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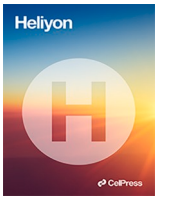

Influencing factors of cancer-related fatigue in acute leukemia patients: A cross-sectional study

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ABSTRACT

Purpose: To investigate influencing factors of cancer-related fatigue (CRF) in adult patients with acute leukemia (AL).

Methods: A total of 288 adult patients diagnosed with acute leukemia in West China Hospital were included in this study. A cross-sectional survey, including the Clinical Information Questionnaire, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Pittsburgh Sleep Quality Index (PSQI), and Hospital Anxiety and Depression Scale (HAD), was provided to the patients. Hierarchical multiple linear regression analyses were conducted to evaluate the associations of the variable factors and the AL patients' CRF.

Results: The CRF score of AL patients was 33.25 ± 10.35. Gender, age, albumin level, depression, anxiety status of the patients and treatment cycles were identified as influencing factors of CRF in AL patients ($P < 0.05$). The CRF level of acute leukemia patients in the complete remission group was lower than that of patients who were not achieving complete remission. Depression, anxiety, age, employment, albumin, and sleep disturbance were independent influencing factors for CRF in patients who were not achieving complete remission.

Conclusions: Acute leukemia patients who are female, older, hypoalbuminemia , or in the induction therapy have a higher risk of developing a high degree of CRF. Clinical staff should pay more attention to the CRF of patients who were not achieving complete remission. Early screening and aggressive intervention could be adopted in caring for these patients.

1. Introduction

Acute leukemia (AL) is a malignant clonal disease of hematopoietic stem cells [1]. Despite a significant improvement in the treatment of AL in recent years, AL patients usually suffer from both the symptoms of the disease and the adverse effect of medicine, both of which have a significant negative impact on the physical and emotional function of the patients [2,3]. Cancer-related fatigue (CRF), defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [4], is one of the most prevalent and persistent symptoms experienced by patients with cancer during and after treatments [4–7].

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According to the literature, the prevalence of CRF in patients varies from 15 % to 90 % and is approximately 30 % in patients even after the end of treatment [8–13]. The range of CRF might be because of the variety of the study populations, the subjective nature of the subtypes of cancer, the treatment modalities, and the CRF evaluation methods. Severe CRF could impair the treatment compliance of the patient and harm the patient's outcome [12,14,15]. CRF could be compromised by health-related quality of life (HRQOL), daily exercise, participation in social activities, maintenance of interpersonal relationships, and personal well-being [13,16]. Accurate recognition and effective intervention of CRF had a beneficial impact on cancer patients [17–19].

The influencing factors of CRF are unclear and are believed to involve multiple factors [20–22]. Previous studies suggested that CRF was associated with anemia, cachexia, cytokine levels, neurological changes, infection, metabolic and endocrine disorders, psychological distress, concomitant medications, antineoplastic side effects, pain, performance status, and so on [7,23–28]. However, very few studies have focused on CRF in Chinese adult AL patients. Therefore, we performed this cross-sectional study to investigate CRF in adult AL patients and analyzed the influencing factors of CRF.

2. Methods

2.1. Design

This cross-sectional study investigated the status of CRF in adult AL patients and analyzed the influencing factors of CRF.

2.2. Patient participants

In this study, AL patients who were aged 18 years and above and who had the capability of understanding and writing informed consent were recruited by convenience sampling in the Department of Hematology, West China Hospital, Sichuan University from June 2020 to October 2020.

2.3. Ethical considerations

This cross-sectional study was approved by the Institutional Review Board of the author's hospital (2020/473).

2.4. Measurements

The charts of included patients were reviewed and collected for demographic and clinical information, including gender, age, education, marital status, employment, income, religion, classification of AL, disease status, treatment cycles, course of the disease, chemotherapy cycles, complete blood count, body mass index (BMI), and body temperature. The study parameters included assessment of CRF, sleep quality, and anxiety/depression assessment as per the following validated tools.

The CRF was evaluated with the Functional Assessment of Chronic Illness Therapy—Fatigue scale (FACIT-F), which is a validated scale to assess the severity of fatigue in cancer patients [29–31]. The FACIT-F is a 13-item, 5-point Likert scale. Each item allows five options from "Not at all" (scored 4) to "Very much" (scored 0). The scale has a cut-off to distinguish fatigued patients from non-fatigued patients, with scores $\leq$34 indicating clinically relevant fatigue. The total FACIT-F scores range from 0 to 52, with a lower score indicating more severe fatigue.

The Pittsburgh Sleep Quality Index (PSQI) was used to assess the sleep quality of the included patients over a 1-month time interval [32]. The PSQI includes 7 subscales. Each item is scored on a scale of 0–3, and the total PSQI scores range from 0 to 21. A higher score indicates worse sleep quality. A PSQI ranging from 1 to 7 is considered normal, whereas a score greater than 7 indicates poor sleep quality.

The self-reported Hospital Anxiety and Depression Scale (HAD) was adopted to screen the anxiety and depression of the patients [33]. The HAD consists of 14 items, including 7 items for depression assessment and 7 items for anxiety assessment, all of which are scored on a scale of 0–3. The evaluation criteria are as follows: 0 to 7 points indicate normal, 8 to 10 points indicate mild abnormalities, and 11 to 21 points indicate severe abnormalities.

2.5. Data collection

The participants were investigated within two weeks after admission by three researchers who received uniform training. Before the investigation, researchers explained the purpose and requirements of the study and strived for the cooperation of the patients. After the patients signed the informed consent form, they answered the questions independently. For items that patients could not understand, the researchers assisted in completing the items and ensuring that the answers reflected the patients' opinions. All questionnaires were retrieved once finished, and the missing items were checked.

2.6. Data analysis

SPSS version 21.0 (Statistical Package for the Social Sciences; IBM Corp., Armonk, NY) was used for data analysis. Descriptive statistics for all variables regarding demographic and clinical data were performed for the participants. Means $\pm$ standard deviations or medians (quartiles) were used to represent the continuous variables. Student's t-test or analysis of variance (ANOVA) was applied

Table 1
Participants' demographic and clinical characteristics (N = 288).

Variables	Number	Percentage (%)[a]
Demographic characteristics		
Gender		
Female	153	53.1
Male	135	46.9
Age (years)		
18-44	138	47.9
45-64	116	40.3
≧65	34	11.8
Marital status		
Divorced/Single	70	24.3
Married	218	75.7
Education		
≦Junior middle school graduate	74	25.7
High school graduate	128	44.4
≧College graduate	86	29.9
Employment		
Employed	106	36.8
Retired	61	21.2
Unemployed	121	42.0
Medical insurance		
No	31	10.8
Yes	257	89.2
Religion		
No	264	91.7
Yes	24	8.3
Medical characteristics		
Cancer type		
ALL	66	22.9
AML	222	77.1
Complete remission[b]		
No[c]	201	69.8
Yes	87	30.2
Treatment cycles		
Induction therapy	216	75.0
Consolidation therapy	72	25.0
Course of disease (months)		
0-3	169	58.7
4-12	83	28.8
>12	36	12.5
Chemotherapy cycles		
0-3	204	71.2
4-6	57	19.8
>6	36	12.5
Hemoglobin (g/L)		
Normal	27	9.4
≥90	66	22.9
60 ~ 89.9	164	56.9
<60	31	10.8
Platelet		
Abnormal	235	81.6
Normal	53	18.4
Albumin		
Abnormal	188	65.3
Normal	100	34.7
Serum potassium		
Hypokalemia	55	19.1
Normal	233	80.9
BMI [d]		
Underweight	21	7.3
Normal	162	56.2
Overweight	105	36.5
Body temperature		
Fever	29	10.1
Normal	259	89.9
PSQI [e]		
Normal (1–7)	156	54.2
Poor (>7)	132	45.8
Anxiety [f]		

(*continued on next page*)

Table 1 (*continued*)

Variables	Number	Percentage (%)[a]
Normal (0–7)	187	64.9
Mild (8–10)	77	26.7
Severe (11–21)	24	8.3
Depression [f]		
Normal (0–7)	199	69.1
Mild (8–10)	59	20.5
Severe (11–21)	30	10.4

Abbreviations: ALL, Acute Lymphocytic Leukemia; AML, Acute Myelocytic Leukemia; BMI, Body Mass Index; PSQI, Pittsburgh Sleep Quality Index.

[a] Percentages may not add to 100 % because of rounding.

[b] Complete remission is defined as having fewer than 5 % blast cells in the bone marrow, blood cell counts that are normal and absence of any disease signs or symptoms.

[c] Including partial remission and no remission.

[d] BMI: Underweight, BMI < 18.5; Normal, 18.5 ≤ BMI < 24; Overweight, BM ≥ 24.

[e] Abnormal PSQI score was defined as greater than 7 on a scale of 1–21. 0 to 7 points indicate normal, 8 to 10 points indicate mild abnormalities, 11 to 14 points indicate moderate abnormality, and 15–21 points indicate severe abnormality.

[f] Hospital Anxiety and Depression Scale was used, 0 to 7 points indicate normal, 8 to 10 points indicate mild abnormalities, 11 to 21 points indicate severe abnormality.

for data with distributions that met parametric assumptions. The Mann–Whitney *U* test was used when the parametric assumptions were not met. Categorical variables were represented as frequencies and percentages, and compared with Pearson's chi-squared test. When the number of observations obtained in an analysis was small, Fisher's exact test was used. A $p < 0.05$ was considered statistically significant. Spearman's rank correlation coefficient was used to explore the correlations between CRF and sleep disturbance, depression, and anxiety. Hierarchical multiple linear regression analyses were conducted to evaluate the associations of the potential influencing factors or CRF. Significant demographic and clinical characteristics in univariate analysis were entered variables in Block 1 and Block 2; the sleep disturbance, depression, and anxiety scores were entered in Block 3.

3. Results

3.1. Study population

Of the 332 AL patients we approached, 300 agreed to participate in the study. After the questionnaire survey, 12 cases were further excluded from the analysis (8 cases because of many missing items in the questionnaires and 4 cases because of invalid questionnaires). Two hundred eighty-eight valid questionnaires were included in the final analysis (Table 1). Acute lymphoblastic leukemia and acute myeloid leukemia were diagnosed in 66 patients (22.9 %) and 222 patients (77.1 %), respectively. The median duration of the disease, which was defined as the time from the diagnosis to the questionnaire survey, was 2 months. A total of 93 patients (32.3 %) had completed three cycles of chemotherapy. Further demographic and clinical characteristics of the included patients are presented in Table 1. The Cronbach's α coefficients of the FACIT-F, PSQI, and HAD were 0.789, 0.767, and 0.858, respectively.

3.2. The association of CRF with demographic and clinical characteristics

The overall FACIT-F score of the included patients was 33.25 ± 10.35. Univariate analysis showed that CRF was inferior in females, old age (≧ 65 years old), married, low level of education (lower than junior middle school), patients not achieving CR, patients undergoing induction therapy, and patients with abnormal hemoglobin, platelet, or serum albumin. Further univariate analysis of the effect of fatigue severity on participants' demographic and clinical characteristics is presented in Table 2.

3.3. Correlation between CRF and sleep disturbance, depression, and anxiety in participants

The median scores of sleep disturbance, depression, and anxiety were 7 (IQR 5–11), 5 (IQR 2–8), and 6 (IQR 3–9), respectively. Spearman correlation showed that the severity of fatigue had mild correlations with sleep disturbance ($r = -0.390$, $P < 0.001$) and a moderate correlation with depression ($r = -0.505$) and anxiety ($r = -0.540$) ($P < 0.001$) (Table 3).

Hierarchical multiple linear regression analyses of the influencing factors for CRF in acute leukemia patients.

CRF was regarded as the dependent variable, while demographic and clinical characteristics were entered as independent variables in Block 1 and Block 2, respectively. The sleep disturbance, depression, and anxiety scores were entered in Block 3 (Table 4). Block 1 (demographic characteristics) and Block 2 (clinical characteristics) accounted for 13.5 % and 22.5 % of the variation in CRF, respectively. The addition of the sleep disturbance, depression and anxiety variables in Block 3 and these entered variables explained 44.3 % of the variance. Age, treatment cycles, serum albumin, depression, and anxiety were independent influencing factors of CRF.

Table 2
Univariate analysis of CRF with participants' demographic and clinical characteristics (N = 288).

Variables	Fatigue Score[a] (mean ± SD)	t/F	*P*
Gender		−2.518	.012[e]*
Female	31.82 ± 10.91		
male	34.87 ± 9.47		
Age (years)		16.116	<.001[f]*
18–44	35.88 ± 10.04		
45–64	32.42 ± 9.53		
≧65	25.41 ± 10.10		
Marital status		3.691	<.001[e]*
Divorced/Single	37.14 ± 9.95		
Married	32.00 ± 10.19		
Education		6.577	.002[f]*
Junior middle school graduate	29.74 ± 10.94		
High school graduate	33.83 ± 9.46		
≧College graduate	35.42 ± 10.45		
Employment		2.989	.052[f]
Employed	33.84 ± 9.82		
Retired	30.41 ± 10.52		
Unemployed	34.17 ± 10.55		
Medical insurance		.113	.910[e]
No	33.45 ± 10.08		
Yes	33.23 ± 10.40		
Religion		1.363	.174[e]
No	33.50 ± 10.38		
Yes	30.50 ± 9.81		
Cancer type		1.743	.082[e]
ALL	35.20 ± 9.76		
AML	32.68 ± 10.48		
Complete remission[b]		−3.831	<.001[e]*
No[c]	31.75 ± 10.56		
Yes	36.72 ± 8.98		
Treatment cycles		−3.326	.001[e]*
Induction therapy	32.10 ± 10.51		
Consolidation therapy	36.71 ± 9.01		
Course of disease (months)		1.563	.211[f]
0–3	32.37 ± 10.52		
4–12	34.30 ± 10.07		
>12	35.00 ± 10.03		
Chemotherapy cycles		1.197	.304[f]
0–3	32.65 ± 10.36		
4–6	34.77 ± 9.82		
>6	34.65 ± 11.38		
Hemoglobin (g/L)[d]		3.604	.014[f]*
Normal	37.81 ± 9.11		
≥90	34.82 ± 9.79		
60 ~ 89	32.46 ± 10.48		
<60	30.13 ± 10.58		
Platelet[d]		−2.121	.035[e]*
Normal	35.96 ± 10.75		
Abnormal	32.64 ± 10.19		
Albumin[d]		−6.093	<.001[e]*
Abnormal	30.89 ± 10.69		
Normal	37.70 ± 8.01		
Serum potassium[d]		−1.699	.090[e]
Normal	33.76 ± 9.97		
Hypokalemia	31.13 ± 11.70		
BMI (kg/m^2)		.484	.617[f]
Underweight	34.76 ± 10.96		
Normal	32.78 ± 10.16		
Overweight	33.69 ± 10.59		
Body temperature		.876	.382[e]
Normal	33.43 ± 10.31		
≥37.3 °C	31.66 ± 10.78		

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F); ALL, Acute Lymphocytic Leukemia; AML, Acute Myelocytic Leukemia; BMI, Body Mass Index; PSQI, Pittsburgh Sleep Quality Index.
*P < 0.05.
[a] Fatigue score was evaluated using FACIT-Fatigue, with total scores ranged from 0 to 52. The lower score indicating more severe fatigue.
[b] Complete remission is defined as having fewer than 5 % blast cells in the bone marrow, blood cell counts that are normal and absence of any disease signs or symptoms.

[c] Including partial remission and no remission.
[d] Normal range: Hemoglobin, male>120 and female>110; Platelet, 100–300 × 10^6/mL; Albumin, >35 g/L; Serum potassium, 3.5–5.5 mmol/L.
[e] Using Student's t-test to establish the p-values.
[f] Using ANOVA to establish the p-values.

Table 3
Analysis of the correlation between sleep disturbance, depression, anxiety and CRF scores (N = 288).

Variables	Correlation coefficient (r)[a]		
	FS	PSQI	HAD (Depression)
PSQI	−.390***		
HAD (Depression)	−.505***	−.458***	
HAD (Anxiety)	−.540***	−.410***	−.700***

Abbreviations: FS, Fatigue score; PSQI, Pittsburgh Sleep Quality; HAD, Hospital Anxiety and Depression Scale (HAD).
***$P < 0.001$.
[a] Using Spearman's rank correlation coefficient to establish the p-values.

Table 4
Hierarchical regression analyses for influencing factors of CRF (N = 288).

	Model 1		Model 2		Model 3	
R^2	.123		.204		.434	
$\triangle R^2$	.108		.179		.409	
P (F)	<.001		<.001		<.001	
	Beta (95%CI)	P[a]	Beta (95%CI)	P[a]	Beta (95%CI)	P[a]
Gender	2.141 (−.193, 4.475)	.072	2.499 (.254, 4.744)	.029*	1.081 (−.843, 3.004)	.052
Age	−3.837 (−5.874, −1.800)	<.001*	−3.381 (−5.356, −1.406)	.001*	−2.616 (−4.299, −.933)	.002*
Marital status	−1.497 (−4.620, 1.626)	.346	−.359 (−3.456, 2.737)	.819	.341 (−2.983, 2.300)	.799
Education	1.215 (−.485, 2.915)	.161	.729 (−.921, 2.380)	0.358	−.649 (−2.073, 0.776)	.371
Treatment cycles			3.072 (.256, 5.887)	.033*	2.675 (1.047, 5.440)	.004*
Anemia			−.053 (−1.755, 1.649)	.951	.075 (−1.369, 1.520)	.918
Platlete			.903 (−2.178, 3.983)	.564	.786 (−1.838, 3.409)	.556
Albumin			5.205 (2.657, 7.752)	<.001*	3.244 (1.047, 5.440)	.004*
Sleep disturbance					−.260 (−.528, .007)	.057
Depression					−.743 (−1.090, −.396)	<.001*
Anxiety					−.665 (−1.006, −.325)	<.001*

*$P < 0.05$.
[a] Using hierarchical multiple linear regression analyses to establish the p-values.

3.4. A group-controlled analysis of the participants in CR versus patients in Non-CR

We performed a group-controlled analysis of the participants in CR versus patients in Non-CR. The demographic and clinical characteristics of each group of participants are shown in Table 5. The CRF level of acute leukemia patients in the complete remission group was lower than that of patients who were not achieving complete remission. Depression and anxiety were independent influencing factors for CRF in both groups of patients, and age, employment, albumin, and sleep disturbance also affected CRF in the Non-CR group (Table 6 and Table 7).

4. Discussion

The results of our study suggested that age, treatment cycles, and abnormality of albumin concentration were influencing factors of CRF. The identification of age as an influencing factor might be explained by the close relationship between the patient's age and the physiological functions of the body. With increasing age, the body's physical functions decline gradually, and the ability to adapt to changes in the internal and external environment is also weakened, making the individual more vulnerable to various chronic diseases [34]. Therefore, elderly patients were more likely to get fatigued when suffering from cancer or receiving various antitumor treatments. Patients in the consolidation therapy often achieve complete remission; at this time, the clinical symptoms usually disappear, and the patient's physiological function gradually recovers. Therefore, as shown in the results of this study, the degree of fatigue in consolidation therapy and complete remission patients was low. Albumin (ALB) is synthesized by liver parenchymal cells [35]. Patients with malignant tumors have various degrees of protein metabolism disorders, and low albumin levels might indicate poor nutritional status due to disease progression or gastrointestinal toxicity caused by chemotherapy drugs [36]. Therefore, it was not surprising to observe that the AL patients with abnormal ALB had severe fatigue.

Our results indicated that depression and anxiety were strongly correlated with CRF. The result was similar to a previous study showing that depression was related to fatigue in survivors of childhood acute lymphoblastic leukemia [37]. Daniel also reported that

Table 5
Participants' demographic and clinical characteristics (N = 288).

Variables	CR group[a] (N = 87)	Non-CR group[b] (N = 201)	χ^2/t	*P*
	n (%)	n (%)		
Gender			.248[f]	.135
Female	51 (58.6)	102 (50.7)		
male	36 (41.4)	99 (49.3)		
Age (years)			6.992[f]	.030*
18–44	43 (49.4)	95 (47.3)		
45–64	40 (46.0)	76 (37.8)		
≧65	4 (4.6)	20 (14.9)		
Marital status			.002[f]	1.000
Divorced/Single	21 (24.1)	49 (24.4)		
Married	66 (75.9)	152 (75.6)		
Education			5.323[f]	.069
Junior middle school graduate	16 (18.4)	58 (28.9)		
High school graduate	38 (43.7)	90 (44.8)		
≧College graduate	33 (37.9)	53 (26.4)		
Employment			.210[f]	.897
Employed	13 (14.9)	30 (14.9)		
Retired	17 (19.5)	44 (21.9)		
Unemployed	57 (65.5)	127 (63.2)		
Medical insurance			5.897[f]	.015*
No	3 (3.4)	28 (13.9)		
Yes	84 (96.6)	173 (86.1)		
Religion			1.630[f]	.202
No	83 (95.4)	181 (90.0)		
Yes	4 (4.6)	20 (10.0)		
Cancer type			.105[f]	.761
ALL	21 (24.1)	45 (22.4)		
AML	66 (75.9)	156 (77.6)		
Treatment cycles			–	<0.001*
Induction therapy	15 (17.2)	201 (100.0)		
Consolidation therapy	72 (82.8)	0 (0.0)		
Course of disease (months)			82.057[f]	<.001*
0–3	17 (19.5)	152 (75.6)		
4–12	53 (60.9)	30 (14.9)		
>12	17 (19.5)	19 (9.5)		
Chemotherapy cycles			44.650[f]	<.001*
0–3	39 (44.8)	166 (82.6)		
4–6	36 (41.4)	21 (10.4)		
>6	12 (13.8)	14 (7.0)		
Hemoglobin (g/L)[c]			59.215[f]	<.001*
Normal	20 (23.0)	7 (3.5)		
≥90	33 (37.9)	33 (16.4)		
60–89	34 (39.1)	130 (64.7)		
<60	0 (0.0)	31 (15.4)		
Platelet[c]			18.506[f]	<.001*
Normal	58 (66.7)	177 (88.1)		
Abnormal	29 (33.3)	24 (11.9)		
Albumin[c]			7.284[f]	.010*
Normal	40 (46.0)	59 (29.5)		
Abnormal	47 (54.0)	141 (70.5)		
Serum potassium[c]			2.270[f]	0.145
Normal	12 (13.8)	43 (21.4)		
Hypokalemia	75 (86.2)	158 (78.6)		
BMI (kg/m^2)			2.454[f]	.303
Underweight	7 (8.0)	14 (7.1)		
Normal	54 (62.1)	105 (53.3)		
Overweight	26 (29.9)	78 (39.6)		
Body temperature			5.033[f]	.025*
Normal	84 (96.6)	175 (87.1)		
≥37.3 °C	3 (3.4)	26 (12.9)		
Fatigue Score (mean ± SD)[d]	36.72 ± 8.98	31.75 ± 10.56	−3.831[e]	<.001*

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F); ALL, Acute Lymphocytic Leukemia; AML, Acute Myelocytic Leukemia; BMI, Body Mass Index; PSQI, Pittsburgh Sleep Quality Index.
*P < 0.05.
[a] CR, complete remission is defined as having fewer than 5 % blast cells in the bone marrow, blood cell counts that are normal and absence of any disease signs or symptoms.
[b] Non-CR group includes partial remission and no remission.
[c] Normal range: Hemoglobin, male >120 and female >110; Platelet, 100–300 × 10^6/mL; Albumin, >35 g/L; Serum potassium, 3.5–5.5 mmol/L.

[d] Fatigue score was evaluated using FACIT-Fatigue, with total scores ranged from 0 to 52. The lower score indicating more severe fatigue.
[e] Using Student's t-test to establish the p-values.
[f] Using chi-squared test to establish the p-values.

Table 6
Hierarchical regression analyses for influencing factors of CRF in the Non-CR group (N = 201).

	Model 1		Model 2		Model 3	
R^2	.127		.193		.425	
$\triangle R^2$	.105		.160		.391	
P (F)	<.001		<.001		<.001	
	Beta (95%CI)	P[a]	Beta (95%CI)	P[a]	Beta (95%CI)	P[a]
Age	−4.154 (−6.498, −1.729)	.001*	−3.713 (−6.023, −1.403)	.002*	−3.000 (−4.975, −1.025)	.003*
Employment	−1.154 (−3.290, .982)	0.288	−1.082 (−3.155, .992)	0.305	−1.839 (−3.613, −.066)	.042*
Albumin			6.616 (3.215, 10.017)	<.001*	3.765 (.797, 6.733)	.013*
Sleep disturbance					−.392 (−.742, −.043)	.028*
Depression					−.829 (−1.264, −.393)	<.001*
Anxiety					−.477 (−.900, −.053)	.028*

CR, complete response.
Non-CR group includes partial response and no response.
*P < 0.05.
[a] Using hierarchical multiple linear regression analyses to establish the p-values.

Table 7
Hierarchical regression analyses for influencing factors of CRF in the complete response group (N = 87).

	Model 1		Model 2		Model 3	
R^2	.136		.166		.444	
$\triangle R^2$	.083		.069		.354	
P(F)	.034		.068		<.001	
	Beta (95%CI)	P[a]	Beta (95%CI)	P[a]	Beta (95%CI)	P[a]
Sex	3.546 (−.349, 7.442)	.074	3.317 (−.629, 7.262)	.098	1.626 (−1.756, 5.008)	.341
Albumin			2.935 (−.991, 6.826)	.141	1.817 (−1.510, 5.144)	.280
Sleep disturbance					−.060 (−.476, .357)	.776
Depression					−.550 (−1.179, −.080)	.036*
Anxiety					−1.058 (−1.662, −.454)	.001*

*P < 0.05.
[a] Using hierarchical multiple linear regression analyses to establish the p-values.

cancer survivors with fatigue showed significantly more depression and anxiety [38]. The relationship between CRF and depression is complex, and they exert reciprocal influences on each other [39]. Depression and fatigue were two conditions that could make someone feel extremely tired. Both conditions might be present at the same time. Fatigue could be a symptom of depression and anxiety. Anxiety and depression could aggravate fatigue. Therefore, depression, anxiety, and fatigue need to be treated as a holistic problem rather than as several separate problems. When patients report severe fatigue, not only should physical exercise be arranged for patients to improve fatigue, but psychotherapy such as cognitive behavior therapy could also be provided for patients to improve anxiety and depression [40,41].

In contrast to studies of another malignant disease [42], which showed that hemoglobin concentration was negatively correlated with the degree of fatigue, our results showed that hemoglobin level was not an influencing factor of AL patients' CRF. A longitudinal study of 77 cancer patients found that changes in hemoglobin were significantly related to changes in the fatigue severity of patients throughout chemotherapy treatment, and greater declines in hemoglobin throughout repeated chemotherapy administrations were accompanied by greater increases in fatigue. Especially when the decline in hemoglobin was to a final value $\leq$ 12 g/dL (120 g/L), changes in fatigue corresponded more closely to changes in hemoglobin in cancer patients [42]. Of note, previous studies in AML also suggested that, unlike CRF in patients with solid tumors, hemoglobin levels in AML did not correlate with the patients' CRF [13,27,43]. A possible explanation for the discrepancy was that moderate or severe anemia was common in the majority of leukemia patients [44]. The correlation between the changes in CRF and alterations in hemoglobin levels might not be captured simply by asking patients to self-assess their fatigue in the past week. Further longitudinal investigations are required to explore the correlation between anemia and CRF in AL patients.

Compared with other CRF studies, our participants received a low CRF score, which indicated a high degree of fatigue. Kapoor et al.'s study showed that adult cancer patients had a mean score of 36 (SD = 3.84) using the same scale, FACIT-F [45]. The FACIT-F subscale scores (means±SDs) of cancer, stroke, and HIV patients were 36.0 ± 12.1, 38.1 ± 9.6 and 34.0 ± 12.6, respectively [46]. The relatively low CRF score might be because most of our participants received the first initial courses of intensive chemotherapy and did not achieve complete remission. According to previous studies, the patient experienced severe symptoms and poor mental status before the disease remission [46,47]. After the leukemia patient achieved complete remission after induction therapy, the clinical symptoms

disappeared, the hemogram tended to become normal, and the patient's physiological function gradually recovered. Therefore, as shown in the results of this study, for the patients who achieved complete remission, the degree of their fatigue was relatively reduced.

In our study, we classified participants into 2 groups based on the disease status of the patients. The hierarchical multiple regression analysis results showed differences in the influencing factors of CRF between the two groups. Anxiety and depression were independent predictors of CRF in the two groups, suggesting that anxiety, depression, and fatigue might coexist. Therefore, depression, anxiety, and fatigue need to be treated as holistic problems, and comprehensive interventions should be implemented. For the Non-CR group, age, employment, albumin, and sleep disturbance were also influencing factors for CRF. Elderly, retired patients were more likely to experience CRF, and those two factors coexisted. A previous study also suggested that because most retired patients were elderly, their physical functions gradually declined, making them more susceptible to disease invasion and fatigue.

We also identified the sleep disturbance was an independent influencing factor of CRF in patients not achieving complete remission. The correlation between sleep disturbance and CRF is controversial. Steur et al.'s study showed that the subjective assessment of fatigue in children with acute lymphoblastic leukemia (ALL) was not correlated with sleep quality [48]. However, several studies have suggested that sleep disturbance is a significant independent predictor of CRF [39,49]. Furthermore, Jim et al.'s study found that sleep disturbance affected the timing, rather than the magnitude, of fatigue [39]. Based on previous publications, as well as our findings, the relationship between sleep disturbance and CRF is still not conclusive and requires further exploration.

Patients with low albumin levels had higher levels of CRF, which was consistent with the results of all participants in the previous section. This study showed that sleep disturbance was also an independent predictor of CRF in patients not achieving complete remission. In patients during the induction chemotherapy, sleeping may be disturbed with intense therapy and persistent intravenous infusion. Almost all patients not achieving complete remission were in the induction chemotherapy, during which sleep problems might significantly affect their physical activity and CRF, and reduce their physical activity, in which higher CRF reduces patients' physical activity while lower levels of physical activity reciprocally increase patients' sensation of CRF [40,50].

There are some limitations in our study. First, the sample size was small. Due to the limitation of manpower and material resources, the study enrolled patients from only one hospital, and the sample size was not sufficiently representative. Second, due to resource constraints, we did not perform repeated measurements within a treatment cycle. This research was only a cross-sectional study, which could only understand the CRF level at a certain stage and limited information about the exact course of fatigue. Therefore, the dynamic trend of CRF in leukemia patients over time requires further longitudinal study.

5. Conclusion

This study demonstrated that females, older age, hypoalbuminemia, and induction therapy in patients with acute leukemia were more likely to have a higher degree of CRF. Psychologically, depression and anxiety were also significant influencing factors for CRF. For the patients not achieving complete remission, age, employment, albumin, and sleep disturbance were also influencing factors for CRF. These results may help caregivers screen patients with high CRF. Early interventions could be adopted, such as close observation and encouragement to participate in fatigue prevention.

Ethical statement

This study was reviewed and approved by the Institutional Review Board of the author's hospital, with the approval number: 2020/473.

All participants/patients (or their proxies/legal guardians) provided informed consent to participate in the study.

All participants/patients (or their proxies/legal guardians) provided informed consent for the publication of their anonymised case details.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Yingli Wang: Conceptualization, Data curation, Formal analysis, Resources, Writing – original draft, Writing – review & editing. **Xinwen Du:** Data curation, Methodology. **Yuping Gong:** Investigation, Methodology. **Yan Jiang:** Investigation, Methodology. **Yuhuan Zheng:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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