



Associations of tumor-related psychiatric symptoms and healthy behaviors with dynamic quality of life after hepatocellular carcinoma hepatectomy

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Abstract

Objective To assess the independent and combined associations of tumor-related psychiatric symptoms (TRPS) with dynamic health-related quality of life (HRQL) in patients with hepatocellular carcinoma (HCC) after hepatectomy and to identify related patterns of health behaviors.

Methods This prospective study included patients with HCC who underwent hepatectomy between September 2021 and May 2022. Independent and combined associations between TRPS and HRQL were identified by generalized linear model and weighted quantile sum model, respectively. Trajectories of HRQL were identified by latent class mixed model.

Results Among the 205 patients, 174 (84.9%) were male. For the outcome of HRQL at 6 months: Anxiety, depression, fatigue, and sleep disorder were independently associated with a decrease of HRQL (all $P < 0.05$). A negative combined effect of TRPS was also found ($\beta = -5.07$, 95% CI, -10.01 to -0.13), with depression emerged as the predominant contributor (49%). The health behaviors of body mass index, smoking, drinking, or physical exercise were not significantly modified the associations between combined TRPS and HRQL (all $P > 0.05$ for interaction). Similar results were also found for the HRQL at baseline and at 1 and 3 months. Three HRQL trajectory groups were identified: recover (44.9%), poor (44.4%), and deteriorating (10.7%). Deteriorating group was associated with higher incidence of TRPS (all $P < 0.05$).

Conclusions TRPS were associated with a decrease of HRQL regardless of healthy behaviors in HCC patients. Therefore, healthy behaviors promotion alone might not substantially increase HRQL associated with TRPS, and other measures tackling TRPS are warranted.

Keywords Hepatocellular carcinoma hepatectomy · Tumor-related psychiatric symptoms · Healthy behaviors; Quality of life

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Introduction

Hepatocellular carcinoma (HCC) is a widely prevalent primary liver cancer that causes substantial cancer-related morbidity and mortality on a global scale [1]. Hepatectomy represents the preferred therapeutic approach for patients with HCC who satisfy the established criteria for operability and has demonstrated efficacy in prolonging patient survival [2, 3]. Nevertheless, the overall prognosis for HCC patients remains suboptimal owing to the condition's significant heterogeneity and high recurrence rate [4, 5]. Hence, there is an urgent need to prioritize health-related quality of life (HRQL) in the management of these patients. Measuring HRQL as an endpoint has become a customary practice in clinical trials evaluating the safety and effectiveness of novel

chemotherapeutic agents in nearly all cancer types, including HCC [6, 7].

Patients with cancer usually present with a wide range of tumor-related psychiatric symptoms (TRPS), such as sleep disorder, fatigue, anxiety, and depression prior to cancer treatments [8–10]. Study has revealed that preexisting TRPS can lead to unfavorable outcomes during and after active treatments, such as poor treatment tolerability (i.e., the extent to which overt adverse effects can be tolerated by the patient [8]), functional decline, and reduced quality of life [11, 12]. Consequently, TRPS, as reported by patients, have increasingly been used as patient-reported outcomes (PROs) to capture symptom burden in cancer patients [13, 14]. Monitoring and managing symptoms using PROs have demonstrated the potential to improve HRQL, decrease emergency department visits, and ensure the continuation of cancer treatments [8, 14]. Despite this progress, the association between TRPS and HRQL in HCC patients after hepatectomy remains unclear. However, considerable inter-individual variability in the longitudinal trajectory of PROs, which may be obscured by a description of the average population level [15]. Few studies comprehensively evaluated dynamic PROs after treatment. Some patient subgroups may follow trajectories at high risk of short-term deterioration in functional health and symptom burden.

Most previous studies [16–18] examining the association between TRPS and HRQL has primarily utilized a binary classification system (e.g., depressed versus non-depressed) or total scores. This approach assumes that all symptoms have equal weight as severity indicators [16], despite the absence of empirical evidence. Furthermore, traditional statistical models have evaluated the impact of individual TRPS without accounting for their combined effects, interactions with other TRPS, and nonlinear association with the outcome variable.

Early identification of high-risk groups for HRQL deterioration is crucial for timely, patient-specific supportive care interventions, including those facilitating a healthy lifestyle [19]. This study was conducted among HCC patients who received hepatectomy, with the following aims: (1) to describe dynamics of patient-reported HRQL over 6 months after hepatectomy; (2) to identify independent and combined associations between TRPS and patient-reported HRQL; and (3) to focus on how modifiable health behaviors are associated with distinct patterns of HRQL.

Methods

Study design and patients

This prospective cohort study recruited patients who underwent hepatectomy for hepatocellular carcinoma (HCC) at

Guangxi Medical University Cancer Hospital in Nanning, China, between September 2021 and May 2022. The inclusive criteria comprise patients diagnosed with HCC through postoperative pathology, who have undergone surgical treatment for the first time in the hospital, aged between 18 and 75 years, with an estimated survival time of at least 12 months. Additionally, patients must be able to complete the questionnaire follow-up independently or under the guidance of the investigator. Conversely, patients who suffer from other types of malignant tumors, severe heart, brain, lung, or kidney diseases, previous mental illness or consciousness disturbances, and those who experience non-illness-related stress factors such as significant family changes during the study period, as well as those who refuse to participate or are lost to follow-up or have died, are excluded from the study.

Prior to commencing the study, the study protocol was reviewed and approved by the Ethics Review Committee of Guangxi Medical University Cancer Hospital, and it was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent in writing was obtained from all patients prior to hepatectomy. Moreover, the study was designed and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. [20]

Assessments of TRPS

We focuses on the TRPS that arise in patients with tumors, encompassing sleep disorder, fatigue, anxiety, and depression. The selection of these particular symptoms was informed by their high prevalence among HCC patients [21–28], as well as the availability of psychometric scales with established reliability and validity to effectively capture and measure their respective impacts [29–32]. TRPS data were collected before hepatectomy.

Sleep disorder was determined through the use of the Pittsburgh Sleep Quality Index (PSQI), a widely utilized, internationally recognized questionnaire designed to assess sleep quality based on a set of 19 self-rated items and five external queries [29]. The PSQI score, which ranges from 0 to 21, is a composite of seven subscales that evaluate different aspects of sleep, including sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep remedies, and daytime fatigue, with each subscale ranging from 0 to 3 points. The instrument has demonstrated high levels of both reliability and validity [29, 33]. The study utilized a PSQI cutoff score of 8 or higher to identify individuals with elevated sleep disorder symptoms [33].

Fatigue was assessed using the Cancer Fatigue Scale (CFS), a 15-item questionnaire that measures fatigue as a construct on a sum scale consisting of three subscales: physical, cognitive, and affective fatigue [30]. The CFS demonstrates robust reliability and validity and captures

the multidimensionality of fatigue using a five-point Likert scale, where higher scores indicate greater levels of fatigue (range 0–60) [30]. Participants were classified as having elevated fatigue if their total score on the CFS was 6 or higher [30].

Anxiety and depression were determined through the use of the Hospital Anxiety and Depression Scale (HADS). HADS consists of two subscales: anxiety (HADS-A) and depression (HADS-D). Each score consists of seven questions, ranging from 0 to 3 (each score is 0–21); depending on the probability of the psychological problem described, patients with a score of 8 or higher can be classified as possibly significant symptoms [31].

Medical coping modes determined through the use of the Medical coping modes questionnaire (MCMQ), which was compiled by Feifel et al. [32] and is used to investigate the psychological and behavioral correlates of patients using primary coping strategies in the treatment of illness. MCMQ has 20 items in 3 dimensions, including confrontation (8 items; score is 0–32), avoidance (7 items; score is 0–28), and resignation (5 items; score is 0–20); each item adopts Likert 4 score method [32]. The scores of three dimensions can reflect the tendency of the patient to adopt coping strategies when facing treatment [32].

Outcomes

The primary outcome was the HRQL at 6 months follow-up after hepatectomy. The secondary outcomes were HRQL at baseline (prior to hepatectomy), and at 1 month and 3 months follow-up after hepatectomy. HRQL data were collected prospectively and were determined through the use of the Functional Assessment of Cancer Therapy-Hepatobiliary questionnaire (FACT-Hep). The 45-item FACT-Hep consists of five subscales: physical well-being, social and family well-being, emotional well-being, functional well-being, and the hepatobiliary cancer subscale (Hep-CS). The Hep-CS includes 18 items that assess specific symptoms of hepatobiliary carcinoma and side-effects of its treatment [19]. Aggregate scores can also be formed, from 0 to 180, higher scores on all scales of the FACT-Hep reflect better quality of life or fewer symptoms [19].

Covariates

At baseline, trained interviewers collected information on sociodemographic status and health-related factors using a structured questionnaire, including age, gender, body mass index, educational level, the night shift due to work requirements, occupational status, self-reported economic pressure, caregiver, and siesta (taking a short afternoon nap at least one to two times per week). Healthy behaviors included self-reported smoking status, drinking status (12 episodes

of drinking a year), and physical exercise. Clinical characteristics included comorbidities, cirrhosis, surgery, tumor size, tumor number, large vessel invasion, postoperative complications, and BCLC stage. Educational level was classified as primary school or below, middle or high school, and college or above. Occupational status was classified as on the job, laid-off or unemployed, and retirement. Economic pressure was classified as very heavy, heavy, generally, and light. Caregiver was classified as spouse, parent or child, and relatives or friends. Comorbidities was classified into two groups: no and yes (diabetes, hypertension, dyslipidemia, and chronic kidney disease). Body mass index was calculated as weight in kilograms divided by height in meters squared; height and weight were measured by a trained nurse. Surgery and postoperative complications were not baseline characteristics (prior to hepatectomy).

Statistical analyses

In this study, categorical variables were described using frequency and percentage, while continuous variables were described using means and standard deviations (SDs) or medians and interquartile ranges (IQRs). To compare quality of life between groups, we employed the Kruskal–Wallis rank sum test. Additionally, we used the Spearman test to assess the correlation between TRPS and social support.

To examine the independent associations between TRPS and HRQL at baseline, and at 1, 3, and 6 months after hepatectomy, we used generalized linear models (GLMs) to estimate the coefficient (β) with 95% confidence intervals (CIs). To conduct these analyses, the score of each TRPS was split into tertiles and included in GLMs, with the first tertile serving as the reference group. Alternatively, for sleep disorder, fatigue, anxiety, and depression, we coded the scores as dichotomous variables using a cutoff. The models were adjusted for age, gender, body mass index, educational level, night shift, occupational status, economic pressure, caregiver, smoking history, drinking history, siesta, physical exercise, comorbidities, cirrhosis, tumor size, tumor number, large vessel invasion, and BCLC stage. We excluded surgery and postoperative complications at baseline since this information was unavailable. To explore potential nonlinear associations, we also employed a restricted cubic spline (RCS) regression model with four knots at the 5th, 35th, 65th, and 95th percentiles of each TRPS score (with the reference being the 5th percentile).

We employed the weighted quantile sum (WQS) regression model to investigate the combined associations between TRPS and HRQL. This analytical approach is designed to estimate the relative contribution of mixed exposures to health outcomes [34]. Specifically, the WQS model assumes a linear relationship between TRPS and HRQL across quantiles of each exposure and calculates a weighted index that

represents the overall burden of these symptoms. The weight index reflects the contribution of each psychiatric symptom to the entire effect and is constrained between 0 and 1, with a sum of 1 [35]. To determine the weights, we used bootstrap resampling methods for 1000 iterations. To identify potential modifying variables of healthy behaviors, stratified analyses were conducted for body mass index, smoking history, drinking history, and physical exercise. We evaluated *P*-values for interaction using interaction terms and likelihood ratio tests.

We employed latent class mixed-effect models (LCMM) to evaluate longitudinal variations in FACT-Hep summary score [36–38]. This analytical approach facilitated the identification of unobserved clusters, or latent trajectory groups, of individuals exhibiting similar patterns of HRQL outcomes over time. Polynomial trajectories were defined through model estimation, with model selection involving the iterative determination of the optimal (1) number of trajectory groups and (2) shape/order of each group, as determined by maximum likelihood methods. To evaluate trajectory groups, we categorized time into monthly intervals. The ideal model should satisfy the following conditions simultaneously: (1) The average posterior probability of each class is greater than 0.7; (2) the proportion of people in a potential category is greater than 5%; (3) entropy > 0.800. Each latent trajectory group was assigned a descriptive label to provide a succinct summary of the associated HRQL outcome pattern. Subsequently, participant characteristics were described for each identified group. Finally, mean scores for all scales included in the FACT-Hep questionnaire were summarized for each trajectory group.

Sensitivity analyses were conducted as follows: (1) non-adjusting for healthy behaviors of body mass index, smoking history, drinking history, and physical exercise, to avoid the impact of potential mediation effects, (2) repeating all analyses using the generalized estimating equation model, and (3) using the *g*-computation approach [39] to account for the combined associations. All analyses were performed using R statistical software version 4.2.2 (R Foundation), and the R packages “gWQS” and “lcmm” were utilized for combined associations analyses and LCMM analyses, respectively. Two-sided *P* < 0.05 was considered as statistically significant (Figs 1, 2, 3, 4 and 5).

Results

Cohort characteristics

A total of 226 patients were initially recruited for the study. After excluding 13 non-HCC patients, 6 who died, 1 who refused evaluation, and 1 who was lost to follow-up, a final sample of 205 patients was included for analysis, with

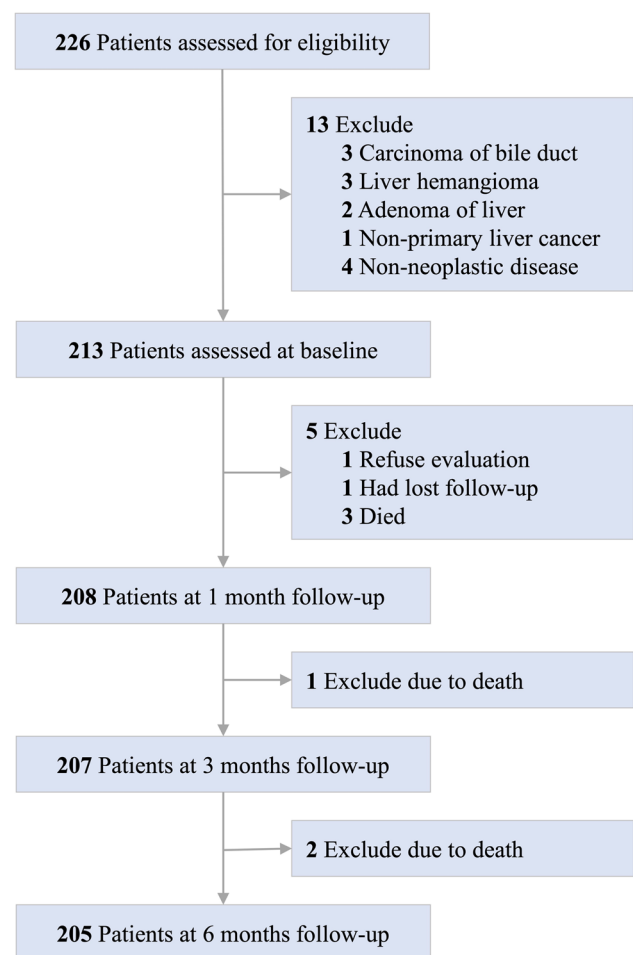


Fig. 1 Study flow diagram in the present study

follow-up assessments conducted at 1, 3, and 6 months (Fig. 6). The mean (SD) age of the included patients at baseline was 52.8 (10.9) years, with an average body mass index of (23.2 ± 2.9) kg/m². Of these patients, 174 (84.9%) were male. Table 1 presents the demographic and clinical characteristics of the study patients.

Independent association between TRPS and HRQL

At baseline, the prevalence of anxiety, depression, fatigue, and sleep disorders were found to be 44.9% (92/205), 40.5% (83/205), 56.1% (115/205), and 56.1% (115/205), respectively. The detailed scores for all scales can be found in e Table 1. Additionally, the quality of life at baseline and post-operative follow-ups of 1, 3, and 6 months were assessed, and the mean (SD) scores were reported as 135.34 ± 17.96 points, 106.92 ± 17.85 points, 119.40 ± 20.88 points, and 129.65 ± 24.68 points, respectively. The detailed scores for all scales can be found in e Table 2.

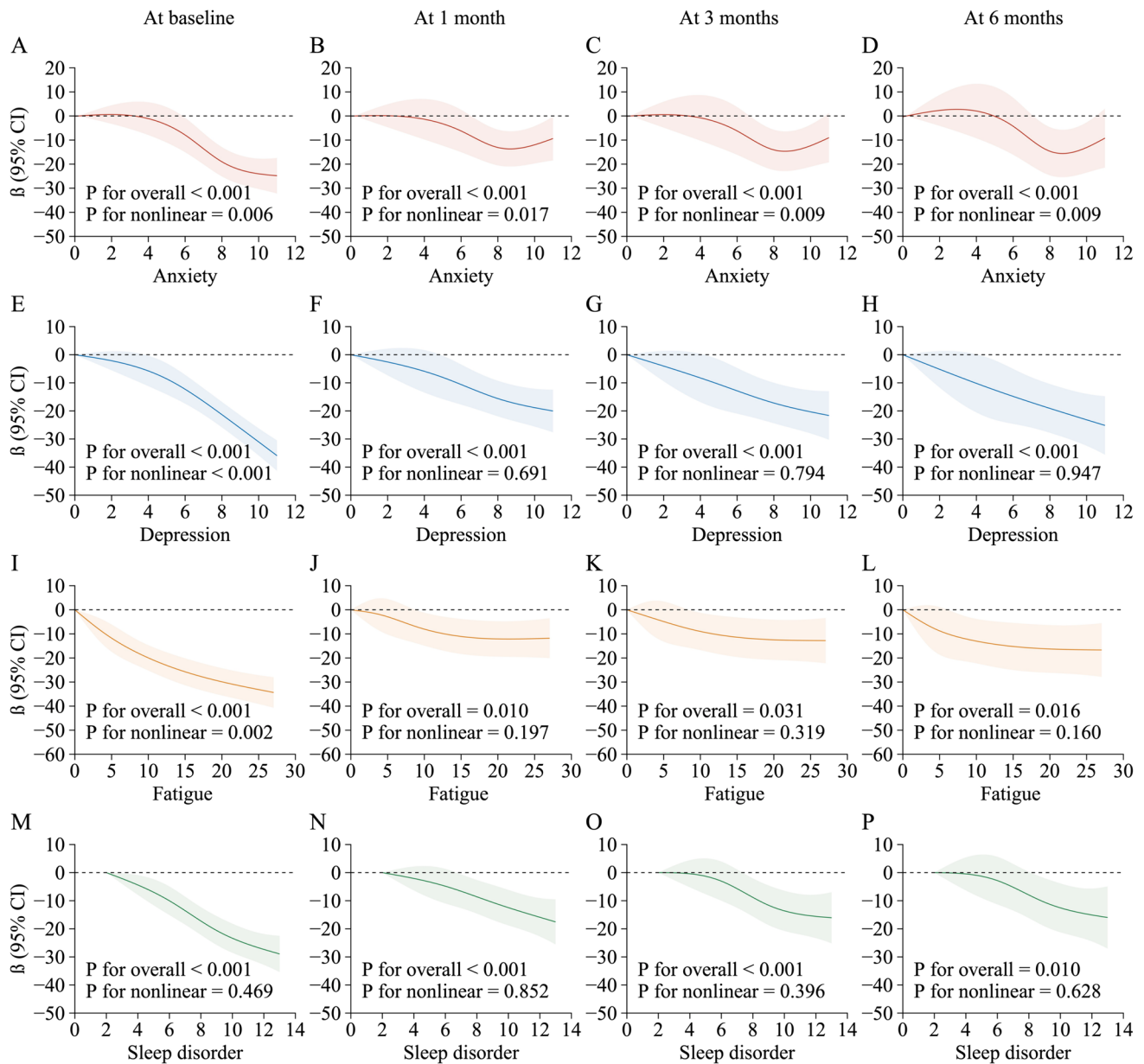


Fig. 2 Nonlinear association between individual tumor-related psychiatric symptoms score and health-related quality of life. Graphs show estimate (β) for quality of life according to anxiety score (A–D), depression (E–H) score, fatigue score (I–L), and sleep disorder score (M–P) at baseline and at 1, 3, and 6 months after hepatectomy. Data were fitted by a restricted cubic spline linear regression model adjusted for age, gender, body mass index, educational level, night shift, occupational status, economic pressure, caregiver, smoking his-

tory, drinking history, siesta, physical exercise, comorbidities, cirrhosis, tumor size, tumor number, large vessel invasion, and BCLC stage, but exclude surgery and postoperative complications at baseline, and the models were conducted with 4 knots at the 5th, 35th, 65th, 95th percentiles of individual tumor-related psychiatric symptoms score (reference is the 5th percentile). Solid lines indicate estimate (β), and shadow shapes indicate 95% CIs. Abbreviation: CI, confidence interval

Table 2 presents the association of individual TRPS and HRQL at baseline and postoperative follow-ups of 1, 3, and 6 months. For the primary outcome of HRQL at 6 months, after adjusting for potential confounders, the presence of symptoms related to anxiety was found to be significantly associated with a decrease of 11.85 points ($\beta = -11.85$, 95% CI, -18.11 to -5.58 ; $P < 0.001$) on HRQL when

compared to patients without such symptoms. Additionally, the presence of symptoms related to depression, fatigue and sleep disorder were also found to be significantly associated with a decrease in HRQL of 14.53 points ($\beta = -14.53$, 95% CI, -20.58 to -8.47 ; $P < 0.001$), 13.61 points ($\beta = -13.61$, 95% CI, -19.91 to -7.32 ; $P < 0.001$), and 12.14 points ($\beta = -12.14$, 95% CI, -18.49 to -5.79 ;

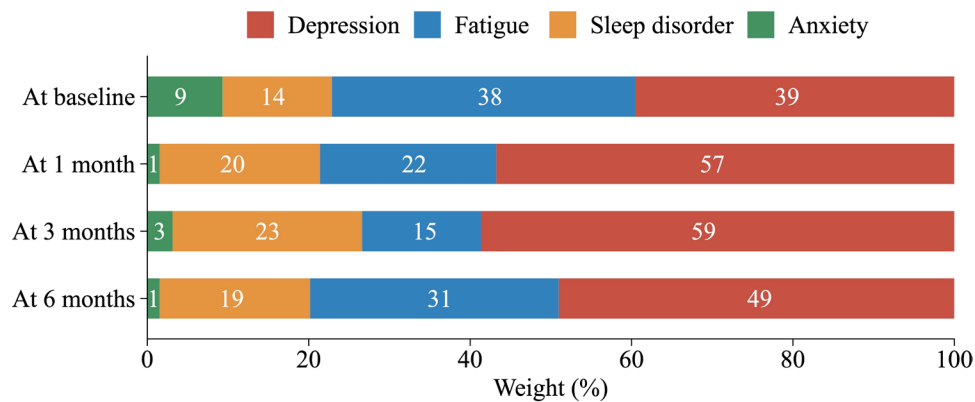


Fig. 3 Estimated weights assigned to individual tumor-related psychiatric symptoms with the WQS model. Weights are in a negative direction and obtained when the effect parameter of WQS model was constrained to the negative direction with 1000 repeated holdout validations. WQS model was adjusted for age, gender, body mass index,

educational level, night shift, occupational status, economic pressure, caregiver, smoking history, drinking history, siesta, physical exercise, comorbidities, cirrhosis, tumor size, tumor number, large vessel invasion, and BCLC stage, but exclude surgery and postoperative complications at baseline. Abbreviation: WQS, weighted quantile sum

$P < 0.001$), respectively, when compared to individuals without these symptoms. Similar results were found when modeling individual TRPS score as tertiles, by comparing tertile 3 with tertile 1, the adjusted β were -13.26 (95% CI, -21.14 to -5.38) for anxiety, -14.83 (95% CI, -23.35 to -6.32) for depression, -13.38 (95% CI, -21.01 to -5.76) for fatigue, -13.68 (95% CI, -21.93 to -5.43) for sleep disorder. Similar results were also found for the HRQL at baseline and at 1 and 3 months.

Figure 1 shows the nonlinear association of individual TRPS and HRQL using RCS regression model. A negative and linear association between depression score, fatigue score, and sleep disorder score with HRQL were found at all time points (for nonlinearity, all $P > 0.05$, except for depression and fatigue at baseline). Notably, anxiety score demonstrates an inverse S-shaped association with HRQL at all time points (for nonlinearity, all $P < 0.05$).

Combined associations between TRPS and HRQL

Table 2 presents the combined effect of TRPS with HRQL, and WQS negative index represent the negative combined effects of TRPS. After adjusting for potential confounders, the WQS negative index was negatively associated with HRQL at all time points (at baseline, $\beta = -14.69$, 95% CI, -17.27 to -12.11 ; at 1 month, $\beta = -4.55$, 95% CI, -8.16 to -0.94 ; at 3 months, $\beta = -4.88$, 95% CI, -8.67 to -1.09 ; at 6 months, $\beta = -5.07$, 95% CI, -10.01 to -0.13). Figure 2 exhibits the weights allocated to individual components comprising the amalgamated impact of TRPS in the WQS regression model. Notably, depression emerged as the predominant contributor in the negative direction at all time points (39% at baseline, 57% at 1 month, 59% at 3 months, 49% at 6 months).

Health behaviors and combined effect

The distribution of health behaviors, as presented in Table 1. Specifically, the proportion of patients with a body mass index less than 23 was found to be 47.8%, while 61.0% of patients reported being non-smokers. Additionally, 72.2% of patients reported being non-drinkers, and 49.8% reported engaging in physical exercise. However, after conducting statistical analyses, we did not find evidence to suggest that the health behaviors of body mass index, smoking, drinking, or physical exercise significantly modified the associations between combined TRPS and HRQL at all time points (all $P > 0.05$ for interaction; Fig. 3).

HRQL trajectory groups and TRPS

The final model generated by our study delineated three trajectory groups (Fig. 4A). Model selection metrics are available in the Table 3. The predominant trajectory group, which comprised a considerable proportion of patients ($n = 92$; 44.9%), exhibited high scores of FACT-Hep at baseline, with some additional negative inflections, and subsequently experienced slow and partial recovery until month 6 (recover group). The second trajectory group ($n = 91$; 44.4%), with overall low scores at baseline, demonstrated similar negative inflections and slowly and partially recovered, yet remained below the average score at month 6 (poor group). The third trajectory group ($n = 22$; 10.7%), displaying very low baseline scores, had a persistent decline in their HRQL throughout the study duration (deteriorating group). The poor trajectory group and deteriorating trajectory group reported mean values below average level at baseline across multiple HRQL domains (Fig. 4A–F).

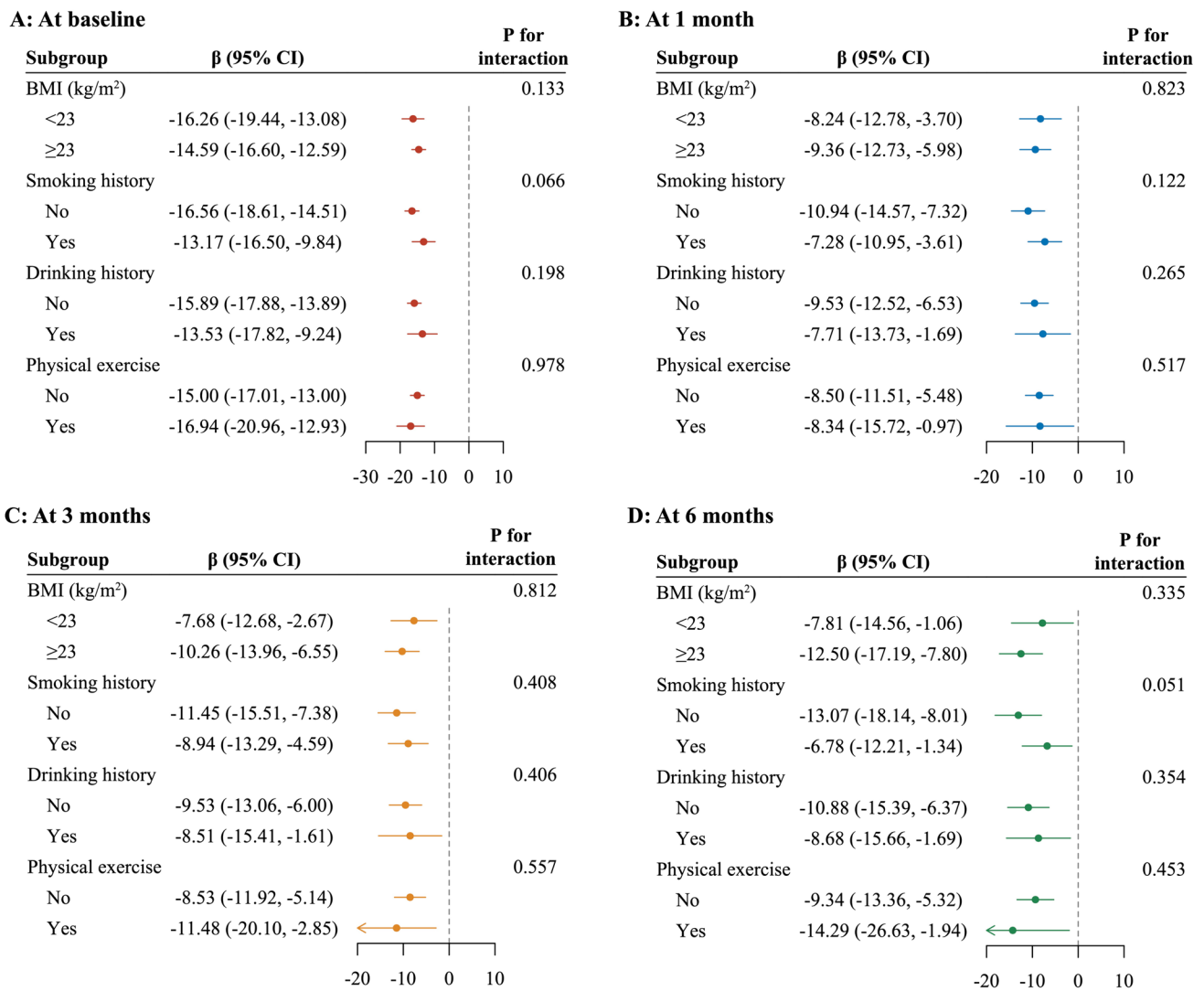


Fig. 4 Distribution of tumor-related psychiatric symptoms by health-related quality of life trajectory group. The bars represent the incidence of tumor-related psychiatric symptoms according health-related quality of life trajectory group. ****P* < 0.001

Table 1 shows patient characteristics by trajectory group. Patients in deteriorating group were more likely to have a lower body mass index, have primary school education, have a laid-off or unemployed occupational status, have a very heavy economic pressure, have a larger tumor size, have postoperative complications, have no siesta, have large vessel invasion, and have C stage of BCLC (all *P* < 0.05).

Figure 5 shows the distribution of TRPS by HRQL trajectory group. Among these groups, the highest prevalence rates of anxiety, depression, fatigue, and sleep disorders were observed in the deteriorating group, with rates of 81.8%, 77.3%, 90.9%, and 81.8%, respectively. The poor group also exhibited notable prevalence rates, which were 62.6%, 61.5%, 72.5%, and 76.9% for anxiety, depression, fatigue, and sleep disorders, respectively. Scores for all scales by HRQL trajectory group are shown in e Table 3.

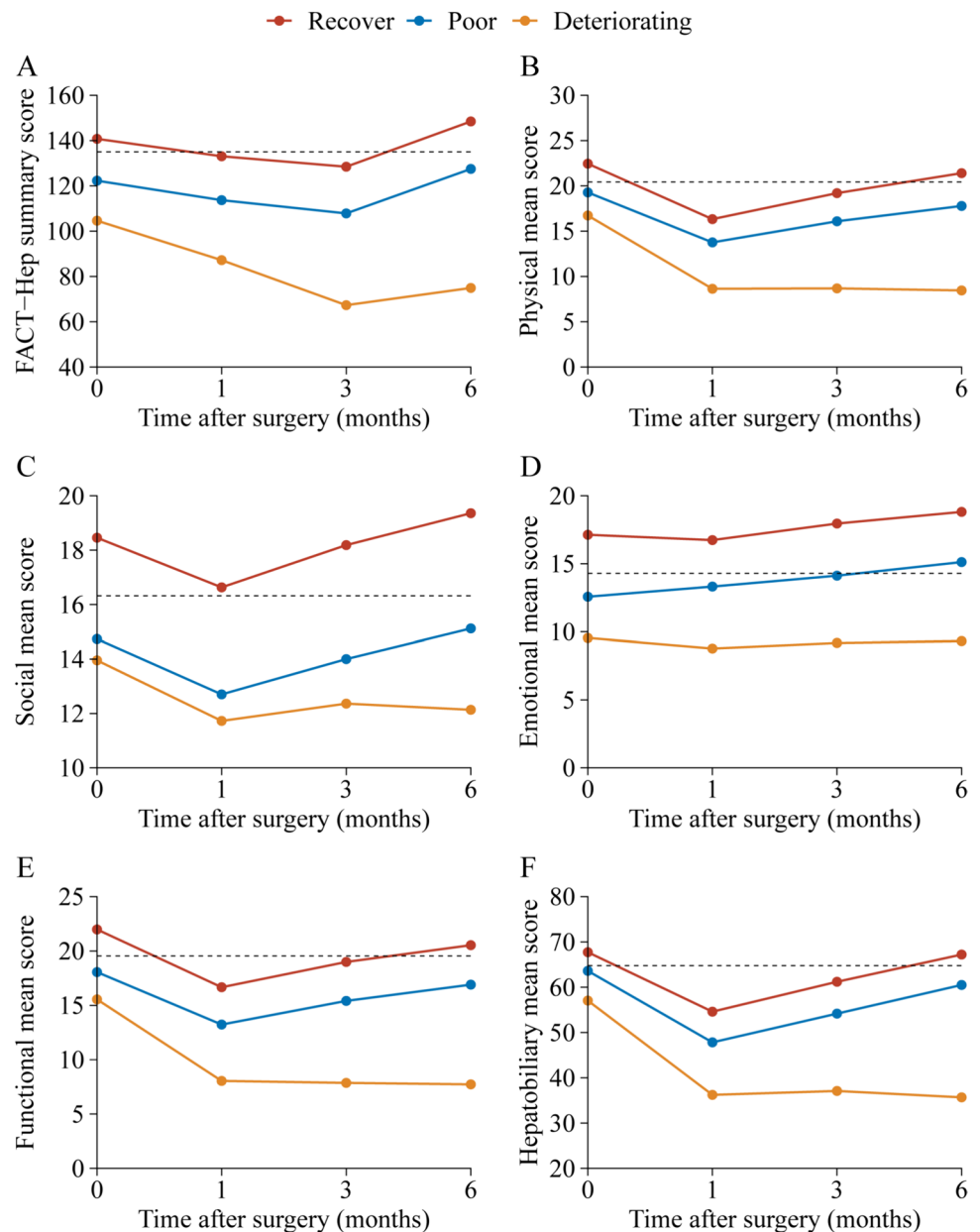
Sensitivity analyses

The results of sensitivity analyses were consistent with main findings when unadjusted for healthy behaviors (e Table 4) or using the generalized estimating equation model (e Table 5). Particularly, the combined associations were also consistent with the WQS model when using the quantile G-computation approach (e Tables 6, 7).

Discussion

In this prospective study, we found that TRPS, including anxiety, depression, fatigue, and sleep disorders, were independently associated with a decrease in HRQL, and a negative combined effect of TRPS was also found by the WQS

Fig. 5 Trajectory groups according to best-fitting model. A Trajectory groups of health-related quality of life measured by the 45-item of FACT-Hep Scale. Mean physical well-being scores (B), mean social well-being scores (C), mean emotional well-being scores (D), mean functional well-being scores (E), and mean hepatobiliary cancer scores (F) by trajectory group and by time point. Respective SDs for the means are available in the eTable 4. Solid lines represent the predicted trajectories, dashed lines represent the mean scores at baseline. Abbreviation: FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary



model, with depression being the predominant contributor. However, health behaviors such as body mass index, smoking, drinking, or physical exercise did not significantly modify the associations between TRPS and HRQL. Using a latent-class analysis, we identified three different trajectories among HCC patients receiving hepatectomy characterized by recover (44.9%), poor (44.4%), and deteriorating (10.7%) patient-reported HRQL patterns, with the deteriorating group being associated with a higher incidence of TRPS. In addition, body mass index, educational level, occupational status, economic pressure, siesta, tumor size, large vessel invasion, postoperative complications, and BCLC stage may be the trajectory group membership.

HCC is a type of liver cancer that can have a significant impact on patients' physical and psychological well-being [40]. Anxiety, depression, fatigue, and sleep disorders are common among HCC patients and can further exacerbate the burden of the disease [18, 41–43]. Studies show that up to 24.1–66.7% of HCC patients experience depression [21–25], while up to 24.3–51.8% experience anxiety [21, 22, 24, 25]. Anxiety and depression can be caused by a variety of factors, including the diagnosis of cancer, the fear of recurrence, and the impact of the disease on daily life [26]. Fatigue is also common among HCC patients; it can be caused by various factors such as treatment side effects, pain, and sleep disturbances [27, 28, 44]. The severity of fatigue

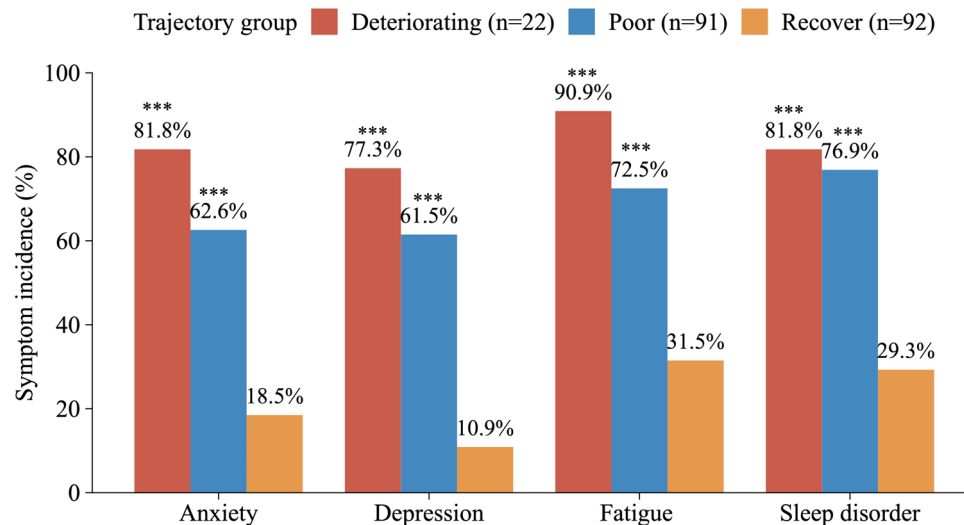


Fig.6 Association between combined tumor-related psychiatric symptoms and health-related quality of life stratified by different health behaviors. Graphs show estimate (β) and 95% CIs for the associations between negative WQS index and health-related quality of life at baseline (A), at 1 month (B), at 3 months (C), and at 6 months (D) adjusted for age, gender, body mass index, educational level, night shift, occupational status, economic pressure, caregiver,

smoking history, drinking history, siesta, physical exercise, comorbidities, cirrhosis, tumor size, tumor number, large vessel invasion, and BCLC stage, but exclude surgery and postoperative complications at baseline. Estimates were interpreted as the effect of increasing the combined tumor-related psychiatric symptoms by one quantile on the health-related quality of life. Abbreviation: WQS, weighted quantile sum

can range from mild to severe, and it can have a significant impact on a patient's daily activities and overall quality of life [28]. Sleep disorders are also prevalent in HCC patients, including difficulty falling asleep, staying asleep, and waking up too early. These sleep disorders can result in fatigue, reduced concentration, and decreased cognitive function, which can negatively affect patients' daily activities and overall quality of life [45–47]. In this study, the incidence of anxiety, depression, fatigue, and sleep disturbance found to be 44.9% (92/205), 40.5% (83/205), 56.1% (115/205), and 56.1% (115/205), respectively, which were consistent with the previous research results. Moreover, a strong association between these symptoms and inferior quality of life has been demonstrated.

Considering the effects of various TRPS on health outcomes, the potential nonlinear associations and the simultaneous exposure to multiple TRPS are more consistent with real-world situations. The combined impact of these factors must therefore be considered. We also utilized RCS regression and WQS regression for the analyses. The RCS regression show that there was a negative and linear association between depression score, fatigue score, and sleep disorder score with HRQL. Notably, there was an inverse S-shaped association of anxiety with HRQL; these seem not to simply explain that it is beneficial when anxiety are at the lowest and highest scores, although we do not yet know the mechanism of this nonlinear association. The WQS models, based on a combination of covariates and interactions among TRPS, are capable of both estimating the overall

effect of multiple TRPS on HRQL, as well as identifying the TRPS in mixed exposures that have a significant impact on outcomes. According to the results of this study, the WQS indices of TRPS were negatively associated with HRQL, which was consistent with our results in the GLMs analysis and supports the robustness of the analyses to some extent. However, the WQS regression model has a drawback in that the cumulative effect of TRPS with diverse modes of action cannot be concurrently examined. Notably, if TRPS have a negative association with HRQL in the WQS regression model, the model deems them to be positively associated and provides them inconsequential weights in the WQS weights [34, 35].

Engaging in healthy behaviors has been associated with improved HRQL in patients with HCC [48, 49]. However, one major finding of this study was that healthy behaviors were not significant modifiers of the associations between TRPS and HRQL. A healthy behaviors, which includes regular exercise, a healthy diet, and avoiding smoking and excessive alcohol consumption, among other things, can help people maintain their physical and mental health [50]. However, when individuals suffer from anxiety, depression, fatigue, and sleep disorders, it can be challenging for them to maintain a healthy behavior. One reason for this is that anxiety, depression, and fatigue can all have a negative impact on individuals' mental and emotional states, making them more prone to unhealthy behaviors [51]. For instance, individuals experiencing these issues may be more likely to engage in emotional eating, and avoid exercise. Additionally, anxiety,

Table 1 Distribution of patient characteristics at baseline by quality of life trajectory group ($n = 205$)^a

Characteristics	Overall ($n = 205$)	Quality of life trajectory group			<i>P</i> value
		Recover ($n = 92$)	Poor ($n = 91$)	Deteriorating ($n = 22$)	
Age (years)					0.072
Mean \pm SD	52.8 \pm 10.9	51.1 \pm 10.4	53.5 \pm 11.5	56.6 \pm 9.3	
< 60	149 (72.7%)	72 (78.3%)	62 (68.1%)	15 (68.2%)	
\geq 60	56 (27.3%)	20 (21.7%)	29 (31.9%)	7 (31.8%)	
Gender					0.138
Male	174 (84.9%)	82 (89.1%)	76 (83.5%)	16 (72.7%)	
Female	31 (15.1%)	10 (10.9%)	15 (16.5%)	6 (27.3%)	
Body mass index (kg/m ²)					0.004
Mean \pm SD	23.2 \pm 2.9	23.9 \pm 3.0	22.8 \pm 2.9	21.9 \pm 2.1	
< 23	98 (47.8%)	37 (40.2%)	47 (51.6%)	14 (63.6%)	
\geq 23	107 (52.2%)	55 (59.8%)	44 (48.4%)	8 (36.4%)	
Educational level					< 0.001
Primary school	55 (26.8%)	13 (14.1%)	29 (31.9%)	13 (59.1%)	
Middle or high school	69 (33.7%)	32 (34.8%)	35 (38.5%)	2 (9.1%)	
College and above	81 (39.5%)	47 (51.1%)	27 (29.7%)	7 (31.8%)	
Night shift					0.390
No	189 (92.2%)	87 (94.6%)	83 (91.2%)	19 (86.4%)	
Yes	16 (7.8%)	5 (5.4%)	8 (8.8%)	3 (13.6%)	
Occupational status					0.002
On the job	82 (40.0%)	49 (53.3%)	29 (31.9%)	4 (18.2%)	
Laid-off or unemployed	92 (44.9%)	28 (30.4%)	50 (54.9%)	14 (63.6%)	
Retirement	31 (15.1%)	15 (16.3%)	12 (13.2%)	4 (18.2%)	
Economic pressure					0.001
Very heavy	30 (14.6%)	5 (5.4%)	16 (17.6%)	9 (40.9%)	
Heavy	49 (23.9%)	19 (20.7%)	26 (28.6%)	4 (18.2%)	
General	62 (30.2%)	30 (32.6%)	27 (29.7%)	5 (22.7%)	
Light	64 (31.2%)	38 (41.3%)	22 (24.2%)	4 (18.2%)	
Caregiver					0.950
Spouse	106 (51.7%)	48 (52.2%)	47 (51.6%)	11 (50.0%)	
Parent or child	78 (38.0%)	33 (35.9%)	36 (39.6%)	9 (40.9%)	
Relatives or friends	21 (10.2%)	11 (12.0%)	8 (8.8%)	2 (9.1%)	
Smoking history					0.305
No	125 (61.0%)	58 (63.0%)	51 (56.0%)	16 (72.7%)	
Yes	80 (39.0%)	34 (37.0%)	40 (44.0%)	6 (27.3%)	
Drinking history					0.116
No	148 (72.2%)	64 (69.6%)	64 (70.3%)	20 (90.9%)	
Yes	57 (27.8%)	28 (30.4%)	27 (29.7%)	2 (9.1%)	
Siesta					< 0.001
No	103 (50.2%)	32 (34.8%)	54 (59.3%)	17 (77.3%)	
Yes	102 (49.8%)	60 (65.2%)	37 (40.7%)	5 (22.7%)	
Physical exercise					0.253
No	156 (76.1%)	65 (70.7%)	73 (80.2%)	18 (81.8%)	
Yes	49 (23.9%)	27 (29.3%)	18 (19.8%)	4 (18.2%)	
Comorbidities					0.117
No	136 (66.3%)	68 (73.9%)	55 (60.4%)	13 (59.1%)	
Yes	69 (33.7%)	24 (26.1%)	36 (39.6%)	9 (40.9%)	
Cirrhosis					0.182
No	75 (36.6%)	39 (42.4%)	31 (34.1%)	5 (22.7%)	
Yes	130 (63.4%)	53 (57.6%)	60 (65.9%)	17 (77.3%)	

Table 1 (continued)

Characteristics	Overall (<i>n</i> = 205)	Quality of life trajectory group			<i>P</i> value
		Recover (<i>n</i> = 92)	Poor (<i>n</i> = 91)	Deteriorating (<i>n</i> = 22)	
Surgery					0.583
Open hepatectomy	139 (67.8%)	59 (64.1%)	64 (70.3%)	16 (72.7%)	
Laparoscopic hepatectomy	66 (32.2%)	33 (35.9%)	27 (29.7%)	6 (27.3%)	
Tumor size (cm)					0.011
< 5	105 (51.2%)	56 (60.9%)	43 (47.3%)	6 (27.3%)	
≥ 5	100 (48.8%)	36 (39.1%)	48 (52.7%)	16 (72.7%)	
Tumor number					0.115
Single	178 (86.8%)	81 (88.0%)	81 (89.0%)	16 (72.7%)	
Multiple	27 (13.2%)	11 (12.0%)	10 (11.0%)	6 (27.3%)	
Large vessel invasion					< 0.001
No	190 (92.7%)	89 (96.7%)	87 (95.6%)	14 (63.6%)	
Yes	15 (7.3%)	3 (3.3%)	4 (4.4%)	8 (36.4%)	
Postoperative complications					0.006
No	130 (63.4%)	68 (73.9%)	53 (58.2%)	9 (40.9%)	
Yes	75 (36.6%)	24 (26.1%)	38 (41.8%)	13 (59.1%)	
BCLC stage					< 0.001
A	141 (68.8%)	71 (77.2%)	65 (71.4%)	5 (22.7%)	
B	36 (17.6%)	16 (17.4%)	16 (17.6%)	4 (18.2%)	
C	28 (13.7%)	5 (5.4%)	10 (11.0%)	13 (59.1%)	

BCLC Barcelona Clinic Liver Cancer

^aData are presented as *n* (%), unless otherwise specified

depression, and fatigue can all cause individuals to lack the motivation and energy necessary to establish and maintain a healthy lifestyle [51]. Sleep disorders, on the other hand, can have a direct impact on an individual's ability to engage in healthy behaviors [52, 53]. Individuals experiencing sleep disturbances, such as insomnia or sleep apnea, may find it challenging to establish a regular exercise routine, prepare healthy meals, or maintain a consistent sleep schedule. In summary, anxiety, depression, fatigue, and sleep disorders can all make it difficult for individuals to maintain a healthy behavior. To address these issues, it is crucial to develop an individualized plan that incorporates mental health interventions, such as therapy and medication, and lifestyle changes, such as regular exercise, healthy eating, and sleep hygiene practices, to support individuals in achieving and maintaining a healthy lifestyle.

Previous literature tried to describe posthepatectomy changes in HRQL; however, most of it only captured population averages or was focused on specific symptoms [54–57]. Here, we present a number of novel findings regarding HRQL trajectories in the 6 months following hepatectomy. We provide a detailed assessment of overall and specific hepatectomy metrics, offering insight into the characteristics of subpopulations that experience persistent deterioration. Although the majority of patients exhibit a return to preoperative HRQL levels by the 6-month mark,

we identified two specific patient clusters for whom short-term HRQL dynamics were notably worse. The group experiencing deteriorating HRQL was most affected by primary treatment, with a significant drop observed from baseline to month 3 that did not recover. This segment exhibited sharp deterioration across multiple functions, including physical, social and family, emotional, functional, and the hepatobiliary cancer subscale. In nearly all cases, median scores for the deteriorating trajectory group were lower than the baseline median level, indicating a need for clinician attention and dedicated supportive care.

Our study additionally revealed that the deteriorating HRQL group had a higher incidence of anxiety, depression, fatigue, and sleep disorders. One possible explanation for this observation is that chronic stress may contribute to immune decline [58–60]. Chronic stress is characterized by a persistent non-specific adaptive response of the body, resulting from the activation of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system in response to physiological and psychological stressors, and is typically manifested as anxiety and depression. Chronic stress can impact the immune system, as prolonged anxiety and depression can negatively affect immune function, leading to a highly immunosuppressed tumor microenvironment (TME). For cancer patients, treatment confidence, treatment side effects, and financial pressures can

Table 2 Associations between tumor-related psychiatric symptoms and health-related quality of life

Symptoms	At baseline		At 1 month		At 3 months		At 6 months	
	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value
Anxiety								
Anxiety symptoms								
No symptoms	Ref		Ref		Ref		Ref	
Symptoms ^a	-18.70 (-22.49, -14.92)	<0.001	-9.83 (-14.44, -5.22)	<0.001	-10.64 (-15.87, -5.41)	<0.001	-11.85 (-18.11, -5.58)	<0.001
Anxiety score, tertile ^b								
Tertile 1	Ref		Ref		Ref		Ref	
Tertile 2	-12.45 (-16.72, -8.18)	<0.001	-8.32 (-13.39, -3.25)	0.002	-9.33 (-15.10, -3.57)	0.002	-12.30 (-19.12, -5.49)	0.001
Tertile 3	-22.29 (-27.14, -17.44)	<0.001	-10.40 (-16.26, -4.53)	0.001	-10.21 (-16.87, -3.55)	0.003	-13.26 (-21.14, -5.38)	0.001
Depression								
Depression symptoms								
No symptoms	Ref		Ref		Ref		Ref	
Symptoms ^c	-19.03 (-22.73, -15.34)	<0.001	-12.40 (-16.81, -7.99)	<0.001	-12.89 (-17.94, -7.85)	<0.001	-14.53 (-20.58, -8.47)	<0.001
Depression score, tertile ^d								
Tertile 1	Ref		Ref		Ref		Ref	
Tertile 2	-11.52 (-15.30, -7.74)	<0.001	-8.12 (-12.96, -3.27)	0.001	-8.64 (-14.21, -3.08)	0.003	-9.12 (-15.83, -2.42)	0.008
Tertile 3	-28.72 (-33.46, -23.97)	<0.001	-14.82 (-20.98, -8.67)	<0.001	-14.17 (-21.23, -7.10)	<0.001	-14.83 (-23.35, -6.32)	0.001
Fatigue								
Fatigue symptoms								
No symptoms	Ref		Ref		Ref		Ref	
Symptoms ^e	-17.10 (-21.16, -13.04)	<0.001	-10.43 (-15.09, -5.77)	<0.001	-10.30 (-15.63, -4.97)	<0.001	-13.61 (-19.91, -7.32)	<0.001
Fatigue score, tertile ^f								
Tertile 1	Ref		Ref		Ref		Ref	
Tertile 2	-11.67 (-16.16, -7.17)	<0.001	-8.60 (-14.10, -3.09)	0.003	-10.19 (-16.41, -3.97)	0.002	-13.60 (-20.95, -6.25)	<0.001
Tertile 3	-22.74 (-27.41, -18.07)	<0.001	-9.66 (-15.37, -3.95)	0.001	-10.34 (-16.80, -3.89)	0.002	-13.38 (-21.01, -5.76)	0.001
Sleep disorder								
Sleep disorder symptoms								
No symptoms	Ref		Ref		Ref		Ref	
Symptoms ^g	-18.80 (-22.60, -14.99)	<0.001	-10.16 (-14.83, -5.50)	<0.001	-11.86 (-17.11, -6.61)	<0.001	-12.14 (-18.49, -5.79)	<0.001
Sleep disorder score, tertile ^h								
Tertile 1	Ref		Ref		Ref		Ref	
Tertile 2	-13.92 (-18.30, -9.55)	<0.001	-5.99 (-11.12, -0.86)	0.023	-7.37 (-13.21, -1.53)	0.014	-6.90 (-14.00, 0.20)	0.058
Tertile 3	-22.16 (-27.06, -17.26)	<0.001	-13.99 (-19.96, -8.03)	<0.001	-14.59 (-21.38, -7.80)	<0.001	-13.68 (-21.93, -5.43)	0.001
Combined effect								
Negative WQS index ⁱ	-14.69 (-17.27, -12.11)	<0.001	-4.55 (-8.16, -0.94)	0.017	-4.88 (-8.67, -1.09)	0.015	-5.07 (-10.01, -0.13)	0.049

All models were adjusted for age, gender, body mass index, educational level, night shift, occupational status, economic pressure, caregiver, smoking history, drinking history, siesta, physical exercise, comorbidities, cirrhosis, tumor size, tumor number, large vessel invasion, and BCLC stage, but exclude surgery and postoperative complications at baseline

CI confidence interval, Ref. reference, WQS weighted quantile sum

^aDefined as a score of 8 or greater on the seven-item of Hospital Anxiety and Depression Scale-A

Table 2 (continued)

^bThe anxiety score, measured by the seven-item of Hospital Anxiety and Depression Scale-A, varies between 0 and 21, with the highest score representing the highest risk of anxiety symptoms

^cDefined as a score of 8 or greater on the seven-item of Hospital Anxiety and Depression Scale-D

^dThe depressive score, measured by the seven-item of Hospital Anxiety and Depression Scale-D, varies between 0 and 21, with the highest score representing the highest risk of depressive symptoms

^eDefined as a score of 6 or greater on the 15-item of the Cancer Fatigue Scale

^fThe fatigue score, measured by the Cancer Fatigue Scale, varies between 0 and 60, with the highest score representing the highest risk of fatigue symptoms

^gDefined as a score of 5 or greater on the 19-item of the Pittsburgh Sleep Quality Index Scale

^hThe sleep disorder score, measured by the 19-item of the Pittsburgh Sleep Quality Index Scale, varies between 0 and 21, with the highest score representing the highest risk of sleep disorder symptoms

ⁱWQS negative index was obtained when the effect parameter of WQS model was constrained to the negative direction with 1000 repeated hold-out validations. Estimates were interpreted as the effect of increasing the combined tumor-related psychiatric symptoms by one quantile on the health-related quality of life

Table 3 Metrics used for comparison across tested trajectory group models

Trajectory groups	AIC	BIC	SABIC	Entropy	Percentage of trajectory groups				
					Class 1	Class 2	Class 3	Class 4	Class 5
1	7401.00	7414.29	7401.62	1.00	100.0%				
2	7093.65	7123.55	7095.04	0.95	12.7%	87.3%			
3	6977.71	7024.23	6979.87	0.82	10.7%	44.9%	44.4%		
4	6975.04	7038.18	6977.98	0.69	10.2%	37.1%	28.8%	23.9%	
5	6963.46	7043.21	6967.17	0.74	2.0%	8.8%	30.7%	37.6%	21.0%

BIC Bayesian information criterion

all contribute to long-term psychological stress, further exacerbating immune suppression [61].

This study has several strengths, including its prospective design and the construction of a combined TRPS variable to comprehensively evaluate the complex relations between healthy behaviors and TRPS with dynamic HRQL. Sensitivity analyses were also conducted to demonstrate the robustness of the findings. However, there are also limitations that must be acknowledged. First, the measurements of TRPS and healthy behaviors were mainly self-reported and were only taken once, resulting in the possibility of measurement errors. Additionally, the long-term trajectories of HRQL and changes in healthy behaviors could not be captured. Secondly, disease status could have influenced both healthy behaviors and TRPS, and while adjustments were made for comorbidities at baseline, the possibility of reverse causation and residual confounding cannot be entirely eliminated. Third, only patients from China were involved in this study; thus, the findings may not fully generalize to other countries. Fourth, we fitted the latent class model with a smaller sample size. Although our sample size may be relatively modest for latent class modeling, but our model evaluation metrics support the suitability of the fitted latent trajectory model, we also conducted several assessments to ensure the robustness of our findings. Fifth, due to the small sample size of the deteriorating group, a multivariate model could not be

utilized to analyze the association between TRPS and health behaviors with HRQL trajectories; thus, future studies with multivariable multinomial logistic regression are preferred. Finally, despite controlling for key personal characteristics and comorbidities, residual confounding remains possible, and causal inference cannot be made due to the nature of observational studies.

Conclusions

Based on this cohorts, TRPS were found to be significantly associated with a decrease of dynamic HRQL, with this association partially mediated by healthy behavior factors. These findings highlight the critical importance of personalized interventions, particularly given the absence of standardized lifestyle-change programs and inconsistent third-party reimbursement of behavioral interventions for patients with cancer [62–64]. To optimize resource allocation, researchers are increasingly exploring the efficacy of targeted lifestyle-promotion interventions and individualized patient support strategies [63, 64]. The current study provides valuable insights into the identification of patient-level risk factors and the development of tailored interventions for the preservation of HRQL, including the early identification of behavioral concerns and the provision of healthy lifestyle support programs.

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Author contribution X.-M. Y conceived the study; all authors participated in the acquisition of the data; F.-R. L and F.-J. Z performed follow-up the data; R.-R.H, F.-J. Z and F.-R. L analyzed data; R.-R.H is a statistician and he checked the statistics. F.-J. Z and X.-M. Y drafted and revised the manuscript; all authors read and approved the final version of the manuscript.

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Data availability Some or all data generated or used during the study are available from the corresponding author by request.

Declarations

Conflict of interest The authors declare no competing interests.

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