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RESEARCH

Identification of distinct fatigue trajectories in patients with nasopharyngeal carcinoma undergoing radiotherapy: an observational longitudinal study

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Abstract

Purpose To investigate the fatigue trajectory types and various influencing factors during intensity-modulated radiotherapy (IMRT) in patients with nasopharyngeal carcinoma (NPC).

Methods Longitudinal data of cancer-related fatigue from 182 participants with NPC were assessed at baseline (T0) and weekly (T1–T7) during radiotherapy via the revised Piper Fatigue Scale. Patient-generated data from the Subjective Global Assessment (PG-SGA) and the Hospital Anxiety and Depression Scale were collected at baseline. Latent growth curve models (LGCM) and latent class growth models (LCGM) were used to explore fatigue trajectories and heterogeneity among fatigue trajectories, respectively. The influencing factors of different trajectories were assessed via multivariate logistic regression analysis.

Results The overall fatigue level during IMRT tended to increase but then decreased, as indicated by the LGCM results ($S = 0.985$, $P < 0.001$), and peaked in the fifth week. The LCGM results fit the following three fatigue trajectories: "mild fatigue persistence" ($n = 54$, 29.7%), "mild fatigue growth" ($n = 95$, 52.2%), and "moderate fatigue persistence" ($n = 33$, 18.1%). PG-SGA score and being married were risk factors for the "mild fatigue growth" group. The risk factors for the "moderate fatigue persistence" group were PG-SGA, anxiety, and being married, whereas a family income < 3000 Y/month was a protective factor.

Conclusions Three types of fatigue trajectories are observed during IMRT in patients with NPC. PG-SGA score, marital status, anxiety, and family income may influence the type of fatigue trajectory in patients, so preventive measures should be taken on the basis of specific circumstances.

Keywords Fatigue · Longitudinal trajectories · Nasopharyngeal carcinoma · Radiotherapy · Intensity-modulated

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor that occurs in the nasopharynx. According to global cancer statistics, in 2020, 62,444 new cases of NPC were diagnosed in China, accounting for 46.8% of the cases worldwide [1]. Non-metastatic NPC is primarily treated via radiotherapy, and intensity-modulated radiotherapy (IMRT) is the most commonly used method because of its relatively high local control and survival rates [2, 3]. However, the proximity of tumors to critical structures at the skull base, such as the salivary glands, optic nerves, and pituitary gland, often leads to significant toxicity [4, 5].

Cancer-related fatigue is a common side effect in patients with cancer that persistently affects patients' quality of life and impedes the treatment course [6]. Patients with NPC are more likely to experience severe fatigue post-treatment than patients with other cancers because the primary treatment for NPC involves radiotherapy or concurrent chemoradiotherapy (CCRT) [7]. The incidence of fatigue in patients undergoing radiotherapy is about 82.5%, with 85.4% experiencing moderate to severe fatigue [8]. Fatigue in patients with NPC during treatment consistently increases in terms of the incidence and severity of fatigue progressively during radiotherapy [9, 10]. Numerous longitudinal studies have demonstrated that fatigue is a significant symptom burden for patients with NPC during treatment. However, the rate of change and important individual differences in the development of fatigue over time may be obscured by traditional longitudinal analysis methods.

Studies have indicated that not all patients experience the same fatigue trend. Doerte et al. [11] assessed fatigue in patients with breast cancer undergoing adjuvant chemotherapy for 28 consecutive days and identified the following three subgroups with different trajectories of fatigue: "low fatigue", "transient fatigue", and "high fatigue." Moreover, persistent high fatigue was shown to be associated with a poorer quality of life [12]. Persistent severe fatigue in Hodgkin's lymphoma survivors hinders reintegration into society and employment while also leading to greater economic problems [6]. Therefore, it is necessary to identify the type of fatigue development trajectory in patients to distinguish those who are at high risk for persistent fatigue.

In addition, different cancer types have distinct fatigue trajectories and variations at various follow-up stages. For example, a longitudinal study of patients with breast cancer at diagnosis and at 1, 2, and 4 years postdiagnosis identified three fatigue development patterns [13]. About 60% were in the "low-risk" group, with consistently low fatigue. The other two "high-risk" and "deteriorating" groups experienced large fluctuations in fatigue in the first year and then stabilized [13]. Another study of patients with breast cancer from 1 week before to 8 months after surgery revealed only "persistently low levels of fatigue" (79%) and "persistently high levels of fatigue" (21%) [14], with the latter showing a downward trend. Two trajectories were also observed in esophageal cancer survivors [15]. One type was consistent with "persistently low levels of fatigue", whereas the other had increased fatigue. To our knowledge, no studies have identified heterogeneity in the development of fatigue during radiotherapy in patients with NPC.

Therefore, this study focused on fatigue changes during IMRT with/without concurrent chemotherapy in patients with NPC. Heterogeneity in the fatigue development trajectories was hypothesized, different trajectory subgroups were explored through the latent class growth model (LCGM), and influencing factors were assessed to provide evidence for identifying high-risk fatigue development trends and early interventions for fatigue.

Method

Study setting and sampling

An observational longitudinal study was designed for this research. Patients were enrolled from July 2021 to January 2024 in the Department of Radiation Oncology, a general hospital in southern China. According to the estimation principle of calculating sample sizes for regression [16], the sample size is required to be 5–10 times the number of independent variables. A lower dropout rate (10%) was considered due to the follow-up of patients during treatment. This study involved 16 variables in total; considering the dropout rate, about 89–177 participants were needed.

Participants

Patients who fulfilled the following inclusion criteria were enrolled: (1) Those who were diagnosed with NPC using histopathological examination (Nasopharyngeal carcinoma 2018 edition 8th UICC/AJCC staging criteria), (2) aged ≥ 18 years, (3) aware of their disease, and (4) scheduled to receive IMRT alone/with chemotherapy within 1 week for the first time. The exclusion criteria were as follows: patients with cognitive or mental disorders, those with physical dysfunction, those complicated by other malignancies or distant metastases, or patients who refused to participate in the questionnaire.

Data collection

At baseline, patients' demographic and clinical information was collected. At 1–7 days before the start of radiotherapy (T0), patients completed the survey of fatigue, nutritional status, anxiety, and depression. Additionally, fatigue was evaluated weekly during the treatment at seven time points (T1–T7). T1, T2, T3, T4, T5, T6, and T7 corresponded to 3–5, 8–10, 13–15, 18–20, 23–25, 28–30, and 30–33 sessions of radiotherapy, respectively.

Measures

The Piper Fatigue Scale-12 (PFS-12) was used to determine overall fatigue [17]. It is mainly suitable for assessing immediate fatigue during or shortly post-treatment [18]. It consists of 12 items within the following four dimensions, with each dimension comprising three items: behavioral, emotional, sensory, and cognitive fatigue. An 11-point Likert scale is used, where higher scores indicate greater fatigue. A score of 0 indicates no fatigue; > 0 to < 4 mild fatigue; ≥ 4 to < 7 moderate fatigue; and ≥ 7 severe fatigue. The PFS-12 in this study demonstrated high internal consistency, with a Cronbach's α of 0.975.

The nutritional status of patients was determined via the Patient Subjective Global Assessment Scale (PG-SGA) [19]. Poorer nutritional status is indicated by higher scores on the PG-SGA. The PG-SGA is recommended as the best tool with high diagnostic accuracy for assessing nutritional status in patients with cancer, with a pooled sensitivity and specificity of 0.964 and 0.905, respectively [19]. Psychological state was analyzed via the Hospital Anxiety and Depression Scale (HADS), which comprises 14 items divided into the following two subscales: the HADS-A for anxiety and the HADS-D for depression [20]. Higher scores indicate more severe anxiety or depressive symptoms. The Cronbach's α of the HADS was 0.877.

Statistical analysis

The data were analyzed using SPSS 26.0 and Mplus 8.3. Continuous variables are presented as the means ± standard deviations, and categorical variables are presented as numbers and variables.

Latent growth curve (LGCM) models were employed to describe changes in fatigue during radiotherapy. Robust maximum-likelihood estimation was used for the LGCM. Both unconditional linear and nonlinear models were developed considering the uncertainty of the fatigue trend. The goodness-of-fit indices of the LGCM were evaluated by χ^2/df, the comparative fit index (*CFI*), the root mean square error of approximation (*RMSEA*), and the standardized root mean square residual (*SRMR*). Acceptable model criteria: $\chi^2/df = 1–3$, $CFI > 0.900$, $SRMR < 0.100$, and $RMSEA < 0.080$ [21, 22]. Concurrent chemotherapy status (0 = no; 1 = yes) during RT was added as a time-varying covariate to assess its impact on fatigue.

An interindividual difference in the fatigue trajectory was hypothesized, and the LCGM was used to explore this heterogeneity. One to four categories were extracted, each representing a distinct fatigue pattern. Model fit was assessed by the Akaike information criterion (AIC), Bayesian information criterion (BIC), and adjusted Bayesian information criterion (aBIC) (lower values indicate better fit), and significant *P* values were obtained for the Lo-Mendell-Rubin (LMR) and bootstrap likelihood ratio test (BLRT) (indicating better fit for the *K* vs. *K*-1 categories) [23]. An entropy > 0.80 suggests good classification accuracy [24]. Trajectory groups with assignment probabilities < 10% were excluded from the final results.

One-way analysis of variance, chi-square tests, and multivariate logistic regression analysis were used to explore factors influencing different trajectory categories. The odds ratios (*OR*s) of risk and 95% confidence intervals (*CI*) are reported. A two-sided test of $P < 0.05$ was considered statistically significant.

For missing data, if the proportion of each time point was < 5%, the average of adjacent points (1 or 2 away) was used. For example, T2 was filled by the average of T1 and T3, and T7 was filled by the average of T5 and T6. Multiple imputations were also used for missing values, with the original data and five generated datasets used for sensitivity analysis to enhance result stability.

Results

Patient characteristics

A total of 182 patients completed baseline assessments from July 2021 to January 2024. Owing to the aggravated toxicities of radiotherapy, three patients declined assessments at T2, T4, and T6, whereas three quit radiotherapy at T7 (Fig. 1). Supplement 1 presents the mean and standard deviation of fatigue at each time point. Table 1 presents the demographic and clinical characteristics of the study participants.

Fatigue trajectories of NPC patients during radiotherapy—LGCM

The unconditional nonlinear LGCM model exhibited a better fit than the unconditional linear LGCM (Table 2). An initial average fatigue level of 1.822 ($P < 0.001$) was demonstrated, with a gradual increase in fatigue during radiotherapy (slope = 0.958, $P < 0.001$), which decreased over

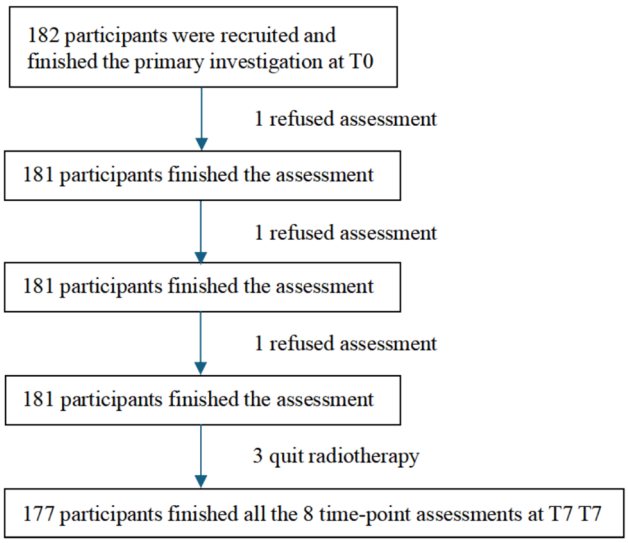

Fig. 1 Flow diagram of participants in the study

time (quadratic slope = –0.079, $P < 0.001$). The notable individual differences in initial fatigue levels and changes over time were denoted by significant variance in the intercept ($\sigma^2 = 2.961$, $P < 0.001$) and quadratic slope ($\sigma^2 = 0.008$, $P < 0.001$). The fatigue level of the participants progressively increased from a mild level to a moderate level after T3, peaked at T6, and then tended to decrease (Fig. 2). The conditional model exhibited an acceptable fit ($\chi^2/df = 1.71$, $CFI = 0.953 > 0.900$, $RMSEA = 0.063 < 0.080$, $SRMR = 0.086 < 0.100$) when concurrent chemotherapy was included as a covariate. Patients who underwent concurrent chemotherapy in the fourth week were revealed to experience higher fatigue levels at T5 ($\beta = 0.330$, $t = 2.577$, $P = 0.010$). The sensitivity analysis results were in accordance with the primary findings (Supplement 2).

Trajectory groups of fatigue of NPC patients during radiotherapy—LCGM

LCGM was performed via a nonlinear model, considering that the LGCM indicated a nonlinear growth trend. Based on the fitted indices for the latent categories grouped into groups 1–4, we recognized that the representation of the heterogeneity of the fatigue trajectories was best through three latent categories (Table 3). The fatigue trajectories were classified into the following groups: A, mild fatigue persistence group ($n = 54$, 29.7%); B, mild fatigue growth group ($n = 95$, 52.2%); and C, moderate fatigue persistence group ($n = 33$, 18.1%) (Fig. 2). Group A was defined as the group of patients who had a mild level of fatigue at baseline, with their fatigue level demonstrating an increasing trend during the treatment period but consistently remaining at a mild level ($I = 1.111$, $P < 0.001$; $S = 0.439$, $P < 0.001$). Moreover, the slope of the curve was –0.019, which was not significantly different ($P > 0.05$). Patients in Group B also had a mild level of baseline fatigue;

Table 1 Patient characteristics ($n = 182$)

Variable	Value
Sex (*N*, %)	
Male	134 (73.63)
Female	48 (26.37)
Age (years, *mean* ± *SD*)	47.46 ± 11.45
BMI (kg/m^2, *mean* ± *SD*)	23.56 ± 3.14
Marital status (*N*, %)	
Married	156 (85.71)
Never married or divorced or widowed	26 (14.29)
Education (*N*, %)	
Primary and below	44 (24.18)
Junior high school	65 (35.71)
High school or technical secondary school	38 (20.88)
College or undergraduate	35 (19.23)
Smoking (*N*, %)	
Yes or ever	87 (47.80)
No	95 (52.20)
Drinking (*N*, %)	
Yes or ever	62 (34.07)
No	120 (65.93)
Employment status (*N*, %)	
Yes	118 (64.84)
No	64 (35.16)
Family incoming (*N*, %)	
< 3000 Y/month	58 (31.87)
3000–5000 Y/month	79 (43.41)
> 5000 Y/month	45 (24.72)
UICC/AJCC stage (*N*, %)	
III and below	97 (53.30)
IV	85 (46.70)
PTVnx (N, %)	
< 70 Gy	74 (40.66)
≥ 70 Gy	108 (59.34)
Induced chemotherapy cycle (*N*, %)	
≤ 2	43 (23.63)
≥ 3	139 (76.37)
Concurrent chemotherapy cycle (*N*, %)	
0	25 (13.74)
1	29 (15.93)
2–3	128 (70.33)
PG-SGA (*mean* ± *SD*)	2.69 ± 2.01
HADS-Anxiety (*mean* ± *SD*)	6.15 ± 3.77
HADS-Depression (*mean* ± *SD*)	5.52 ± 3.34

UICC Union for International Cancer Control, *AJCC* American Joint Committee on Cancer, *BMI* body mass index, *PG-SGA* Patient-Generated Subjective Global Assessment, *HADS* Hospital Anxiety and Depression Scale

Table 2 LGCM model fitting results of CRF in NPC patients during radiotherapy ($n = 182$)

	χ^2 (*df*)	*P*	*CFI*	*RMSEA*	*SRMR*	Coefficient			Variable coefficient		
						Intercept	Slope	Slope of curve	Intercept	Slope	Slope of curve
Linear unconditional model	205.395 (31)	< 0.001	0.752	0.176	0.128	2.656*	0.349*		2.191*	0.066*	
Nonlinear unconditional model	50.050 (27)	0.0045	0.967	0.068	0.070	1.822*	0.958*	− 0.079*	2.961*	0.627*	0.008*

LGCM latent growth curve model, *CFI* comparative fit index, *RMSEA* root mean square error of approximation, *SRMR* standardized root mean square residual

*$P < 0.001$

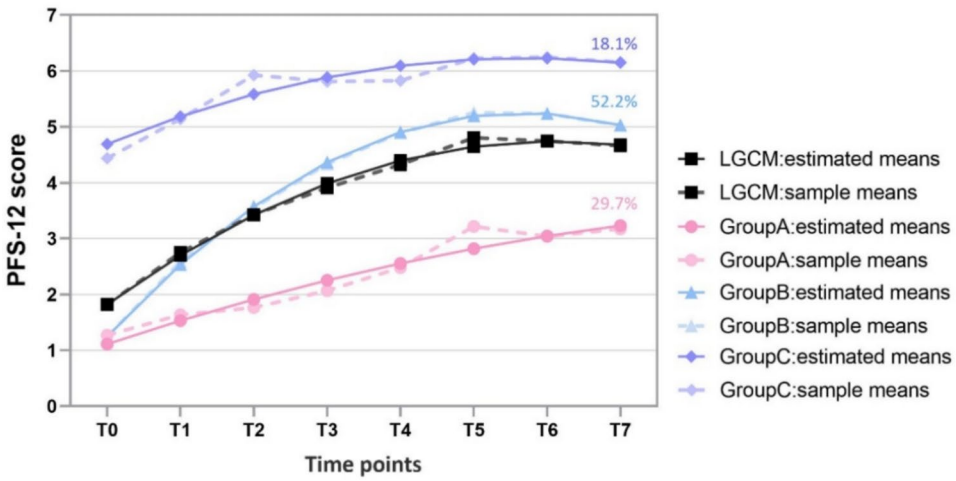

Fig. 2 Latent fatigue trajectories in 182 patients during intensity-modulated radiation therapy (IMRT) at eight time points for global fatigue. The solid lines represent the estimated means; the dotted lines represent the sample means. Group A: Mild fatigue persistence group. Group B: Mild fatigue growth group. Group B: Moderate-fatigue persistence group

Table 3 LCGM model fit results of CRF in NPC patients during radiotherapy ($n = 182$)

Class	AIC	BIC	aBIC	Entropy	*P* value		Class probability (%)
					LMR	BLRT	
1	5388.877	5427.325	5389.320	-	-	-	-
2	5126.527	5177.791	5127.117	0.795	0.0127	< 0.001	0.401/0.599
3	4994.063	5058.143	4994.801	0.841	0.0397	< 0.001	0.181/0.297/0.522
4	4959.983	5036.880	4960.869	0.861	0.1403	< 0.001	0.148/0.308/0.060/0.484

LCGM latent class growth model, *AIC* Akaike information criterion, *BIC* Bayes information criterion, *aBIC* adjusted Bayes information criterion, *LMR* Lo-Mendell-Rubin, *BLRT* bootstrap likelihood ratio test

however, the level continued to increase and eventually remained at a moderate level, with a progressively slower rate of increase ($I = 1.247$, $P < 0.001$; $S = 1.414$, $P < 0.001$; $Q = –0.125$, $P < 0.001$). Patients in Group C had a mean level of baseline fatigue of 4.691, which was moderate, and fatigue increased slowly during the treatment period ($I = 4.691$, $P < 0.001$; $S = 0.541$, $P < 0.05$). The slope of the curve was –0.047, which was not significantly different ($P > 0.05$). Additionally, the trend plots of the fatigue trajectories of the three groups demonstrated that the fatigue levels of both Groups A and B peaked at T6, which was consistent with the overall fatigue development trajectory. The mild fatigue persistence group did not peak. The sensitivity analysis results were similar to the main results above (Supplement 3).

Predictors of different groups of fatigue trajectories

The results of the one-way analysis of variance revealed statistically significant differences in marital status ($\chi^2 = 7.85$, $P = 0.020$), family income ($\chi^2 = 13.07$, $P = 0.011$), number of cycles of concurrent chemotherapy ($\chi^2 = 14.03$, $P = 0.007$), PG-SGA ($F = 7.56$, $P = 0.001$), anxiety ($F = 15.60$, $P < 0.001$), and depression ($F = 12.94$, $P < 0.001$) between the different fatigue trajectories. The above variables were incorporated into the logistic regression analysis. Age, BMI, disease stage, and PTVnx were included in the regression equation combined with clinical experience and previous studies.

The demographic and clinical characteristics of each group are presented in Table 4, along with the risk factors observed in the more severe fatigue trajectory group. The results revealed significant risk factors belonging to poorer trajectory groups (mild fatigue growth and moderate fatigue persistence groups), including the PG-SGA score and marital status. A higher PG-SGA score indicated a greater probability of belonging to the mild fatigue growth and moderate fatigue persistence groups, with OR (95% *CI*) of 1.43 (1.09 and 1.90) and 1.52 (1.10 and 2.11), respectively. Moreover, the risk of experiencing mild fatigue growth and moderate fatigue persistence was greater in patients who were married than in those without a partner, with OR (95% *CI*) of 4.47 (1.36 and 14.87) and 39.91 (2.79 and 570.66), respectively.

Table 4 Distribution of patient characteristics across different fatigue trajectories and multivariate logistic regression of predictive factors of the fatigue trajectory group. (vs. Group A)

Patient characteristic	Group of fatigue trajectory ($n = 182$)						
	Group A[a] ($n = 54$ [29.7%])	Group B[b] ($n = 95$ [52.2%])			Group C[c] ($n = 33$[18.1%])		
	No. (%)	No. (%)	*OR* (95% *CI*)	*P*	No. (%)	*OR* (95% *CI*)	*P*
Age (*mean* ± *SD*)	48.15 ± 12.90	47.62 ± 11.03	0.96 (0.92, 1.00)	0.0584	46.88 ± 10.37	0.96 (0.91, 1.01)	0.1126
BMI (*mean* ± *SD*)	23.89 ± 2.83	23.31 ± 3.36	0.94 (0.82,1.08)	0.3800	23.72 ± 2.97	0.98 (0.82,1.18)	0.8451
PG-SGA (*mean* ± *SD*)	2.00 ± 1.24	3.03 ± 2.07	1.43 (1.09, 1.90)	0.0112*	2.82 ± 2.54	1.52 (1.10, 2.11)	0.0113*
HADS-Anxiety (*mean* ± *SD*)	4.11 ± 2.96	6.69 ± 3.49	1.07 (0.93, 1.24)	0.3484	7.91 ± 4.40	1.27 (1.06, 1.53)	0.0115*
HADS-Depression (*mean* ± *SD*)	3.72 ± 2.81	6.16 ± 3.17	1.18 (1.00, 1.40)	0.0511	6.64 ± 3.52	1.25 (1.00, 1.56)	0.0520
Marital status							
Married	41 (26.28)	83 (53.21)	4.47 (1.36, 14.87)	0.0145*	32 (20.51)	39.91 (2.79, 570.66)	0.0066*
Never married or divorced or widowed	13 (50.00)	12 (46.15)	Ref		1 (3.85)	Ref	
Family incoming							
< 3000Y/month	15 (25.86)	39 (67.24)	1.52 (0.48, 4.82)	0.4772	4 (6.90)	0.14 (0.02, 0.76)	0.0228*
3000–5000 Y/month	21 (26.58)	40 (50.63)	1.36 (0.51, 3.62)	0.5413	18 (22.78)	0.77 (0.23, 2.56)	0.6650
> 5000 Y/month	18 (40.00)	16 (35.56)	Ref		11 (24.44)	Ref	
UICC/AJCC stage							
III and below	26 (26.80)	55 (56.70)	1.49 (0.66, 3.37)	0.3392	16 (16.49)	1.02 (0.35, 2.96)	0.9679
IV	28 (32.94)	40 (47.06)	Ref		17 (20.00)	Ref	
Total radiation dose							
< 70 Gy	15 (20.27)	45 (60.81)	1.73 (0.71, 4.20)	0.2258	14 (18.92)	1.72 (0.53, 5.74)	0.3698
≥ 70 Gy	39 (36.11)	50 (46.30)	Ref		19 (17.59)	Ref	
Concurrent chemotherapy cycle							
0	2 (8.00)	20 (80.00)	4.32 (0.74, 25.35)	0.1054	3 (12.00)	1.65 (0.17, 15.66)	0.6614
1	6 (20.69)	19 (65.52)	2.20 (0.71, 6.79)	0.1690	4 (13.79)	0.75 (0.16, 3.54)	0.7144
2–3	46 (35.94)	56 (43.75)	Ref		26 (20.31)	Ref	

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *PG-SGA* Patient-Generated Subjective Global Assessment, *HADS* Hospital Anxiety and Depression Scale

[a]Mild fatigue persistence group

[b]Mild fatigue growth group

[c]Moderate-fatigue persistence group

*$P < 0.05$

The participants with higher anxiety were more likely to be in the moderate-fatigue persistence group, whereas those with a family income < 3000 Y/month were less likely to be in this group.

Discussion

To our knowledge, this is the first study exploring the heterogeneity of fatigue trajectories and their influencing factors in patients with NPC during radiotherapy. Trajectory category analysis revealed continuous fatigue changes and inter-group disparities. The study demonstrated that mild-to-moderate fatigue was prevalent during radiotherapy, with overall fatigue increasing at a gradually slower rate. We also found that concurrent chemotherapy may exacerbate fatigue 1 week later, particularly in the second cycle. Furthermore, three fatigue patterns were identified: mild persistent, mild increasing, and moderate persistent fatigue, influenced by factors such as PG-SGA, marital status, anxiety, and family income.

Like previous studies [9, 25, 26], an overall mild-to-moderate trend during NPC radiotherapy was observed, with peak fatigue at T6. Similar results were reported in earlier observational studies of patients with head and neck cancer [27]. In our earlier smaller sample study ($n = 105$), the severity and changing trend of fatigue were found to be similar; however, peak fatigue appeared at T5 [28]. This difference may be due to sampling and statistical errors, as the fatigue at T5 closely approached the peak observed at T6. Owing to the particularity of the radiation target area, the pituitary function of patients with NPC is prone to radiation damage [10, 29]. When the pituitary radiation dose reaches 50–60 Gy (the cumulative irradiation dose to the patient at T5 is within this interval), the risk of hypopituitarism is greatly increased, and the main manifestation of functional decline is fatigue [30, 31]. Studies have established a dose-fatigue relationship by revealing a significant correlation between fatigue during radiotherapy and the average dose received by the pituitary gland [10, 32]. Therefore, as treatment progresses and radiation accumulates, fatigue increases. Additionally, 70.33% of patients completed a second cycle of concurrent chemotherapy before the fatigue peak, exacerbating acute toxicity [33, 34]. Adding a time covariate (with or without CCRT) showed that patients who underwent a second cycle at week 4 experienced heightened fatigue about 1 week later. Therefore, the most severe fatigue in patients with NPC occurred at T5–T6, possibly owing to the combined effect of radiotherapy and chemotherapy.

This study further verified the nonlinear trajectory of fatigue through the LGCM. The rate of increase in fatigue decreases with increasing radiotherapy, which is partly attributed to the "response shift" [35]. A response shift refers to a change in internal standards and values or the reconceptualization of quality of life owing to altered health status [36], which functions as an adaptive psychological mechanism in patients with cancer [37]. As patients adapt to the side effects of treatment, their perception of fatigue severity decreases. Considering that our fatigue assessments were subjective, this adaptation possibly contributed to the observed deceleration in fatigue escalation during later stages of treatment.

Three trajectories of fatigue were identified in the present study: the "mild fatigue persistent" (29.7%), "mild fatigue growth" (52.2%), and "moderate fatigue persistent" groups (18.1%), representing different fatigue patterns in patients with NPC during radiotherapy. Since no other relevant studies have investigated fatigue trajectories during treatment in patients with head and neck cancer, for the discussion, we chose to compare the types of fatigue trajectories during treatment with those of patients with other types of cancer, reflecting the differences between them. A longitudinal study among patients with breast cancer over 28 consecutive days of a chemotherapy cycle revealed the following three fatigue trajectories ($n = 77$): "low fatigue" (23%), "transient fatigue" (27%), and "high fatigue" (50%) [11]. All three groups were characterized by a significant decline following an initial increase in fatigue, demonstrating an "inverted U" pattern, differing from the findings of this study. In our study, only the "mild fatigue increase" and "moderate fatigue persistence" groups exhibited slight remission at the last assessment. This difference may be attributed to the primary treatment modality. Chemotherapy involves periodic drug administration, with the plasma concentration rapidly peaking post-infusion, effectively targeting tumor cells but also impacting normal cells. This leads to a peak in fatigue within a week post-treatment, followed by gradual alleviation—creating a "roller coaster" effect [38, 39]. In contrast, radiotherapy gradually increases in dosage through fractionated sessions, resulting in sustained fatigue that tends to gradually increase over the course of treatment [40, 41].

The "mild fatigue growth" group (52.2%) formed the largest cluster, indicating that most patients experienced rapid progression from mild to moderate fatigue during radiotherapy, which was consistent with the overall trend. In a trajectory analysis of symptom burden among patients with head and neck cancer undergoing radiotherapy or chemoradiotherapy, the largest clusters showed a mild to moderate increase in symptom burden, regardless of whether the trajectories were grouped into 2 or 4 clusters (68% and 44%) [42]. Although this study was not solely focused on fatigue, the symptom burden score was based on the average of the five most severe symptoms in the M. D. Anderson Symptom Inventory-Head and Neck module [43], with fatigue among them. In contrast, different patterns were observed in breast cancer. Rosas et al. [41] identified four trajectories, with

the "low fatigue" group being the largest (46.3%). This discrepancy may result from differences in the radiotherapy dose and follow-up time points. An earlier study focused on patients with breast cancer who underwent adjuvant radiotherapy after breast-conserving surgery [41], with a lower frequency and dose than our study did [44]. Additionally, Rosas et al. continued to assess fatigue in the first and second years post-radiotherapy [41], covering both treatment and recovery. The "low-fatigue" group usually becomes the most common when fatigue trajectories extend into the rehabilitation period [15, 40, 45], suggesting that although patients often experience increased fatigue during treatment, acute fatigue may turn into low-intensity chronic fatigue during recovery.

The percentage of patients in the "moderate fatigue persistence" group was the lowest (18.1%). This group developed at a relatively slow pace. Patients reporting moderate or higher fatigue at baseline typically experienced slower or smaller increases in fatigue during treatment [11, 46], thus indicating a ceiling effect. This suggests a maximum threshold for fatigue during treatment, warranting further investigation through a large multicenter study.

Identifying factors that influence fatigue trajectories during radiotherapy is critical for developing prevention strategies, identifying at-risk patients, and providing targeted interventions to improve quality of life. In our research, certain risk factors were identified for patients in the "mild fatigue increase" and "moderate fatigue persistence" groups. First, patients with higher baseline PG-SGA scores were more likely to belong to these groups than to the "mild fatigue persistence" group, with the PG-SGA effect size being greater in the "moderate fatigue persistence" group. The nutritional status of patients with head and neck cancer deteriorates continuously during radiotherapy [47], and poor status is associated with a greater increase in severe fatigue [48], particularly in those with greater initial nutritional risk [49]. The PG-SGA is a reliable tool for assessing the nutritional status of patients with cancer [50], and previous studies have shown its ability to accurately predict fatigue levels in the following week [28]. Therefore, early interventions to manage patient fatigue may be implemented via the PG-SGA for nutritional screening before radiotherapy.

Additionally, being married was also a risk factor for the two groups. However, a larger sample size is needed to improve reliability, as the uneven marital status distribution in the "moderate fatigue persistence" group increased uncertainty in the estimates. In parallel with a Taiwanese longitudinal study on breast cancer patients [51], married women diagnosed with breast cancer in Taiwan may exhibit increased fatigue levels due to the combined pressures of work, childcare, and other responsibilities throughout their illness. Compared with unmarried patients, married patients often shoulder a wider array of familial duties. In this study, the majority of patients with NPC were male. During treatment, patients' familial roles often shift from caregiver to care recipient, a significant transition that may lead to maladjustment [52]. Especially within the context of Chinese socio-cultural norms, where men are typically the primary financial providers, patients may express concerns about their family's economic stability due to treatment costs and reduced income. The interplay of these psychological stressors and role conflicts may exacerbate fatigue.

Anxiety serves as a predictor of chronic fatigue in patients with head and neck cancer at both 3 months and 5 years post-treatment [53]. Our findings suggest that anxiety also influences the presentation of acute fatigue in patients with NPC during radiotherapy, with more severe anxiety correlated with "moderate fatigue persistence." The same phenomenon was found in breast cancer patients. Bower et al. [40] noted five fatigue trajectories and identified a strong association between "stable high" fatigue and initial psychological factors. This may be due to the decreased self-regulation capacity of patients with higher baseline anxiety, impairing their ability to manage treatment side effects [54]. We found that the only protective factor in this study was a family income of less than 3000 yuan per month. This could be attributed to patients with low income often engaging in heavy physical labor, potentially resulting in better muscle mass and physical fitness [55]. However, direct evidence that muscle mass mediates the relationship between physical labor and fatigue is lacking. Thus, objective physiological indicators such as lean body mass and muscle mass can be added to explore this relationship in future studies.

This study also has several limitations. First, fatigue assessment is subjective, as patients may perceive their fatigue differently, and the use of subjective questionnaires moderately reduces data accuracy. However, objective diagnostic criteria are lacking because of the ambiguous fatigue mechanism involved [18]. When selecting validated, high-quality assessment tools, the ease of administration and the dimensions covered by the scale should be considered with respect to the study's objectives [56]. Second, some crucial and objective indicators, such as tumor volume and irradiation field size and inflammatory indicators, are absent, making multiple regression exploratory. Finally, patients were not followed up postradiotherapy; thus, changes occurring post-treatment in those who experienced severe fatigue during treatment were undetermined. Thus, longer-term follow-up is needed to determine the fatigue-development trajectory and influencing factors during treatment and recovery, providing important evidence for preventing chronic fatigue during the recovery phase.

Conclusions

To conclude, this study elucidates the nonlinear progression of fatigue and three distinct fatigue trajectories during radiotherapy in patients with NPC. The fatigue trajectories regulated by nutritional status, anxiety, marital status, and family income were determined. Therefore, medical staff must identify the development trend of fatigue in patients with NPC during radiotherapy according to specific conditions and formulate precise intervention strategies to alleviate it.

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Author contributions JLW collected the data, performed the data analysis, and drafted the original manuscript; XRY, QQH, ZLW, LTZ collected the data and conducted the data curation; ZYZ interpreted the results and provided statistical methodology support; LS, WLY collected the samples; LS, JRY, XRS, JSH, JHS supervised the study; JSH, JHS conceived the study; LS, JHS revised the manuscript. All authors contributed to critical reading of and commented on the manuscript, helped to interpret the data, and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board (IRB) of Fujian Medical University (FMU2021[114]). Each participant provided informed content before each survey.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

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