symptom cluster severity scores and QOL-LC domain scores across phases. Where significant effects were observed, post-hoc pairwise comparisons were performed using Bonferroni correction. Symptom cluster severity was calculated as the mean severity score of all symptoms within a cluster, following established methods from longitudinal oncology symptom research. Spearman's rank correlation was used to assess associations between symptom clusters and quality-of-life domains. Finally, stepwise multiple linear regression was employed to determine the influence of demographic variables and symptom cluster severity on overall quality of life in patients undergoing targeted plus immune therapy for liver cancer.

Results

Baseline Characteristics of the Study Sample

A total of 150 patients with primary liver cancer receiving combined targeted and immune therapy were enrolled. The mean age was 53.62 years. The sex distribution was relatively balanced, with a slightly higher proportion of female patients (54.67%). The majority resided in urban or suburban areas (41.33%), while 30.00% and 28.67% lived in cities and rural regions, respectively. Most participants were married (65.33%), and 60.00% had completed junior high school or below. Notably, 27.33% had only primary education or less. A majority (84.67%) reported having children. In terms of employment status, 52.67% were actively employed, while the remainder were retired or unemployed. Medical insurance was the primary means of healthcare coverage for 79.33% of patients, whereas 20.67% paid entirely out of pocket. Monthly household income most frequently ranged between 3000–5000 RMB (38.00%).

In terms of pathological subtype, hepatocellular carcinoma (HCC) was the most prevalent diagnosis (67.33%), followed by intrahepatic cholangiocarcinoma (19.33%) and mixed-type liver cancer (13.33%). Patients were relatively evenly distributed across treatment phases, with the largest proportions in phase 1 (25.33%) and phase 2 (30.67%), followed by phase 4 (24.67%) and phase 3 (19.33%). According to tumor stage, the majority were classified as stage IIIa or IIIb (combined 55.34%), while 16.00% were stage IV (Table 1).

Symptom Prevalence and Severity Across Treatment Periods

Several symptoms, including fatigue, dry mouth, weight loss, and altered taste perception, were consistently prevalent across all four treatment phases (Table 2). Fatigue increased from 60.00% at T1 to 80.67% at T4; dry mouth rose from 56.67% to 80.00%. Taste alterations escalated from 44.00% at T1 to 80.67% at T4, and weight loss increased from 52.67% to 74.00%. Sleep- and mood-related symptoms also demonstrated progressive upward trends: insomnia rose progressively, reaching 76.67% at T4; somnolence and anxiety increased from 55.33% and 49.33% at T1 to 78.67% and 79.33% at T4, respectively. Emotional symptoms such as sadness and irritability showed similar late-phase intensification, with anxiety demonstrating the most pronounced increase.

Pain prevalence increased from 43.33% at T1 to 69.33% at T4. Nausea rose from 37.33% to 70.00%, and dizziness from 35.33% to 60.67%. Other physical symptoms, such as alopecia and limb swelling, also rose substantially, from 16.00% and 37.33% at T1 to 58.00% and 54.67% at T4, respectively. In contrast, specific symptoms remained consistently infrequent (<10%) throughout treatment, including sexual dysfunction, dysuria, and dysphagia. Other symptoms, such as oral ulcers, cough, vomiting, and dyspnea, remained relatively uncommon (<15%).

Symptom severity fluctuated across treatment phases. Fatigue presented a median severity score of 1 (IQR: 0, 3) at T1, increasing to 2 (1, 3) from T2 through T4. Dry mouth rose from 1 (0, 2) at T1 to 2 (1, 3) thereafter. Similar trajectories were observed for taste alteration and weight loss, with median scores stabilizing at 2 (1, 3) by T3 and T4. Insomnia increased from 0 (0, 2) at baseline to 2 (1, 3) at T4. Anxiety severity rose from 0 (0, 2.75) at T1 to 2 (1, 3) at T4, indicating a notable progression of mood and sleep disturbances. Nausea worsened from 0 (0, 2) to 2 (0, 3) by T4.

Pain was mild in early phases (T1 median = 0 [0, 2]) but increased significantly after T2, reaching 2 (0, 3) at T4. Somnolence maintained a consistent median of 2 (1, 3) during T3 and T4. Abdominal distension peaked at T2 and T3 (2 [1, 3]) but declined slightly at T4 (1 [0, 3]). Mild increases were also observed for dizziness and nausea in late stages. Symptoms such as cough, dyspnea, vomiting, sex-

Table 1. Demographic and clinical characteristics of patients with primary hepatic malignancies receiving combination targeted and immune therapy (n = 150).

Variables	Total (n = 150)
Age, Mean ± SD	53.62 ± 9.47
Sex, n (%)	
Male	68 (45.33)
Female	82 (54.67)
Place of residence, n (%)	
Urban	45 (30.00)
Town	62 (41.33)
Rural	43 (28.67)
Marital status, n (%)	
Unmarried	29 (19.33)
Married	98 (65.33)
Widowed	23 (15.33)
Educational level, n (%)	
Primary school or below	41 (27.33)
Middle school	49 (32.67)
High school/vocational school	37 (24.67)
College or above	23 (15.33)
Children, n (%)	
No	23 (15.33)
Yes	127 (84.67)
Employment status, n (%)	
Unemployed/retired	71 (47.33)
Employed	79 (52.67)
Medical payment method, n (%)	
Medical insurance	119 (79.33)
Self-pay	31 (20.67)
Monthly household income, n (%)	
<3000 RMB	49 (32.67)
3000–5000 RMB	57 (38.00)
>5000 RMB	44 (29.33)
Pathological type, n (%)	
Intrahepatic cholangiocarcinoma	29 (19.33)
Hepatocellular carcinoma	101 (67.33)
Combined hepatocellular-cholangiocarcinoma	20 (13.33)
Treatment phase, n (%)	
Phase 1	38 (25.33)
Phase 2	46 (30.67)
Phase 3	29 (19.33)
Phase 4	37 (24.67)
Tumor stage, n (%)	
Stage Ia	6 (4.00)
Stage Ib	9 (6.00)
Stage IIa	12 (8.00)
Stage IIb	16 (10.67)
Stage IIIa	43 (28.67)
Stage IIIb	40 (26.67)
Stage IV	24 (16.00)

SD, Standard deviation. 1 USD ≈ 7.12 RMB.

ual dysfunction, dysuria, dysphagia, oral ulcers, and sweating demonstrated negligible severity throughout (all medians = 0 [0, 0]). Emotional symptoms, including nervousness, sadness, and irritability, exhibited minor fluctuation in severity over time (Table 2).

Symptom Cluster Structure

Across the four observation points, the dominant symptoms and factor loadings exhibited dynamic changes, reflecting the stage-specific characteristics of patients' symptom profiles during combination targeted and immune therapy (Table 3). The neurocognitive cluster included insomnia, fatigue, dizziness, and difficulty concentrating. At T1 and T2, insomnia was the dominant symptom with the highest factor loadings (0.79 and 0.88, respectively). At T3, dizziness became predominant (loading = 0.76), while fatigue was dominant at T4 (loading = 0.87). This cluster remained structurally stable across time, with strong consistency among core symptoms.

The hepatic-metabolic cluster consistently included pain, dry mouth, and abdominal distension, with changes in taste food, loss of appetite, and weight loss emerging at specific time points. Pain was dominant at T1 (loading = 0.79), dry mouth at T2 (0.87), and pain again at T3 and T4 (0.77 and 0.76, respectively).

The emotional-psychological cluster comprised irritability, sadness, anxiety, and nervousness. This cluster remained stable across phases, with irritability consistently demonstrating the highest loading, peaking at T4 (0.80). The gastrointestinal cluster was primarily defined by nausea, anorexia, and taste alteration. These core symptoms demonstrated strong loadings at T1, T2, and T4, with anorexia reaching a loading of 0.83 at T2. Other digestive symptoms, including vomiting, constipation, and diarrhea, appeared intermittently with lower loadings, suggesting peripheral contributions to the cluster. The dermatologic–peripheral neuropathy cluster comprised limb swelling, extremity numbness/tingling, and alopecia. Limb swelling remained the central symptom at T1, T3, and T4, with the highest loading observed at T4 (0.65). Notably, alopecia and peripheral neuropathy symptoms gained prominence in later stages.

Sentinel Symptoms in Symptom Clusters

Using the Apriori association rule algorithm, incorporating the timing of symptom onset, sentinel symptoms within each symptom cluster were identified across treatment stages. At T1, nausea emerged as the primary sentinel symptom within the gastrointestinal symptom cluster. It demonstrated a moderate association with altered taste perception (support = 52.00%, confidence = 66.67%, lift = 1.06). Loss of appetite and vomiting also showed substantial co-occurrence with altered taste (support = 60.00% and 62.67%, respectively). In the liver function-metabolic cluster, dry mouth and abdominal distension were frequently

Table 2. Symptom prevalence (%) and severity [median (P25, P75)] across treatment phases (n = 150).

Symptoms	T1		T2		T3		T4	
	Occurrence, n (%)	Severity	Occurrence, n (%)	Severity	Occurrence, n (%)	Severity	Occurrence, n (%)	Severity
Difficulty concentrating	83 (55.33%)	1 (0, 2)	71 (47.33%)	0 (0, 2.75)	100 (66.67%)	2 (0, 3)	84 (56.00%)	1 (0, 3)
Pain	65 (43.33%)	0 (0, 2)	97 (64.67%)	2 (0, 3)	94 (62.67%)	1.5 (0, 3)	104 (69.33%)	2 (0, 3)
Fatigue	90 (60.00%)	1 (0, 3)	116 (77.33%)	2 (1, 3)	118 (78.67%)	2 (1, 3)	121 (80.67%)	2 (1, 3)
Cough	15 (10.00%)	0 (0, 0)	16 (10.67%)	0 (0, 0)	12 (8.00%)	0 (0, 0)	13 (8.67%)	0 (0, 0)
Feeling nervous	51 (34.00%)	0 (0, 1)	52 (34.67%)	0 (0, 2)	68 (45.33%)	0 (0, 2)	52 (34.67%)	0 (0, 2)
Dry mouth	85 (56.67%)	1 (0, 2)	115 (76.67%)	2 (1, 3)	116 (77.33%)	2 (1, 3)	120 (80.00%)	2 (1, 3)
Nausea	56 (37.33%)	0 (0, 2)	79 (52.67%)	1 (0, 3)	85 (56.67%)	1 (0, 3)	105 (70.00%)	2 (0, 3)
Drowsiness	83 (55.33%)	1 (0, 3)	95 (63.33%)	2 (0, 3)	117 (78.00%)	2 (1, 3)	118 (78.67%)	2 (1, 3)
Extremity numbness or tingling	29 (19.33%)	0 (0, 0)	28 (18.67%)	0 (0, 0)	34 (22.67%)	0 (0, 0)	29 (19.33%)	0 (0, 0)
Restless sleep	67 (44.67%)	0 (0, 2)	72 (48.00%)	0 (0, 3)	90 (60.00%)	2 (0, 3)	115 (76.67%)	2 (1, 3)
Abdominal distension	81 (54.00%)	1 (0, 3)	116 (77.33%)	2 (1, 3)	115 (76.67%)	2 (1, 3)	88 (58.67%)	1 (0, 3)
Difficulty urinating	3 (2.00%)	0 (0, 0)	2 (1.33%)	0 (0, 0)	6 (4.00%)	0 (0, 0)	0 (0.00%)	0 (0, 0)
Vomiting	14 (9.33%)	0 (0, 0)	16 (10.67%)	0 (0, 0)	19 (12.67%)	0 (0, 0)	13 (8.67%)	0 (0, 0)
Shortness of breath	17 (11.33%)	0 (0, 0)	15 (10.00%)	0 (0, 0)	16 (10.67%)	0 (0, 0)	20 (13.33%)	0 (0, 0)
Diarrhea	24 (16.00%)	0 (0, 0)	29 (19.33%)	0 (0, 0)	77 (51.33%)	1 (0, 3)	59 (39.33%)	0 (0, 2)
Feeling sad	66 (44.00%)	0 (0, 2)	63 (42.00%)	0 (0, 2)	77 (51.33%)	1 (0, 3)	68 (45.33%)	0 (0, 2)
Sweating	10 (6.67%)	0 (0, 0)	17 (11.33%)	0 (0, 0)	8 (5.33%)	0 (0, 0)	4 (2.67%)	0 (0, 0)
Feeling anxious	74 (49.33%)	0 (0, 2.75)	99 (66.00%)	2 (0, 3)	110 (73.33%)	2 (0, 3)	119 (79.33%)	2 (1, 3)
Difficulty with sexual activity	5 (3.33%)	0 (0, 0)	10 (6.67%)	0 (0, 0)	3 (2.00%)	0 (0, 0)	4 (2.67%)	0 (0, 0)
Itchy skin	22 (14.67%)	0 (0, 0)	34 (22.67%)	0 (0, 0)	50 (33.33%)	0 (0, 2)	31 (20.67%)	0 (0, 0)
Loss of appetite	87 (58.00%)	1 (0, 3)	106 (70.67%)	2 (0, 3)	110 (73.33%)	2 (0, 3)	98 (65.33%)	1 (0, 3)
Dizziness	53 (35.33%)	0 (0, 2)	77 (51.33%)	1 (0, 3)	94 (62.67%)	1 (0, 3)	91 (60.67%)	1 (0, 2)
Difficulty swallowing	2 (1.33%)	0 (0, 0)	2 (1.33%)	0 (0, 0)	0 (0.00%)	0 (0, 0)	1 (0.67%)	0 (0, 0)
Irritability	53 (35.33%)	0 (0, 2)	68 (45.33%)	0 (0, 2)	68 (45.33%)	0 (0, 2)	74 (49.33%)	0 (0, 2)
Oral ulcers	4 (2.67%)	0 (0, 0)	22 (14.67%)	0 (0, 0)	14 (9.33%)	0 (0, 0)	5 (3.33%)	0 (0, 0)
Changes in food taste	66 (44.00%)	0 (0, 2)	97 (64.67%)	2 (0, 3)	115 (76.67%)	2 (1, 3)	121 (80.67%)	2 (1, 3)
Weight loss	79 (52.67%)	1 (0, 3)	111 (74.00%)	2 (0, 3)	113 (75.33%)	2 (1, 3)	111 (74.00%)	2 (0, 3)
Hair loss	24 (16.00%)	0 (0, 0)	38 (25.33%)	0 (0, 0.75)	83 (55.33%)	1 (0, 3)	87 (58.00%)	1 (0, 3)
Constipation	27 (18.00%)	0 (0, 0)	21 (14.00%)	0 (0, 0)	24 (16.00%)	0 (0, 0)	35 (23.33%)	0 (0, 0)
Limb swelling	56 (37.33%)	0 (0, 2)	77 (51.33%)	1 (0, 3)	97 (64.67%)	2 (0, 3)	82 (54.67%)	1 (0, 2)
Feeling unlike oneself	22 (14.67%)	0 (0, 0)	20 (13.33%)	0 (0, 0)	19 (12.67%)	0 (0, 0)	24 (16.00%)	0 (0, 0)
Changes in skin	64 (42.67%)	0 (0, 2)	74 (49.33%)	0 (0, 3)	57 (38.00%)	0 (0, 2)	55 (36.67%)	0 (0, 2)

Note: Prevalence: %; Severity: median (25th percentile, 75th percentile). T1–T4: assessments conducted on Day 7 of treatment Cycles 1–4.

Table 3. Composition of symptom clusters across treatment phases (T1–T4) in patients receiving combination targeted and immune therapy.

Symptom cluster	T1 symptom	Factor loading (T1)	T2 symptom	Factor loading (T2)	T3 symptom	Factor loading (T3)	T4 symptom	Factor loading (T4)
Psychiatric Cluster	Restless sleep	0.79	Restless sleep	0.88	Dizziness	0.76	Fatigue	0.87
	Fatigue	0.73	Drowsiness	0.74	Restless sleep	0.76	Drowsiness	0.76
	Dizziness	0.67	Dizziness	0.74	Drowsiness	0.63	Dizziness	0.69
	Impaired concentration	0.59	Impaired concentration	0.50	Impaired concentration	0.42	Restless sleep	0.57
Hepatic–Metabolic Cluster	Pain	0.79	Dry mouth	0.87	Pain	0.77	Pain	0.76
	Dry mouth	0.74	Abdominal distension	0.77	Dry mouth	0.77	Abdominal distension	0.68
	Abdominal distension	0.70	Pain	0.72	Changes in taste food	0.73	Dry mouth	0.55
	–	–	–	–	Loss of appetite	0.72	Weight loss	0.50
	–	–	–	–	Weight loss	0.50	–	–
Emotional–Psychological Cluster	Irritability	0.75	Irritability	0.75	Feeling sad	0.68	Irritability	0.80
	Feeling sad	0.72	Feeling nervous	0.64	Irritability	0.63	Feeling nervous	0.62
	Feeling anxious	0.65	Feeling anxious	0.61	Feeling nervous	0.62	Feeling anxious	0.56
	Feeling nervous	0.44	Feeling sad	0.54	Feeling anxious	0.52	–	–
Gastrointestinal Cluster	Nausea	0.74	Loss of appetite	0.83	–	–	Nausea	0.73
	Changes in taste of food	0.63	Nausea	0.69	–	–	Changes in food taste	0.69
	Loss of appetite	0.53	Vomiting	0.53	–	–	Loss of appetite	0.55
	Vomiting	0.42	Constipation	0.46	–	–	Constipation	0.47
Dermatologic–Peripheral Neurological Cluster	Limb swelling	0.58	–	–	Limb swelling	0.59	Limb swelling	0.65
	Extremity numbness or tingling	0.45	–	–	Hair loss	0.41	Hair loss	0.54
	–	–	–	–	Extremity numbness or tingling	0.41	Extremity numbness or tingling	0.42

Table 4. Intra-cluster symptom associations at T1 in patients receiving combination targeted and immune therapy.

Symptom cluster	Antecedent symptom	Consequent symptom	Support (%)	Confidence (%)	Lift
Gastrointestinal Cluster	Nausea	Changes in taste of food	52.00	66.67	1.06
	Loss of appetite	Changes in taste of food	60.00	65.56	1.05
	Vomiting	Changes in taste of food	62.67	62.77	1.05
	Changes in taste of food	Nausea	60.00	60.00	1.04
Hepatic–Metabolic Cluster	Dry mouth	Abdominal distension	67.33	68.32	1.00
	Abdominal distension	Dry mouth	68.00	67.65	1.00
	Pain	Dry mouth	61.33	65.22	0.97
	Pain	Abdominal distension	61.33	65.22	0.96
Emotional–Psychological Cluster	Feeling sad	Feeling nervous	54.67	68.29	1.06
	Irritability	Feeling nervous	61.33	67.39	1.04
	Feeling nervous	Irritability	64.67	63.92	1.04
	Feeling anxious	Irritability	56.67	63.53	1.04
Psychiatric Cluster	Restless sleep	Dizziness	61.33	65.22	1.03
	Fatigue	Dizziness	56.67	64.71	1.02
	Dizziness	Restless sleep	63.33	63.16	1.03

co-reported (support = 67.33%, confidence = 68.32%). Pain also showed high confidence levels (>65.00%) with both symptoms, underscoring its central bridging role in this cluster. In the emotional–psychological cluster, sadness was identified as a sentinel symptom, strongly associated with psychological tension (support = 54.67%, confidence = 68.29%). In the psychological–cognitive cluster, dizziness was the predominant early indicator, closely linked with sleep disturbance (support = 61.33%, confidence = 65.22%) (Table 4).

At T2, nausea emerged as the dominant sentinel symptom within the gastrointestinal cluster. It was associated with loss of appetite (support = 65.33%, confidence = 70.41%, lift = 1.09) and showed sequential progression patterns with vomiting and constipation. In the psychological–cognitive cluster, dizziness and impaired concentration appeared as early indicators. Dizziness showed a strong association with sleep disturbance (confidence = 76.92%, lift = 1.17), while impaired concentration was linked to sleep disturbance (support = 63.33%, confidence = 73.68%, lift = 1.12). Within the emotional–psychological cluster, irritability emerged as an early and frequent symptom, associated with sadness and psychological tension (support >58.00%, confidence >65.00%). In the liver function–metabolic cluster, pain was the sentinel symptom, associated with abdominal distension (support = 55.33%, confidence = 63.86%) and dry mouth (support = 58.00%, confidence = 60.92%) (Table 5).

At T3, the strongest symptom pair in the psychological–cognitive cluster was impaired concentration and dizziness (support = 63.33%, confidence = 69.47%), indicating early neurocognitive disruption. Fatigue and sleep disturbance also demonstrated moderate associations. In the emotional cluster, psychological tension was the sentinel symptom, reciprocally linked to anxiety (support ~60.00%, confidence >64.00%). In the liver function–metabolic cluster, dry mouth emerged as the sentinel symptom, associated with pain and abdominal distension (support = 62.67% and 61.33%, respectively). Abdominal distension was further correlated with weight loss (Table 6).

At T4, loss of appetite became the dominant sentinel symptom in the gastrointestinal cluster, with strong associations with nausea and constipation (support = 60.67% and 52.67%, confidence >65.00%). In the psychological–cognitive cluster, sleep disturbance was the early indicator, closely associated with fatigue (support = 61.33%, confidence = 64.13%). Within the emotional–psychological cluster, psychological tension and irritability demonstrated a bidirectional association (support = 62.00%, confidence = 64.52%). In the liver function-metabolic cluster, pain again served as the sentinel symptom, with the highest stage-specific confidence in its association with weight loss (support = 54.67%, confidence = 73.17%). Dry mouth was also associated with weight loss (support = 55.33%, confidence = 65.06%) (Table 7).

Longitudinal Trends in Symptom Cluster Severity and Quality of Life Scores Across Four Treatment Phases

All five symptom clusters exhibited a statistically significant increase in severity scores from T1 to T4, indicating a pronounced time effect. For the gastrointestinal symptom cluster, severity scores remained relatively stable between T1 and T2, followed by a marked escalation at T4, reaching 3.02 $\pm$ 0.50 ($F = 52.19$, $p < 0.001$). The hepatic–metabolic cluster showed a progressive increase from 1.63 $\pm$ 0.51 at T1 to 2.57 $\pm$ 0.52 at T4 ($F = 68.24$, $p < 0.001$), with T3 and T4 significantly higher than T1 and T2 (all $p < 0.001$). The emotional–psychological cluster increased from 1.85 $\pm$ 0.50 at T1 to 2.77 $\pm$ 0.51 at T4 ($F = 96.61$, $p < 0.001$), with significant differences observed across all timepoints ($p < 0.001$). The psychiatric symp-

Table 5. Intra-cluster symptom associations at T2 in patients receiving combination targeted and immune therapy.

Symptom cluster	Antecedent symptom	Consequent symptom	Support (%)	Confidence (%)	Lift
Gastrointestinal Cluster	Nausea	Loss of appetite	65.33	70.41	1.09
	Constipation	Nausea	58.00	63.22	1.05
	Loss of appetite	Nausea	58.00	62.07	1.07
	Nausea	Vomiting	58.00	62.07	1.07
Psychiatric Cluster	Dizziness	Restless sleep	52.00	76.92	1.17
	Impaired concentration	Restless sleep	63.33	73.68	1.12
	Dizziness	Impaired concentration	52.00	71.79	1.13
	Restless sleep	Impaired concentration	66.00	70.71	1.12
	Dizziness	Drowsiness	52.00	65.38	1.05
Emotional–Psychological Cluster	Irritability	Feeling sad	61.33	67.39	1.01
	Feeling nervous	Irritability	58.67	65.91	1.07
	Irritability	Feeling nervous	61.33	63.04	1.07
Hepatic–Metabolic Cluster	Pain	Abdominal distension	55.33	63.86	1.05
	Dry mouth	Pain	58.00	60.92	1.00

Table 6. Intra-cluster symptom associations at T3 in patients receiving combination targeted and immune therapy.

Symptom cluster	Antecedent symptom	Consequent Symptom	Support (%)	Confidence (%)	Lift
Psychiatric Cluster	Difficulty concentrating	Dizziness	63.33	69.47	1.05
	Drowsiness	Dizziness	56.67	69.41	1.05
	Restless sleep	Dizziness	58.00	67.82	1.03
	Dizziness	Impaired concentration	66.00	66.67	1.05
Emotional–Psychological Cluster	Feeling nervous	Feeling anxious	59.33	66.29	1.09
	Feeling anxious	Feeling nervous	60.67	64.84	1.09
Hepatic–Metabolic Cluster	Dry mouth	Pain	62.67	62.77	1.04
	Abdominal distension	Weight loss	62.67	62.77	1.03
	Pain	Dry mouth	63.33	62.11	1.04
	Dry mouth	Abdominal distension	61.33	63.04	1.00
	Changes in taste of food	Loss of appetite	53.33	66.25	1.16

tom cluster increased gradually from 1.95 ± 0.50 at T1 to 2.54 ± 0.47 at T4, indicating a clear time effect (F = 41.98, $p < 0.001$), with all inter-timepoint comparisons statistically significant ($p < 0.05$). A similar upward trend was observed for the cutaneous–peripheral nervous cluster (F = 37.82, $p < 0.001$) (Table 8).

In parallel, QOLscores across all domains declined to varying degrees. The physical functioning domain showed an overall reduction (F = 10.63), with the lowest score observed at T3 (41.54 ± 14.08). Although a slight rebound occurred at T4 (43.24 ± 10.20), it remained significantly lower than T1 (47.84 ± 10.25; $p < 0.001$). Psychological functioning scores declined progressively (F = 6.76), with significant reductions at T3 and T4 relative to T1 ($p < 0.01$ and $p < 0.001$, respectively), suggesting an increasing emotional burden. Social functioning scores decreased consistently (F = 7.68), reaching the lowest point at T3 (33.71 ± 11.33), with T4 scores remaining significantly lower than T1 ($p < 0.001$). In contrast, side effect scores increased steadily over the treatment course, from 34.65 ± 9.97 at T1 to 43.35 ± 6.58 at T4 (F = 20.05), with significant differences evident from T2 onward. The total QOL score declined markedly with treatment progression (F = 34.66), reaching its lowest value at T4 (157.64 ± 23.10), significantly lower than T1 (178.96 ± 18.87) and all intermediate timepoints ($p < 0.001$). Self-evaluation scores followed a similar downward trajectory (F = 9.57), with T4 (58.91 ± 16.73) significantly lower than T1 through T3 (all $p < 0.05$) (Table 9).

Correlations Between Symptom Clusters and Quality of Life

At baseline (T1), the psychiatric symptom cluster exhibited moderate negative correlations with most QOL domains, with the strongest associations observed for overall QOL (r = –0.51), psychological functioning (r = –0.48), physical functioning (r = –0.47), and self-evaluation (r = –0.46), all statistically significant ($p < 0.01$). The emotional–psychological symptom cluster showed strong inverse correlations with psychological functioning (r = –0.46) and self-evaluation (r = –0.47). The hepatic–metabolic symptom cluster was primarily associated with self-evaluation (r = –0.47). The gastrointestinal symptom cluster demonstrated moderate negative correlations with physical functioning (r = –0.37) and self-evaluation (r = –0.47). In contrast, the cutaneous–peripheral nervous symp-

Table 7. Intra-cluster symptom associations at T4 in patients receiving combination targeted and immune therapy.

Symptom cluster	Antecedent symptom	Consequent symptom	Support (%)	Confidence (%)	Lift
Gastrointestinal Cluster	Loss of appetite	Nausea	60.67	67.03	1.03
	Loss of appetite	Constipation	52.67	65.82	1.01
	Constipation	Loss of appetite	54.00	65.43	1.00
Psychiatric Cluster	Restless sleep	Fatigue	61.33	64.13	1.05
	Fatigue	Restless sleep	61.33	64.13	1.05
	Dizziness	Drowsiness	55.33	63.86	1.04
	Dizziness	Fatigue	55.33	62.65	1.02
Emotional–Psychological Cluster	Feeling nervous	Irritability	62.00	64.52	1.03
	Irritability	Feeling nervous	62.67	63.83	1.03
	Feeling anxious	Feeling nervous	56.67	61.18	0.99
	Feeling anxious	Irritability	56.67	60.00	0.96
Hepatic–Metabolic Cluster	Pain	Weight loss	54.67	73.17	1.11
	Dry mouth	Weight loss	55.33	65.06	1.03
	Weight loss	Pain	66.00	60.61	1.10

Table 8. Longitudinal changes in the severity of individual symptom clusters across four treatment phases.

Symptom cluster	T1 (Mean ± SD)	T2 (Mean ± SD)	T3 (Mean ± SD)	T4 (Mean ± SD)	F	*p*-value
Psychiatric cluster	1.95 ± 0.50	2.16 ± 0.50 ***	2.40 ± 0.48 ***/###	2.54 ± 0.47 ***/###/^	41.98	<0.001
Liver function-metabolic cluster	1.63 ± 0.51	2.22 ± 0.50 ***	2.50 ± 0.49 ***/###	2.57 ± 0.52 ***/###	68.24	<0.001
Emotional–psychological cluster	1.85 ± 0.50	2.28 ± 0.48 ***	2.58 ± 0.51 ***/###	2.77 ± 0.51 ***/###/^^	96.61	<0.001
Gastrointestinal cluster	1.99 ± 0.49	2.07 ± 0.53	–	3.02 ± 0.50 ***/###	52.19	<0.001
Cutaneous–peripheral neuropathy cluster	1.75 ± 0.45	–	2.34 ± 0.49 ***	2.45 ± 0.48 ***/^	37.82	<0.001

Notes: ***$p < 0.001$ vs. T1; $^{###}p < 0.001$ vs. T2; ^$p < 0.05$, ^^$p < 0.01$ vs. T3.

tom cluster displayed overall weak correlations, most of which were not significant. For the side-effect domain, all symptom clusters were positively correlated, particularly the psychiatric (r = 0.49) and hepatic–metabolic clusters (r = 0.44) (Fig. 1A).

At T2, correlations strengthened. The psychiatric cluster showed the strongest inverse associations with overall QOL (r = –0.55), physical functioning (r = –0.54), and self-evaluation (r = –0.51), all highly significant ($p < 0.001$). The emotional–psychological cluster maintained moderate-to-strong negative correlations with social functioning (r = –0.51), psychological functioning (r = –0.48), and self-evaluation (r = –0.51). Notably, the hepatic–metabolic cluster showed an increased positive correlation with the side-effect domain (r = 0.51). Meanwhile, the gastrointestinal cluster continued to display moderate negative correlations with overall QOL (r = –0.41) and self-evaluation (r = –0.46) (Fig. 1B).

By T3, the strength of associations further intensified. The psychiatric cluster showed the most pronounced inverse correlations, particularly with psychological functioning (r = –0.63), overall QOL (r = –0.62), and self-evaluation (r = –0.57). The emotional–psychological cluster maintained moderate-to-strong negative correlations with psychological functioning (r = –0.60) and self-evaluation (r = –0.56). The hepatic–metabolic cluster demonstrated stronger negative associations, most notably with physical functioning (r = –0.53), overall QOL (r = –0.55), while showing a positive correlation with side effects (r = 0.60). The cutaneous–peripheral nervous cluster remained weakly correlated (Fig. 2A).

At T4, correlation coefficients reached their peak. The psychiatric symptom cluster showed significant negative associations across all QOL domains, including psychological functioning (r = –0.65), overall QOL (r = –0.64), physical functioning (r = –0.59), and self-evaluation (r = –0.60), all at $p < 0.001$. The hepatic–metabolic cluster also demonstrated strong associations, especially with physical functioning (r = –0.60), side effects (r = 0.60), overall QOL (r = –0.63), and self-evaluation (r = –0.63). The gastrointestinal cluster exhibited stronger correlations at this stage, particularly with self-evaluation (r = –0.64), psychological functioning (r = –0.58), and physical functioning (r = –0.58). The cutaneous–peripheral nervous cluster re-

Table 9. Longitudinal changes in quality-of-life (QOL) dimension scores across four treatment phases.

QOL Domain	T1 (Mean ± SD)	T2 (Mean ± SD)	T3 (Mean ± SD)	T4 (Mean ± SD)	F	*p*-value
Physical domain	47.84 ± 10.25	45.57 ± 8.69 *	41.54 ± 14.08 ***/##	43.24 ± 10.20 ***/#	10.63	<0.001
Psychological domain	48.87 ± 9.20	47.18 ± 9.54	45.95 ± 8.82 **	44.31 ± 9.88 ***/#	6.76	<0.001
Social domain	38.99 ± 7.21	36.70 ± 10.59 *	33.71 ± 11.33 ***/#	35.52 ± 8.86 ***	7.68	<0.001
Side-effect domain	34.65 ± 9.97	38.37 ± 8.16 ***	39.79 ± 9.51 ***	43.35 ± 6.58 ***/###/^^^	20.05	<0.001
Overall QOL score	178.96 ± 18.87	169.13 ± 18.87 ***	159.51 ± 24.10 ***/###	157.64 ± 23.10 ***/###	34.66	<0.001
Self-evaluation	69.39 ± 14.92	65.31 ± 18.23 *	63.03 ± 19.38 **	58.91 ± 16.73 ***/###/^	9.57	<0.001

Notes: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. T1; #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$ vs. T2; ^$p < 0.05$, ^^^$p < 0.001$ vs. T3.

mained the least correlated, with consistently weak coefficients across most QOL domains (Fig. 2B).

Collectively, the psychiatric and emotional–psychological clusters emerged as the primary determinants of QOL across all four treatment phases, with their negative associations becoming progressively stronger over time. The influence of hepatic–metabolic and gastrointestinal clusters was more pronounced at T3 and T4, particularly for side effects, physical functioning, and self-evaluation. In contrast, the influence of the cutaneous–peripheral nervous cluster remained minimal throughout the study period.

Multivariate Regression Analysis

To examine the impact of demographic characteristics and symptom clusters on QOL in patients with hepatocellular carcinoma receiving combination targeted and immunotherapy, stepwise multivariate linear regression analyses were performed at each treatment time point.

At baseline (T1), the psychiatric symptom cluster ($\beta = -16.13$, $p < 0.001$) and emotional–psychological cluster ($\beta = -12.76$, $p < 0.001$) were significant negative predictors of overall QOL. Male sex was positively associated with QOL ($\beta = 9.25$, $p = 0.012$), suggesting greater self-reported well-being among male patients. Although other symptom clusters (hepatic–metabolic, gastrointestinal, and cutaneous–peripheral nervous) did not reach statistical significance ($p > 0.05$), the negative direction of their coefficients suggested a consistent adverse trend across domains (Fig. 3A).

At T2, the psychiatric cluster ($\beta = -23.01$, $p < 0.001$), emotional–psychological cluster ($\beta = -11.69$, $p = 0.0019$), and gastrointestinal cluster ($\beta = -9.93$, $p = 0.016$) remained significant negative predictors. The hepatic–metabolic cluster and parental status showed marginal significance ($p = 0.051$), but both contributed consistently to the model. Educational attainment was not significantly associated with QOL (Fig. 3B).

By T3, the psychiatric ($\beta = -17.63$, $p < 0.001$), emotional–psychological ($\beta = -13.32$, $p < 0.001$), and hepatic–metabolic ($\beta = -7.66$, $p = 0.022$) all exerted significant adverse effects on QOL (Fig. 3C).

At T4, this pattern persisted. The psychiatric cluster ($\beta = -15.74$, $p < 0.001$), emotional–psychological cluster ($\beta = -15.95$, $p < 0.001$), hepatic–metabolic cluster ($\beta = -15.49$, $p < 0.001$), and gastrointestinal cluster ($\beta = -8.95$, $p = 0.022$) were independently associated with poorer QOL. Additionally, treatment duration emerged as a significant predictor ($\beta = -5.26$, $p = 0.0044$), reflecting cumulative burden. Although marital status and tumor histology did not achieve statistical significance, both variables approached the threshold, suggesting potential explanatory relevance (Fig. 3D).

Model diagnostics using residual plots confirmed the adequacy of the linear regression assumptions. Across all four time points, residuals were symmetrically distributed around zero and exhibited random scatter without evidence of heteroscedasticity or systematic deviation, indicating robust model fit and compliance with linear regression assumptions (Fig. 4).

Subgroup Multivariate Regression Analyses by Pathological Type

To further elucidate the associations between symptom clusters and overall QOL across pathological subtypes, subgroup multivariate regression analyses were conducted for T1–T4 (**Supplementary Figs. 1–4**). At T1, the psychiatric cluster emerged as a significant negative predictor for both ICC ($\beta = -31.33$, $p = 0.031$) and CHC ($\beta = -38.43$, $p = 0.019$). Additionally, the hepatic–metabolic cluster exhibited adverse effects in HCC (**Supplementary Fig. 1**). At T2, the psychiatric cluster remained significant in ICC ($\beta = -43.86$, $p = 0.023$), while the gastrointestinal cluster demonstrated a borderline effect. In contrast, HCC was characterized by a positive association of the hepatic–metabolic cluster with QOL ($\beta = 20.21$, $p = 0.036$). For CHC, the emotional–psychological cluster was the primary driver of reduced QOL ($\beta = -37.54$, $p = 0.01$) (**Supplementary Fig. 2**).

At T3, the effect of the psychiatric cluster weakened in ICC ($\beta = -11.71$, $p = 0.05$), while the emotional–psychological cluster demonstrated a positive association ($\beta = 31.23$, $p = 0.041$). In HCC, both the hepatic–metabolic ($\beta = -14.90$, $p = 0.03$) and emotional–psychological clusters ($\beta = -18.01$, $p = 0.025$) exerted adverse predictive effects (**Supplementary Fig. 3**). At T4, the psychiatric cluster again exerted strong negative effects across all pathological subtypes: ICC ($\beta = -39.91$, $p = 0.0022$), HCC (β

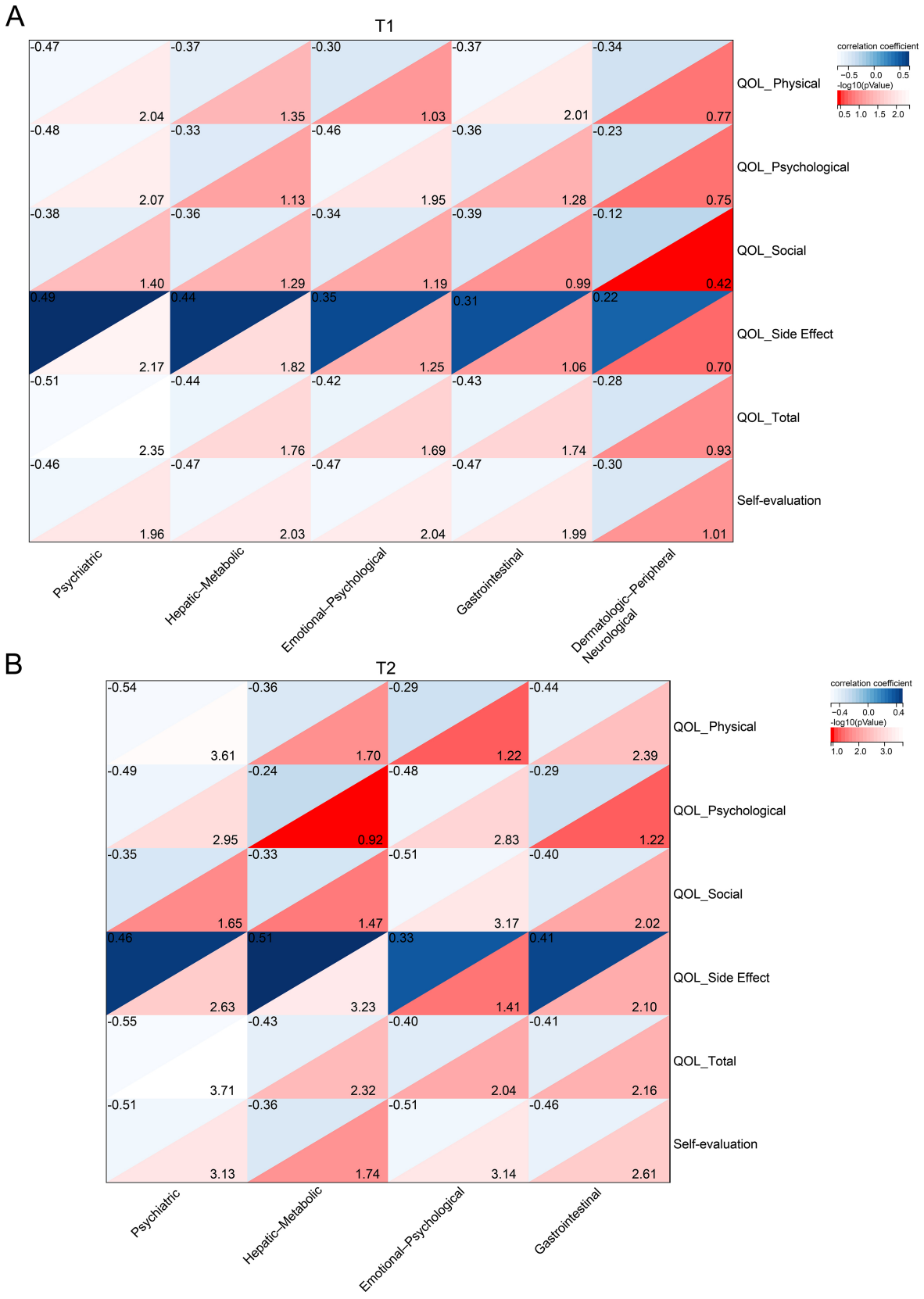

Fig. 1. Heatmaps of correlations between symptom clusters and quality of life (QOL) domains at T1 (A) and T2 (B). Each matrix cell is divided into two triangles: the upper-left displays Spearman correlation coefficients (r), while the lower-right triangle shows statistical significance as $-\log_{10}(p)$. Significance thresholds are defined as $-\log_{10}(p) > 1.3$ ($\approx p < 0.05$), >2 ($\approx p < 0.01$), >3 ($\approx p < 0.001$).

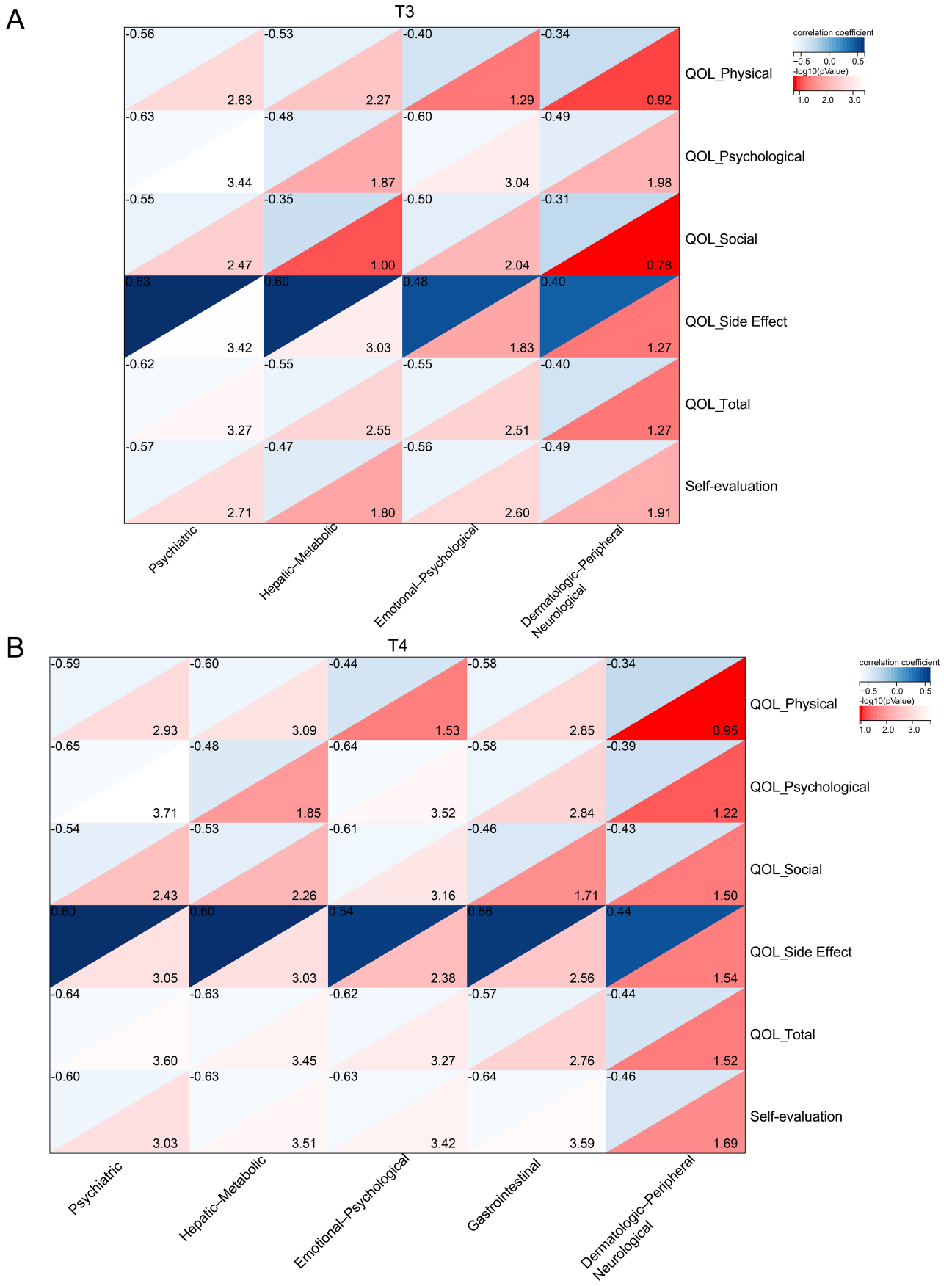

Fig. 2. Heatmaps of correlations between symptom clusters and QOL domains at T3 (A) and T4 (B). Spearman correlation coefficients (r) are shown in the upper-left triangle of each cell, and $-\log_{10}(p)$ values are presented in the lower-right triangle.

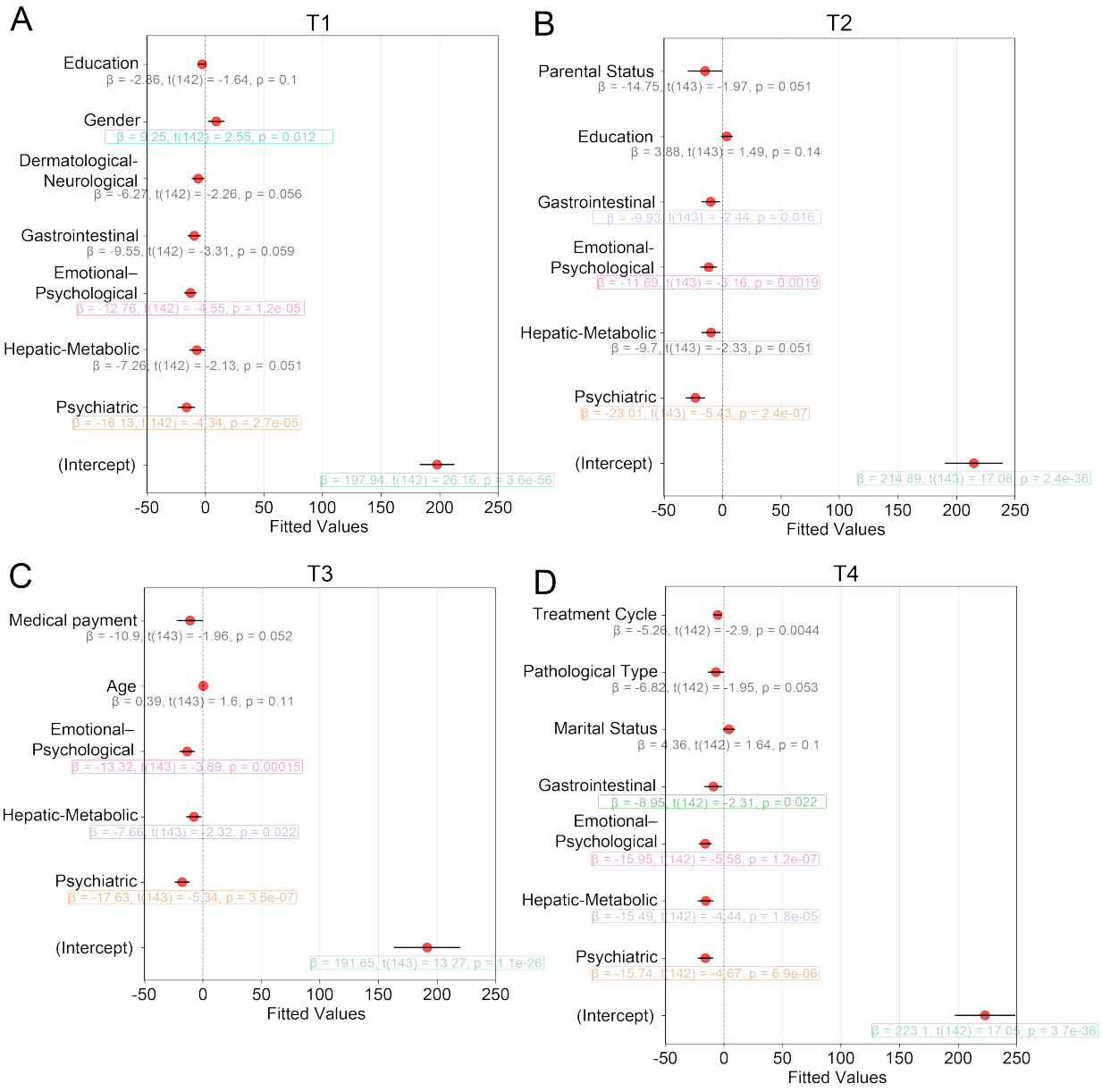

Fig. 3. Stepwise multivariate linear regression models predicting overall QOL scores from symptom clusters and demographic covariates across four treatment stages (T1–T4). Panels (A–D) correspond to T1 through T4, respectively. The x-axis shows fitted standardized regression coefficients (β), indicating the direction and magnitude of impact for each variable on QOL. The y-axis lists the predictor variables, including five symptom clusters and relevant demographic covariates. Red dots denote β estimates, and horizontal lines indicate 95% confidence intervals. Values in parentheses report β, degrees of freedom, *t*-statistics, and *p*-values.

= –17.55, p = 0.016), and CHC (β = –59.44, p = 0.024) (**Supplementary Fig. 4**). Concurrently, the hepatic–metabolic cluster remained a consistent negative predictor in ICC (β = –14.45, p = 0.02) and HCC (β = –12.59, p = 0.038). Collectively, these findings indicate that the psychiatric cluster consistently represents a universal negative driver of QOL across pathological subtypes and treatment phases. In contrast, the hepatic–metabolic and emotional–psychological clusters exhibited more subtype-specific effects, with stronger influences observed in HCC and CHC patients.

Discussion

This study systematically evaluated symptom prevalence, symptom cluster structures, and their impact on QOL across four treatment phases in patients with primary liver malignancies undergoing combined targeted therapy and immune checkpoint inhibition. Systemic symptoms such as fatigue, appetite loss, and weight loss were frequently reported [14] and progressively worsened, consistent with the established adverse effects of targeted agents and disease progression. Agents such as lenvatinib are

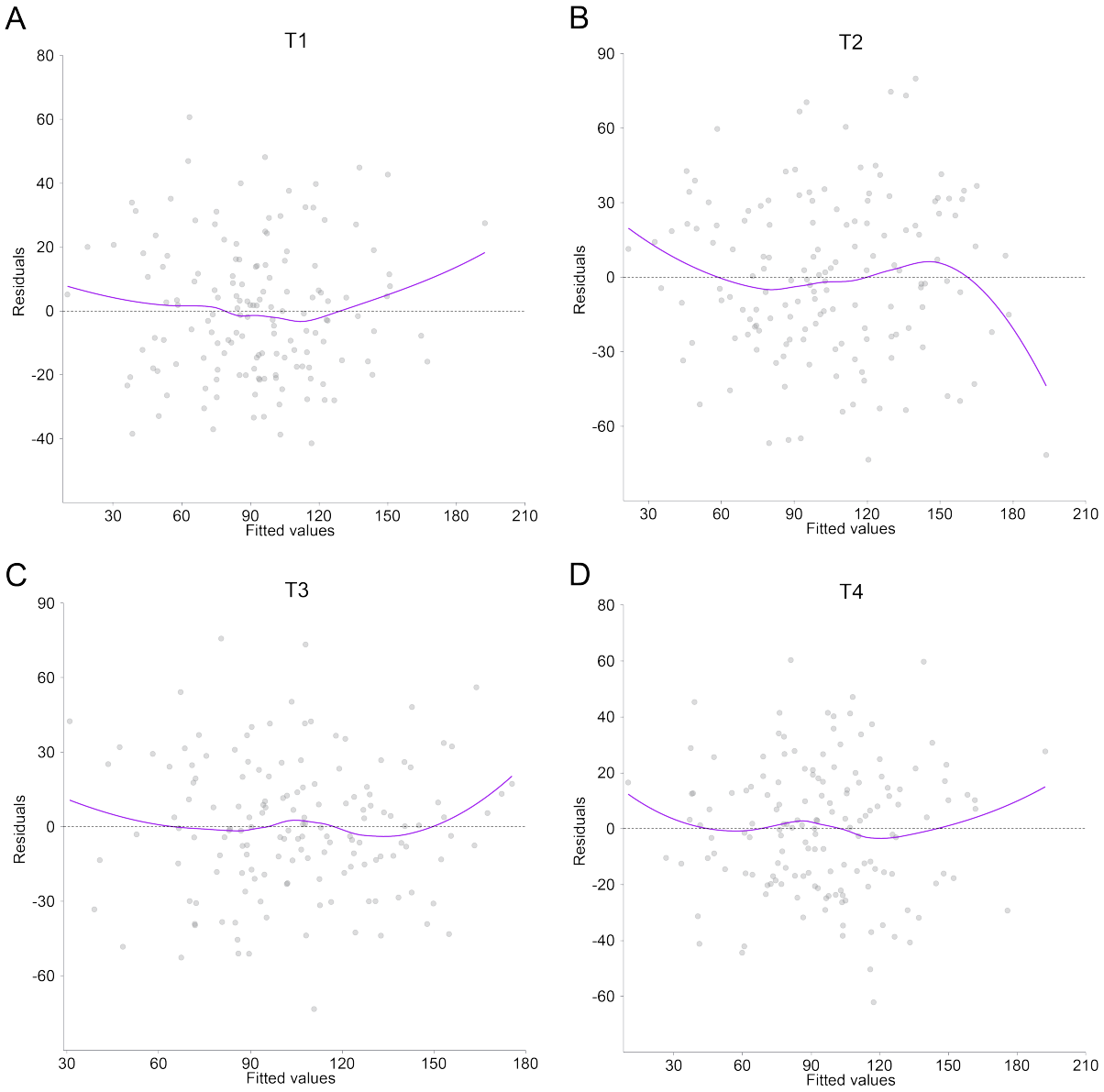

Fig. 4. Residual plots for multivariate linear regression models predicting QOL across T1–T4 (A–D). Each plot displays standardized residuals plotted against predicted QOL scores to evaluate model validity. Symmetrical, pattern-free distributions confirm that regression assumptions were satisfied.

frequently associated with anorexia and weight loss [15], which may explain the increased prevalence of xerostomia, dysgeusia, and weight loss observed in our cohort. The frequent co-occurrence of xerostomia and taste alterations suggests mucosal or salivary gland involvement, consistent with previously reported strong associations between "taste alteration–dry mouth" clusters in patients receiving combined immunotherapy [9]. The high prevalence of emotional tension and anxiety likely reflects the substantial psychological burden experienced by patients with advanced hepatocellular carcinoma (HCC). A previous study has shown that 64–65% of advanced HCC patients present with anxiety or depression, with significant adverse effects on QOL [16]. In our study, the prevalence of anxiety symptoms approached 80% at later treatment stages. One previous study identified a high-risk subgroup of patients whose quality of life progressively deteriorated during immunotherapy, particularly with respect to fatigue and emotional functioning, findings consistent with the adverse influence of psychiatric and emotional–psychological symptom clusters observed in our cohort [17]. The progressive increase in sleep disturbances may reflect a bidirectional interaction with pain and anxiety, contributing to a self-perpetuating phase of insomnia, fatigue, and cognitive decline. These findings are consistent with previous symptom cluster analyses in HCC populations, including the high-

frequency clusters described by Ryu *et al*. [18], such as "pain–appetite loss", "fatigue-related", and "gastrointestinal" clusters. While combination therapy has significantly extended survival, it also imposes cumulative toxicities that intensify symptom burden during prolonged treatment.

The types and compositions of symptom clusters identified at each treatment phase differed, indicating stage-dependent structural variations, with dominant symptoms dynamically evolving as treatment progressed. For example, in the hepatic–metabolic cluster, pain served as the central symptom, frequently co-occurring with xerostomia and abdominal bloating. This pattern resembles the "pain–bloating" bridging cluster reported by Chen *et al*. [9] in patients receiving immune-based therapy. Symptom complexes such as xerostomia, anorexia, abdominal distension, and cachexia are recognized features of HCC-related syndromes [8]. Furthermore, a study has demonstrated that patients treated with sorafenib often experience appetite loss and malnutrition, occasionally requiring dose reduction or discontinuation [19]. Therefore, the hepatic–metabolic cluster may serve as a clinical surrogate for hepatic decompensation and systemic catabolism. Early recognition of xerostomia, abdominal distension, or unexplained weight loss should prompt timely liver function reassessment and initiation of anti-inflammatory and nutritional support to delay organ failure and mitigate symptom burden.

Gastrointestinal toxicity, including anorexia and diarrhea, is frequently reported with tyrosine kinase inhibitors used in liver cancer [20]. Similarly, immune-related adverse events (irAEs) involving the gastrointestinal tract, such as anorexia, nausea, vomiting, diarrhea, and constipation, are commonly observed in patients receiving immune checkpoint blockade [21]. In our study, early treatment phases (T1–T2) identified nausea as the sentinel symptom within the gastrointestinal cluster, possibly reflecting the acute effects of inflammation and treatment-related toxicity. By T4, anorexia became the primary complaint. These findings suggest that sentinel gastrointestinal symptoms reflect the cumulative effects of tumor burden, hepatic insufficiency, and therapy-induced toxicity, underscoring the need for early, targeted symptom management, especially for nausea and appetite loss.

The emotional–psychological cluster was characterized by symptoms including sadness, psychological tension, anxiety, and irritability, which are common manifestations of depressive and anxious states. In the psychiatric cluster, sleep disturbance predominated during the early phases, whereas dizziness and fatigue became more prominent at T3–T4, reflecting a progressive decline in cognitive and physical functioning. Epidemiological evidence indicates that approximately 25% of patients with HCC experience depressive symptoms, and about 22% report anxiety [22], highlighting the clinical significance of mood disorders in this population. Emotional symptoms such as sadness and anxiety frequently appear in early disease stages and may exacerbate physical complaints such as fatigue as the disease advances [8,22]. Therefore, routine psychological screening should be incorporated into HCC care pathways, with early intervention for patients exhibiting signs of emotional distress, as this may help reduce overall symptom burden and improve clinical outcomes.

Symptom severity scores increased significantly over time across all clusters, indicating a progressive escalation in symptom burden. Gastrointestinal symptoms remained relatively stable during the first two treatment phases but exhibited marked exacerbation by the fourth phase. In contrast, the hepatic–metabolic and emotional symptom clusters demonstrated a continuous upward trajectory. Previous studies have consistently shown that higher symptom burden is associated with poorer QOL [16,18], a finding corroborated by our results. Patients with elevated symptom burden exhibited substantially worse functional status and QOL. Notably, in a comparative study of immunotherapy plus VEGF inhibition (atezolizumab plus bevacizumab) versus sorafenib, although dual therapy conferred superior survival benefits, patient-reported outcomes also demonstrated more clinically meaningful improvements in QOL, functional status, and symptom control [23]. These observations underscore the significance of symptom management even within the context of more effective combination regimens. In our study, increasing side effect scores, coupled with significantly reduced global QOL scores by the fourth phase, suggest a clear deterioration in patients' subjective well-being across functional and symptomatic dimensions. Collectively, these findings emphasize the critical role of comprehensive symptom-targeted interventions in preserving QOL during treatment.

Our analysis revealed that a constellation of co-occurring symptoms exerts a pronounced negative impact on QOL in patients with advanced liver cancer receiving targeted immunotherapy. Among these, psychiatric symptoms, including fatigue, cognitive dysfunction, and sleep disturbance, together with mood-related symptoms such as anxiety and depression, emerged as principal drivers of diminished QOL. These symptom clusters exhibited robust inverse associations with both global and psychological QOL domains across all treatment phases, with this negative correlation intensifying over time. Previous literature has demonstrated significant associations between pain, fatigue, and reduced health-related QOL in hepatocellular carcinoma, suggesting that both physical discomfort and psychological distress compromise the lived experience of patients. Furthermore, fatigue is a frequently reported irAE associated with checkpoint inhibitors [24], potentially exacerbating psychiatric and emotional symptomatology. These findings highlight the need for proactive monitoring and management of psychiatric and emotional symptoms throughout the course of targeted immunotherapy to mitigate their cumulative impact on QOL.

The adverse effects of hepatic–metabolic and gastrointestinal symptom clusters became increasingly evident during later stages of treatment. Although these clusters demonstrated relatively weak associations with QOL during early phases (T1–T2), their negative correlations with global scores, self-perceived health status, and physical and treatment-related domains intensified markedly in phases T3 and T4, peaking in the final phase. This trajectory likely reflects cumulative treatment toxicity in conjunction with advancing disease. For example, an IMbrave150 trial and related study reported that approximately 20% of patients receiving atezolizumab–bevacizumab therapy developed elevated liver enzymes and hepatic dysfunction, while 17–18% experienced gastrointestinal toxicities such as diarrhea and anorexia [25]. These adverse events not only indicate organ impairment but also directly compromise the physical functioning and subjective well-being of patients, thereby lowering both physiological and overall QOL scores. Hepatotoxicity (e.g., elevations in AST/ALT) and persistent gastrointestinal disturbances have been recognized as frequent and potentially long-lasting immune-related toxicities [26]. In our regression models, coefficients for hepatic–metabolic and gastrointestinal symptom clusters increased progressively over time, suggesting that their predictive value for QOL deterioration strengthened during later treatment phases. These findings highlight the importance of early and continuous monitoring of liver function and nutritional status, with timely management of metabolic disturbances, anorexia, and gastrointestinal symptoms, to preserve QOL throughout therapy.

Multivariate regression analyses further quantified the independent predictive contributions of each symptom cluster to QOL. Across all timepoints, psychiatric symptoms consistently exhibited the strongest negative regression coefficients, underscoring their role as robust predictors of QOL decline, even after adjusting for other covariates. Emotional–psychological symptoms also emerged as significant negative predictors across all treatment stages. Conversely, hepatic–metabolic and gastrointestinal clusters entered the regression models only during later treatment phases (T3 and T4), suggesting that their influence on QOL becomes more pronounced as cumulative toxicity develops. Male sex was associated with better QOL at baseline (T1), potentially reflecting sex-related differences in physiological or psychological resilience. However, this effect was not sustained in subsequent phases, likely due to the overriding influence of accumulating symptom burden. Notably, treatment duration emerged as a significant negative predictor at T4, implying that extended treatment is associated with progressive QOL decline, most likely reflecting cumulative toxicity and disease progression. Overall, the multivariate findings were consistent with univariate correlations, reinforcing the central role of psychiatric and emotional symptom clusters in determining QOL outcomes. Consistent with these observations, Chen *et al*. [9] demonstrated that interventions targeting core and "bridge" symptoms can disrupt symptom cluster dynamics and improve patient-reported outcomes. The quantitative evidence from our study provides a rationale for precision-targeted interventions. Previous research has similarly identified fatigue, emotional distress, and impaired social functioning as the most prevalent and disruptive determinants of QOL in HCC patients, aligning with our findings that psychiatric and emotional–psychological symptom clusters exert a predominant negative influence [27].

The present study is among the first to apply a symptom cluster analytical framework to patients with hepatocellular carcinoma (HCC) undergoing combined targeted and immune-based therapies. It systematically evaluated the temporal and multidimensional dynamics between symptom clusters and QOL. Several limitations warrant consideration. First, the study was conducted in a single tertiary hospital, which may limit the generalizability of the findings. Multicenter investigations with larger and more diverse cohorts are warranted to validate these results. Second, symptom assessment relied exclusively on patient-reported outcomes, which, while effectively capturing subjective experiences, are inherently susceptible to recall bias and underreporting. Incorporating objective biomarkers such as liver function indices, cytokine profiles, or imaging parameters in future studies could enhance the biological validity of symptom cluster identification. Third, the follow-up period was restricted to four treatment phases, precluding assessment of delayed immune-related toxicities and long-term quality-of-life trajectories. Extending follow-up to at least 6–12 months in future studies would allow a more comprehensive evaluation of symptom evolution and cumulative therapeutic burden.

Conclusions

This study provides a comprehensive assessment of longitudinal changes in QOL, symptom cluster structures, and sentinel symptom characteristics in patients with liver cancer receiving targeted immunotherapy. We observed that overall QOL progressively declined throughout the treatment course, particularly during phases T3 and T4, reflecting the cumulative impact of treatment-related toxicities and hepatic impairment on physical, psychological, and social functioning. Gastrointestinal, psychiatric, emotional, and metabolic clusters demonstrated stable co-occurrence patterns across treatment stages, suggesting strong interdependence and dynamic co-evolution. Sentinel symptoms identified via the Apriori algorithm, such as nausea, dizziness, tension, and pain, demonstrated distinct temporal progression and strong co-associations with other symptoms, highlighting their pivotal role in the formation and amplification of symptom clusters. These findings underscore the need for stage-specific, coordinated symptom management strategies in clinical practice. Targeting sentinel symptoms

may facilitate personalized, anticipatory care models. Furthermore, dynamic monitoring tools should be integrated into routine care to facilitate longitudinal assessment and remote management of QOL during systemic treatment.

Availability of Data and Materials

The datasets analyzed during current study are available from the corresponding author upon reasonable request.

Author Contributions

BH and MXQ performed most of the experiments, analyzed the data, and drafted the manuscript. LH was mainly involved in the acquisition of data and article writing. WW and SMC interpreted the data and critically revised the manuscript. MYH and DM contributed to experiment coordination, data verification and critical manuscript revision. CJC contributed to the project design and critically revised the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted with the authorization of Medical Research Ethics Review Committee of Qingyuan Affiliated Hospital of Guangzhou Medical University (Ethical approval No.: IRB-2025-025), and was conducted following the guidelines outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202537202.227.

References

[1] Li Q, Cao M, Lei L, Yang F, Li H, Yan X, *et al*. Burden of liver cancer: From epidemiology to prevention. Chinese Journal of Cancer Research = Chung-kuo Yen Cheng Yen Chiu. 2022; 34: 554–566. https://doi.org/10.21147/j.issn.1000-9604.2022.06.02.

[2] Li M, He H, Zhao X, Guan M, Khattab N, Elshishiney G, *et al*. Trends in burden of liver cancer and underlying etiologies in China, 1990−2021. The Lancet Regional Health – Western Pacific. 2025; 55: 101385. https://doi.org/10.1016/j.lanwpc.2024.101385.

[3] Wu Y, Lin H, You X, Guo T, Sun T, Xu H, *et al*. Immune Checkpoint Blockade in Chinese Patients With Hepatocellular Carcinoma: Characteristics and Particularity. Frontiers in Oncology. 2022; 12: 764923. https://doi.org/10.3389/fonc.2022.764923.

[4] Yan H, Xu J, Li Z, Li N, Guo X, Wu M, *et al*. Efficacy of radiotherapy combined with targeted therapy and immunotherapy for lymph node metastasis of liver cancer. Journal of Cancer Research and Clinical Oncology. 2025; 151: 129. https://doi.org/10.1007/s00432-025-06182-1.

[5] Huang A, Yang XR, Chung WY, Dennison AR, Zhou J. Targeted therapy for hepatocellular carcinoma. Signal Transduction and Targeted Therapy. 2020; 5: 146. https://doi.org/10.1038/s41392-020-00264-x.

[6] Gan B, Wu L, Zhou S, Chen Z, Wu F, Xu L, *et al*. Comprehensive analysis of publications concerning combinations of immunotherapy and targeted therapies for hepatocellular carcinoma: a bibliometric study. Frontiers in Immunology. 2025; 16: 1476146. https://doi.org/10.3389/fimmu.2025.1476146.

[7] Zheng J, Wang S, Xia L, Sun Z, Chan KM, Bernards R, *et al*. Hepatocellular carcinoma: signaling pathways and therapeutic advances. Signal Transduction and Targeted Therapy. 2025; 10: 35. https://doi.org/10.1038/s41392-024-02075-w.

[8] Pathomjaruwat T, Matchim Y, Armer JM. Symptoms and symptom clusters in patients with hepatocellular carcinoma and commonly used instruments: An integrated review. International Journal of Nursing Sciences. 2024; 11: 66–75. https://doi.org/10.1016/j.ijnss.2023.09.009.

[9] Chen M, Li S, Jin G, Li R, Qi Z, He Y. Symptom clusters and network analysis of patients with intermediate and advanced liver cancer treated with targeted immunotherapy. Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer. 2024; 32: 580. https://doi.org/10.1007/s00520-024-08784-w.

[10] Lam WWT, Law CC, Fu YT, Wong KH, Chang VT, Fielding R. New insights in symptom assessment: the Chinese Versions of the Memorial Symptom Assessment Scale Short Form (MSAS-SF) and the Condensed MSAS (CMSAS). Journal of Pain and Symptom Management. 2008; 36: 584–595. https://doi.org/10.1016/j.jpainsymman.2007.12.008.

[11] Fu L, Hu Y, Lu Z, Zhou Y, Zhang X, Chang VT, *et al*. Validation of the Simplified Chinese Version of the Memorial Symptom Assessment Scale-Short Form Among Cancer Patients. Journal of Pain and Symptom Management. 2018; 56: 113–121. https://doi.org/10.1016/j.jpainsymman.2018.03.024.

[12] Wan C, Fang J, Yang Z, Zhang C, Luo J, Meng Q, *et al*. Development and validation of a quality of life instrument for patients with liver cancer QOL-LC. American Journal of Clinical Oncology. 2010; 33: 448–455. https://doi.org/10.1097/COC.0b013e3181b4b04f.

[13] Zhu BH, Wan CH, Wang K, Yuan JK, Xu CZ, Meng Q. Comparisons among FLIC, SF-36 and QOL-LC in Measuring Quality of Life of Patients with Liver Cancer. Chinese Journal of Evidence-Based Medicine. 2012; 12: 1175–1179.

[14] Imai K, Takai K, Aiba M, Unome S, Miwa T, Hanai T, *et al*. Adverse Events in Targeted Therapy for Unresectable Hepatocellular Carcinoma Predict Clinical Outcomes. Cancers (Basel). 2024; 16: 3150. https://doi.org/10.3390/cancers16183150.

[15] Kim BH, Yu SJ, Kang W, Cho SB, Park SY, Kim SU, *et al*. Expert consensus on the management of adverse events in pa-

tients receiving lenvatinib for hepatocellular carcinoma. Journal of Gastroenterology and Hepatology. 2022; 37: 428–439. https://doi.org/10.1111/jgh.15727.

[16] Hendi M, Zhang B, Lv JM, Cai XJ. Factors influencing anxiety and depression in advanced hepatocellular carcinoma patients and their impact on quality of life. World Journal of Psychiatry. 2025; 15: 104995. https://doi.org/10.5498/wjp.v15.i5.104995.

[17] You XM, Lu FC, Li FR, Zhao FJ, Huo RR. Dynamics trajectory of patient-reported quality of life and its associated risk factors among hepatocellular carcinoma patients receiving immune checkpoint inhibitors: a prospective cohort study. Frontiers in Immunology. 2024; 15: 1463655. https://doi.org/10.3389/fimmu.2024.1463655.

[18] Ryu E, Kim K, Cho MS, Kwon IG, Kim HS, Fu MR. Symptom clusters and quality of life in Korean patients with hepatocellular carcinoma. Cancer Nursing. 2010; 33: 3–10. https://doi.org/10.1097/NCC.0b013e3181b4367e.

[19] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, *et al*. Sorafenib in advanced hepatocellular carcinoma. The New England Journal of Medicine. 2008; 359: 378–390. https://doi.org/10.1056/NEJMoa0708857.

[20] An LJ, Zhang X, Yang Y, Sha HY, Huang S, Wang YD. Clinical significance of the management of adverse events and symptom cluster associated with advanced hepatocellular carcinoma after lenvatinib treatment. Journal of Clinical Hepatology. 2019; 35: 1505–1508.

[21] Lou S, Cao Z, Chi W, Wang X, Feng M, Lin L, *et al*. The safety concerns regarding immune checkpoint inhibitors in liver cancer patients rising mainly from CHB. Frontiers in Pharmacology. 2023; 14: 1164309. https://doi.org/10.3389/fphar.2023.1164309.

[22] Tan DJH, Quek SXZ, Yong JN, Suresh A, Koh KXM, Lim WH, *et al*. Global prevalence of depression and anxiety in patients with hepatocellular carcinoma: Systematic review and meta-analysis. Clinical and Molecular Hepatology. 2022; 28: 864–875. https://doi.org/10.3350/cmh.2022.0136.

[23] Galle PR, Finn RS, Qin S, Ikeda M, Zhu AX, Kim TY, *et al*. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. The Lancet. Oncology. 2021; 22: 991–1001. https://doi.org/10.1016/S1470-2045(21)00151-0.

[24] Song YG, Yoo JJ, Kim SG, Kim YS. Complications of immunotherapy in advanced hepatocellular carcinoma. Journal of Liver Cancer. 2024; 24: 9–16. https://doi.org/10.17998/jlc.2023.11.21.

[25] Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, *et al*. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. The New England Journal of Medicine. 2020; 382: 1894–1905. https://doi.org/10.1056/NEJMoa1915745.

[26] Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, *et al*. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. Journal of Hepatology. 2022; 76: 862–873. https://doi.org/10.1016/j.jhep.2021.11.030.

[27] Sangro B, Galle PR, Kelley RK, Charoentum C, De Toni EN, Ostapenko Y, *et al*. Patient-Reported Outcomes From the Phase III HIMALAYA Study of Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2024; 42: 2790–2799. https://doi.org/10.1200/JCO.23.01462.