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Reduced Sleep Quality and Increasing Fatigue in Patients with Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization

Paula Bark

paula.bark@unimedizin-mainz.de

University Medical Center of the Johannes Gutenberg University Mainz

Jan Weerts

University Medical Center of the Johannes Gutenberg-University Mainz

Alper Cankaya

University Medical Center of the Johannes Gutenberg-University Mainz

Akin Kapucu

University Medical Center of the Johannes Gutenberg-University Mainz

Simon Sachse

Charité - Universitätsmedizin Berlin

Lukas Müller

University Medical Center of the Johannes Gutenberg University Mainz

Fabian Stoehr

University Medical Center of the Johannes Gutenberg University Mainz

Dirk Graafen

University Medical Center of the Johannes Gutenberg University Mainz

Felix Hahn

University Medical Center of the Johannes Gutenberg University Mainz

Tilman Emrich

University Medical Center of the Johannes Gutenberg University Mainz

Michael B. Pitton

University Medical Center of the Johannes Gutenberg University Mainz

Jens Mittler

University Medical Center of the Johannes Gutenberg University Mainz

Beate Katharina Straub

University Medical Center of the Johannes Gutenberg University Mainz

Carolin Zimpel

University Hospital Schleswig-Holstein

Jens Uwe Marquardt

University Hospital Schleswig-Holstein
Christian Labenz
University Medical Center of the Johannes Gutenberg University Mainz
Simon Johannes Gairing
University Medical Center of the Johannes Gutenberg University Mainz
Kateryna Shmanko
University Medical Center of the Johannes Gutenberg University Mainz
Roman Kloeckner
University Hospital Schleswig-Holstein
Tobias Bäuerle
University Medical Center of the Johannes Gutenberg University Mainz
Christian M. Lange
University Medical Center of the Johannes Gutenberg University Mainz
Peter Robert Galle
University Medical Center of the Johannes Gutenberg University Mainz
Arndt Weinmann
University Medical Center of the Johannes Gutenberg University Mainz
Marcus-Alexander Wörns
Klinikum Dortmund
Friedrich Foerster
University Medical Center of the Johannes Gutenberg University Mainz

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Research Article

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Reduced Sleep Quality and Increasing Fatigue in Patients with Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization

Running head: Sleep Quality and Fatigue in HCC Patients Undergoing TACE

Paula Bark[1, †], Jan Weerts[1], Alper Cankaya[1], Akin Kapucu[1], Simon Sachse[1], Lukas Müller[2], Fabian Stoehr[2], Dirk Graafen[2], Felix Hahn[2], Tilman Emrich[2], Michael B. Pitton[2], Jens Mittler[3], Beate Katharina Straub[4], Carolin Zimpel[1,5], Jens Uwe Marquardt[1,5], Christian Labenz[1], Simon Johannes Gairing[1], Kateryna Shmanko[1], Roman Kloeckner[2,6], Tobias Bäuerle[2], Christian M. Lange[1], Peter Robert Galle[1], Arndt Weinmann[1], Marcus-Alexander Wörns[1,7], Friedrich Foerster[1]

Affiliations:

[1] Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[2] Department of Diagnostic and Interventional Radiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[3] Department of General, Visceral and Thoracic Surgery, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[4] Institute of Pathology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[5] Department of Internal Medicine I, University Medical Center Schleswig-Holstein – Campus Lübeck, Lübeck, Germany

[6] Institute of Interventional Radiology, University Medical Center Schleswig-Holstein – Campus Lübeck, Lübeck, Germany

[7] Department of Gastroenterology, Hematology, Oncology and Endocrinology, Klinikum Dortmund, Klinikum of the University Witten/Herdecke, Dortmund, Germany

[†]Corresponding author

Paula Bark, MD

Department of Internal Medicine I

University Medical Center of the Johannes Gutenberg-University Mainz

Langenbeckstr. 1, 55131 Mainz, Germany

Phone: +49 (0) 6131 17-4406

E-mail: paula.bark@unimedizin-mainz.de

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Abbreviations

AFP – alpha-fetoprotein

AIH – autoimmune hepatitis

ALBI – Albumin–Bilirubin score

BCLC – Barcelona Clinic Liver Cancer classification

CI – confidence interval

CLDQ – Chronic Liver Disease Questionnaire

COPD – chronic obstructive pulmonary disease

CRP – C-reactive protein

CT – computed tomography

ECOG – Eastern Cooperative Oncology Group performance status

HCC – hepatocellular carcinoma

HR – hazard ratio

HRQoL – health-related quality of life

INR – international normalized ratio

IQR – interquartile range

MELD – Model for End-Stage Liver Disease

MELD-Na – Model for End-Stage Liver Disease incorporating serum sodium

mRECIST – modified Response Evaluation Criteria in Solid Tumors

MRI – magnetic resonance imaging

NAFLD – non-alcoholic fatty liver disease

NYHA – New York Heart Association

OS – overall survival

PSQI – Pittsburgh Sleep Quality Index

QoL – quality of life

SE – standard error

TACE – transarterial chemoembolization

TARE – transarterial radioembolization

tEND – last available study visit

Abstract

Background: Sleep quality and health-related quality of life (HRQoL) remain underassessed in hepatocellular carcinoma (HCC). We prospectively assessed sleep quality and HRQoL in patients with HCC undergoing transarterial chemoembolization (TACE), their association with liver function, and prognostic value for survival.

Methods: 29 patients with HCC undergoing TACE were included. Sleep quality and HRQoL were assessed at baseline (t1), after the first TACE (t2), and at end of follow-up (tEND) using the Pittsburgh Sleep Quality Index (PSQI) and Chronic Liver Disease Questionnaire (CLDQ). Associations with liver function were evaluated using Spearman correlation; overall survival (OS) was analyzed by Kaplan–Meier and Cox regression.

Results: Among 26 patients with questionnaire data, median baseline PSQI was 6.5 (IQR 3.5–9.0); 73.1% had impaired sleep quality (PSQI ≥5). Patients with children had significantly better sleep quality than those without. Overall HRQoL was stable during TACE (p=0.601), while fatigue worsened significantly (p=0.016). CLDQ correlated with liver function (Child–Pugh: rho=-0.668, p<0.001); PSQI did not. Sleep quality and HRQoL were strongly inversely correlated (rho=-0.806, p<0.001). Median OS was 15.7 months (95% CI 12.1–42.7), numerically longer in patients with good sleep quality (32.0 vs. 12.1 months; p=0.064). ALBI score was the only independent predictor of OS (HR 10.52, 95% CI 3.40–32.60, p<0.001).

Conclusions: Sleep quality and HRQoL are commonly impaired in HCC patients undergoing TACE and closely correlated, with fatigue the most sensitive domain. Neither independently predicted OS after adjustment for liver function. Routine assessment of both parameters should be considered in this population.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer-related mortality worldwide, with an estimated 906,000 new cases and 830,000 deaths annually. [1] In the majority of patients, HCC develops on the background of liver cirrhosis, which not only constitutes a major risk factor for malignant transformation but also limits available treatment options and independently impairs prognosis. [2] According to the Barcelona Clinic Liver Cancer (BCLC) staging system, transarterial chemoembolization (TACE) represents the recommended first-line treatment for patients with intermediate-stage disease (BCLC B). [3]

Sleep disturbances represent another frequently underrecognized dimension of impaired wellbeing in patients with chronic liver disease. Up to 80% of patients with liver cirrhosis report poor sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI). The underlying mechanisms are multifactorial and include altered melatonin secretion, hepatic encephalopathy, pruritus, and psychosocial distress. While sleep disturbances are well recognized in patients with liver cirrhosis, prospective data specifically addressing sleep quality in patients with HCC undergoing locoregional therapy remain scarce, and sleep quality continues to be underassessed in this oncological setting. [4]

Beyond serving as the site of tumor development, the liver is essential for metabolic and systemic homeostasis. Progressive hepatic dysfunction therefore affects multiple organ systems and contributes directly to the complex symptom burden experienced by patients with chronic liver disease and HCC. Given the palliative nature of TACE in most patients, health-related quality of life (HRQoL) has emerged as an increasingly important outcome measure alongside traditional endpoints such as overall survival and tumor response. [4, 5] Patients with HCC face a dual burden of an underlying progressive liver disease and an oncological diagnosis, both of which contribute to

physical and psychological impairment. A growing body of evidence suggests that baseline HRQoL is not only impaired in patients with HCC compared to the general population, but may also carry independent prognostic value for survival. [6–8] In particular, fatigue and physical functioning have been identified as prognostically relevant QoL domains in multivariate analyses across several cohorts. [7, 8]

A recent prospective study in HCC patients demonstrated significant correlations between PSQI subcategories and all HRQoL domains measured by the SF-36, yet the prognostic relevance of sleep quality in this population has not been systematically evaluated. [9]

The Chronic Liver Disease Questionnaire (CLDQ) is a validated disease-specific instrument for the assessment of HRQoL in patients with chronic liver disease, comprising six subscales including fatigue, abdominal symptoms, systemic symptoms, activity, emotional function, and worry. [10] The German version has been shown to have good reliability and validity across different etiologies of chronic hepatopathy. [11] While the CLDQ has been applied in several studies of patients with chronic liver disease and cirrhosis, prospective longitudinal data specifically examining CLDQ trajectories and their correlation with liver function during TACE are limited. In a prospective cohort of 190 patients with chronic liver disease it has recently been demonstrated that CLDQ scores correlated more strongly with the Child-Pugh score than with the albumin-bilirubin (ALBI) score, and suggested a potential prognostic utility of the CLDQ in clinical practice. [12]

The ALBI score has been established as an objective, evidence-based tool for liver function assessment in patients with HCC, demonstrating consistent prognostic value across different treatment modalities including TACE. [13, 14] However, the relationship between ALBI score and patient-reported outcomes such as HRQoL and sleep quality has not been prospectively examined in a TACE-treated HCC cohort.

The present study aimed to prospectively assess sleep quality and HRQoL during TACE therapy in patients with HCC, evaluate their longitudinal changes and associations with established liver function parameters, and determine their independent prognostic value for overall survival in a cohort with extended follow-up.

Methods

Study Design and Patients

This prospective single-center observational study was conducted at the Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg University Mainz, Germany. The study was approved by the ethics committee of the Medical Association of Rhineland-Palatinate, Mainz, Germany (permit number 837.242.17 [11076]) and conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). Written informed consent was obtained from all patients prior to study inclusion.

Patients were enrolled as part of a parent study investigating early prediction of liver function decline in patients with HCC undergoing TACE, using LiMAX testing alongside complementary clinical parameters — including health-related quality of life, sleep quality, and minimal hepatic encephalopathy — as potential earlier indicators than established laboratory-based scores such as Child–Pugh stage or MELD score. CLDQ and PSQI assessments were performed as part of this parent study protocol at each visit. As enrollment was linked to participation in this parent study, not all patients receiving TACE at our center during the study period were consecutively included.

Between December 2017 and May 2022, 30 patients with HCC were enrolled in the study. Eligible patients had histologically and/or radiologically confirmed HCC with BCLC stage A, B or C tumor burden, were scheduled to receive palliative TACE by decision of the institutional multidisciplinary tumor board, had a life expectancy of at least 3 months, were aged ≥18 years, had an ECOG performance status of 0–2, and had preserved liver function (Child–Pugh A or B). Patients were excluded if they had previously received transarterial therapy (TACE or TARE), had received oncological

treatment within four weeks prior to the first TACE, were on concomitant sorafenib therapy, were pregnant, had severe comorbidities (chronic renal failure requiring dialysis, severe heart failure NYHA >II, severe COPD GOLD >II), had a psychiatric disorder, or declined study participation.

Study Procedures and Data Collection

At each study visit, patients underwent clinical assessment including physical examination, vital signs, body weight and height, and documentation of current medication and ECOG performance status. Blood samples were obtained at every visit as part of routine clinical care, including measurements of sodium, potassium, creatinine, urea, total bilirubin, total protein, albumin, CRP, prothrombin time, INR, and AFP. The Child–Pugh score, MELD score, MELD-Na score, and ALBI score were calculated from these parameters at each time point.

Imaging follow-up was performed by CT or MRI of the abdomen approximately every 6 weeks, with tumor response assessed according to modified Response Evaluation Criteria in Solid Tumors (mRECIST). Treatment decisions, including continuation or discontinuation of TACE, were made by the institutional multidisciplinary tumor board. Study participation ended for each patient upon change of treatment modality, transition to best supportive care, or death. Survival data were updated in January 2026.

Assessment of Health-Related Quality of Life and Sleep Quality

Sleep quality was assessed using the validated German version of the Pittsburgh Sleep Quality Index (PSQI). This self-rated instrument covers 19 items across seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction.

Component scores are summed to yield a global score ranging from 0 to 21, with higher values indicating worse sleep quality. A validated global score of ≥5 indicates poor sleep quality, with a reported sensitivity of 89.6% and specificity of 86.5%.

HRQoL was assessed in parallel at each study visit using the validated German version of the Chronic Liver Disease Questionnaire (CLDQ). This self-administered instrument comprises 29 items grouped into six subscales: abdominal symptoms, fatigue, systemic symptoms, activity, emotional function, and worry. Responses are rated on a 7-point Likert scale ranging from "always" to "never", with higher scores reflecting better HRQoL. The German version has demonstrated good reliability, with test-retest reliability of 0.79–0.88 and internal consistency (Cronbach's alpha) of 0.69–0.95.

Both questionnaires were administered independently by patients before commencement of each TACE intervention. For the present analyses, three time points were defined: baseline before the first TACE (t1), after the first TACE approximately six weeks later (t2), and the last available assessment at the end of the study period (tEND).

Statistical Analysis

Overall survival (OS) was defined as the time from the date of first TACE to death from any cause. Patients alive at the time of analysis were censored at the date of last contact. Median follow-up was estimated using the reverse Kaplan–Meier method.

Continuous variables are presented as median with interquartile range (IQR); categorical variables as absolute numbers and percentages. Normal distribution was assessed using the Shapiro-Wilk test. Given the small sample size and non-normal distribution of most variables, non-parametric tests were applied throughout. Longitudinal changes in QoL, sleep quality, and liver function parameters were assessed using the paired Wilcoxon signed-rank test comparing t1 with tEND.

Associations between QoL, sleep quality, and liver function parameters were quantified using Spearman rank correlation coefficients.

Survival probabilities were estimated using the Kaplan–Meier method and compared between groups using the log-rank test. For Kaplan–Meier analyses, PSQI, CLDQ total score, and CLDQ fatigue subscale were each dichotomized at the respective median. Although a PSQI score ≥5 represents the validated threshold for poor sleep quality, the highly unequal group sizes resulting from this cut-off (n=7 vs. n=19) precluded meaningful survival analysis. Therefore, median split was applied for Kaplan–Meier analyses as a sensitivity approach, while the validated cut-off was used for descriptive characterization of sleep quality prevalence only. Associations with OS were evaluated using Cox proportional hazards regression. Univariable Cox models were applied to all prespecified variables. Given the primary aim of evaluating QoL parameters as potential independent prognostic factors, PSQI was additionally included alongside ALBI score – the strongest univariable predictor – in a multivariable Cox model. PSQI was selected over CLDQ total score and fatigue subscale as the primary QoL covariate for the main multivariable model, as it fulfilled the proportional hazards assumption (Schoenfeld residuals p=0.286), whereas the model including CLDQ showed a violation of this assumption (p=0.028). Due to the limited sample size, multivariable models were restricted to two covariates to avoid overfitting, following the commonly applied rule of approximately one variable per ten events. Additional multivariable models are provided in Additional file 1. An exploratory post-hoc subgroup analysis was performed comparing patients with and without children with respect to baseline QoL and sleep quality, based on findings reported in a prior analysis of this cohort.

All analyses were performed using R (version 4.4.3; R Core Team, Vienna, Austria) with the packages survival, survminer, tableone, dplyr, and ggplot2. [15–19] A two-

sided p-value <0.05 was considered statistically significant. Bilirubin concentrations were analyzed and are reported in μmol/L throughout.

Results

Baseline Characteristics

A total of 30 patients with HCC were enrolled between December 2017 and May 2022. After excluding one patient in whom OS could not be calculated due to missing procedural data, 29 patients were included in the final analysis (Figure 1). Of these, 26 patients had complete sleep quality and quality of life assessments and were included in the longitudinal QoL analysis.

Baseline demographic and clinical characteristics are summarized in Table 1. The median age was 70.0 years (IQR 67.0–75.0), and 24 patients (82.8%) were male. The most common etiology of underlying liver disease was alcohol-related (n=18, 62.1%), followed by other/cryptogenic causes (n=5, 17.2%) and hepatitis B (n=3, 10.3%). The majority of patients presented with BCLC stage B disease (n=25, 86.2%). Liver function was preserved in the majority of patients, with Child–Pugh A in 17 patients (58.6%), Child–Pugh B in 10 (34.5%), and Child–Pugh C in 2 (6.9%). Median MELD score was 11.0 (IQR 7.0–13.0) and median ALBI score was -2.11 (IQR -2.57– -1.79). ECOG performance status was 0 in 9 patients (33.3%), 1 in 14 (51.9%), and 2 in 4 (14.8%). Nineteen of 26 patients with available data (73.1%) had children and 22 of 27 patients with available data (81.5%) were in a partnership. Among the 26 patients with available questionnaire data, median CLDQ score at baseline was 5.98 (IQR 4.85–6.25). Median PSQI score was 6.5 (IQR 3.5–9.0), with 19 of 26 patients (73.1%) scoring ≥5, indicating impaired sleep quality according to the validated threshold proposed by Buysse et al. Median fatigue subscale score was 5.70 (IQR 5.20–6.35).

Sleep Quality During TACE Therapy

Sleep quality, assessed by the PSQI, showed a non-significant trend towards deterioration over the study period (Table 2). Median PSQI score was 6.5 (IQR 3.5–9.0) at t1, 6.0 (IQR 5.0–9.5) at t2, and 7.5 (IQR 5.2–9.0) at tEND (p=0.323).

A strong and consistent inverse correlation between sleep quality and quality of life was observed throughout the entire observation period (t1: rho=-0.806, p<0.001; t2: rho=-0.559, p=0.013; tEND: rho=-0.775, p<0.001), indicating that patients with better quality of life consistently reported better sleep quality across all time points.

Notably, the proportion of patients with impaired sleep quality (PSQI ≥5) remained consistently high throughout the observation period, underscoring the persistent nature of sleep disturbances in this population.

Quality of Life During TACE Therapy

At baseline (t1), median CLDQ score was 5.98 (IQR 4.85–6.25), declining to 5.69 (IQR 4.74–6.27) after the first TACE (t2) and 5.54 (IQR 4.79–6.27) at the end of the study period (tEND; Table 2). This decrease did not reach statistical significance (paired Wilcoxon test, p=0.601).

Among the six CLDQ subscales, fatigue showed the most pronounced and clinically relevant deterioration over the study period. Median fatigue score declined from 5.70 (IQR 5.20–6.35) at t1 to 4.80 (IQR 4.10–5.80) at t2 and 5.00 (IQR 3.85–5.75) at tEND, reaching statistical significance (p=0.016; Table 2). No significant changes were observed in the remaining subscales.

Changes in Liver Function During TACE Therapy

Changes in liver function parameters over the course of TACE therapy are summarized in Table 2. A significant decline in serum albumin was observed from t1 to tEND

(median 35.0 g/L vs. 32.0 g/L, p=0.032). ALBI score and MELD-Na showed trends towards deterioration that did not reach statistical significance (p=0.061 and p=0.064, respectively). Child–Pugh points, MELD, bilirubin, INR, and CRP did not change significantly over the observation period.

Correlation of Quality of Life and Sleep Quality with Liver Function

Correlations between QoL, sleep quality, and liver function parameters at baseline are summarized in Table 3. CLDQ score showed significant inverse correlations with all major liver function parameters, including Child–Pugh points (rho=-0.668, p<0.001), MELD (rho=-0.567, p=0.003), MELD-Na (rho=-0.510, p=0.008), ALBI (rho=-0.446, p=0.022), bilirubin (rho=-0.405, p=0.040), INR (rho=-0.425, p=0.030), and CRP (rho=-0.414, p=0.035), as well as a significant positive correlation with albumin (rho=+0.409, p=0.043) and AFP (rho=+0.578, p=0.002).

In contrast, PSQI score showed no significant correlations with liver function scores, with the exception of AFP (rho=-0.573, p=0.002). Trends towards positive correlation were observed with Child–Pugh points (rho=0.334, p=0.096) and MELD-Na (rho=0.366, p=0.066).

Subscale analysis revealed that the fatigue subscale showed the broadest and strongest associations with liver function, with significant inverse correlations with Child–Pugh points (rho=-0.599, p=0.001), MELD (rho=-0.626, p=0.001), MELD-Na (rho=-0.506, p=0.008), ALBI (rho=-0.428, p=0.029), bilirubin (rho=-0.456, p=0.019), and CRP (rho=-0.533, p=0.005). Full subscale correlation data are provided in Additional file 2.

Exploratory Subgroup Analysis: Patients with and without Children

Patients with children (n=19) demonstrated significantly better sleep quality compared to patients without children (n=6) at baseline, with a median PSQI of 5.0 (IQR 2.0–8.0) versus 9.0 (IQR 7.5–9.0; p=0.032). A trend towards better overall quality of life was also observed in patients with children (median CLDQ 6.10, IQR 5.80–6.45 vs. 5.26, IQR 4.80–5.72; p=0.074). No significant difference was observed for the fatigue subscale (p=0.140).

Overall Survival

After a median follow-up of 69.2 months (reverse Kaplan–Meier method), 25 of 29 patients (86.2%) had died. Median OS for the complete cohort was 15.7 months (95% CI 12.1–42.7; Figure 2). The estimated 1-year and 2-year survival rates were 65.5% (95% CI 50.3–85.3%) and 43.7% (95% CI 28.7–66.5%), respectively. The restricted mean survival time was 27.5 months (SE 4.3).

Quality of Life, Sleep Quality, and Overall Survival

Kaplan–Meier analyses according to baseline sleep quality and QoL are shown in Figure 3.

Stratification by baseline sleep quality showed a clinically meaningful separation of survival curves, with patients with good sleep quality (PSQI ≤median) demonstrating a median OS of 32.0 months compared to 12.1 months in patients with poor sleep quality (PSQI >median; log-rank p=0.064; Figure 3A). Stratification by baseline fatigue subscale score did not reveal a significant difference in overall survival (median OS 28.5 months for low fatigue vs. 15.5 months for high fatigue; log-rank p=0.964; Figure 3B).

Stratification by CLDQ score (median split) did not reveal a significant difference in overall survival between the high QoL group (median OS 15.5 months) and the low QoL group (median OS 17.0 months; log-rank p=0.138; Figure 3C). Of note, the survival curves crossed during follow-up.

Univariable and Multivariable Cox Regression Analyses

Results of univariable and multivariable Cox regression analyses are summarized in Table 4. In univariable analysis, Child–Pugh points (HR 1.45, 95% CI 1.04–2.02, p=0.029), ALBI score (HR 12.04, 95% CI 4.06–35.70, p<0.001), and bilirubin (HR 1.03 per µmol/L, 95% CI 1.01–1.06, p=0.017) were significantly associated with overall survival. Neither CLDQ (HR 0.87, 95% CI 0.61–1.24, p=0.431), PSQI (HR 1.05, 95% CI 0.96–1.15, p=0.317), nor fatigue subscale (HR 0.99, 95% CI 0.91–1.08, p=0.836) were significant in univariable analysis.

Given the primary research aim of evaluating QoL parameters as independent prognostic factors, PSQI was additionally included in a multivariable model alongside ALBI as the strongest univariable predictor. In this model, ALBI remained a strong and independent predictor of overall survival (HR 10.52, 95% CI 3.40–32.60, p<0.001), while PSQI did not retain independent prognostic significance (HR 1.04, 95% CI 0.94–1.14, p=0.492). Additional multivariable models including CLDQ and fatigue subscale are provided in Additional file 1.

The proportional hazards assumption was confirmed for the multivariable model including ALBI and PSQI (Schoenfeld residuals: ALBI p=0.370, PSQI p=0.286; global p=0.396).

Discussion

Main Findings

In this prospective single-center cohort of 29 patients with HCC undergoing TACE, sleep quality, assessed by the PSQI, was impaired in nearly three quarters of patients at baseline and showed a non-significant trend towards further deterioration during therapy. Overall HRQoL as measured by the CLDQ remained stable over the study period, while the fatigue subscale showed a significant and clinically relevant deterioration from baseline to study end. CLDQ correlated significantly with all major liver function parameters, while PSQI showed no significant associations with liver function scores beyond AFP.

In multivariable Cox regression, the ALBI score was the only independent predictor of overall survival, while neither CLDQ, PSQI, nor fatigue subscale retained prognostic significance after adjustment for liver function. These findings add prospective longitudinal evidence on HRQoL and sleep quality to a well-characterized TACE cohort with a high event rate and extended follow-up of 69.2 months.

Sleep Quality in HCC Patients Undergoing TACE

The high prevalence of impaired sleep quality at baseline (73.1%, PSQI ≥5) observed in our cohort is consistent with reported rates of up to 80% in patients with liver cirrhosis. [4] Hepatic dysfunction, tumor burden, and treatment-related stress may all contribute to sleep disturbances in this patient population. Prospective studies in patients with HCC undergoing locoregional therapy have also shown significant associations between sleep quality and multiple domains of health-related quality of life, highlighting the close relationship between sleep and overall patient wellbeing. [9]

The strong inverse correlation between CLDQ and PSQI consistently observed throughout the study (t1: rho=-0.806; t2: rho=-0.559; tEND: rho=-0.775; all $p<0.05$) confirms that patients with better overall quality of life consistently report better sleep quality, and vice versa.

Quality of Life During TACE Therapy

The overall stability of HRQoL during TACE therapy observed in the present study is consistent with prior evidence. Several prospective studies have demonstrated that TACE does not lead to significant deterioration of overall HRQoL over time. [20, 21] This finding may reflect adaptation to chronic illness, treatment-related stabilization of disease burden, or limitations of global HRQoL scores in capturing domain-specific changes, particularly in patients with substantial baseline impairment, where floor effects may reduce sensitivity to further deterioration. Systematic analyses recently confirmed that HRQoL after TACE is influenced by a complex interplay of clinical, psychological, and social factors, and that global scores may mask deterioration in specific domains. [22]

In contrast, the fatigue subscale worsened significantly over time ($p=0.016$) and was the only CLDQ domain to reach statistical significance. This observation is consistent with the multifactorial nature of fatigue in patients with chronic disease, encompassing progressive liver dysfunction, systemic inflammation, tumor burden, and the psychological stress associated with an oncological diagnosis. [12, 23]

The strong inverse correlations observed between fatigue and liver function parameters – including Child-Pugh points (rho=-0.599, $p=0.001$) and MELD (rho=-0.626, $p=0.001$) – further support the concept that fatigue in this population is closely linked to the severity of hepatic impairment. Fatigue scores correlated more strongly

with liver function parameters than any other CLDQ subscale, consistent with findings from a prospective cohort of chronic liver disease patients. [12]

CLDQ and Liver Function

The significant inverse correlations between CLDQ and all major liver function parameters at baseline, including Child-Pugh points, MELD, MELD-Na, ALBI, bilirubin, and INR, confirm that in patients with HCC undergoing TACE, HRQoL closely mirrors the severity of hepatic dysfunction. This finding is consistent with the original CLDQ validation, which demonstrated a gradient in HRQoL scores across Child-Pugh stages, and has subsequently been corroborated in prospective cohorts of patients with chronic liver disease. [10, 12] The particularly strong correlation between fatigue and MELD (rho=-0.626) adds to a growing body of evidence linking chronic fatigue in cirrhosis to portal hypertension and its systemic consequences. [23]

In contrast to CLDQ, PSQI did not show significant correlations with liver function scores, suggesting that sleep disturbances in this population may be driven by factors not captured by standard liver function parameters – such as psychological distress, pain, pruritus, or nocturia – rather than by hepatic dysfunction itself. This suggests that sleep quality and HRQoL represent partially distinct constructs warranting separate clinical assessment.

Prognostic Value of Sleep Quality and QoL

In contrast to several studies in larger and more heterogeneous HCC cohorts, neither overall sleep quality nor HRQoL emerged as independent predictors of overall survival in the present cohort after adjustment for liver function. [6–8] In univariable analysis, ALBI score, bilirubin, and Child–Pugh points were all significantly associated with overall survival (Table 4); given their different scales, these hazard ratios are not

directly comparable in magnitude. The crossing of survival curves during follow-up further argues against a consistent prognostic role of baseline CLDQ in this setting. These findings are consistent with the established prognostic hierarchy in TACE-treated HCC, in which liver function dominates over other clinical variables. [13, 14]

The borderline significant separation of survival curves according to sleep quality (log-rank p=0.064), with patients in the good sleep group demonstrating a nearly threefold longer median OS compared to poor sleepers (32.0 vs. 12.1 months), represents a numerically meaningful but statistically non-significant finding. Of note, when PSQI was analyzed as a continuous variable in univariable Cox regression, no significant association with OS was observed (p=0.317), suggesting that the survival difference observed on Kaplan–Meier analysis may reflect the specific dichotomization applied rather than a robust continuous prognostic effect.

The limited sample size of the present study may have precluded detection of a true prognostic association. In larger cohorts, sleep quality has been linked to survival outcomes in patients with cancer through mechanisms including immune dysregulation, neuroendocrine disruption, and circadian rhythm alterations. [24] Whether similar mechanisms operate in TACE-treated HCC patients warrants investigation in future studies with larger sample sizes.

The lack of prognostic significance for QoL in the present cohort may also reflect the dominance of liver function as a competing prognostic factor. In patients whose prognosis is largely determined by hepatic reserve, patient-reported outcomes may add limited incremental prognostic information beyond established liver function scores. This interpretation is supported by the very high HR observed for ALBI in multivariable models (HR ~10.5), which likely attenuated the potential contributions of QoL parameters.

Social Factors and QoL

Patients with children demonstrated significantly better sleep quality (p=0.032) and a trend towards better overall HRQoL (p=0.074) compared to childless patients. This may reflect the beneficial effects of social support and family connectedness on psychological coping in this population, consistent with observations in other oncological cohorts. [25, 26] Given the median age of 70 years in our cohort, the presence of children likely implies an established social network and regular social interactions, which may attenuate the psychological distress associated with an HCC diagnosis and TACE therapy.

Strengths and Limitations

Strengths of this study include the prospective design, standardized TACE protocol within an interdisciplinary tumor board framework, the use of two validated patient-reported outcome instruments, and the extended follow-up with a high event rate of 86.2%, enabling mature survival analyses including multivariable Cox regression.

The primary limitation is the small sample size of 29 patients, which restricts statistical power and limits the generalizability of findings. In particular, the absence of a statistically significant association between QoL parameters and survival should be interpreted in the context of this limited power rather than as definitive evidence of the absence of a true association. The single-center design, enrollment linked to a parent study rather than consecutive real-world inclusion, and the predominance of alcohol-related HCC etiology (62.1%) may further limit external validity. The PSQI has not been specifically validated in patients with HCC undergoing TACE, and its susceptibility to cognitive impairment and reporting bias should be acknowledged. Finally, the absence

of a structured assessment of depression and anxiety as potential confounders of both HRQoL and sleep quality represents a limitation, as the prevalence of depression in patients with liver cirrhosis has been reported to be up to 63%. [27]

Conclusion

In patients with HCC undergoing TACE, impaired sleep quality and HRQoL are common and closely linked to hepatic dysfunction. Fatigue emerged as the most sensitive HRQoL domain in relation to liver disease severity and longitudinal deterioration during follow-up. While ALBI score remained the dominant predictor of overall survival, sleep quality showed a numerical association with survival outcomes that warrants further investigation in larger cohorts.

These findings support the integration of patient-reported outcome measures, including sleep and HRQoL assessments, into routine clinical care of patients undergoing TACE. Future prospective studies should evaluate whether structured supportive interventions targeting fatigue and sleep impairment may improve patient wellbeing during locoregional HCC treatment.

Ethics approval and consent to participate

This prospective single-center observational study was conducted at the Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg University Mainz, Germany. The study was approved by the ethics committee of the Medical Association of Rhineland-Palatinate, Mainz, Germany (permit number 837.242.17 [11076]) and conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). Written informed consent was obtained from all patients prior to study inclusion.

Consent for publication

Not applicable.

Competing interests

PB has received reimbursement of meeting attendance fees and travel expenses from AstraZeneca.

FF has received honoraria as a speaker and/or consultant from AstraZeneca, Bluejay Therapeutics, BMS, Eisai, Lilly, MSD, Pfizer, Roche, Taiho and Takeda and reimbursement of meeting attendance fees and travel expenses from BeOne Medicines, Merck KGaA and Servier.

SJG has received travel expenses from Ipsen, Gilead, and Merz.

AW has received honoraria as a speaker and/or consultant from Bayer, BMS, Sanofi, Roche, AstraZeneca, Servier, Taiho, MSD, Eisai, Ipsen and Norgine and reimbursement of meeting attendance fees and travel expenses from Merck KGaA and Servier.

BKS has received honoraria as a speaker and/or consultant from Bayer HealthCare, Boehringer Ingelheim, AstraZeneca, med update, Bristol Myers Squibb as well as from IMPP. In addition, BKS holds a cooperation with Resolve Biosciences.

RK has received consultancy fees from Boston Scientific, Bristol-Myers Squibb, Guerbet, Roche, and SIRTEX, and lecture fees from AstraZeneca, BTG, Eisai, Guerbet, Ipsen, Roche, Siemens, SIRTEX, and MSD Sharp & Dohme.

CML has received honoraria as a speaker and/or consultant from AbbVie, AstraZeneca, Boston Scientific, CSL Behring, Cook, Eisai, Falk, Gilead, Gore, Mirum, Sobi, Shionogi, and reimbursement of meeting attendance fees and travel expenses from AbbVie, Gilead, Ipsen.

CL: Lecture and consultant fees: Merz Therapeutics, Alfasigma, Norgine, Gilead Sciences, Abbvie, Ipsen, Falk Foundation e.V., CSL Behring, Ewimed, Boehringer Ingelheim, Novartis. Research grants: Merz Therapeutics, Norgine.

PRG has received honoraria as a speaker and/or consultant from Bayer, AstraZeneca, BMS, MSD, and Roche and reimbursement of meeting attendance fees and travel expenses from BMS and AstraZeneca.

TE: Speaker and Travel Support from Siemens Healthineers, Institutional Research Support from Siemens Healthineers. Consultant for Circle Cardiovascular Imaging. All of these roles are not related to this project.

MAW has received honoraria as a speaker and/or consultant from AbbVie, AstraZeneca, Boston Scientific, Bristol-Myers Squibb, Dr. Falk Pharma, Gilead Sciences, Incyte, Ipsen, MSD Sharp & Dohme, Norgine, Nordic Pharma, Roche

Pharma, Sirtex and reimbursement of meeting attendance fees and travel expenses from AstraZeneca.

All other authors declare no potential financial or non-financial conflicts of interest.

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Authors' contributions

PB: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. JW: Investigation, Data curation. AC: Investigation, Data curation. AK: Investigation, Data curation. SS: Investigation, Data curation. SJG: Investigation, Data curation. KS: Investigation, Data curation. CZ: Investigation, Data curation. MAW: Investigation, Data curation, Supervision, Writing – review & editing. JUM: Investigation, Data curation, Supervision, Writing – review & editing. LM: Resources. FS: Resources. DG: Resources. FH: Resources. TE: Resources. MBP: Resources. JM: Resources. BKS: Resources. RK: Resources, Supervision. TB: Resources, Supervision. CL: Supervision, Writing – review & editing. CML: Supervision, Writing – review & editing. PRG: Supervision, Writing – review & editing. AW: Supervision, Writing – review & editing. FF: Conceptualization, Methodology, Supervision, Writing – review & editing.

All authors reviewed and approved the final manuscript.

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Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the author(s) used Claude (Anthropic) for editing and language refinement of the manuscript text. The author(s) reviewed and edited the output as needed and take full responsibility for the content of the published article.

Availability of data and materials

The data that support the findings of this study are not publicly available due to patient data privacy regulations. Data are available from the corresponding author upon reasonable request and subject to institutional data sharing agreements.

Additional files

Additional file 1: Additional multivariable Cox proportional hazards regression models for overall survival. Model 1 includes ALBI score and CLDQ total score as covariates. Model 2 includes ALBI score and CLDQ fatigue subscale as covariates.

Additional file 2: Spearman rank correlations between CLDQ subscale scores and liver function parameters at baseline (t1, n=26). Rho values are shown; asterisks indicate level of significance. ns, not statistically significant (p≥0.05).

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Tables

Table 1. Baseline demographic and clinical characteristics of the study cohort (n=29).

Variable	Overall (n=29)
Demographics	
Age, years, median (IQR)	70.0 (67.0–75.0)
Male sex, n (%)	24 (82.8)
Partnership, n (%)	22 (81.5)
Children, n (%)	19 (73.1)
Etiology of liver disease, n (%)	
Alcohol-related	18 (62.1)
Hepatitis B	3 (10.3)
NAFLD	2 (6.9)
AIH	1 (3.4)
Other/cryptogenic	5 (17.2)
Tumor characteristics	
BCLC stage A, n (%)	3 (10.3)
BCLC stage B, n (%)	25 (86.2)
BCLC stage C, n (%)	1 (3.4)
Liver function	
Child–Pugh A, n (%)	17 (58.6)
Child–Pugh B, n (%)	10 (34.5)
Child–Pugh C, n (%)	2 (6.9)
MELD score, median (IQR)	11.0 (7.0–13.0)
ALBI score, median (IQR)	-2.11 (-2.57– -1.79)
Performance status	

ECOG 0, n (%)	9 (33.3)
ECOG 1, n (%)	14 (51.9)
ECOG 2, n (%)	4 (14.8)
Quality of life (n=26)	
PSQI total score, median (IQR)	6.5 (3.5–9.0)
Poor sleep quality (PSQI ≥5), n (%)	19 (73.1)
CLDQ total score, median (IQR)	5.98 (4.85–6.25)
CLDQ fatigue subscale, median (IQR)	5.70 (5.20–6.35)

Baseline demographic and clinical characteristics of the study cohort (n=29). Continuous variables are presented as median (interquartile range). Categorical variables are presented as absolute numbers and percentages. Sleep quality and quality of life data were available for 26 of 29 patients. Partnership and children data were available for 27 and 26 patients, respectively.

AIH, autoimmune hepatitis; ALBI, Albumin–Bilirubin score; BCLC, Barcelona Clinic Liver Cancer classification; CLDQ, Chronic Liver Disease Questionnaire (scale 1–7, higher scores indicate better quality of life); ECOG, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; NAFLD, non-alcoholic fatty liver disease; PSQI, Pittsburgh Sleep Quality Index (scale 0–21, higher scores indicate worse sleep quality).

Table 2. Longitudinal changes in sleep quality, quality of life, and liver function parameters during TACE therapy (n=26 for QoL, n=27–29 for liver function).

Variable	t1	t2	tEND	p-value (t1 vs. tEND)
Sleep quality (n=26)				
PSQI total score	6.5 (3.5–9.0)	6.0 (5.0–9.5)	7.5 (5.2–9.0)	0.323
Quality of life (n=26)				
CLDQ total score	5.98 (4.85–6.25)	5.69 (4.74–6.27)	5.54 (4.79–6.27)	0.601
— Abdominal symptoms	6.48 (5.08–7.00)	6.30 (5.00–6.80)	6.15 (5.00–7.00)	0.589
— Fatigue	5.70 (5.20–6.35)	4.80 (4.10–5.80)	5.00 (3.85–5.75)	**0.016**
— Systemic symptoms	5.80 (5.00–6.80)	5.80 (5.00–6.30)	5.60 (5.05–6.35)	0.255
— Activity	6.00 (5.00–6.69)	6.00 (5.00–6.83)	6.00 (4.68–6.69)	0.438
— Emotional function	6.19 (5.19–6.75)	6.00 (4.94–6.45)	5.71 (5.16–6.62)	1.000
— Worry	5.40 (4.25–6.20)	5.80 (4.40–6.40)	5.70 (4.80–6.35)	0.486

Liver function scores				
Child–Pugh points	6.0 (5.0–7.0)	5.0 (5.0–6.0)	6.0 (5.0–7.0)	0.667
MELD	11.0 (8.8–13.0)	11.0 (8.0–13.2)	11.0 (9.0–14.0)	0.118
MELD-Na	11.0 (8.8–13.2)	12.0 (10.0–14.5)	12.0 (10.0–16.0)	0.064
ALBI score	-2.12 (-2.49–-1.62)	-2.20 (-2.52–-1.68)	-1.88 (-2.29–-1.54)	0.061
Laboratory parameters				
Bilirubin, µmol/L	20.5 (13.7–35.4)	16.2 (11.1–29.9)	22.2 (11.5–34.7)	0.887
Albumin, g/L†	35.0 (30.2–38.0)	35.0 (30.2–38.8)	32.0 (29.0–35.5)	**0.032**
INR	1.20 (1.10–1.30)	1.20 (1.00–1.30)	1.30 (1.10–1.33)	0.180
CRP, mg/L	8.6 (2.6–15.5)	14.0 (6.1–25.0)	11.0 (5.7–25.0)	0.163

Longitudinal changes in sleep quality, quality of life, and liver function parameters during TACE therapy. All values are presented as median (interquartile range). P-values refer to paired Wilcoxon signed-rank tests comparing baseline (t1) and study end (tEND). Bold p-values indicate statistical significance (p<0.05). t1, baseline assessment before first TACE; t2, assessment after first TACE (approximately 6 weeks); tEND, last available assessment. n=19

for t2 quality of life assessments; n=18–20 for t2 liver function parameters, reflecting patients who received a second TACE and had available data. †n=25 at t1, n=18 at t2, n=27 at tEND due to missing values.

ALBI, Albumin–Bilirubin score; CLDQ, Chronic Liver Disease Questionnaire (scale 1–7, higher scores indicate better quality of life); CRP, C-reactive protein; INR, international normalized ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; MELD-Na, MELD incorporating serum sodium; PSQI, Pittsburgh Sleep Quality Index (scale 0–21, higher scores indicate worse sleep quality).

Table 3. Spearman correlations between quality of life, sleep quality, and liver function parameters at baseline (t1, n=26).

Variable	CLDQ total score		PSQI total score	
	rho	p-value	rho	p-value
Liver function scores				
Child–Pugh points	-0.668	<0.001	0.334	0.096
MELD	-0.567	0.003	0.314	0.119
MELD-Na	-0.510	0.008	0.366	0.066
ALBI score	-0.446	0.022	0.309	0.124
Laboratory parameters				
Bilirubin, µmol/L	-0.405	0.040	0.284	0.159
Albumin, g/L	+0.409	0.043	-0.323	0.115
INR	-0.425	0.030	0.322	0.108
CRP, mg/L	-0.414	0.035	0.269	0.183
AFP, ng/mL	+0.578	0.002	-0.573	0.002
CLDQ-PSQI correlation				
PSQI total score	-0.806	<0.001	—	—

Spearman rank correlations between health-related quality of life (CLDQ), sleep quality (PSQI), and liver function parameters at baseline (t1, n=26). Bold values indicate statistical significance (p<0.05). Negative rho values for CLDQ indicate that worse liver function is associated with poorer quality of life. Positive rho values for PSQI indicate that worse liver function is associated with poorer sleep quality. n=25 for correlations involving albumin due to one missing value.

AFP, alpha-fetoprotein; ALBI, Albumin–Bilirubin score; CLDQ, Chronic Liver Disease Questionnaire; CRP, C-reactive protein; INR, international normalized ratio; MELD, Model for

End-Stage Liver Disease; MELD-Na, MELD incorporating serum sodium; PSQI, Pittsburgh Sleep Quality Index; rho, Spearman correlation coefficient.

Table 4. Univariable and multivariable Cox proportional hazards regression analyses for overall survival.

Variable	Univariable HR	95% CI	p	Multivariable HR	95% CI	p
Liver function						
ALBI score	12.04	4.06–35.70	<0.001	10.52	3.40–32.60	<0.001
Child–Pugh points	1.45	1.04–2.02	0.029	—	—	—
Bilirubin, μmol/L	1.03	1.01–1.06	0.017	—	—	—
MELD	1.03	0.92–1.14	0.653	—	—	—
Performance status						
ECOG	1.32	0.70–2.51	0.393	—	—	—
Quality of life						
PSQI total score	1.05	0.96–1.15	0.317	1.04	0.94–1.14	0.492

CLDQ total score	0.87	0.61–1.24	0.431	—	—	—
Fatigue subscale	0.99	0.91–1.08	0.836	—	—	—

Univariable and multivariable Cox proportional hazards regression analyses for overall survival. The multivariable model includes ALBI score and PSQI as covariates, with all quality of life parameters entered as continuous variables. Dashes indicate variables not included in the multivariable model. Bold p-values indicate statistical significance (p<0.05). Univariable analyses: n=29 (25 events) for liver function and performance status variables; n=26 (23 events) for QoL parameters. Multivariable model: n=26, 23 events.

ALBI, Albumin–Bilirubin score; CI, confidence interval; CLDQ, Chronic Liver Disease Questionnaire; ECOG, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; PSQI, Pittsburgh Sleep Quality Index.

Figure Legends

Figure 1. Flowchart of patient selection and allocation. A total of 30 patients were enrolled in the study between December 2017 and May 2022. One patient was excluded due to missing survival data, leaving 29 patients for the overall survival analysis. Of these, 26 patients with complete quality of life and sleep quality assessments were included in the longitudinal QoL analysis. Follow-up was updated in January 2026.

CLDQ, Chronic Liver Disease Questionnaire; PSQI, Pittsburgh Sleep Quality Index; QoL, quality of life; tEND, last available study visit.

Figure 2. Kaplan–Meier curve of overall survival for the complete study cohort (n=29). Tick marks indicate censored observations. The median overall survival was 15.7 months (95% CI 12.1–42.7). At the time of analysis, 25 of 29 patients (86.2%) had died. The restricted mean survival time was 27.5 months (SE 4.3).

CI, confidence interval; SE, standard error.

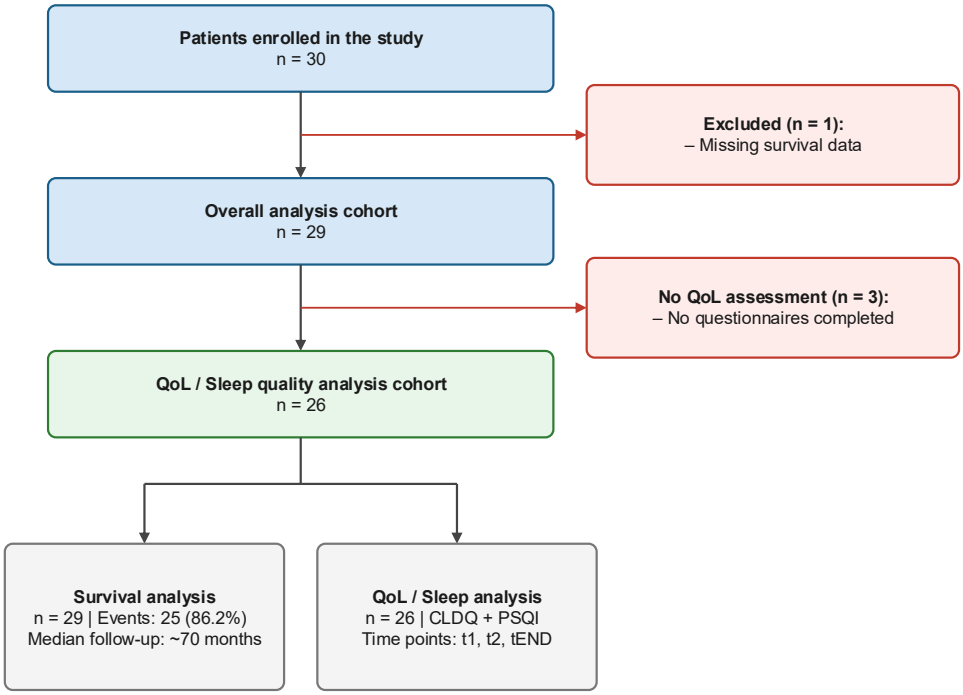
Figure 3. Kaplan–Meier curves for overall survival stratified by baseline quality of life and sleep quality parameters. (A) Overall survival according to PSQI total score, stratified by median split (median 6.5). Patients with good sleep quality (≤median, n=13) had a median overall survival of 32.0 months compared to 12.1 months in patients with poor sleep quality (>median, n=13; log-rank p=0.064). (B) Overall survival according to CLDQ fatigue subscale score, stratified by median split (median 5.70). Patients with low fatigue (≥median, n=13) had a median overall survival of 28.5 months compared to 15.5 months in patients with high fatigue (<median, n=13; log-rank p=0.964). (C) Overall survival according to CLDQ total score, stratified by median split (median 5.98). Patients with high QoL (≥median, n=13) had a median overall survival

of 15.5 months compared to 17.0 months in patients with low QoL (<median, n=13; log-rank p=0.138). Tick marks indicate censored observations.

CLDQ, Chronic Liver Disease Questionnaire (scale 1–7, higher scores indicate better quality of life); PSQI, Pittsburgh Sleep Quality Index (scale 0–21, higher scores indicate worse sleep quality); QoL, quality of life.

Figures

Fig. 1



CLDQ, Chronic Liver Disease Questionnaire; PSQI, Pittsburgh Sleep Quality Index; QoL, quality of life; tEND, last available study visit.

Fig. 2

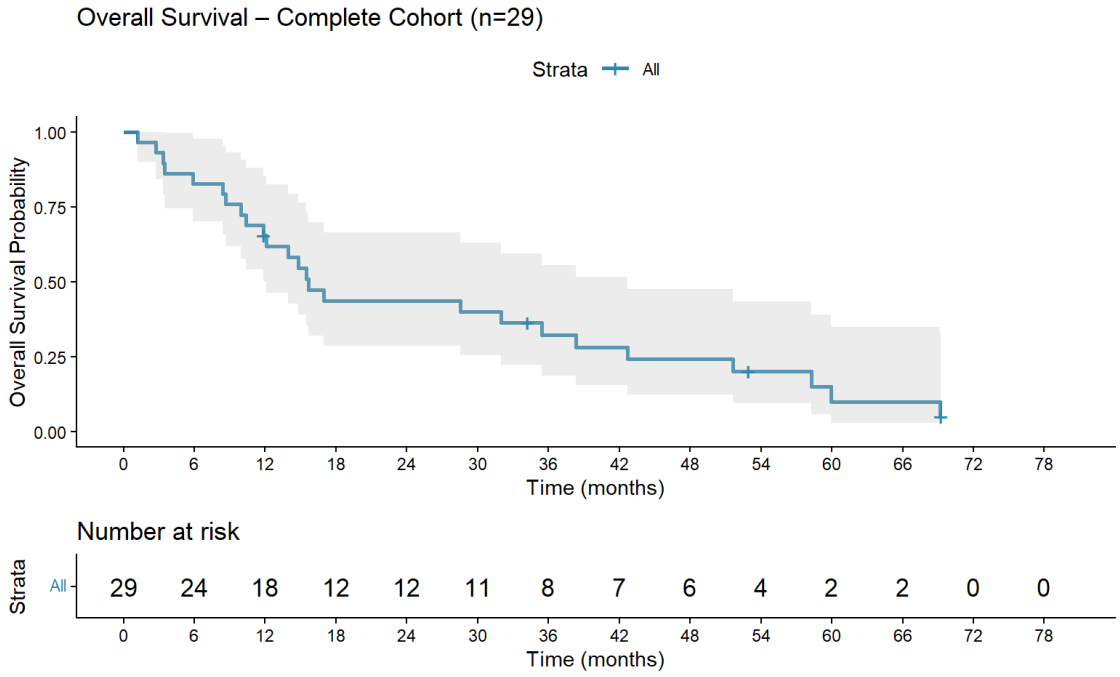

Overall Survival – Complete Cohort (n=29)
Strata All
Overall Survival Probability
1.00
0.75
0.50
0.25
0.00
0 6 12 18 24 30 36 42 48 54 60 66 72 78
Time (months)
Number at risk
Strata
All
29 24 18 12 12 11 8 7 6 4 2 2 0 0
0 6 12 18 24 30 36 42 48 54 60 66 72 78
Time (months)

Fig. 3A

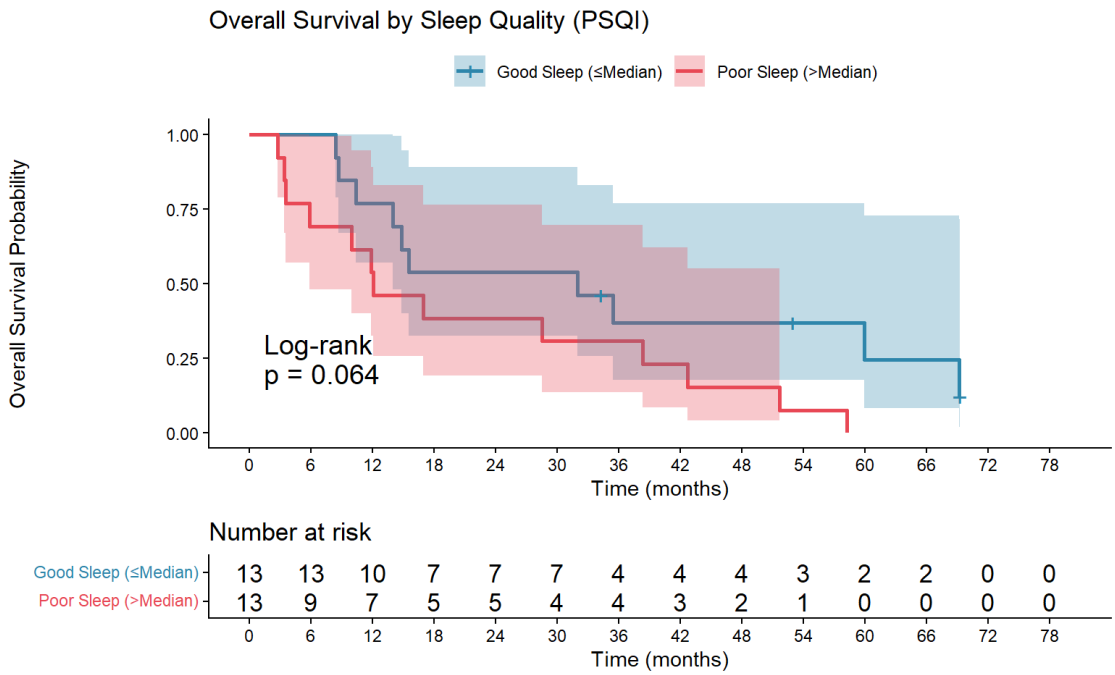

Overall Survival by Sleep Quality (PSQI)
Good Sleep (≤Median)
Poor Sleep (>Median)
Overall Survival Probability
1.00
0.75
0.50
0.25
0.00
Log-rank
p = 0.064
0 6 12 18 24 30 36 42 48 54 60 66 72 78
Time (months)
Number at risk
Good Sleep (≤Median) 13 13 10 7 7 7 4 4 4 3 2 2 0 0
Poor Sleep (>Median) 13 9 7 5 5 4 4 3 2 1 0 0 0 0
0 6 12 18 24 30 36 42 48 54 60 66 72 78
Time (months)

Fig. 3B

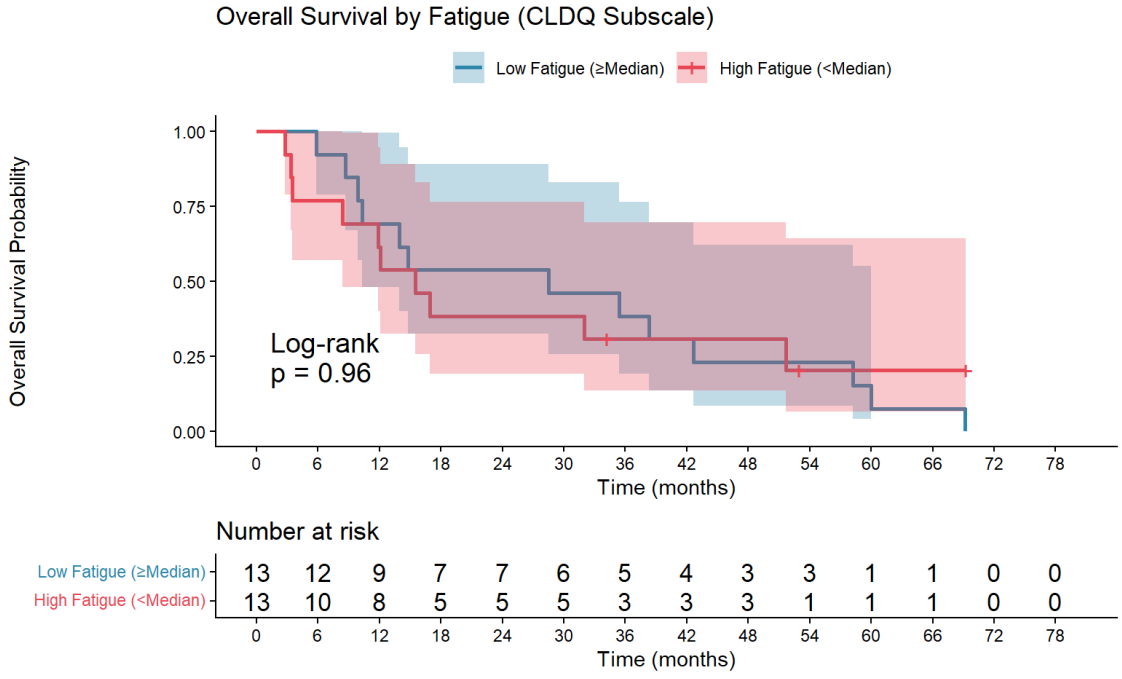
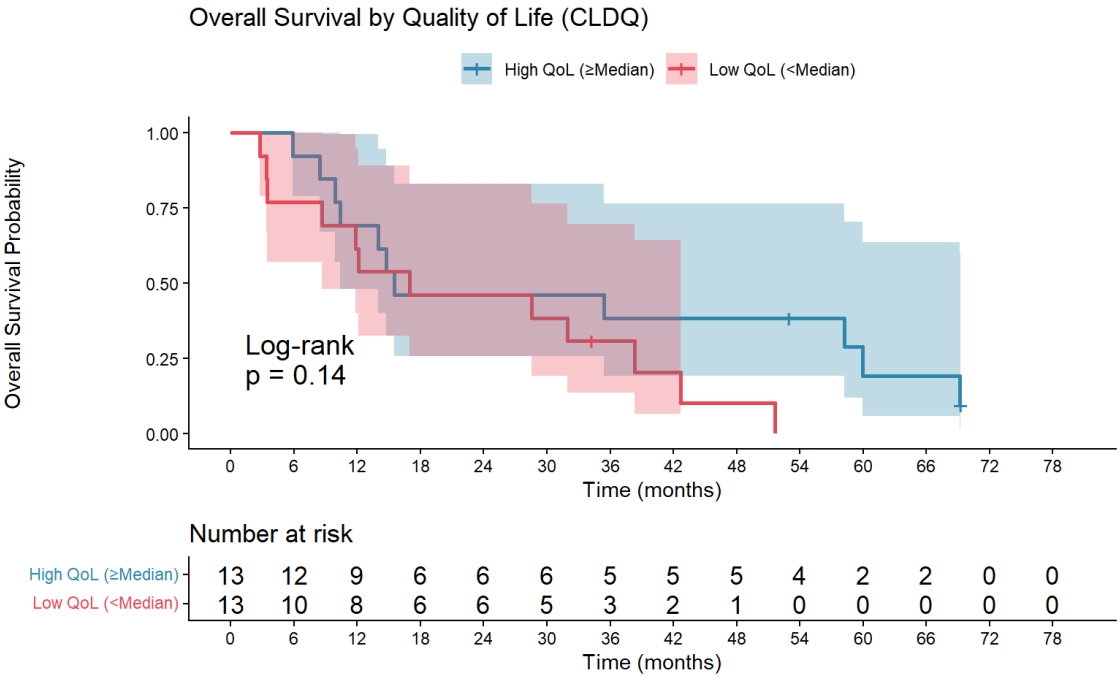

Overall Survival by Fatigue (CLDQ Subscale)
Low Fatigue (≥Median)
High Fatigue (<Median)
Overall Survival Probability
1.00
0.75
0.50
0.25
0.00
Log-rank
p = 0.96
0 6 12 18 24 30 36 42 48 54 60 66 72 78
Time (months)
Number at risk
Low Fatigue (≥Median) 13 12 9 7 7 6 5 4 3 3 1 1 0 0
High Fatigue (<Median) 13 10 8 5 5 5 3 3 3 1 1 1 0 0
0 6 12 18 24 30 36 42 48 54 60 66 72 78
Time (months)

Fig. 3C


Overall Survival by Quality of Life (CLDQ)
High QoL (≥Median)
Low QoL (<Median)
Overall Survival Probability
1.00
0.75
0.50
0.25
0.00
Log-rank
p = 0.14
0
6
12
18
24
30
36
42
48
54
60
66
72
78
Time (months)

Number at risk
High QoL (≥Median) 13 12 9 6 6 6 5 5 5 4 2 2 0 0
Low QoL (<Median) 13 10 8 6 6 5 3 2 1 0 0 0 0 0
0
6
12
18
24
30
36
42
48
54
60
66
72
78
Time (months)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFilesHCCTACESleepFatigue.docx