Nutritional and prognostic value of bioelectrical phase angle as a potentially modifiable marker in acute myeloid leukemia

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Abstract. Phase angle (PhA), as measured by bioelectrical impedance analysis, is an important parameter in nutritional assessment and is highly predictive of clinical outcomes in various diseases; however, there is little research on its use in acute myeloid leukemia (AML). Therefore, the present study was conducted to determine the association between PhA and malnutrition and to clarify the prognostic significance of PhA for progression-free survival (PFS) and overall survival (OS) in adult patients with AML (excluding acute promyelocytic leukemia) who were undergoing chemotherapy. A total of 70 patients with newly diagnosed AML were enrolled. After chemotherapy, the nutritional risk for patients with a reduced baseline PhA increased significantly. Disease progression occurred in 28 patients, of which 23 died, with a median follow-up of 9.3 months. A reduced baseline PhA was associated with poor PFS (7.1 months vs. 11.6 months; P=0.001) and OS (8.2 months vs. 12.1 months; P=0.011). A multivariate analysis revealed that a reduced PhA was an independent risk factor for disease progression (hazard ratio, 3.13; 95% CI, 1.21-8.11; P=0.019). Overall, these results suggested that PhA is an effective and sensitive indicator that may provide important nutritional and prognostic information in patients with AML.

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Introduction

Acute myeloid leukemia (AML) is a group of aggressive heterogeneous malignancies. The backbone of therapy for AML is a combination of cytarabine- and anthracycline-based regimens with hematopoietic stem-cell transplantation (HSCT) for eligible candidates (1). Acute promyelocytic leukemia (APL) is a special disease entity of AML, known as type M3, which is characterized by a specific t(15;17) chromosome translocation that generates the promyelocytic leukemia/retinoic acid receptor-α fusion gene (2). Differentiation therapy with all-trans retinoic acid has been a very successful therapeutic strategy and has transformed APL into the most curable form of AML (3). However, the increased demand for nutrients and energy caused by tumor invasion, as well as chemotherapy-related gastrointestinal mucositis, may affect the nutritional status of patients (4). An insufficient nutrient supply can easily lead to malnutrition, which can result in decreased chemotherapy tolerance and an increased incidence of adverse complications (5,6). Thus, nutritional status is directly associated with treatment success.

It has been confirmed that under- and overweight patients are at an increased risk of complications, non-relapse mortality and shorter overall survival (OS) after chemotherapy and HSCT (7). However, as the most commonly used nutritional indicator in AML, body mass index (BMI) may not be feasible for the detection of early physical changes, thereby compromising timely and effective intervention (6). To increase the long-term survival rate of patients, more sensitive clinical nutritional parameters should be established, and clinical nutritional interventions should be implemented for patients with a combined nutritional risk or those with previous malnutrition.

Phase angle (PhA), which is determined by bioelectrical impedance analysis (BIA), indicates the amount and quality of soft tissue. When interpreting PhA in patient populations, a decrease in PhA is due to loss of soft tissue and could be seen as an indicator of nutritional status (8). Additionally, PhA has been used in clinical practice to detect cellular membrane function and fluid balance that may reveal cellular health and is highly predictive of impaired clinical outcomes and mortality in renal disease, human immunodeficiency virus infections, allogeneic HSCT and surgical patients (9-12). Previous studies have shown that PhA can be used to predict adverse clinical

outcomes, including survival time, financial cost of disease and incidence of post-operative complications (11-13).

To the best of our knowledge, few studies have evaluated the use of PhA in AML. It has been reported by univariable, but not multivariable analyses, that low baseline PhA is associated with increased incidence of 60-day mortality (13). Decreases in morbidity and mortality of patients warrant improving the understanding of the nutritional and prognostic value of using PhA in AML. Therefore, the present study aimed to prospectively evaluate PhA as a prognostic indicator of the nutritional status and mortality of patients with AML who were undergoing chemotherapy, excluding APL for which retinoic acid-based therapeutics have been developed as aforementioned.

Materials and methods

Study design and population. The present study was conducted in the Department of Hematology at the First Affiliated Hospital of Chongqing Medical University (Yuzhong, China) in accordance with the principles of the Declaration of Helsinki (approval no. 2020-589).

A total of 100 patients were enrolled from July 2020 to February 2021. Baseline clinical data, including age and sex, are presented in Table I. The inclusion criteria were as follows: i) Adult patients were aged 19 to 85 years with a diagnosis of AML confirmed by morphology, immunology, cytogenetics and molecular diagnosis system (14); and ii) indications for chemotherapy evaluated by a hematologist. The critical exclusion criteria were as follows: i) Patients diagnosed with APL (type M3); ii) patients with severe heart failure, liver and kidney dysfunctions or other concomitant severe diseases, with an absence of tolerability to chemotherapy after active treatment for the aforementioned contraindications; iii) pregnant patients; iv) patients who could not cooperate to complete the BIA testing; and v) chronic drug use that may affect the body fluid balance. A flowchart of the study design and patient selection criteria is presented in Fig. 1.

All patients with AML (excluding M3) were given the standard 3+7 induction chemotherapy comprising idarubicin (10 mg/m^{2}d) or daunorubicin (60 mg/m^{2}d) on days 1-3 plus cytarabine (Ara-c; 100-200 mg/m^{2}d) on days 1-7. Consolidation chemotherapy consisted of high-dose Ara-c-based regimens (1-3 g/m^2 every 12 h) for a 4-week cycle for 3~6 courses. According to disease remission, risk stratification, physical status and economic level, patients could choose whether to undergo HSCT after induction and consolidation chemotherapy.

Measurements. Anthropometric variables including height (cm) and weight (kg) were measured by doctors. Nutritional Risk Screening 2002 (NRS-2002) system was implemented to screen nutritional risk (15). Routine laboratory tests were performed in the Department of Laboratory at the First Affiliated Hospital of Chongqing Medical University. The data of tumor-specific variables with prognostic significance were collected at initial diagnosis of AML, including lactate dehydrogenase (LDH) level, white blood cell count, creatinine (Cre) and cytogenetic risk group (based on bone marrow biopsy) (16).

A direct segmental multi-frequency BIA device (InBody S10; InBody Co., Ltd.) was used to determine the values of body composition indicators and PhA at 50 kHz before the initiation of fluid treatment. The participants were instructed not to eat or drink and to avoid strenuous activity for 2 h before BIA testing. The results of the parameter tests were obtained using a standard montage of outer and inner electrodes on the right hand and foot while patients were laid down with parted legs. All measurements were undertaken at the time of initial diagnosis of AML and after completion of therapy. The body composition indicators, including skeletal muscle mass (SMM), soft lean mass (SLM), percentage of body fat, fat-free mass (FFM), body cell mass (BCM), intracellular water (ICW), extracellular water (ECW), total body water (TBW) and mineral and protein contents, were measured and recorded. The parameters of resistance and reactance were determined using an electric alternating current flow of 800 mA and frequencies of 5, 50 and 250 kHz. PhA was calculated using the following equation: PhA (˚)=(arc tangent reactance/resistance) x (180˚/π). Reduced PhA was defined as PhA <5˚ for male or PhA <4.6˚ female patients (17). According to this established standard, the study population was divided into normal PhA and reduced PhA groups.

Statistical analysis. The Kolmogorov-Smirnov test was used to analyze data normality. Normally distributed continuous variables were presented as the mean ± standard deviation, while non-normally distributed variables were presented as the median with upper and lower quartiles. A two-way mixed ANOVA followed by Bonferroni's post hoc test was used for the comparison of normally distributed body composition variables between and within groups. For non-normally distributed body composition variables, a Bonferroni correction after either Wilcoxon signed-rank test or Mann-Whitney U test was used. An unpaired Student's t-test or Mann-Whitney U test was used to analyze the rest of the comparisons. Categorical variables were presented as frequency (proportions) and compared using Chi-square test or Fisher's exact test as appropriate. The Kaplan-Meier method was used to estimate the survival probabilities and the log-rank test was utilized to compare the differences in progression-free survival (PFS) and OS between the patient subgroups. A multivariate analysis was performed by fitting the Cox proportional hazards model to assess the effects of PhA and other characteristics on PFS and OS. PFS was defined as the time from diagnosis to relapse, progression or death from any cause. OS was defined as the time from diagnosis to the date of the last follow-up examination or the date of death from any cause. All statistical analyses were performed using SPSS 21.0 software (IBM Corp.). P<0.05 was considered to indicate a statistically significant difference.

Results

Patients and basic characteristics. According to the established process of patient selection, 70 patients consented, underwent baseline laboratory and BIA measurements and completed the follow-up. The median age of the patients at diagnosis was 52 years and 50% were males. Of the enrolled patients, 55.7% had intermediate to adverse cytogenetic risk. Due to their financial status and treatment tolerance, only

Table I. Comparison of baseline clinical and body composition indicators according to the baseline PhA.

A, Clinical data

Variable	Total (n=70)	Normal PhA group (n=51)	Reduced PhA group (n=19)	P-value
Age, years	51.9±14.0	49.7±12.8	58.0±15.6	0.025
Sex, male	35 (50.0%)	27 (52.9%)	8 (42.1%)	0.420
BMI, kg/m^2	22.7±2.8	23.2±2.9	21.4±2.1	0.009
SBP, mmHg	121.0±12.8	117.1±11.4	113.3±9.0	0.647
DBP, mmHg	70.7±9.8	70.5±7.3	66.8±10.0	0.466
NRS-2002 score				0.034
≥3	50 (71.4)	40 (78.4)	10 (52.6)	
<3	20 (28.6)	11 (21.6)	9 (47.4)	

B, Laboratory parameters

Variable	Total (n=70)	Normal PhA group (n=51)	Reduced PhA group (n=19)	P-value
WBC, 10^9/l	10.3 (2.7-37.8)	13.5 (2.5-44.0)	14.0 (8.4-286.0)	0.219
Hb, g/l	74.2±24.3	83.5±26.6	53.5±24.4	0.283
Ure, mmol/l	315 (229-407)	299 (233-402)	326 (245-341)	0.858
Cre, μmol/l	66.7±16.8	63.1±14.4	75.7±31.9	0.085
Alb, g/l	41 (38-44)	41 (38-43)	40 (37-56)	0.196
LDH, U/l	574 (261-1,398)	404 (182-1,489)	736 (478-1,646)	0.093
hs-CRP, mg/l	10.0 (2.3-20.0)	1.5 (1.0-7.7)	15.1 (13.5-20.0)	0.197

C, Body composition indicators

Variable	Total (n=70)	Normal PhA group (n=51)	Reduced PhA group (n=19)	P-value
TBW, kg	33.6±5.7	34.0±0.9	32.3±4.4	0.280
ECW, kg	13.0±2.2	13.0±2.3	13.0±1.9	0.992
ICW, kg	19.8 (17.8~22.4)	21.4 (18.1~23.0)	19.6 (16.8~21.8)	0.117
Protein, kg	8.7 (7.7~9.6)	9.2 (7.8~10.0)	8.5 (7.3~9.4)	0.125
Fat, kg	13.1 (9.6~16.4)	14 (9.7~16.6)	11.5 (7.1~15.6)	0.088
SMM, kg	24.3 (21.3~27.1)	25.9 (21.6~27.8)	23.5 (20.3~26.3)	0.121
SLM, kg	43.0±7.3	43.7±7.9	41.2±5.5	0.220
PBF, kg	22.5±7.1	23.2±7.0	20.6±7.2	0.169
FFM, kg	45.6±7.7	46.3±8.3	43.9±5.8	0.246
BCM, kg	29.5±5.1	30.2±5.5	27.8±3.6	0.122
PhA, °	5.4±0.9	5.9±0.7	4.2±0.6	0.001

D, Molecular tests

Variable	Total (n=70)	Normal PhA group (n=51)	Reduced PhA group (n=19)	P-value
FLT3	10 (14.3)	7 (13.7)	3 (15.8)	0.548
WT1	15 (21.4)	12 (23.5)	3 (15.8)	0.365

E, Cytogenetic risk

Variable	Total (n=70)	Normal PhA group (n=51)	Reduced PhA group (n=19)	P-value
Risk group				0.413
Favorable	31 (44.3)	25 (49)	6 (31.6)	
Intermediate	14 (20)	9 (17.6)	5 (26.3)	
Adverse	25 (35.7)	17 (33.3)	8 (42.1)	

Table I. Continued.

F, HSCT				
Variable	Total (n=70)	Normal PhA group (n=51)	Reduced PhA group (n=19)	P-value
Transplant type				0.308
Auto-HSCT	6 (8.6)	5 (9.8)	1 (5.3)	
Allo-HSCT	17 (24.3)	10 (19.6)	7 (36.8)	
Non-HSCT	47 (67.1)	36 (70.6)	11 (57.9)	

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NRS-2002, Nutritional Risk Screening 2002; WBC, white blood cell; Hb, hemoglobin; Ure, urea nitrogen; Cre, creatinine; Alb, albumin; LDH, lactate dehydrogenase; hs-CRP, hypersensitive C-reactive protein; TBW, total body water; ECW, extracellular water; ICW, intra cellular water; SMM, skeletal muscle mass; SLM, soft lean mass; PBF, percentage of body fat; FFM, fat free mass; BCM, body cell mass; PhA, phase angle; FLT3, FMS-like tyrosine kinase 3; WT1, Wilms' tumor antigen 1; HSCT, hematopoietic stem cell transplantation.

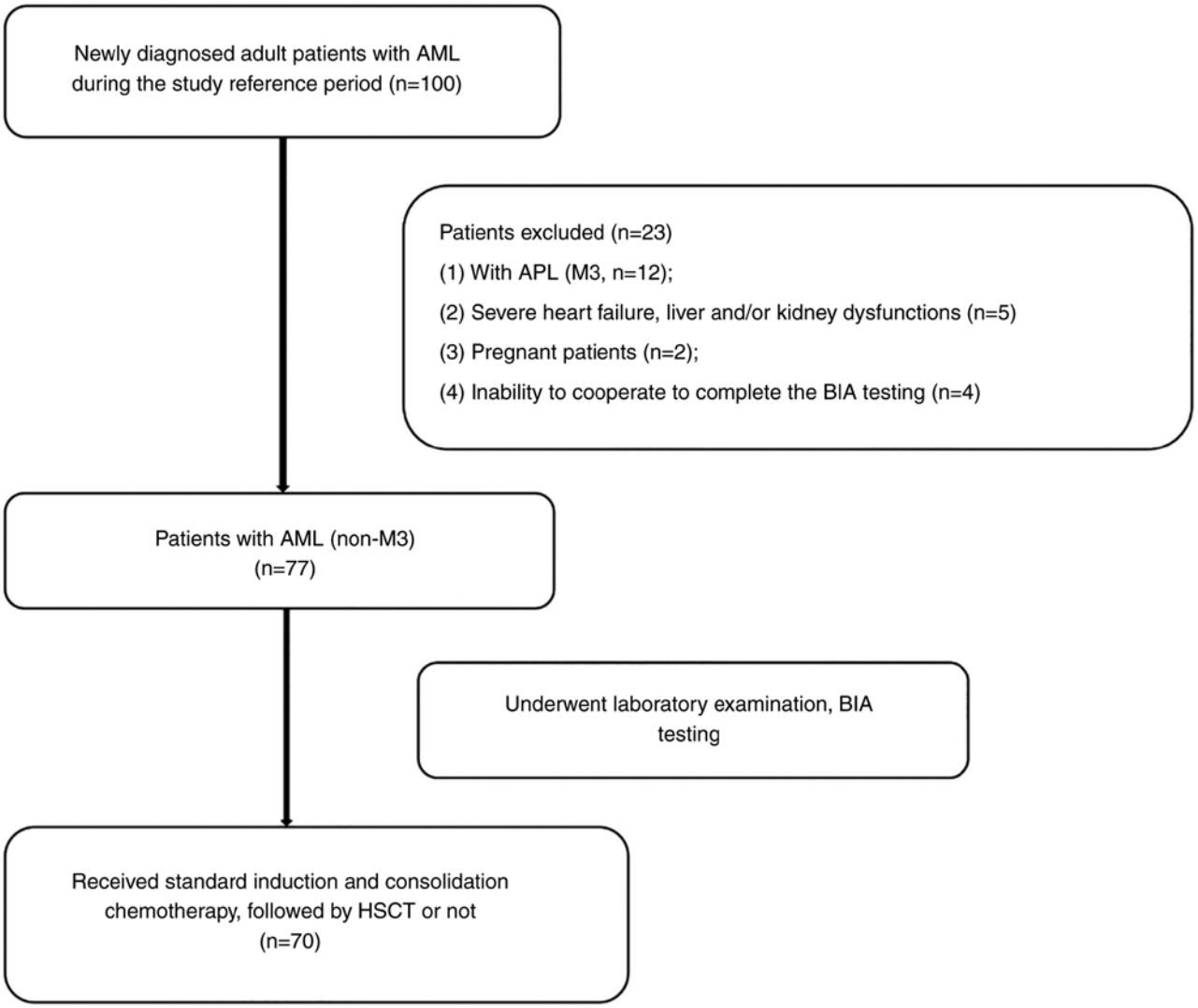

Figure 1. Flow chart of the study design and patient selection criteria. AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BIA, bioelectrical impedance analysis; HSCT, hematopoietic stem-cell transplantation.

32.9% of the patients underwent HSCT. At initial diagnosis of AML, 28.6% were at nutritional risk according to the NRS-2002 scoring system and 27.1% had decreased PhA values. The population and basic characteristics of the normal PhA and reduced PhA groups are summarized in Table I. There were no significant statistical differences between the

Table II. Comparison of body composition indicators at the end of therapy according to the baseline PhA.

Variable	Total (n=70)	Normal PhA group (n=51)	Reduced PhA group (n=19)	P-value
TBW, kg	30.7 (27.9-35.0)	34.8 (28.9-39.7)	27.9 (25.4-34.6)[a]	0.002
ECW, kg	12.1 (10.8-14.0)	13.6 (11.2-15.1)	11.2 (10.1-12.8)[a]	0.005
ICW, kg	19.4±3.8	21.1±3.8	17.5±2.6[a]	0.003
Protein, kg	8.4±1.7	9.1±1.7	7.6±1.1[a]	0.003
Fat, kg	14.8±6.3	18.4±7.2	11.5±5.1[a]	0.008
SMM, kg	23.3±5.0	25.6±5.0	20.8±3.4[a]	0.003
SLM, kg	39.1 (35.7-44.9)	44.4 (37.0-51.0)	35.7 (32.5-41.7)[a]	0.002
PBF, kg	24.9±7.1	26.1±7.7	22.4±5.1	0.062
FFM, kg	41.7 (38.0-47.5)	47.1 (39.2-54.1)	38.0 (34.8-44.1)	0.002
BCM, kg	27.8±5.5	30.3±5.5	25.1±3.7[a]	0.007

[a]P<0.05 vs. baseline levels. TBW, total body water; ECW, extracellular water; ICW, intra cellular water; SMM, skeletal muscle mass; SLM, soft lean mass; PBF, percentage of body fat; FFM, fat free mass; BCM, body cell mass.

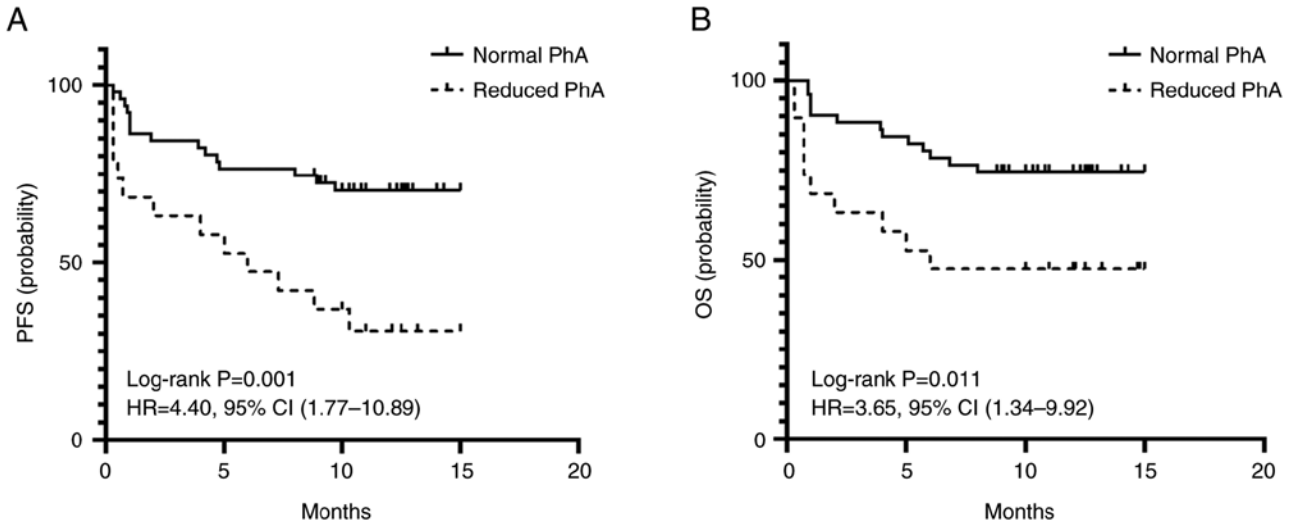

Figure 2. Kaplan-Meier curves for (A) PFS and (B) OS. PFS, progression-free survival; OS, overall survival; PhA, phase angle; HR, hazard ratio; CI, confidence interval.

two groups in laboratory data, body composition indicators and molecular testing results. Notably, the patients in the normal PhA group were younger and their basic nutritional risk was lower compared with the reduced PhA group due to higher BMI and NRS-2002 scores (Table I).

Body composition index after antitumor therapy. A decrease in body composition parameters from baseline was observed after chemotherapy or HSCT, although statistically significant differences existed only in the reduced PhA group. The post-treatment body composition parameters of the patients with AML with a reduced baseline PhA were significantly lower compared with patients with normal PhA, including TBW, ECW, ICW, protein, fat, SMM, SLM, FFM and BCM (Table II).

PFS and OS from initial diagnosis of AML according to baseline PhA. In total, 28 patients experienced progressive disease (PD), of which 23 deaths occurred at a median observation time of 9.3 months. Of these deaths, 13 were due to progressive AML, three deaths were related to treatment complications following HSCT and 7 patients died of severe infection or acute cerebral hemorrhage secondary to myelosuppression after chemotherapy. All the patients were subjected to survival outcome measurements based on an intention-to-treat analysis.

The 1-year PFS and OS rates of the reduced PhA group were 36.8 and 47.4%, respectively, while those of the normal PhA group were 76.5 and 76.5%, respectively. The PFS and OS rates of the reduced PhA group, estimated by Kaplan-Meier analysis, were shorter compared with those of the patients in the normal PhA group (median PFS: 7.1 months vs. 11.6 months, P=0.001; median OS: 8.2 months vs. 12.1 months, P=0.011) (Fig. 2).

Cox proportional hazards model for assessing the association of baseline PhA with PFS and OS. Univariate analysis suggested that both PFS (hazard ratio [HR], 3.14; 95%CI],

Table III. Cox proportional hazards model for assessing the association of baseline phase angle with PFS and OS.

Model	PFS [HR (95% CI)]	OS [HR (95% CI)]
Univariate	3.14 (1.49-6.63)[a]	2.76 (1.21-6.31)[a]
Multivariate[b]	3.13 (1.21-8.11)[a]	2.19 (0.76-6.30)

[a]P<0.05; [b]adjusted for the confounding factors age, BMI, Nutritional Risk Screening 2002 score, creatinine and lactate dehydrogenase. PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

1.49-6.63; P=0.003) and OS (HR, 2.76; 95% CI, 1.21-6.31, P=0.016) were significantly worse in patients with reduced baseline PhA. Multivariate adjustments for age, BMI, NRS-2002 score, LDH and Cre levels confirmed the prognostic value of PhA in adult patients with AML. A reduced PhA was associated with decreased PFS (HR, 3.13; 95% CI, 1.21-8.11; P=0.019), but it was not a significant predictor of OS (HR, 2.19; 95% CI, 0.76-6.30; P=0.147) (Table III).

Discussion

In the present study, the potential association of PhA, obtained using BIA, with malnutrition and prognosis was explored in adults with newly diagnosed AML who were undergoing chemotherapy. The results demonstrated that chemotherapy caused a reduction in nutrients, such as water, protein, fat and minerals, and that these changes were more pronounced in patients with a reduced baseline PhA. The results also showed that a reduction in the baseline PhA was significantly associated with an increased risk of PD and death in AML. When adjusted for age, BMI, NRS-2002 score, Cre and LDH, the present study revealed a reduced baseline PhA to be a significant predictor of PFS.

Malnutrition is a challenging clinical syndrome in onco-hematology because of its adverse effects on the patients' quality of life and survival (18). Furthermore, malnutrition has been confirmed as a risk factor for infectious complications, treatment intolerance, prolonged hospitalization and impaired quality of life (19-23). A previous study found malnutrition to be highly prevalent, occurring in 40-80% of patients with cancer (24). In the current study, 28.6% of patients were at nutritional risk according to the NRS-2002 score estimated at the time of diagnosis, possibly due to the increased metabolic demands caused by high tumor load and nutrient consumption (25). Subsequent chemotherapy-related mucositis and gastrointestinal side effects, including nausea and vomiting, may have led to reduced food intake and nutrient absorption dysfunction, thus further worsening the nutritional status of patients (26).

At the time of the initial AML diagnosis, ~30% of the study population had reduced PhA. PhA has been suggested as an indicator of cellular health, in which higher values reflect higher cellularity, cell membrane integrity and improved cell function; therefore, the reduction in baseline PhA can be attributed to the combination of cell death and the loss of cellular integrity, as well as changes in membrane selective permeability and fluid balance (27).

Our previous study revealed that the incidence of sarcopenia is associated with chemotherapy of patients with AML, as reflected by body composition changes (28). The present study also observed that the body composition indicators, including water, muscle mass, protein and BCM, were significantly decreased after antitumor therapy in patients with baseline reduced PhA. It is likely that these patients suffered from malnutrition due to an early shift in terms of an increased extracellular-to-intracellular fluid ratio and decreased BCM, both of which lowered PhA (29). In addition, there was no significant difference between the two groups in baseline hypersensitive C-reactive protein, thereby excluding the effect of inflammation-associated excessive hydration on PhA (30). Thus, low PhA could specifically reflect impaired nutritional status. The negative association between PhA and malnutrition shows its predictive value for disease prognosis.

Previous research has confirmed that standardized PhA (sPhA) is an independent prognostic factor for the 2-year OS rate in patients with AML that undergo HSCT (11). In another study, the change in sPhA has been confirmed as a significant predictor of OS, as it increases the 60-day mortality for patients in the lower 25th percentile of baseline sPhA values; however, this association is statistically significant only in univariable analysis (13). A limitation of the aforementioned studies is the lack of validated cut-offs for PhA, due to previous studies only focusing on healthy German populations. Thus, PhA was standardized according to reference values for healthy German populations as follows: sPhA=observed PhA (˚)-PhA medium for sex, age and BMI (˚)/standard deviation of PhA for sex, age and BMI. In this way, the external validity of the results is thereby reduced (31).

In 2012, Kyle *et al* (17) evaluated the accuracy of PhA in identifying the presence of nutritional risk in a large cohort of patients at the time of hospital admission compared with age-, sex- and height-matched healthy controls. It was revealed that the cut-offs for PhA at 5.0˚ in men and 4.6˚ in women are prognostically relevant and give the highest sensitivity, specificity and area under the receiver operating characteristic curve. This established standard was used as the basis for classifying the patient population in the present study. The present results add to the growing body of evidence supporting the prognostic significance of PhA in patients with AML. To the best of our knowledge, the present study is the first to identify the association between baseline PhA and disease progression. Reduced baseline PhA is one of the few predictors of PFS, besides age and cytogenetic risk, in both univariate and multivariate analyses (32). These exploratory analyses suggest that the effect of the baseline PhA on survival may be due to a combination of the patients' disease response and nutritional status.

Tumor-specific factors, such as cytogenetics and gene mutations and other patient-specific factors, including age and Eastern Cooperative Oncology Group (ECOG) performance status, have been used to create a prognostic scoring system for OS (33,34). Thus, the aforementioned prognostic factors were examined in the present study. In the study population, ~65% had a favorable or intermediate cytogenic risk. No significant differences in molecular testing and cytogenetic risk data have been observed between the two groups. Previous studies have not confirmed the potential association between PhA and

genetic markers for leukemia (11,13). These findings considerably reduce the influence of disease severity on clinical outcomes, improving the interpretation of the independent effect of PhA on the studied outcomes.

The current study has certain limitations. Firstly, a follow-up study with an increased sample size is needed to clarify the impact of PhA on long-term complications and mortality. Secondly, since there were no data to assess the burden of leukemia in the bone marrow, it was not possible to determine whether PhA affects the complete remission status of patients, leading to a worse prognosis.

In summary, the findings of the present study demonstrated that PhA is a reproducible and high-precision indicator that may provide important nutritional and prognostic information in patients with newly diagnosed AML (excluding type M3). An increased risk of PD and death exists in patients with a reduced baseline PhA. Previous studies have suggested that 12 weeks of progressive resistance training may improve PhA, and nutritional support can minimize sarcopenia and increase muscle function in patients with low PhA (35,36). Future prospective studies are necessary to elucidate the efficacy of PhA while further exploring the influence of strength training and personal nutritional support on PhA and clinical outcomes.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TJ designed the study, recruited patients, collected and analyzed data and drafted the manuscript. YW contributed to data collection and critically reviewed the data analysis and manuscript preparation. NZ and XT contributed to the data analysis and interpretation as well as the critical writing and revision of the manuscript. All authors have read and approved the final manuscript. TJ and XT confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The protocols involving patients were approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Yuzhong, China; approval no. 2020-589). The patients enrolled in this research provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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