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Original Article

Trajectories of postoperative fatigue and their association with physical and mental health among patients with peritoneal metastases from colorectal and appendiceal cancer after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a 1-year longitudinal study

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Abstract: Postoperative fatigue (POF) is a common complication following major or medium-sized surgeries. It is influenced by surgical trauma, pain, sleep quality, nutrition, and mental state, and can significantly hinder postoperative recovery. As enhanced recovery protocols become more widely adopted in perioperative care, attention to the prevention and management of POF has increased. This 1-year longitudinal study enrolled patients with peritoneal metastases from colorectal and appendiceal cancer following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) at two tertiary hospitals. Participants completed self-administered questionnaires at discharge, and at 3, 6, 9, and 12 months after surgery. POF was assessed using the 10-item Identity-Consequence Fatigue Scale (ICFS-10). Group-based trajectory modeling (GBTM) was utilized to identify distinct POF trajectories, and multivariable models were fitted to examine their associations with sleep quality, pain, and physical and mental conditions over time. The reporting of this study adhered to the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) checklist. Among 182 participants who experienced POF during follow-up, three distinct fatigue trajectories were identified: high-increasing (29.67%), moderate-increasing (37.36%), and low-increasing (31.87%). Poor sleep quality, inadequate pain management, and compromised physical and mental conditions were linked to trajectory groups with more severe fatigue symptoms. After adjusting for covariates, the high-increasing trajectory group demonstrated significantly lower scores in mental dimensions at 12 months post-discharge. This study presents the cumulative incidence and longitudinal trajectories of POF over a 1-year postoperative period, analyzing the relationship between physical and mental conditions in peritoneal metastatic cancer survivors. Our findings underscore the importance of early identification and targeted treatment of high-risk patients to prevent the chronic progression of POF. These trajectory patterns provide potential clinical avenues for the early detection and management of persistent fatigue based on a patient's evolving symptom profile.

Keywords: Peritoneal metastatic cancer, postoperative fatigue, physical and mental condition, health related quality of life

Introduction

Peritoneal cancer - including primary peritoneal carcinoma and metastases from gastrointestinal or gynecological malignancies - represents a growing global health burden. Its incidence has increased in recent years, partly attributed to population aging, improved diagnostic imaging, and prolonged survival in malignancies such as ovarian, colorectal, and gastric cancers that commonly metastasize to the peritoneum [1]. Despite advances in CRS-HIPEC, the disease continues to carry significant morbidity and a poor long-term prognosis [2]. Survival outcomes vary widely depending on tumor origin, completeness of cytoreduction, and bio-

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logical aggressiveness, but mortality rates remain high, particularly among advanced-stage patients [3]. Postoperative fatigue (POF) is one of the most frequent and distressing symptoms experienced by patients undergoing CRS-HIPEC [4]. Epidemiological studies report that cancer-related fatigue may persist for months or even years following surgery, affecting more than half of patients during postoperative recovery [5]. Fatigue is influenced by surgical complexity, systemic inflammatory responses, nutritional status, anemia, psychological stress, and chemotherapy-induced toxicity [6]. Severe fatigue significantly impairs physical functioning, daily living activities, and health-related quality of life, posing major challenges for survivorship care. Additionally, persistent POF has been associated with delayed rehabilitation, higher readmission rates, reduced treatment tolerance, and inferior overall and progression-free survival [7]. Although POF has been widely reported in cancer populations, little is known about its longitudinal trajectories among patients with peritoneal metastatic cancer following CRS-HIPEC.

Given the growing number of patients living with or beyond peritoneal cancer, understanding the epidemiological characteristics and long-term outcomes of POF is critical. Existing literature consistently indicates that cancer-related fatigue often coexists with symptoms such as sleep disorders, pain, anxiety, and depression, forming a symptom cluster [8]. There are complex interactions and common mechanisms among these factors, including inflammatory responses, energy metabolism disorders, and neuroendocrine imbalances [9]. Physical and mental conditions not only serve as significant risk factors for fatigue but may also exacerbate its persistence and fluctuation. Moreover, fatigue has a significant negative impact on patients' emotions, cognition, social functions, and daily activities, and is often underestimated or overlooked in clinical management. Mapping fatigue trajectories enables the identification of distinct symptom patterns - such as rapid recovery, gradual improvement, or persistent long-term fatigue - which may be driven by differing biological, psychological, and treatment-related mechanisms [10]. Understanding these patterns is essential for recognizing high-risk subgroups who may benefit from early supportive interventions.

Group-based trajectory modeling (GBTM) is a person-centered statistical approach used to identify latent subgroups of individuals who share similar developmental trajectories over time. The method assumes that the population is composed of a finite number of distinct trajectory groups, each characterized by its own polynomial function. Individuals within each group are assumed to follow the same trajectory pattern without random effects [11]. Posterior probabilities are estimated for each individual to determine the likelihood of belonging to each trajectory group. Therefore, the objectives of this research are to: (1) identify latent subgroups of POF trajectories among metastatic peritoneal cancer survivors over a 1-year period using GBTM; (2) explore how sleep quality, pain, physical and mental status, and several sociodemographic factors at baseline can discriminate among trajectory memberships; and (3) examine the association between POF trajectories and physical and mental health status at 12 months post-operation.

Methods

Study design

This is a prospective longitudinal cohort study, conducted at two tertiary hospitals in Hangzhou city from February 2021 to March 2024. Patients were eligible if they met the following criteria: (1) age ≥ 19 years; (2) a diagnosis of peritoneal metastases (The determination criteria are based on the pathological results and clinical diagnosis). Exclusion criteria were as follows: (1) severe cognitive impairment or psychiatric disorders preventing the completion of the questionnaire; and (2) expected survival < 3 months. The rationale for this exclusion is twofold: clinically, end-of-life fatigue associated with terminal decline or cancer cachexia differs fundamentally in etiology from postoperative recovery fatigue; methodologically, early mortality would severely limit the availability of repeated longitudinal measures necessary for robust Group-Based Trajectory Modeling over the 1-year follow-up, thereby confounding the survivorship recovery trajectories. The convenience sampling method was used to collect data from colorectal cancer patients and received surgical treatment in the surgery department of two tertiary hospitals in Hangzhou city.

This report was subject to GRoLTS-Checklist: Guidelines for Reporting on Trajectory Studies.

Participants and sample size

Although formal power calculation methods for GBTM are limited, our sample size justification was based on established methodological recommendations. Methodologically, for longitudinal trajectory modeling incorporating repeated measurements, a minimum sample size of 200 is widely recommended to ensure robust model convergence and trajectory stability [12]. Furthermore, to ensure the adequacy of the sample size for the subsequent multinomial logistic regression, we adhered to the widely accepted rule of thumb requiring at least 10 events per predictor variable (EPV) [13]. Given the 16 independent variables evaluated, a minimum of 160 participants was necessary. Accounting for an estimated 10% attrition rate, our target sample was at least 176. The final modeled sample of 182 patients, with 100% completing at least three follow-up assessments, well exceeded these minimum requirements. Additionally, the smallest identified trajectory group comprised 55 patients, safely exceeding the 5% viability threshold for GBTM. This robust sample size ensured stable standard errors and reliable confidence intervals for the reported odds ratios (ranging from 1.67 to 4.56) in our regression models.

Ethical consideration

The investigation conformed to the principles outlined in the Declaration of Helsinki. Institutional Review Board (IRB) approval was obtained from the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (Approval No: (2020) Ethical Review Research No. 914), where the participants were enrolled. Furthermore, this study was registered with the Chinese Clinical Trial Registry (Registration No: ChiCTR26001-25214). Researchers explained the study purpose, procedures, and the right to voluntarily withdraw at any time to all eligible patients. Participants provided informed consent.

Procedures and measurements

Patients were consecutively screened for eligibility when they were scheduled for surgery at the two participating hospitals. Those who met the inclusion criteria and provided written informed consent were enrolled in the study.

Socio-demographic data: Socio-demographic data were collected using a self-administered questionnaire. The variables included sex, age, educational level, marital status, monthly per-capita household income, etc.

Clinical and laboratory information: Clinical and laboratory information was obtained from medical records. The variables included body mass index (BMI), hemoglobin, systemic immune-inflammation index (SII), prognostic nutritional index (PNI), therapeutic schedule, and comorbidities.

Postoperative Fatigue (POF): We used the Chinese version of the Identity-Consequence Fatigue Scale (ICFS) to evaluate perioperative fatigue status. The ICFS was developed by Paddison et al. in 2006 based on the self-regulation theory of the common-sense model, which consists of 5 dimensions and 31 items. In 2016, Nøstdahl et al. extracted 3 common factors and 10 items. Items 1-7 were scored using a 6-point Likert scale, and items 1, 3, and 7 were reverse scored. Items 8-10 were scored using a 5-point Likert scale, with an additional "not for me" option provided. The total score of the Chinese version of the ICFS-10 was the sum of the scores of each item, with a higher total score indicating more severe POF. The cutoff value of the Chinese version of the ICFS-10 for the diagnosis of POF in postoperative patients with gastrointestinal cancer is 24. Because fatigue is highly subjective and individual scores may vary over time, we evaluated the overall longitudinal burden of fatigue. The cumulative incidence of POF was defined as having an ICFS-10 score > 24 at any of the five follow-up time points (≥ 1 positive assessment). Additionally, the point prevalence of POF was calculated independently at discharge, and at 3, 6, 9, and 12 months postoperation. Although not specifically validated in patients with peritoneal metastasis undergoing CRS-HIPEC, this threshold was deemed clinically appropriate for our cohort. The primary tumor origins (colorectal and appendiceal) highly overlap with the validated gastrointestinal population, and the underlying pathophysiological mechanisms of postoperative inflam-

matory response and energy depletion share similarities with major abdominal surgeries.

Sleep quality: The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep quality at all survey points. The PSQI total score represents the sum of component scores for subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. A PSQI score of > 5 indicates poor sleep quality. Higher scores indicate lower sleep quality or more severe sleep disturbance. The reliability and validity of the Chinese version of the PSQI have been satisfactorily established. In our study, Cronbach's α for PSQI domains ranged from 0.63 to 0.75.

Chronic pain: The Numeric Rating Scale (NRS) was used to assess chronic pain among patients with peritoneal metastases. The NRS is a widely adopted unidimensional measure of pain intensity in which individuals rate their pain on an 11-point scale ranging from 0 ("no pain") to 10 ("worst imaginable pain"). Owing to its simplicity, minimal respondent burden, and strong interpretability, the NRS has been recommended for both clinical and research settings involving patients with advanced cancer.

Physical and mental status: The 12-Item Short Form Health Survey (SF-12) is a widely used, validated instrument designed to measure health-related quality of life across various populations, including those with chronic health conditions. The SF-12 is a shorter version of the SF-36, maintaining a focus on both physical and mental health components. It consists of 12 items that evaluate functional health and well-being, yielding two summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The SF-12 is structured to provide a comprehensive snapshot of an individual's health status while minimizing respondent burden, making it particularly useful in large-scale studies and clinical settings. The SF-12 has been used extensively in research on cancer survivorship. In the present study, the categorization of SF-12 score into ≤ 60, 60-70, and ≥ 70 was based on the distribution of scores in our cohort and was used only for descriptive baseline comparison. These categories were intended to describe relatively lower, intermediate, and higher levels of health-related quality of life within this study population, rather than to represent validated clinical cutoffs.

Statistical methods

Data were double-entered and cross-checked to reduce error or bias. Missing data patterns were examined using independent t-tests and χ^2 tests comparing groups with and without missing data. A "missingness" indicator for ICFS scores at each time point was created, assigning "1" for missingness and "0" for not missing. Independent t-tests and χ^2 tests were conducted between missingness groups on both baseline and terminal variables to determine whether characteristics varied systematically. Since no significant differences were found between groups, the missing data were considered "Missing Completely at Random" (MCAR) and were handled using listwise deletion for baseline analyses. Descriptive statistics (mean, standard deviation, frequency, and percentage) were used to describe the sample characteristics. GBTM was used to identify subgroups of participants with distinct POF trajectories. The distribution of each latent profile in demographic data was compared using ANOVA or χ^2 tests.

The point prevalence of POF across baseline characteristics was analyzed using the χ^2 test. For our primary aim, GBTM was used to detect different longitudinal trajectories of POF with 5 waves of data throughout discharge to 1-year post-operation, utilizing the traj add-on in RStudio version 4.0. We specified a censored normal distribution (CNORM) for the continuous dependent variables. Models with up to four groups were estimated. Cubic, quadratic, linear coefficients, and intercepts were considered to fit the best models. The optimal model was selected based on the lowest Bayesian Information Criterion (BIC) value, interpretability, and adequate group size (> 5%). This procedure handles missing longitudinal data using a maximum likelihood algorithm that utilizes all available data. For our second aim, baseline characteristic differences among trajectories were examined with the Kruskal-Wallis test and one-way ANOVA. Significant variables were then entered into a multinomial logistic regression as independent predictors of trajectory classification. Notably, the adjustment set was strictly limited to baseline (preoperative or at discharge) characteristics. Time-varying covariates occurring during follow-up, such as disease progression or subsequent treatments, were intentionally excluded to prevent reverse causality and over-adjustment bias. This design aligns with our primary clinical objective of

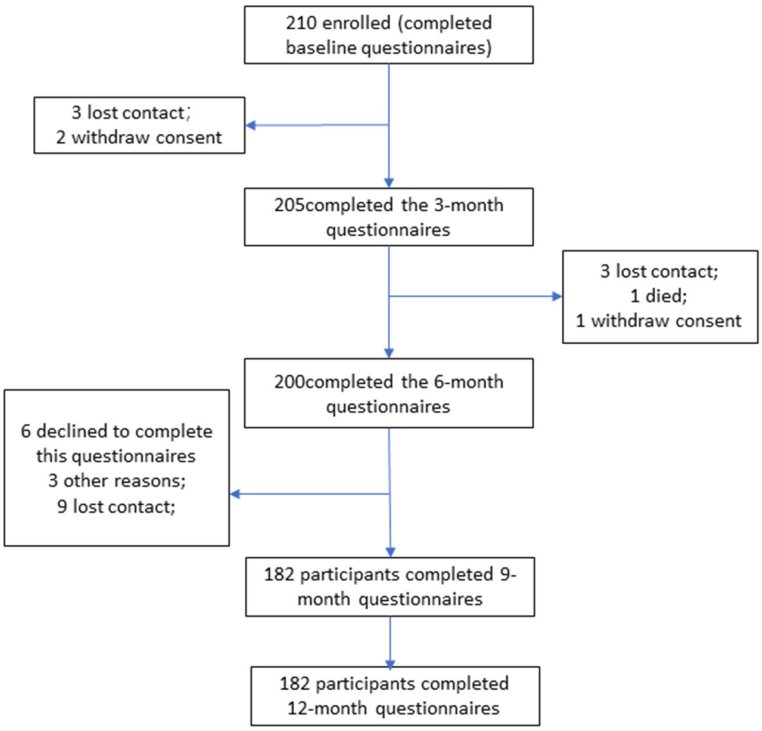

Figure 1. Flowchart of study.

identifying high-risk patients early at the time of discharge, rather than retroactively assessing risk. For our third aim, ANOVA was used to explore whether physical and mental status at 12 months post-operation differed among the fatigue trajectory groups. Since adjusting for physical and mental status at baseline is necessary, the analyses were also replicated exclusively for patients without poor physical or mental status at baseline. To further evaluate whether the identified trajectory pattern depended on the diagnostic cutoff used to define postoperative fatigue, we performed additional sensitivity analyses. First, the trajectory analyses were repeated using alternative ICFS-10 cutoff scores of 22 and 26. Second, we conducted a complementary GBTM using the raw continuous ICFS-10 scores across the five follow-up time points, without applying any diagnostic cutoff. For this continuous-score sensitivity analysis, a censored normal distribution was specified, and two-, three-, and four-class models were compared using log-likelihood, AIC, BIC, trajectory interpretability, and the requirement that each latent class contain more than 5% of the modeled sample. The objective of this analysis was to determine whether the same high-, moderate-, and low-fatigue trajectory patterns could be reproduced when trajectory classification was based directly on continuous symptom severity rather than threshold-defined fatigue status. Statistical analyses were conducted using Stata 14.0 and SPSS 17.0, and statistical significance was set at $P < 0.05$ (two-tailed).

Results

Participant flow

The participant enrollment and retention process throughout the 12-month follow-up is shown in **Figure 1**. Of the 210 participants enrolled at baseline, 205 completed the 3-month assessment, 200 completed the 6-month assessment, and 182 completed both the 9- and 12-month assessments. The final trajectory analysis therefore included 182 participants.

Identifying postoperative fatigue trajectory subgroups

Baseline characteristics across the three postoperative fatigue trajectory groups are presented in **Table 1**. Significant between-group differences were observed in age, household income, hemoglobin, PCI, surgery type, pain intensity, sleep quality, chemotherapy, immunotherapy, SII, PNI, SF-12 score, PCS score, and MCS score (all $P < 0.05$), whereas sex, marital status, educational level, and BMI did not differ significantly across trajectory groups. Overall, patients assigned to the high-increasing trajectory tended to present with lower hemoglobin and PNI, higher PCI and SII, more severe pain, poorer sleep quality, and worse baseline physical and mental health, suggesting that greater disease burden and symptom burden were associated with a more unfavorable fatigue trajectory.

The model fit indices for the candidate trajectory models are shown in **Table 2**. The three-class model was selected as the optimal solution based on the BIC and AIC values of

Table 1. Baseline characteristics across postoperative fatigue trajectory groups (n = 182)

Characteristics	High-increasing (n = 55)	Moderate-increasing (n = 69)	Low-increasing (n = 58)	*P*-value
Age (years), n (%)				< 0.001
18-29	20 (36.36)	11 (15.94)	0 (0.00)	
30-39	22 (40.00)	14 (20.29)	2 (3.45)	
40-59	12 (21.82)	27 (39.13)	37 (63.79)	
≥ 60	1 (1.82)	17 (24.64)	19 (32.76)	
Sex, n (%)				0.995
Male	27 (49.09)	34 (49.28)	29 (50.00)	
Female	28 (50.91)	35 (50.72)	29 (50.00)	
Marital status, n (%)				0.969
Married	31 (56.36)	40 (57.97)	34 (58.62)	
Single/other	24 (43.64)	29 (42.03)	24 (41.38)	
Educational level, n (%)				0.088
Primary	13 (23.64)	18 (26.09)	18 (31.03)	
College	21 (38.18)	20 (28.99)	14 (24.14)	
Bachelor	12 (21.82)	25 (36.23)	24 (41.38)	
Postgraduate	9 (16.36)	6 (8.70)	2 (3.45)	
Household income, n (%)				< 0.001
3000-5000	52 (94.55)	33 (47.83)	18 (31.03)	
5000-10000	2 (3.64)	31 (44.93)	35 (60.34)	
> 10000	1 (1.82)	5 (7.25)	5 (8.62)	
BMI (kg/m^2), Mean ± SD	25.61 ± 4.24	25.60 ± 5.09	23.87 ± 4.20	0.062
Hb (g/L), Mean ± SD	104.16 ± 14.31	125.80 ± 19.01	142.14 ± 12.26	< 0.001
PCI index, n (%)				< 0.001
3-9	10 (18.18)	24 (34.78)	38 (65.52)	
10-19	20 (36.36)	25 (36.23)	18 (31.03)	
≥ 20	25 (45.45)	20 (28.99)	2 (3.45)	
Surgery type, n (%)				< 0.001
CRS only	9 (16.36)	19 (27.54)	33 (56.90)	
CRS + HIPEC	46 (83.64)	50 (72.46)	25 (43.10)	
NRS, n (%)				< 0.001
0	5 (9.09)	17 (24.64)	21 (36.21)	
1-3	21 (38.18)	30 (43.48)	28 (48.28)	
4-6	25 (45.45)	18 (26.09)	9 (15.52)	
7-10	4 (7.27)	4 (5.80)	0 (0.00)	
PSQI index, n (%)				< 0.001
0-5	0 (0.00)	19 (27.54)	16 (27.59)	
6-10	9 (16.36)	26 (37.68)	27 (46.55)	
11-15	30 (54.55)	22 (31.88)	15 (25.86)	
16-21	16 (29.09)	2 (2.90)	0 (0.00)	
Chemotherapy (Yes), n (%)	55 (100.00)	44 (63.77)	2 (3.45)	< 0.001
Immunotherapy (Yes), n (%)	44 (80.00)	12 (17.39)	0 (0.00)	< 0.001
SII index, Mean ± SD	1,411.60 ± 738.54	617.97 ± 444.33	361.03 ± 118.23	< 0.001
PNI index, Mean ± SD	39.32 ± 2.22	45.04 ± 3.92	48.60 ± 2.12	< 0.001
SF-12 score, n (%)				< 0.001
≤ 60	50 (90.91)	41 (59.42)	50 (86.21)	
60-70	3 (5.45)	24 (34.78)	3 (5.17)	
≥ 70	2 (3.64)	4 (5.80)	5 (8.62)	

PCS score, Mean ± SD	34.29 ± 3.69	50.25 ± 7.72	49.93 ± 3.29	< 0.001
MCS score, Mean ± SD	33.31 ± 4.14	51.59 ± 8.28	50.30 ± 3.68	< 0.001

Notes: Data are presented as n (%) for categorical variables and Mean ps (n = 182)er patients: a systemacentages represent column percentages, calculated based on the total number of patients within each respective trajectory group (i.e., n = 55, n = 69, and n = 58). Statistical differences across the three trajectory groups were evaluated using Pearson's χ^2 test or Fisher's exact test for categorical variables, and one-way ANOVA for continuous variables. BMI, body mass index; Hb, hemoglobin; PCI, Peritoneal Cancer Index; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; NRS, Numeric Rating Scale; PSQI, Pittsburgh Sleep Quality Index; SII, systemic immune-inflammation index (calculated as platelet count × neutrophil-to-lymphocyte ratio); PNI, prognostic nutritional index (calculated as serum albumin [g/L] + 0.005 × total lymphocyte count [per mm^3]); SF-12, 12-Item Short Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary. Consistent with our overall cohort analyses, specific HIPEC drug regimens were collapsed into a single "CRS + HIPEC" category.

Table 2. Model comparison results

Model	ng	logLik	AIC	BIC
1-class	1	-1687.74	3389.49	3411.91
2-class	2	-1655.79	3335.59	3374.04
3-class*	3	-1621.21	3276.41	3330.88
4-class	4	-1610.27	3264.55	3335.03

Notes: ng, number of groups; logLik, log-likelihood; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion. *The 3-class model was selected as the optimal model based on the lowest BIC value, robust clinical interpretability, and the requirement of maintaining an adequate sample size (> 5%) in each trajectory subgroup.

the one-class model (BIC = 3411.91, AIC = 3389.49), two-class model (BIC = 3374.04, AIC = 3335.59), three-class model (BIC = 3330.88, AIC = 3276.41), and four-class model (BIC = 3335.03, AIC = 3264.55). Cubic coefficients were removed from the final model. As shown in **Figure 2**, group-based trajectory modeling identified three distinct postoperative fatigue trajectories over the 12-month follow-up, with all groups showing an upward trend: a high-increasing group (n = 55, 30.22%), a moderate-increasing group (n = 69, 37.91%), and a low-increasing group (n = 58, 31.87%).

Predictors of postoperative fatigue trajectories and sensitivity analyses

Multinomial logistic regression was performed to further identify baseline factors associated with postoperative fatigue trajectory membership, using the moderate-increasing trajectory as the reference category. As shown in **Table 3**, several clinical and patient-reported variables were significantly associated with trajectory assignment. Compared with patients in the moderate-increasing group, those in the high-increasing group were more likely to report poor sleep quality (PSQI > 5; OR 1.99, 95% CI 1.37-2.89, P < 0.001), impaired mental health (MCS < 45; OR 2.03, 95% CI 1.41-2.90, P < 0.001), lower hemoglobin levels (< 120 g/L; OR 4.56, 95% CI 1.05-19.82, P = 0.043), intermediate PCI burden (10-19 vs 3-9; OR 1.67, 95% CI 1.32-2.11, P = 0.013), and greater pain intensity (NRS ≥ 4; OR 2.09, 95% CI 1.41-3.12, P = 0.023). By contrast, PCI ≥ 20 was not significantly associated with membership in the high-increasing trajectory (OR 2.34, 95% CI 0.78-9.11, P = 0.116). Thus, poorer symptom control, lower hemoglobin, and worse mental health independently predicted unfavorable fatigue progression. When the low-increasing trajectory was compared with the moderate-increasing trajectory, poor sleep quality remained significantly associated with trajectory membership (OR 2.17, 95% CI 1.82-2.98, P = 0.005). In addition, lower hemoglobin (< 120 g/L; OR 1.97, 95% CI 1.33-2.91, P < 0.001) and higher PCI were also significant correlates, including PCI 10-19 (OR 1.88, 95% CI 1.52-2.14, P < 0.001) and PCI ≥ 20 (OR 2.08, 95% CI 1.45-2.99, P < 0.001). In contrast, MCS < 45 and NRS ≥ 4 were not significantly associated with the low-increasing trajectory relative to the moderate-increasing group (P = 0.254 and P = 0.104, respectively). Overall, these results suggest that postoperative fatigue trajectory membership is shaped by a multidimensional constellation of clinical and symptom-related factors. In particular, sleep disturbance, anemia, and greater peritoneal tumor burden emerged as the most consistent correlates across trajectory comparisons, highlighting their potential importance for early risk stratification and targeted supportive care in patients with peritoneal metastatic cancer.

To ensure the robustness of the trajectory classifications, sensitivity analyses were performed

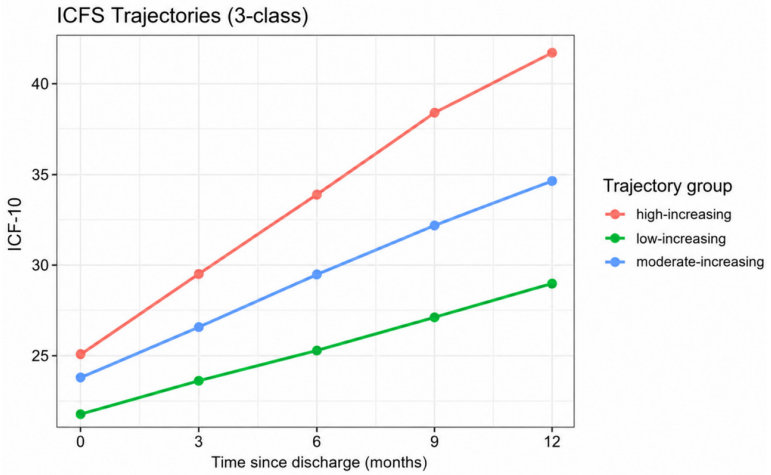

Figure 2. Longitudinal trajectories of postoperative fatigue over a 12-month follow-up period. Three distinct latent groups were identified using group-based trajectory modeling: high-increasing (red line), moderate-increasing (blue line), and low-increasing (green line). The x-axis represents the time points of assessment (months after discharge), and the y-axis represents the mean score of the 10-item Identity-Consequence Fatigue Scale (ICFS).

using alternative ICFS-10 diagnostic cutoffs of 22 and 26 and using raw continuous ICFS-10 scores without applying any cutoff. As detailed in Supplementary Table 1, the three-class model consistently showed the most favorable fit based on BIC, clinical interpretability, and adequate trajectory group size across all sensitivity analyses. When alternative cutoffs of 22 and 26 were applied, the three-trajectory structure remained stable, and the relative proportions of the high-, moderate-, and low-increasing groups showed only minor variation. Importantly, the continuous-score GBTM also reproduced a similar three-class solution, with high-, moderate-, and low-increasing fatigue trajectories. These findings indicate that the identified trajectory structure was robust and was not artifactually driven by the selection of a single ICFS-10 diagnostic cutoff.

Physical and mental condition and postoperative fatigue trajectory

Significant differences in health-related quality of life, assessed by the SF-12, were observed across trajectory groups at the composite and domain-specific levels (**Figures 3**-**5**). At the composite level, both the PCS and MCS scores differed significantly among the three trajectory groups. Participants in both the moderate-increasing and low-increasing groups exhibited significantly higher PCS and MCS scores than those in the high-increasing group. These differences were statistically significant ($P < 0.05$ or $P < 0.01$) and were consistently observed across multiple comparisons, indicating a robust association between an unfavorable fatigue trajectory (high-increasing) and impaired overall physical and mental health.

Domain-specific analyses of the PCS revealed significant differences among trajectory groups in bodily pain (BP), general health (GH), physical functioning (PF), and role physical (RP). Across all PCS domains, both the moderate- and low-increasing groups reported significantly higher scores than the high-increasing group ($P < 0.05$ or $P < 0.01$), with no significant differences observed between the moderate- and low-increasing groups. Similarly, significant group differences were observed across all MCS subdomains, including mental health (MH), role emotional (RE), social functioning (SF), and vitality (VT). Overall, the high-increasing group consistently demonstrated the poorest performance across all physical and mental health domains, whereas the moderate- and low-increasing groups maintained comparable, higher functional levels. Collectively, these findings indicate that membership in the high-increasing POF trajectory is closely linked to comprehensive and graded impairments in both the physical and mental dimensions of health-related quality of life.

Discussion

In this 12-month longitudinal study, we identified three distinct POF trajectories among patients with peritoneal metastatic cancer, namely the high-increasing, moderate-increasing, and low-increasing groups. These findings suggest that POF does not follow a uniform recovery pattern, but instead evolves heterogeneously across individuals [14]. Notably, rather than remaining stable or self-resolving over time, fatigue severity demonstrated a progressive, upward trajectory across all three

Table 3. Multinomial logistic regression analysis of factors associated with postoperative fatigue trajectory membership

Variable	Category	Low-increasing vs Moderate-increasing OR (95% CI)	*P*-value	High-increasing vs Moderate-increasing OR (95% CI)	*P*-value
Sleep quality (PSQI)	≤ 5	Reference	-	Reference	-
	> 5	1.99 (1.37 to 2.89)	< 0.001	2.17 (1.82 to 2.98)	0.035
Mental health (MCS)	≥ 45	Reference	-	Reference	-
	< 45	2.03 (1.41 to 2.90)	< 0.001	1.70 (0.68 to 4.23)	0.254
Hemoglobin (g/L)	≥ 120	Reference	-	Reference	-
	< 120	4.56 (1.05 to 19.82)	0.043	1.97 (1.33 to 2.91)	< 0.001
PCI	3-9	Reference	-	Reference	-
	10-19	1.67 (1.32 to 2.11)	0.013	1.88 (1.52 to 2.14)	0.034
	≥ 20	2.34 (0.78 to 9.11)	0.116	2.08 (1.45 to 2.99)	< 0.001
Pain intensity (NRS)	< 4	Reference	-	Reference	-
	≥ 4	2.09 (1.41 to 3.12)	0.023	1.70 (0.90 to 3.21)	0.104

Notes: OR, odds ratio; CI, confidence interval; PSQI, Pittsburgh Sleep Quality Index; MCS, Mental Component Summary; PCI, Peritoneal Cancer Index; NRS, Numeric Rating Scale. The moderate-increasing trajectory group served as the predefined reference outcome category for the dependent variable in the multinomial logistic regression model. Statistical significance was set at P < 0.05.

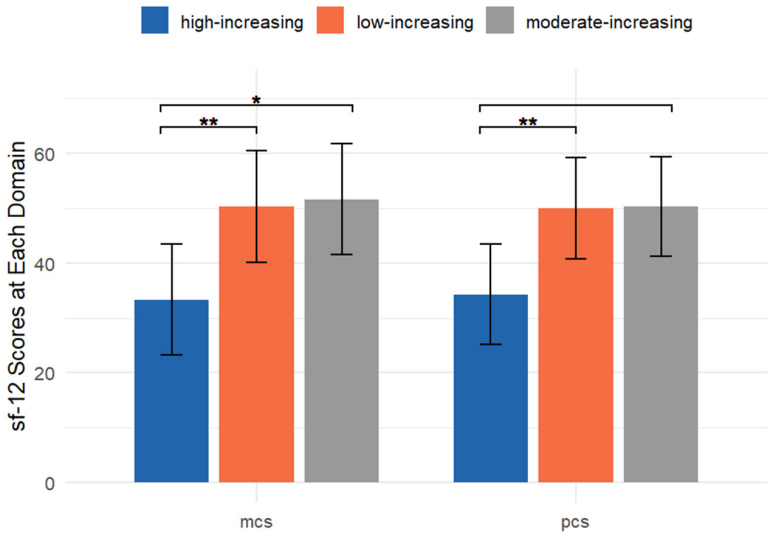

Figure 3. Comparison of the composite physical and mental health scores across the three postoperative fatigue trajectory groups. The high-increasing group demonstrated significantly lower scores compared to the moderate- and low-increasing groups. SF-12, 12-Item Short Form Health Survey; PCS, Physical Component Summary; MCS, Mental Component Summary. *P < 0.05, **P < 0.01.

groups. For instance, even the low-increasing group experienced a continuous escalation in symptom burden from discharge to 12 months [15]. This pattern is clinically important because cancer-related fatigue is increasingly recognized as a persistent and function-limiting symptom that may continue well beyond active treatment, substantially impairing daily functioning, rehabilitation, and health-related quality of life [16]. In patients undergoing intensive procedures such as cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC), the cumulative impact of surgical trauma, inflammatory activation, nutritional depletion, and adjuvant treatment may further amplify the long-term burden of fatigue and survivorship-related symptoms [17].

A key finding is that unfavorable fatigue trajectories were linked to multiple baseline vulnerabilities. Patients in the high-increasing trajectory tended to have lower hemoglobin and PNI, higher PCI and SII, more severe pain, poorer sleep quality, and worse physical and mental health at baseline. This supports the view that cancer-related fatigue is not isolated but reflects interactions among biological burden, symptom distress, and reduced functional reserve. Prior research has shown that cancer-related fatigue frequently clusters with pain

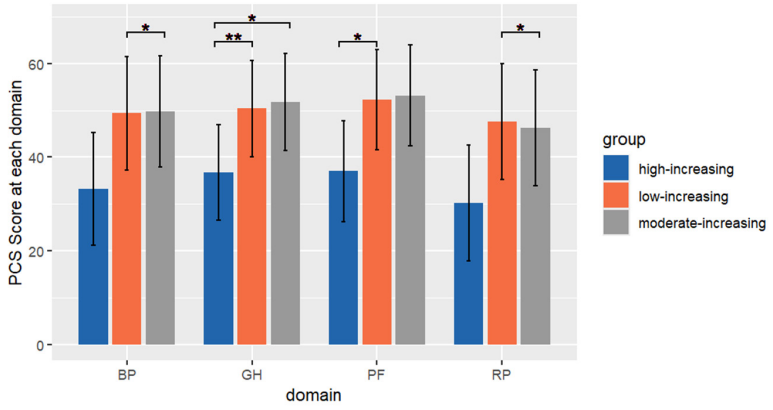

Figure 4. Comparison of the physical health domain scores across the three postoperative fatigue trajectory groups. PCS, Physical Component Summary; BP, bodily pain; GH, general health; PF, physical functioning; RP, role physical. *P < 0.05, **P < 0.01.

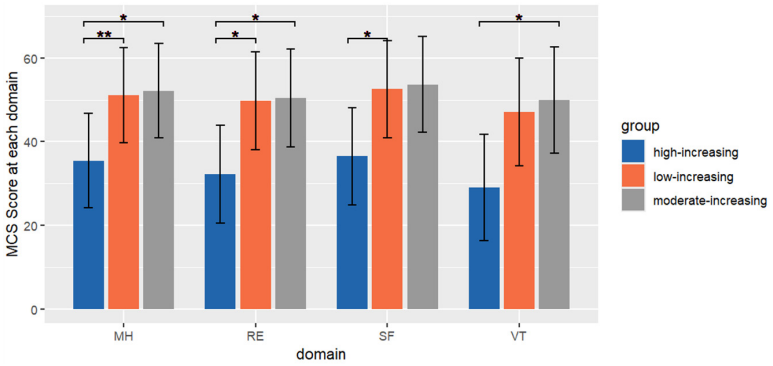

Figure 5. Comparison of the mental health domain scores across the three postoperative fatigue trajectory groups. MCS, Mental Component Summary; MH, mental health; RE, role emotional; SF, social functioning; VT, vitality. *P < 0.05, **P < 0.01.

and sleep disturbance, forming a symptom cluster with shared behavioral and biological mechanisms [18]. Neuroendocrine-immune models further suggest that inflammatory signaling may contribute simultaneously to fatigue, sleep disruption, depressed mood, and cognitive or behavioral changes, providing a plausible mechanistic explanation for the co-occurrence of these symptoms in patients with advanced cancer [19].

Our multinomial logistic regression findings further highlight sleep disturbance, anemia, and tumor burden as the most consistent correlates of trajectory membership. Poor sleep quality was significantly associated with both high-increasing and low-increasing trajectories relative to the moderate-increasing group, suggesting that sleep disruption may represent an early and broadly relevant marker of altered fatigue progression. This is consistent with prior evidence that sleep disturbance is both highly prevalent in cancer survivors and closely intertwined with fatigue severity and persistence. Similarly, hemoglobin < 120 g/L was significantly associated with unfavorable trajectory membership. This finding is clinically plausible, as anemia is a well-established contributor to cancer-related fatigue, diminished exercise tolerance, and poorer quality of life. In practice, this suggests that routine postoperative monitoring of hemoglobin and timely correction of reversible anemia may be important components of fatigue prevention and survivorship care. Greater PCI was also associated with more unfavorable trajectories, indicating that disease burden may shape long-term postoperative symptom evolution [20]. Patients with higher peritoneal tumor burden generally undergo more extensive surgery and may experience greater metabolic stress, inflammatory activation, and prolonged recovery, all of which could contribute to worsening fatigue over time.

Another notable observation is that impaired mental health and greater pain intensity were more strongly associated with the high-increasing trajectory than with the low-increasing trajectory. This may indicate that psychological distress and inadequate symptom control are particularly relevant to the development of more severe fatigue patterns. The National Comprehensive Cancer Network (NCCN) and survivorship guidelines emphasize that fatigue screening should be accompanied by the assessment of distress, sleep, pain, medical contributors, and functional impairment, because effective management often requires

a multimodal rather than symptom-specific approach [21]. Our findings support this perspective and suggest that patients with early evidence of poor sleep, pain burden, psychological distress, anemia, or high PCI may benefit from proactive surveillance and individualized supportive care after discharge [22]. Such interventions may include symptom monitoring, rehabilitation, sleep-focused strategies, nutritional and anemia management, and psychosocial support. Nonpharmacologic approaches targeting the pain-fatigue-sleep symptom cluster have also shown promise and may be relevant for this population.

Several limitations should be acknowledged. First, this was a two-center study using convenience sampling at two tertiary hospitals in Hangzhou city, which limits the generalizability of our findings. Patients referred to these specialized academic centers for CRS-HIPEC often present with higher disease complexity, more extensive surgical interventions, or better socio-economic support compared to the general peritoneal metastatic cancer population. Consequently, this sampling approach may impact external validity, potentially overestimating the severity of POF trajectories or failing to capture the symptom evolution of patients managed in community or rural healthcare settings. Second, fatigue, sleep quality, pain, and health status were assessed using self-reported instruments and may be subject to reporting bias. Additionally, the ICFS-10 cutoff of 24 was originally validated in general gastrointestinal cancer populations rather than specifically in peritoneal metastasis. To address potential variations in baseline symptom burden due to the extensive surgical trauma of CRS-HIPEC, we performed sensitivity analyses using alternative diagnostic thresholds. These analyses consistently yielded the optimal three-trajectory model, confirming the robustness of our trajectory classification irrespective of minor cutoff variations. Third, although several baseline factors were associated with fatigue trajectory membership, the observational design does not permit causal inference. Finally, while the GBTM method inherently accounts for the fixed 12-month follow-up time frame, we did not incorporate time-varying covariates - such as disease progression, cumulative chemotherapy cycles, or targeted therapy during the follow-up period - into our regression models. Including these events, which occur concurrently with the development of fatigue, as baseline predictors would introduce temporal ambiguity and over-adjustment bias. However, we acknowledge that these factors profoundly influence fatigue severity. Future studies employing joint modeling of longitudinal and survival data or time-dependent Cox models are warranted to explore the dynamic interplay between these oncologic events and fatigue trajectories. Despite these limitations, our study adds longitudinal evidence that POF in patients with peritoneal metastatic cancer is highly heterogeneous and closely linked to sleep disturbance, anemia, tumor burden, and impaired physical and mental well-being. These findings may help inform early risk stratification and support the development of individualized supportive care strategies for patients at greatest risk of persistent or worsening fatigue.

Conclusions

Distinct longitudinal trajectories of POF were identified among patients with peritoneal metastatic cancer. Poor sleep quality, severe pain, and psychological distress at baseline were strongly associated with more severe and progressive fatigue trajectories over time. Although future studies using formal diagnostic interviews are needed to confirm psychiatric comorbidities (e.g., anxiety and depressive disorders), our findings remain clinically meaningful. They successfully identify a high-risk subset of patients - based on specific baseline characteristics - who are highly vulnerable to elevated physical and psychological distress during their postoperative recovery. Early recognition of these vulnerability factors provides a critical window for targeted interventions, ultimately helping to mitigate the development and chronicity of POF in cancer survivors.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Sensitivity analysis: Model fit indices for GBTM under alternative ICFS-10 cutoffs

Analysis approach	Model	logLik	AIC	BIC	Trajectory proportions (%)
Cutoff = 22	2-class	-1701.32	3426.64	3465.12	41.2%, 58.8%
	3-class*	-1668.45	3370.90	3425.41	32.4% High, 39.1% Moderate, 28.5% Low
	4-class	-1659.18	3362.36	3432.88	15.2%, 22.3%, 34.1%, 28.4%
Cutoff = 26	2-class	-1612.45	3248.90	3287.35	35.5%, 64.5%
	3-class*	-1575.22	3184.44	3238.92	27.8% High, 36.4% Moderate, 35.8% Low
	4-class	-1569.81	3183.62	3254.10	12.1%, 18.5%, 31.2%, 38.2%
Continuous ICFS-10 score	2-class	-3894.26	7812.52	7857.47	42.6%, 57.4%
	3-class*	-3788.91	7611.82	7675.49	24.7% High, 36.9% Moderate, 38.4% Low
	4-class	-3774.60	7593.20	7675.59	8.1%, 18.5%, 35.6%, 37.8%

Notes: GBTM, group-based trajectory modeling; ICFS-10, 10-item Identity-Consequence Fatigue Scale; logLik, log-likelihood; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion. *The 3-class model was selected as the optimal model based on BIC, clinical interpretability, and adequate group size greater than 5%. For the continuous-score sensitivity analysis, raw ICFS-10 scores across five follow-up time points were modeled directly without applying a diagnostic cutoff.