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Changes in physical fitness in acute leukemia patients during chemotherapy

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This study aimed to investigate the changes in physical fitness and patient-reported outcomes as well as the correlation between these two factors in adult patients with newly diagnosed acute leukemia during chemotherapy. This was a longitudinal observational study. Patients were recruited from a tertiary hospital in China with a follow-up period of less than 90 days. Physical fitness was assessed using body mass index (BMI), mean skinfold thickness, waist-to-hip ratio, spirometry, mean grip strength, and flexibility at T1 (before chemotherapy), T2 (7–14 days after initial chemotherapy), and T3 (completely relieved or after two chemotherapy courses). A repeated-measures analysis of variance was used to analyze the physical fitness changes during follow-up. Multiple linear regression was used to analyze the factors influencing patient-reported outcomes. The study analyzed 121 patients. Changes in physical fitness during chemotherapy, including BMI, mean skinfold thickness, lung capacity and flexibility were not all equal at all three time points ($F = 38.477$, $P < 0.001$; $F = 44.506$, $P < 0.001$; $F = 70.948$, $P < 0.001$; and $F = 70.965$, $P < 0.001$), and post-hoc tests showed that they all trended to be decreasing before they were elevated (T2 < T3 < T1). The waist-to-hip ratio decreased and then increased ($F = 12.138$, $P < 0.001$, T2 < T3 = T1) and the mean grip strength remained stable ($F = 0.137$, $P = 0.718$). The total patient-reported outcome scale score decreased and subsequently increased ($F = 362.507$, $P < 0.001$, T2 < T1 < T3). BMI, mean skinfold thickness, spirometry, and flexibility influenced the patient-reported outcomes ($B = 1.427$, $P < 0.001$; $B = -15.340$, $P < 0.001$; $B = 0.002$, $P = 0.014$; $B = 0.249$, $P < 0.001$). Physical fitness affects patient-reported outcomes in those with acute leukemia. During chemotherapy, especially myelosuppression, healthcare providers should monitor patients' physical fitness and implement positive patient-appropriate interventions, such as exercise interventions, to promote better outcomes.

Acute leukemia (AL) is characterized by acute onset, high malignancy, difficult treatments, and poor survival rates and is more prone to recurrence than solid tumors[1,2]. Chemotherapy is widely used as an effective treatment to ameliorate overall survival rates and the physical activity status in patients with AL[3].

Physical fitness is defined by the ability to perform daily tasks with energy and alertness, without undue fatigue, and with sufficient energy to enjoy leisure activities and handle unexpected situations[4]. The American College of Sports Medicine guidelines for exercise testing and prescription describe physical fitness as a collection of measurable health-related and skill-related attributes, including cardiorespiratory fitness, power, coordination, agility, flexibility, reaction time, balance, body composition, and muscular fitness, that encompasses muscular strength and endurance[5]. Cardiorespiratory fitness can be assessed to some extent by the 6-minute walk test (6MWT)[6]. The hand dynamometer can be used to measure grip strength quantitatively; it serves as the easiest method recommended for evaluating muscle strength in clinical practice[7].

AL is life-threatening and can be highly distressing, with significant physical suffering and a relatively high risk of death. According to scientific statements from the American Heart Association[8], physical fitness is associated with mortality risk in various cancer types. Kirkham et al.[9] developed a standardized physical fitness assessment protocol for cancer survivors, confirming the feasibility of standardized physical fitness measures for this group of patients that are also applicable to those with hematological malignancies. Hence, it should be feasible to perform standardized physical fitness measures in patients with AL. Previous longitudinal studies

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on the physical fitness levels in adult patients with lymphoma showed that the 6MWT and grip strength was decreased before, during, and after chemotherapy[10].

As the global disease spectrum changes and the biopsychosocial model of medicine becomes more recognized, the acceptance of the patient-centered medical model continues to grow[11]. Many scholars have successfully studied patient-reported clinical outcomes[12]. Patient-Reported Outcomes (PROs) are defined in the guidelines as "a report that is derived directly from all aspects of the patient's perception of his or her health status, functional status, and overall feelings about treatment, excluding the interpretation of health care professionals and any other person"[13]. Studies have shown that patients' subjective perceptions and laboratory indicators complement each other in diagnosing the disease[14]. The PROs contain the patient's symptom function, health-related quality of life, treatment compliance, and satisfaction with the outcome of the treatment, which can reflect the changes in laboratory indicators and provide a comprehensive evaluation of the patient's overall health status[15]. Thus, adding patient reporting of treatment outcomes to the clinical efficacy evaluation is necessary. A prior study showed that PROs were directly derived from patients and are relatively easy to measure[16]. Healthcare professionals can potentially improve their clinical decision-making by fully utilizing PROs information[17]. Various researchers have already included PROs in their clinical guidelines as relevant findings for efficacy evaluation[18]. Consequently, the PROs can compensate for the shortcomings of clinical efficacy evaluation systems and provide a basis for selecting the best treatment plan and nursing care decisions for patients.

The Theory of Unpleasant Symptoms (TOUS) suggests that symptoms are composed of the symptom itself, the influencing factors, and the symptom outcome, and that there is a bi-directional correlation between these three. In the AL patient population, symptoms can be quantified to some extent with the help of PROs. Possible influencing factors include psychological, psychiatric, and social factors, while the outcome of the symptom is the prognosis of the patient. In addition, PROs may be influenced by the patient's physical condition, which may lead to changes in symptom outcomes[19,20].

To our knowledge, no longitudinal studies have been conducted in China to address changes in physical fitness and PROs during chemotherapy in adult acute leukemia patients. Most studies have used cross-sectional designs, which are deficient in analyzing the dynamic trajectory of changes in patients' physical fitness[21,22]. Therefore, given the importance of physical fitness and PROs for patients with AL as well as the lack of relevant previous studies, studying the relationship between physical fitness and PROs longitudinally in adult patients with AL undergoing chemotherapy is necessary to provide reference information for predicting the prognosis of the disease, choosing appropriate chemotherapy regimen, and guiding rehabilitation measures to be taken during chemotherapy in these patients. The objective of this study was to (i) assess the level of physical fitness among adult patients with AL, (ii) explore the changes in PROs among adult patients with AL, and (iii) investigate the correlation between physical fitness status and PROs in adult patients with AL during chemotherapy. This study will provide further theoretical support for the subsequent implementation of positive interventions such as exercise interventions for patients during chemotherapy, which will in turn improve their symptom experience during chemotherapy.

Methods

Design

This study is based on the TOUS and used a longitudinal design to investigate changes in physical fitness levels during chemotherapy in adult patients with AL, including cardiorespiratory fitness, body composition, flexibility, and muscular fitness. Questionnaires and index measurements were conducted at three time points: before chemotherapy (T1), 7–14 days after the first chemotherapy session (myelosuppression stage, T2), and after 1–2 courses of treatment (complete remission stage, T3). In reporting this study, STROBE guidelines for observational research were followed, as detailed in Supplementary file 1 as a supplementary table.

Study setting and sampling

This study used a cluster sampling method. A survey was conducted to select adult patients with AL from the hematology department of a tertiary hospital (Fujian Medical University Union Hospital) in China between December 2020 and December 2021. The sample size was calculated using the repeated-measures analysis module of PASS 15.0, and the sample size calculation principle was based on two previous studies[23,24]. According to the index of physical fitness, the sample size was calculated to be 9–102 cases. Assuming that 20% are lost to follow-up, the required sample size was calculated to be 11–128 cases. According to the total Patient-Reported Outcome Scale for Acute Leukemia (ALPRO) score, the required sample size consisted of six cases; assuming that 20% are lost to follow-up, the required sample size consisted of eight cases. Since the sample size calculated from the total ALPRO score was too small, the sample size calculated from the physical fitness index was used instead. The final sample size was 128, and 132 cases were included for follow-up; the sample size calculation details are shown in Supplementary file 2 as a supplementary table.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (a) newly diagnosed with AL; (b) aged ≥ 18 years old (based on the standard of the Department of Adult Hematology in Fujian, China); (c) patients' awareness of their cancer diagnosis; (d) able to communicate fluently in Mandarin Chinese; (e) willing to consciously participate in this study; and (f) initiated treatment but not yet receiving chemotherapy. The exclusion criteria were as follows: (a) diagnosed with a severe disease of vital organs, a disorder of consciousness, or a mental illness (e.g., dementia, unconsciousness, delirium, depression, or stroke), who were at risk for or unable to cooperate well with the investigator in performing the fitness measurements; and (b) chemotherapy not included in the patient's treatment plan, and

there were significant differences in the indicators between patients who did not receive chemotherapy and those who did receive chemotherapy. There were substantial differences.

Variables and instrument

Demographic characteristics

The questionnaire was developed for this study. Demographic characteristics, including employment status, age, medical payment method, religion, sex, permanent residence, marital status, number of children, level of education, per capita income class (yuan), type of family living, and movement intention (divided into five levels, T1) were collected. The details are presented in Supplementary file 3 as a supplementary table.

Disease characteristics

The questionnaire was developed for this study. Disease characteristics collected included disease classification, number of underlying diseases or comorbidities, chemotherapy regimens, duration of chemotherapy (days), prognostic assessment, hematological indices, white blood cells (WBC), neutrophil granulocytes (GRAN), hemoglobin (HGB), and platelets (PLT). Hematological indices were tested at all three time points. The details are presented in Supplementary file 4 as a supplementary table.

Physical fitness measurement record form

During the course of this study, the investigators did not provide patients with any exercise interventions, other than standard care. At the end of the study, the investigators provided patients with appropriate exercise recommendations. The Physical Fitness Measurement Record Form, including body mass index (BMI), mean skinfold thickness, waist-to-hip ratio, spirometry, 6MWT, mean grip strength, flexibility. In this study, each index was measured as follows: BMI = weight (kg)/[height (m)]^2, height was measured using a rigid ruler and measured in centimeters; weight was determined by weighing scale and measured in KG. skinfold thickness was measured with the help of skinfold thickness meter (JiXing, PZJ − 01) and measured in centimeters. Waist and hip circumference were measured in centimeters using a soft ruler for measurement operations. Spirometry was measured in mL using a spirometer (Naili, NL-100) in a sitting position in the ward or clinic. 6MWT Fold measurements were carried out in a corridor of 30 m in length and were expressed in meters. Grip strength was measured using an electronic grip strength meter (XiangShan, EH − 101) in KG. Flexibility was assessed using an upper limb back grip test, where the distance between the middle fingers of both hands was measured using a soft ruler in centimeters, and the specific measurement methods, is shown in Supplementary file 5 for supplementary tables and text.

ALPRO

The ALPRO, which was used to assess the PROs, was developed by the research team[25] in 2018. It consists of 42 items covering four dimensions: physiological, psychological, social, and therapeutic. The total score ranges from 42 to 210, with higher scores indicating more desirable clinical outcomes. The Cronbach's α coefficient for the total scale was 0.897, and the content validity of the total scale was 0.907.

Data collection

Basic patient information and ALPRO were collected using a face-to-face survey method. Patients' physical fitness was determined using an on-site measurement method, and routine blood results were extracted from patients' medical records and recorded. Demographic and disease characteristics were collected before chemotherapy, and physical fitness measurement record forms and ALPRO scores were collected at all three time points. Because patients generally felt tired, fell easily, and had reduced platelets after chemotherapy, they were advised to rest in bed during the myelosuppression phase; therefore, the 6MWT was not performed at 7–14 days after the first chemotherapy session (myelosuppression phase)[26–28]. All questionnaires were completed by the respondents. Before the survey, the investigators (WKX and ZJL) explained the study's purpose, significance, and method of completion to the patients. After the patients provided their consent and cooperation and signed an informed consent form for the study, the questionnaires were distributed, and instructions given to them how to complete the questionnaires. Both investigators were master's degree students in nursing who had obtained a Nurse Qualification Certificate and had experience in operational training for the measurement of physical fitness indicators. All scales were collected on the spot, and the investigator checked the completion, corrected, and supplemented the information when missing or wrong items were found.

Fidelity of the study

The investigators (WKX and ZJL) measured physical fitness indicators. A nursing specialist and a chief hematology-oncology physician provided guidance, supervision, and coordination for the implementation of the study. Data from 121 adult patients with AL were included in this study. Two researchers (WKX and ZJL) independently checked and input data using EpiData 3.1 software to ensure the validity and completeness of the questionnaire. After all data entries were completed, a consistency check was performed, and inconsistent data were confirmed and corrected by querying the original records.

Statistical analysis

Statistical software (SPSS 26.0) was used for the data analysis. Indicators that conform to a normal distribution and those that do not are expressed as mean ± standard deviation ($\overline{x}\pm$ SD) and median (P25, P75), respectively. For comparisons between the groups included in the analysis and those lost to follow-up, the t-test was used for continuous variables if they were normally distributed and satisfied chi-square; if they were not normally

distributed, the Mann - Whiney U rank sum test was used. For count data, the Fisher's exact test was used. Count data are statistically described using frequency and composition ratios. One-way repeated-measures ANOVAs were used to analyze changes in patients' ALPRO and physical fitness status during chemotherapy, post-hoc tests at each time point using the least significant difference (LSD) method, and effect sizes were evaluated using the means difference and their 95% confidence intervals (95% CI). Given that the follow-up period of this study was less than 90 days, and thus the time effect was relatively weak, multiple linear regression analysis was used to explore the correlation between physical health status and ALPRO in patients with AL[29]. Prior to the multiple linear regression analysis, the data were transformed into time-cross-section data (long form data). Using the stepwise method (entry: 0.05, exclusion: 0.1), the variance inflation factor (VIF) and tolerance were used to determine multicollinearity between variables, and severe multicollinearity was considered when VIF > 10 or tolerance < 0.1. Differences were considered statistically significant at $P < 0.05$. Any lost follow-up data were removed.

Results

Recruitment and follow-up of participants

A total of 224 patients with AL were initially screened in this study, of which 84 did not meet the inclusion criteria, and 8 refused to participate for various reasons, resulting in a refusal rate of 5.7%. A total of 132 patients with AL who met the inclusion criteria were ultimately included in the study. After completing the first measurement (T1), one patient was subsequently excluded due to a change of diagnosis and eight were lost overall. After completing the second measurement (T2), 2 more patients were lost; finally, 121 patients with AL were included in the analysis, as detailed in Fig. 1. The total rate of loss to follow-up in this study was 8.33%.

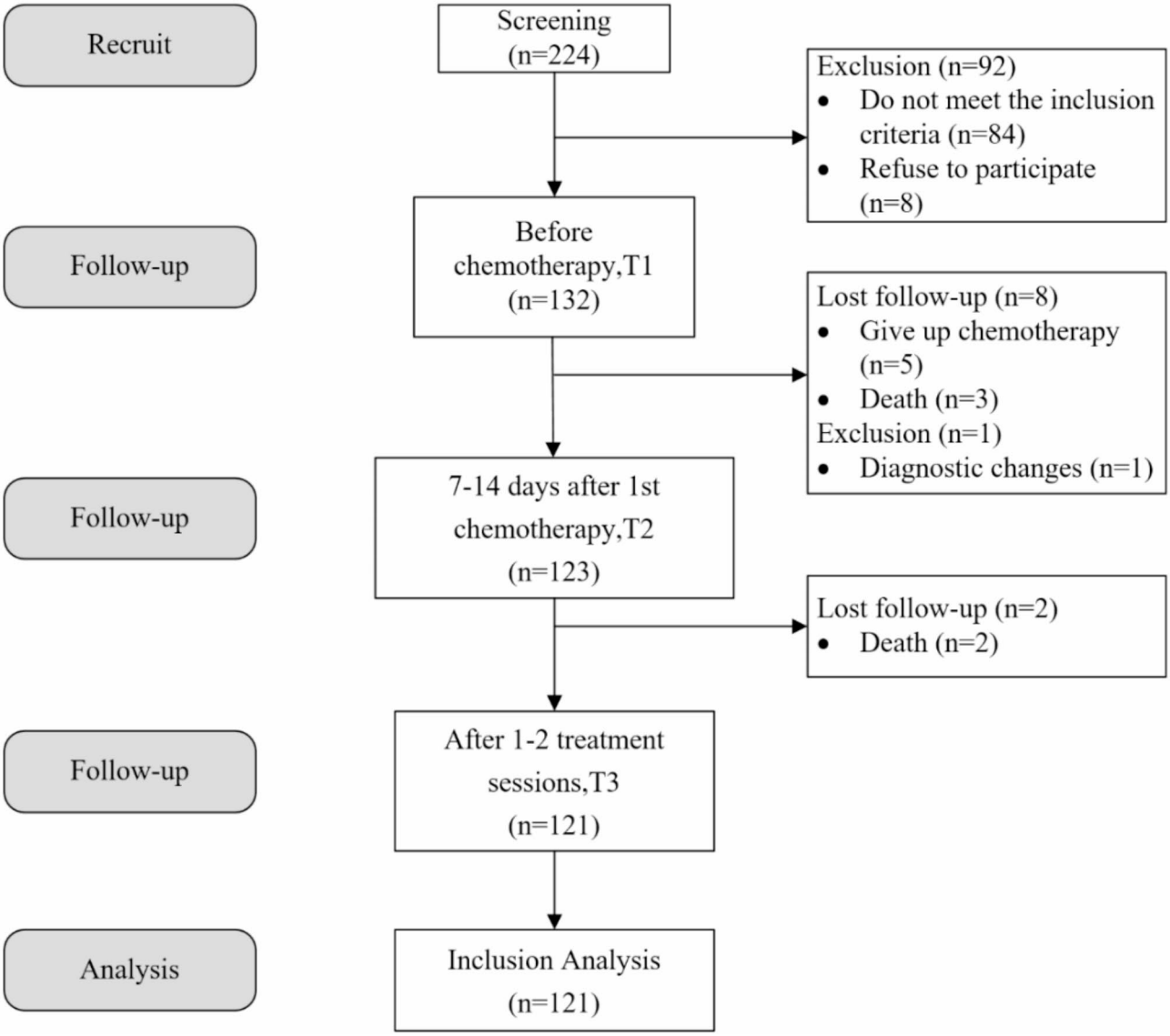

Fig. 1. Flow chart for inclusion of study subjects.

During the in-depth profiling of loss to follow-up, the occurrence of specific adverse events was observed in the lost to follow-up group, with 5 patients voluntarily abandoning the chemotherapy intervention, 5 patients having a fatal outcome, and 1 patient having a change in initial diagnosis to multiple myeloma. Comparative analysis of the inclusion group and the lost-to-follow-up group showed that the age of the lost-to-follow-up group was significantly higher than that of the inclusion group ($P<0.001$), and the proportion of males in this group was also higher than that of the inclusion group ($P<0.001$). The mean skinfold thickness and flexibility were lower in the lost-follow-up group than in the inclusion group ($P=0.006$, $P=0.040$). In addition, the total ALPRO score and its physical and psychological dimensions were lower in the lost-to-follow-up group than in the inclusion group ($P<0.001$).

Characteristics of the sample

The basic characteristics of the 121 patients included in this study were analyzed, the details are presented in Table 1.

Changes in physical fitness of patients with acute leukemia during chemotherapy

There were statistically significant differences in BMI, mean skinfold thickness, waist-to-hip ratio, spirometry, 6MWT, and flexibility in patients with AL during chemotherapy among the three measurement time points ($P<0.001$). The overall trends in BMI, mean skinfold thickness, spirometry, and flexibility were first decreased and then increased. The overall trend in the waist-to-hip ratio was initially decreased and then increased. The mean grip strength of both hands remained stable during chemotherapy and the 6MWT score before chemotherapy was higher than that during complete remission. The details are presented in Table 2 and Table 3. Variable line graphs of the data are presented as supplementary figures in Supplementary file 6.

Changes in PROs of patients with acute leukemia during chemotherapy

The overall trend for the total ALPRO, physiological dimension, and psychological dimension scores was initially decreased and then increased, whereas that for the social and therapeutic dimensions consistently increased. The details are presented in Table 4 and Table 5. Variable line graphs of the data are presented as supplementary figures in Supplementary file 7.

Multiple linear regression analysis of the correlation between physical fitness status and PROs in patients with acute leukemia during chemotherapy

A multifactorial analysis of the total ALPRO score in patients with AL showed correlations between physical fitness status and PROs during chemotherapy sessions. BMI, mean skinfold thickness, spirometry, and flexibility were influential factors for ALPRO. Details are presented in Table 6.

Discussion

This study focuses on the dynamics of physical fitness, patient-reported outcomes, and the correlations between these changes in the course of chemotherapy in a population of adult patients newly diagnosed with acute leukemia. The results of this study revealed that the overall trend in BMI, waist-to-hip ratio, mean skinfold thickness, spirometry, and flexibility during chemotherapy in patients with AL was decreased and then increased, and the 6MWT at T3 decreased compared with T1. Mean grip strength remained stable during chemotherapy, and no significant changes in muscle fitness were observed. The overall trend in the total ALPRO score initially decreased but then increased afterward.

Analysis of the loss of follow-up showed that the mean age and proportion of males in the loss of follow-up group was significantly higher than that in the inclusion group. The potential reason for this may be that older male AL patients tend to trivialize the significance of chemotherapy due to their pessimistic prognosis. Meanwhile, in the Chinese cultural context, men have a heavier financial burden and are more inclined to forgo chemotherapy and follow-up in view of the cost of long-term cancer treatment[30]. In terms of physiological indicators, the skinfold thickness, flexibility, total ALPRO score and its dimensions were significantly lower in the loss group than in the inclusion group, which implies that poorer basic physiological conditions, lower fat reserves, poor overall status and weaker disease coping ability might have weakened the tolerance level of chemotherapy and ultimately led to the loss of follow-up.

During chemotherapy, AL patients are prone to a variety of treatment-related symptoms. A previous study[31]showed that most patients with AL experienced nausea and vomiting during chemotherapy. Our study showed that body composition (including BMI, mean skinfold thickness, and waist-to-hip ratio) was reduced in AL patients at T2 compared with T1. This may be related to the nausea and vomiting caused by chemotherapy drugs, which reduce appetite and dietary intake, affect nutritional status, and cause decreases in BMI, mean skinfold thickness, and waist-to-hip ratio[32,33]. Two weeks after stopping chemotherapy, the patient's appetite was gradually recovered, and other symptoms reduced, which could be why the trend of the three indicators (BMI, mean skinfold thickness, and waist-to-hip ratio) in patients showed an initial decrease and then increase ($T2<T3<T1$).

Chemotherapy can significantly impair cardiopulmonary function. During the myelosuppressive phase, lung volumes decrease more dramatically. Even in complete remission, lung volumes remain lower than pre-chemotherapy levels, with a trend of $T2<T3<T1$. For the 6MWT, only T1 and T3 were measured in view of the risk of bleeding associated with thrombocytopenia during myelosuppression, and the results showed that the 6MWT index was lower at T3 than at T1. This finding is consistent with the results of a previous study[34]. This may be related to the multiple reasons for prolonged bed rest and the adverse effects of various chemotherapeutic drugs. Patients with AL experience numerous symptoms during chemotherapy, including fatigue, bleeding, and anemia. Fatigue is one of the most common and distressing symptoms experienced by patients undergoing

Variable	Inclusion group($n=121$) mean ± SD /n (%)	Lost-to-follow-up group($n=11$) mean ± SD /n (%)	t/χ^2	P
Age				
mean ± SD	44.45 ± 13.01	61.45 ± 13.51	−4.139	< 0.001
Gender			15.260	< 0.001
Male	63(52.1)	10(90.9)		
Female	58(47.9)	1(9.1)		
Marital status			1.790	0.592
Unmarried	16(13.2)	0(0.0)		
Married	100(82.6)	11(100.0)		
Divorce	2(1.7)	0(0.0)		
Bereaved spouse	3(2.5)	0(0.0)		
Level of education			4.354	0.102
Less than primary education	28(23.2)	5(45.5)		
Junior high school /High school/technical school	66(54.5)	6(54.5)		
University or above	27(22.3)	0(0.0)		
Employment status			1.877	0.198
Not at work	41(33.9)	6(54.5)		
At work	80(66.1)	5(45.5)		
Medical payment method			4.299	0.207
Resident Medical Insurance	82(67.8)	9(81.8)		
Employee Medical Insurance	34(28.1)	1(9.1)		
Commercial Insurance + Resident Medical Insurance	2(1.7)	1(9.1)		
No medical insurance	3(2.4)	0(0.0)		
Per capita income class (yuan)			3.367	0.282
< 1000	12(9.9)	3(27.3)		
1000–3000	73(60.3)	7(63.6)		
3001–6000	26(21.5)	1(9.1)		
> 6000	10(8.3)	0(0.0)		
Disease classification			2.346	0.282
AML (not APL)	72(59.5)	9(81.8)		
ALL	28(23.1)	2(18.2)		
AML (APL)	21(17.4)	0(0.0)		
Number of underlying diseases or comorbidities				
Median(25% Digits,75% Digits)	1(0,2)	/	/	/
Chemotherapy regimens			8.300	0.124
IA	56(46.3)	9(81.8)		
DA	6(5.0)	2(18.2)		
TKI + VD(I)CP	7(5.8)	0(0.0)		
VD(I)CLP	21(17.4)	0(0.0)		
AZA Vinecla	5(4.1)	0(0.0)		
ATRA + ATO	21(17.3)	0(0.0)		
AZA/D + GHA	5(4.1)	0(0.0)		
Duration of chemotherapy (days)				
Mean ± SD	14.81 ± 10.36	/	/	/
Prognostic assessment			/	/
No relief (NR)	25(20.7)	/		
Complete relief (CR)	92(76.0)	/		
Partial relief (PR)	4(3.3)	/		
BMI	23.14 ± 3.17	22.24 ± 2.88	0.907	0.366
Waist-hip ratio	0.90 ± 0.07	0.89 ± 0.06	0.191	0.849
Mean skinfold thickness (cm)	0.83 ± 0.26	0.60 ± 0.27	0.278	0.006
Spirometry (mL)	2453.07 ± 859.14	2102.90 ± 801.11	1.244	0.216
6MWT (m)	259.71 ± 10.75	268.50 ± 160.26	−0.220	0.827
Mean grip strength (kg)	24.98 ± 0.88	26.17 ± 12.91	−0.359	0.720
Flexibility	−12.12 ± 1.05	−20.00 ± 12.15	2.069	0.040
The total score of ALPRO	162.82 ± 1.05	96.82 ± 13.55	17.887	< 0.001
Continued				

Variable	Inclusion group($n=121$) mean ± SD /n (%)	Lost-to-follow-up group($n=11$) mean ± SD /n (%)	t/χ^2	P
physiological	63.84 ± 0.53	29.64 ± 3.36	19.059	< 0.001
Psychological	55.31 ± 0.59	18.73 ± 5.88	17.907	< 0.001
Social	15.59 ± 0.19	17.36 ± 3.91	−2.425	0.017
Therapeutic	28.07 ± 0.36	31.09 ± 6.52	−2.251	0.026

Table 1. Comparison of basic information between the inclusion group and the lost-to-follow-up group. Note: SD: standard deviation; AML (non-APL): acute myeloid leukemia other than acute promyelocytic leukemia, including acute myeloid leukemia minimally differentiated (M0), acute granulocytic leukemia undifferentiated (M1), acute granulocytic leukemia partially differentiated (M2), acute granulocytic leukemia (M4), acute monocytic leukemia (M5), acute erythroleukemia (M6) and acute megakaryocytic leukemia (M7). ALL: Acute lymphoblastic leukemia. APL: Acute promyelocytic leukemia. IA: desmethoxy erythromycin + cytarabine. DA: erythromycin + cytarabine. TKI + VD(I)CP: Tyrosine kinase inhibitor + vincristine/vincristine + erythromycin/demethoxylated erythromycin + cyclophosphamide + prednisone. VD(I)CLP: vincristine/vincristine + erythromycin/demethoxyzolomycin + cyclophosphamide + levomepromazine + prednisone. AZA + Vinecla:5-azacytidine + vinecla (B-cell lymphoma factor-2 inhibitor). ATRA + ATO: all-trans retinoic acid + arsenic trioxide. AZA/D + GHA:5-azacytidine/decitabine + granulocyte colony factor + hypertriglyceride + arsenic.

Variable	T1	T2	T3	F	P	Post hoc test
BMI	23.14 ± 3.17	22.26 ± 3.03	22.68 ± 3.05	38.477	< 0.001	T2 < T3 < T1*
Waist-hip ratio	0.90 ± 0.07	0.88 ± 0.07	0.90 ± 0.07	12.138	< 0.001	T2 < T3*,T2 < T1*, T1 = T3
Mean skinfold thickness (cm)	0.83 ± 0.26	0.72 ± 0.26	0.77 ± 0.26	44.506	< 0.001	T2 < T3 < T1*
Spirometry (mL)	2453.07 ± 859.14	1998.18 ± 831.12	2294.58 ± 783.83	70.948	< 0.001	T2 < T3 < T1*
6MWT (m)	259.71 ± 10.75	/	239.67 ± 9.36	19.105	< 0.001	T3 < T1*
Mean grip strength (kg)	24.98 ± 0.88	25.76 ± 3.28	24.37 ± 0.85	0.137	0.718	T1 = T2 = T3
Flexibility	−12.12 ± 1.05	−15.87 ± 1.18	−13.50 ± 1.09	70.965	< 0.001	T2 < T3 < T1*

Table 2. Changes in the physical fitness situation of AL patients during chemotherapy. Note: T1: before chemotherapy; T2:7–14 days after the 1st chemotherapy (myelosuppression stage); T3:1–2 courses of treatment (complete remission stage); Flexibility: distance between the middle fingers of both hands for the upper limb grip back test; * $P < 0.05$, after LSD correction; comparisons were made using one-way repeated measures ANOVA with post hoc tests using the LSD method.

chemotherapy[26]. Chemotherapy in patients with AL may lead to increased fatigue[28]. Therefore, healthcare professionals recommend that patients stay in bed for a long duration and as a result, their capability to exercise is limited because of the weakness[35,36]. Another reason for the reduced cardiopulmonary fitness during chemotherapy may be related to anthracycline-induced cardiotoxicity (AIC). Anthracyclines (doxorubicin, daunorubicin, epirubicin, and idarubicin) are the main drugs used to treat patients with AL, and anthracyclines' most serious and prominent adverse effect is AIC[37,38].

In this study, flexibility showed a decrease from T1 to T2 and an increase from T2 to T3, but it was still lower than the T1 level. This may be due to the effects of chemotherapeutic agents on flexibility during chemotherapy. For example, a previous animal study reported that cisplatin administration may induce muscle atrophy[39]. This reduces the fitness levels in patients with head and neck cancer, especially the flexibility[40]. However, the underlying mechanisms underlying the increase in flexibility from myelosuppression to complete remission are currently unknown, and the number of studies on changes in flexibility during chemotherapy in AL patients is scarce. Previous studies[41,42] have shown that glucocorticoids used during chemotherapy in patients with AL lead to a reduction in muscle strength and flexibility. However, further research is needed on the mechanisms underlying changes in flexibility during chemotherapy in patients with AL.

The effects of chemotherapy on muscle strength in adults remain controversial. A previous study showed that muscle strength was decreased in adult patients after intensive chemotherapy[43]. The adult patients with AL in this study did not experience significant changes in muscle fitness (mean grip strength) during chemotherapy. This was consistent with the results of another previous study[44]. The main factors influencing muscle strength during chemotherapy are nutritional status, physical activity, and exercise self-efficacy[45]. Although the patients' BMI was decreased within one to two chemotherapy sessions, fat was the main source of energy intake during this short interval, and protein consumption was relatively low. This may explain why the effect of muscle strength was not significant in the present study.

The total ALPRO score in patients with AL showed a decrease followed by an increase, indicating that most patients tended to exhibit a good status when first diagnosed with AL and that chemotherapeutic agent use caused many adverse effects that led to a decrease in the total ALPRO score in patients during the myelosuppression

Variable	Time point	Mean difference	Standard error	*P*	Lower of 95%CI	Upper of 95%CI
BMI	T1 VS T2	0.878*	0.106	< 0.001	0.667	1.088
	T1 VS T3	0.460*	0.111	< 0.001	0.241	0.679
	T2 VS T3	−0.418*	0.080	< 0.001	−0.577	−0.258
Waist-hip ratio	T1 VS T2	0.013*	0.004	< 0.001	0.006	0.020
	T1 VS T3	< 0.001	0.003	0.961	−0.007	0.007
	T2 VS T3	−0.013*	0.002	< 0.001	−0.016	−0.009
Mean skinfold thickness (cm)	T1 VS T2	0.118*	0.016	< 0.001	0.087	0.149
	T1 VS T3	0.600*	0.012	< 0.001	0.036	0.085
	T2 VS T3	− 0.058*	0.009	< 0.001	−0.074	−0.041
Spirometry (mL)	T1 VS T2	454.882*	46.167	< 0.001	363.474	546.290
	T1 VS T3	158.488*	33.901	< 0.001	91.366	225.609
	T2 VS T3	−296.394*	35.043	< 0.001	−365.777	−227.011
6MWT (m)	T1 VS T3	20.041*	4.585	< 0.001	10.963	29.120
Mean grip strength (kg)	T1 VS T2	−0.785	3.260	0.810	−7.240	5.670
	T1 VS T3	0.611	0.416	0.145	−0.213	1.435
	T2 VS T3	1.396	3.266	0.670	−5.070	7.863
Flexibility	T1 VS T2	3.752*	0.398	< 0.001	2.964	4.541
	T1 VS T3	1.380*	0.272	< 0.001	0.842	1.918
	T2 VS T3	−2.372*	0.268	< 0.001	−2.903	−1.840

Table 3. Effect sizes for post hoc tests of physical fitness. Note: * $P < 0.05$, after LSD correction; 95% CI: 95% confidence intervals.

Dimension	T1	T2	T3	F	*P*	Post hoc test
The total score of ALPRO	162.82 ± 1.05	158.54 ± 1.49	189.96 ± 1.20	362.507	< 0.001	T2 < T1 < T3*
physiological	63.84 ± 0.53	55.74 ± 0.47	67.04 ± 0.46	178.770	< 0.001	T2 < T1 < T3*
Psychological	55.31 ± 0.59	52.51 ± 0.86	58.31 ± 0.69	43.601	< 0.001	T2 < T1 < T3*
Social	15.59 ± 0.19	19.31 ± 0.15	23.70 ± 0.16	808.796	< 0.001	T1 < T2 < T3*
Therapeutic	28.07 ± 0.36	30.98 ± 0.42	40.90 ± 0.34	517.218	< 0.001	T1 < T2 < T3*

Table 4. Comparison of ALPRO scores during chemotherapy in patients with acute leukemia. Note: * $P < 0.05$, after LSD correction; comparisons were made using one-way repeated-measures ANOVA with post hoc tests using the LSD method.

Variable	Time point	Mean difference	Standard error	*P*	Lower of 95%CI	Upper of 95%CI
The total score of ALPRO	T1 VS T2	4.281*	1.231	0.001	1.844	6.718
	T1 VS T3	−27.140*	1.322	< 0.001	−29.758	−24.523
	T2 VS T3	−31.421*	1.243	< 0.001	−33.882	−28.961
physiological	T1 VS T2	8.099*	0.630	< 0.001	6.851	9.347
	T1 VS T3	−3.198*	0.697	< 0.001	−4.579	−1.818
	T2 VS T3	−11.298*	0.504	< 0.001	−12.296	−10.299
Psychological	T1 VS T2	2.802*	0.626	< 0.001	1.563	4.041
	T1 VS T3	−3.000*	0.667	< 0.001	−4.321	−1.679
	T2 VS T3	−5.802*	0.567	< 0.001	−6.925	−4.679
Social	T1 VS T2	−3.719*	0.198	< 0.001	−4.111	−3.327
	T1 VS T3	−8.116*	0.251	< 0.001	−8.613	−7.619
	T2 VS T3	−4.397*	0.143	< 0.001	−4.679	−4.115
Therapeutic	T1 VS T2	−2.901*	0.391	< 0.001	−3.674	−2.127
	T1 VS T3	−12.826*	0.434	< 0.001	−13.686	−11.967
	T2 VS T3	−9.926*	0.429	< 0.001	−10.774	−9.077

Table 5. Effect sizes for post hoc tests of ALPRO. Note: * $P < 0.05$, after LSD correction; 95% CI: 95% confidence intervals.

Variables	B	SE	b	t	*P*	R^2	Adjusted R^2	F	*P*
Constant	111.651	6.535		17.086	< 0.001	0.320	0.318	49.385	< 0.001
Chemotherapy stage	14.042	0.984	0.585	14.270	< 0.001				
Spirometry(mL)	0.004	0.001	0.164	3.886	< 0.001				
BMI	1.508	0.308	0.238	4.893	< 0.001				
Flexibility	0.239	0.075	0.150	3.196	< 0.001				
Mean skinfold thickness(cm)	−11.358	3.669	−0.152	−3.095	0.002				

Table 6. Correlation between physical fitness status and patient-reported outcomes for AL patients during chemotherapy. Note: Data transformed into time-series data; Time variable: chemotherapy stage; Analysis of ALPRO and physical fitness correlations using multiple linear regression.

phase. Since 79.3% of patients achieved remission (complete remission or partial remission) after 1–2 courses of chemotherapy, the ALPRO scores were increased substantially during the complete remission phase, and patients reported better clinical outcomes than before chemotherapy, indicating that chemotherapy significantly improved the clinical outcomes in the patients. Overall, the myelosuppression phase is the period of greatest concern for healthcare professionals. Nursing staff should implement various early preventive measures to reduce the incidence of adverse clinical outcomes in patients with AL.

This study showed that BMI, mean skinfold thickness, spirometry, and flexibility were factors influencing ALPRO. Weight loss in patients with AL is common during chemotherapy[32,33], and those with low BMI become frailer during this process. The present study found that the higher the BMI, the less severe the patient's response to chemotherapy was and the more tolerant the patient was to chemotherapy, which was in line with the findings of earlier research[46,47]. Cardiorespiratory fitness and flexibility are thought to correlate with cognitive function in AL[48]. Patients with better cardiorespiratory fitness and flexibility have a lower probability of developing adverse reactions after chemotherapy[49]; therefore, they have higher ALPRO scores. The mean skinfold thickness reflects the body fat profile of the patient. Excessive body fat percentage reduces chemotherapy drug metabolism, resulting in suboptimal patient-reported clinical outcomes[50].

Improving the fitness level in patients with AL during chemotherapy by considering appropriate interventions for their specific physical condition is fundamental. We recommend that patients adopt a high-protein, high-vitamin, and moderate-fat diet to strengthen their immunity at T1. In addition, appropriate weight gain before chemotherapy can help provide better physical fitness. Moderate weight loss in adult patients with AL was shown to be associated with the highest remission rates; therefore, we advise that the patient's weight loss should be limited to 10 kg at T2[51]. Simultaneously, increasing a patient's appetite and nutritional intake is feasible by treating the nausea and vomiting symptoms. To prepare for the next course of chemotherapy, our recommendations for patients at T3 were the same as those before chemotherapy.

Exercise intervention can potentially enhance physical fitness[52]. Previous research has shown that exercise interventions can be safe and effective in improving patients' fitness levels with AL[53]. Aerobic exercise training before and after chemotherapy has been shown to prevent cardiac injury, which may help avoid an excessive reduction in cardiorespiratory fitness[54]. Exercising during the early remission period after chemotherapy has been demonstrated to aid in restoring body function[55]. Current guidelines for cancer survivors, including adult patients with AL, indicate that exercising for 150 min per week with moderate-intensity aerobic exercise and two resistance training sessions is necessary[56]. Medical professionals should assist patients in selecting the most effective type and frequency of exercise to aid in recovery because not all exercises provide the same benefits for early recovery[57].

Limitations

This study has some limitations. First, this study had a limited sample size from a single tertiary hospital, which may have affected the generalizability of the findings. Second, the follow-up period was short and only covered 1–2 chemotherapy sessions; therefore, changes during complete remission and recovery at home were not tracked. Future studies should extend the follow-up period and expand the study sites. Finally, due to manpower, material, and space constraints, omissions in measuring physical fitness indicators may be present. Therefore, future studies may consider measuring more health-related fitness indicators to ensure safety.

Conclusion

During chemotherapy, patients with AL experienced varying degrees of decline in different physical fitness indicators, except for mean grip strength, suggesting that healthcare providers should pay more attention to the physical condition of patients undergoing chemotherapy, especially during the period of myelosuppression. Based on the trajectory of ALPRO during chemotherapy, social and therapeutic aspects need to be focused on before chemotherapy and physical and psychological aspects during myelosuppression. Patient-reported outcomes are influenced by BMI, mean skinfold thickness, lung capacity, and flexibility, so it is necessary to monitor patient health during chemotherapy, especially during myelosuppression, and implement active interventions such as exercise interventions and nutritional support to improve health. Given the limitations of this study, such as a single sample source, short follow-up time, and lack of measurement of all fitness indicators, future studies need to explore the long-term effects of chemotherapy on fitness and quality of life in AL patients

to gain insight into post-treatment recovery management, and to investigate the underlying mechanisms of fitness decline to see if interventions can prevent or reverse the changes.

Data availability

The datasets used and/or analysed during the current study are available by emailing ronghu1246@fjmu.edu.cn from the corresponding author on reasonable request.

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Author contributions

WKX and ZJL contributed equally to this study. WKX and ZJL were responsible for collecting data and manuscript preparation. RH and YW contributed to the design of the study, critical revision of the manuscript, and supervised the research. CFW and JYC contributed to the critical revision of the manuscript. All the authors have reviewed and approved the manuscript.

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Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the guidelines of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants were informed of the voluntary nature of the study and their participation and provided informed consent. All collected data were kept confidential and anonymous. The study was approved by the Biological and Medical Research Ethics Committee of Fujian Medical University (IRB Ref No: 2017/00049) in September 2017.

Competing interests
The authors declare no competing interests.

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