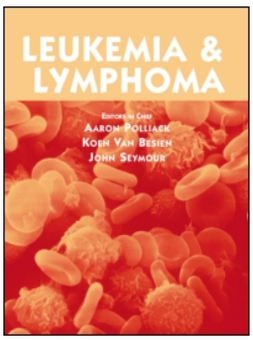

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ORIGINAL ARTICLE

Prognostic value of hypoalbuminemia at diagnosis in *de novo* non-M3 acute myeloid leukemia

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ABSTRACT

The association between serum albumin level and clinical outcomes has been reported for several hematological malignancies. Our study aimed to identify the relationship between serum albumin level at the time of diagnosis and subsequent clinical outcomes in patients with newly diagnosed acute myeloid leukemias (AMLs) other than acute promyelocytic leukemias (APLs). A total of 243 patients with *de novo* non-M3 AML were enrolled in this study. Variables including gender, age, serum albumin, white blood cell (WBC) count, hemoglobin (Hb), platelet (PLT) count, blasts at peripheral blood (PB) and bone marrow (BM), immunophenotype and cytogenetics at diagnosis, BM response after one course of chemotherapy and hematopoietic stem cell transplantation (HSCT) treatment were studied. We found that normal albumin level (serum albumin >3.5 g/dL) was significantly associated with superior overall survival (HR = 0.375, $p < .001$) and leukemia-free survival (HR = 0.411, $p < .001$). These results demonstrate that albumin could serve as a simple, cheap, and objective prognostication factor in refinement of AML regimens.

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Acute myeloid leukemia; serum albumin; overall survival; leukemia-free survival

Introduction

Acute myeloid leukemia (AML) is a rare but highly lethal malignancy, with uncontrollable growth of myeloid blasts and blockage of cell maturation [1,2]. Despite significant advancements in the treatment and supportive care for AML patients, the long-term survivals remain poor with estimated 10,590 deaths in the United States in 2017 [3]. Currently, the selection of appropriate regimen for AML mainly depends on the age of patient and risk stratification, including cytogenetic and molecular features [4]. It is important to identify additional prognostic markers to optimize risk stratification, by which clinicians could better estimate prognosis and clinical outcomes of AML patients.

Hypoalbuminemia (serum albumin <3.5 g/dL) is a frequently observed finding [5], and has shown to have strong predictive value on mortality and morbidity of hematological malignancies, such as multiple myeloma, pediatric acute lymphoblastic leukemia and diffuse large B-cell lymphoma [6–8]. Besides, the association of severe hypoalbuminemia (serum albumin <3.0 g/dL) with myeloid diseases has garnered attention in recent years. Komrokji et al. reported that severe hypoalbuminemia is an independent predictor of overall survival (OS) in patients with myelodysplastic syndromes (MDSs) [9]. In addition, Sorror et al. developed a novel AML composite model, which includes albumin level, to better predict survival outcomes at 1 year [10]. Filliatre-Clement et al. proposed that AML patients with serum albumin <3.0 g/dL showed a reverse trend to relapse and death when compared with patients with body mass index <25 kg/m^2. It appears that serum albumin provided a better overall assessment of the basal nutritional status in AML patients [11].

Our study aimed to evaluate the relationship between serum albumin level at the time of AML diagnosis and clinical outcomes in patients with newly diagnosed AML.

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Supplemental data for this article can be accessed here.

Methods

We conducted a retrospective chart review of patients diagnosed with *de novo* non-M3 AML treated at our institution between January 2010 and December 2016 using electronic medical records. All data concerning clinical characteristics and subsequent therapeutic regimens were extracted and analyzed in accordance with the Declaration of Helsinki. The study was approved by the institutional review board of the First Affiliated Hospital of Wenzhou Medical University. Also, consent was waived by the institutional review board due to retrospective nature of this study, yet confidentialities of patients were protected.

Patients

Inclusion criteria used for selection of patients were: (1) age 14 years or older, (2) newly diagnosed non-M3 AML at the First Affiliated Hospital of Wenzhou Medical University from January 2010 to December 2016, and (3) initial induction chemotherapy given during this period.

Exclusion criteria used were: (1) secondary AML in patients with preceding hematological disorders and (2) patients receiving palliative chemotherapy or supportive care only.

De novo AML was diagnosed and classified based on the morphological, immunophenotypic, cytogenetic, and molecular features of myeloid blasts according to FAB [12] and WHO 2016 criteria [13].

Figure 1 displays the therapies and outcomes of the patients. All patients received conventional '3 + 7' induction regimen after the initial diagnosis: idarubicin 8–10 mg/m^2 at day 1–3 and cytarabine 100 mg/m^2 at day 1–7. One hundred and thirty-one patients achieved complete remission (CR) after the first induction regimen. Of the 93 patients who did not achieve CR after the first induction regimen, 43 patients received a second course of induction therapy with '3 + 7' regimen, 35 patients received second-line induction regimens as depicted in Supplementary Table 1. For 190 patients who achieved CR after induction and re-induction chemotherapies, consolidation therapy with intermediate-dose cytarabine (2000 mg/m^2 every 12 h at day 1–3; total six doses) was administrated in 172 patients. Among all patients included in our study, 54 underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) as post remission therapy, while the maintenance therapy was applied in the remaining 64 patients. For patients with favorable risk group, intermediate-dose cytarabine based maintenance was used, while 14 patients underwent allo-HSCT after relapse. For patients with intermediate-risk group, many patients were administered repetitive cycles of intermediate-dose cytarabine, while HSCT was administered for 30 patients. The patients with adverse-risk AML received cytarabine only and 10 underwent alloHSCT. Patients who were unable to receive the transplant due to age, complications, and economic status, were treated with different maintenance therapies consisting of regular doses of different drugs. By 1 June 2018, 73 patients were found to be in remission (Figure 1).

Source of data

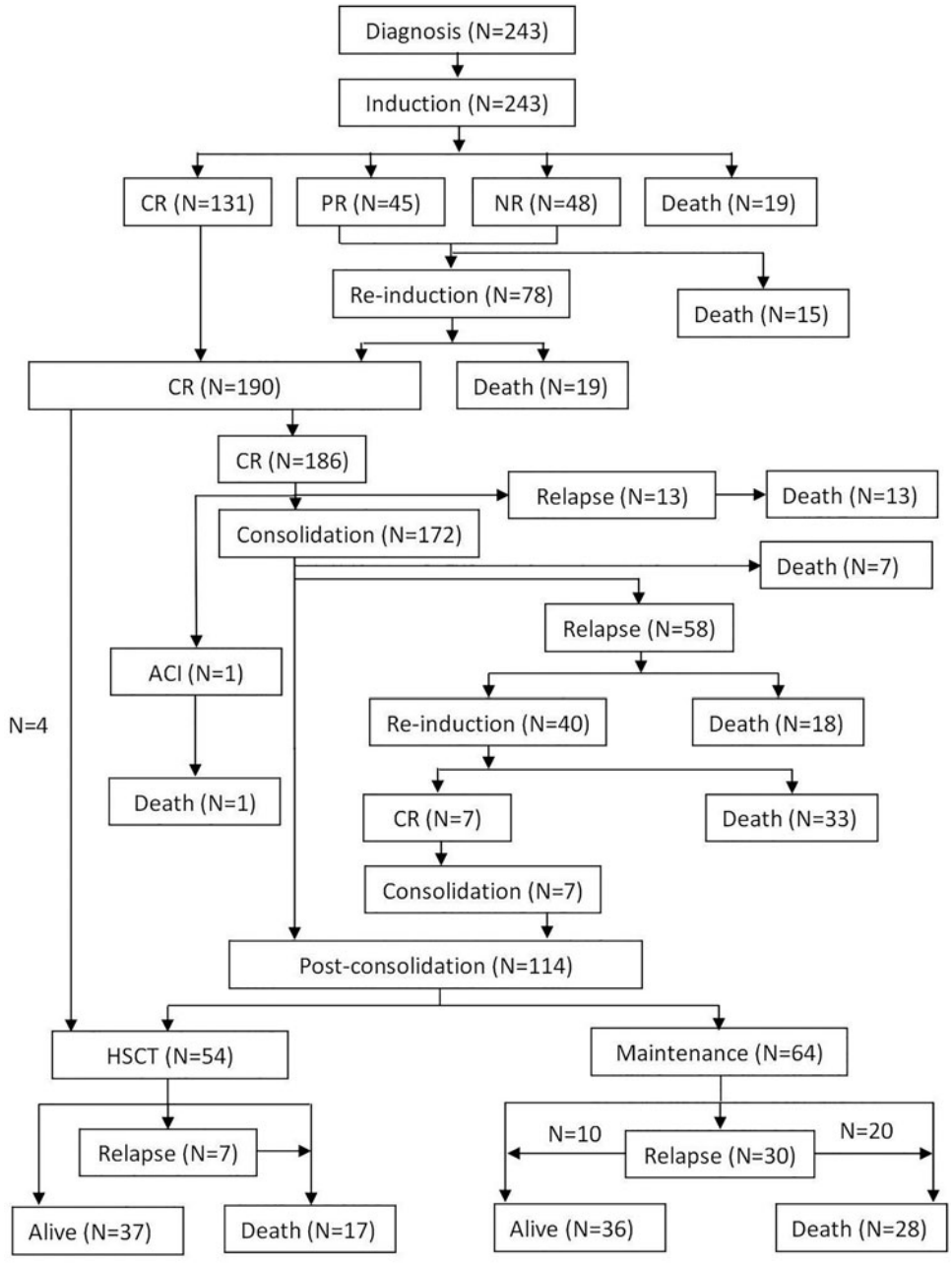
Variables such as age, gender, serum albumin, white blood cell (WBC) count, hemoglobin (Hb), platelet (PLT) count, blasts at peripheral blood (PB) as well as bone marrow (BM), immunophenotype and cytogenetics at diagnosis before chemotherapy, BM response after one course of chemotherapy and hematopoietic stem cell transplantation (HSCT) treatment were abstracted and reviewed. If patients had multiple serum albumin measurements before chemotherapy after admission, only the first measurement was recorded.

Hypoalbuminemia was defined as a serum albumin $\leq$3.5 g/dL [5]. Early BM response was evaluated through BM inspection on day 14–21 of initial regimen, and BM result was defined as CR, partial remission (PR), or non-remission (NR) if the residual blast percentages were $<$5, 5–20, or $>$20, respectively. Additionally, the criteria of CR in AML included morphologically normal hematopoiesis, recovery of PB cell counts to normal levels, and without extramedullary disease [4,14–16].

For the cytogenetic studies, BM samples obtained at diagnosis were tested by R- and/or G-banding techniques systematically for karyotype descriptions, and were classified on the basis of the International System for Human Cytogenetic Nomenclature [17]. At least 20 metaphases of each BM sample were observed. For nine patients, karyotype descriptions could not be observed in 20 metaphases.

Outcome

The primary endpoint and outcome of interest was death from initial diagnosis, which could be a result of chemotherapy related toxicity, the lack of response, progression of disease or any other reasons (Supplementary Table 2). Relapse or death was analyzed as the secondary end point. Relapse was defined



Abbreviations: CR, complete remission; PR, partial remission; NR, non-remission; ACI, acute cerebral infarction; HSCT, hematopoietic stem cell transplantation.

Figure 1. Flowchart of the patients.

as BM containing 5% blasts unrelated to recovery from prior chemotherapy [18,19]. The data collectors of clinical information at initial diagnosis were blinded to the survival data.

Statistical analysis

The aim of this study was to discover the impact of initial serum albumin on clinical outcomes of non-M3 *de novo* AML patients. Patients were divided into two groups: hypoalbuminemia ($\leq$3.5 g/dL) and normoalbuminemia (>3.5 g/dL) based on the serum albumin level [5]. The cutoff of the serum albumin was validated by ROC curve and the selection was made by combination of Youden's index and clinical use. Patient baseline characteristics were compared using the Wilcoxon rank-sum test for numerical covariates and Chi-square test or Fisher's exact test for categorical covariates. Comparisons for cause of mortality were done by Chi-square test or Fisher's exact test.

Overall survival was calculated from the date of diagnosis to the date of death from any cause or last follow-up. Leukemia-free survival (LFS) was measured from the date of CR to the date of the first event (induction failure, relapse, or death from any cause) occurrence or last follow-up. The analyses of survival between hypoalbuminemia and normo-albuminemia groups were performed using the Kaplan–Meier method and compared via the log-rank test. The univariable and multivariable analyses were performed by the Cox proportional hazards models. All variables with a p value $<.1$ in the univariable analysis were subsequently included in the multivariable Cox proportional hazards model. C-index was calculated to see the prediction accuracy of the multivariable Cox proportional hazards model by internal validation. All tests were two-sided and these tests with p value $<.05$ considered statistically significant. All statistical analyses were performed using the SPSS 19 statistical software (SPSS Inc./IBM, Armonk, NY) and R version 3.6.0.

Results

Patient characteristics

A total of 243 patients with non-M3 *de novo* AMLs were enrolled in this retrospective study with clinical characteristics as summarized in Table 1. Median age of the population studied was 47 years (range: 14–80 years). One hundred and thirty-three (54.7%) patients were male, while remaining 110 (45.3%) were female. The median WBC count at diagnosis was 19.40×10^9/L (range: 0.70–330.20 $\times 10^9$/L). The median Hb level was 80.0 g/L (range: 26.0–162.0 g/L) and median PLT count was 37×10^9/L (range: 3–708 $\times 10^9$/L). The median percentages of blasts in PB and BM were 59.0% (range: 0.0–98.0%) and 65.6% (range: 9.6–98.9%), respectively. Based on the FAB classification, there was 1 (0.4%) AML M1, 44 (18.1%) AML M2, 108 (44.4%) AML M4, 75 (30.9%) AML M5, 4 (1.6%) AML M6, 1 (0.4%) AML M7, and remaining 10 (4.1%) patients failed to morphologically classify. Cytogenetic risk analyses were performed at the time of initial diagnosis, in which 51 (21.0%), 139 (57.2%), and 44 (18.1%) patients displayed favorable, intermediate, and unfavorable karyotypes, respectively. The median follow-up for the entire cohort of 243 patients was 14 months (range: 0–99 months). The number of recorded deaths and relapses were 170 and 108, respectively (Figure 1). The estimated 5-year OS and LFS were 28% (95% confidence interval (CI): 25–31%) and 22% (95%CI: 18–25%), respectively.

According to ROC curve (Supplementary Figure 1), the optimal cutoff of serum albumin for grouping was 3.58 g/dL with a Youden index of 0.377. For clinical purposes, we chose 3.50 g/dL as the cutoff with sensitivity of 0.822 and specificity of 0.527.

The median serum albumin level at diagnosis was 3.58 g/dL (range: 2.32–5.19 g/dL), with 104 (42.8%) patients showed low serum albumin ($\leq$3.5 g/dL) and 139 (57.2%) patients showed normal (>3.5 g/dL). Patients with hypoalbuminemia had high WBC count

Table 1. Baseline patient characteristics [median (range) or n (%)].

Characteristics	All patients ($N = 243$)	Hypoalbuminemia ($N = 104$)	Normo-albuminemia ($N = 139$)	p Value
Age (years)	47 (14–80)	55 (17–80)	40 (14–75)	<.001
Male/female	133/110	55/49	78/61	.617
WBC count ($\times 10^9$/L)	19.40 (0.70–330.20)	34.12 (0.70–330.20)	11.81 (0.74–313.52)	<.001
Hemoglobin (g/L)	80.0 (26.0–162.0)	75.5 (34.0–142.0)	86.0 (26.0–162.0)	.004
Platelets ($\times 10^9$/L)	37 (3–708)	33 (4–708)	40 (3–293)	.366
Blasts in PB (%)	59 (0–98)	70 (0–98)	49 (0–98)	<.001
Blasts in BM (%)	65.59 (9.59–98.89)	75.25 (9.50–98.00)	57.50 (13.00–98.80)	<.001
FAB subtypes				
M0	0 (0.0)	0 (0.0)	0 (0.0)	–
M1	1 (0.4)	1 (1.0)	0 (0.0)	.428
M2	44 (18.1)	15 (14.4)	29 (20.9)	.197
M4	108 (44.4)	51 (49.0)	57 (41.0)	.213
M5	75 (30.9)	33 (31.7)	42 (30.2)	.800
M6	4 (1.6)	1 (1.0)	3 (2.2)	.638
M7	1 (0.4)	0 (0.0)	1 (0.7)	1.000
Unclassified	10 (4.1)	3 (2.9)	7 (5.0)	.611
Cyto/molecular genetic risk group				
Favorable	51 (21.0)	18 (17.3)	33 (23.7)	.223
Intermediate	139 (57.2)	64 (61.5)	75 (54.0)	.237
Unfavorable	44 (18.1)	18 (17.3)	26 (18.7)	.780
Missing	9 (3.7)	4 (3.8)	5 (3.6)	1.000
CR[a]	131 (53.9)	45 (43.3)	86 (61.9)	.004
No. of patients who underwent HSCT	54 (22.2)	17 (16.3)	37 (26.6)	.057

WBC: white blood cell; PB: peripheral blood; BM: bone marrow; FAB: French-American-British; CR: complete remission; HSCT: hematopoietic stem cell transplant.
[a]Achieved CR after one course of induction therapy.

($p < .001$) and low Hb level ($p = .004$) when compared to patients with normal albumin levels. Additionally, patients with hypoalbuminemia had high percentages of blasts in PB ($p < .001$) and BM ($p < .001$). Patients with normal serum albumin level at diagnosis were more likely to achieve CR after induction and re-induction therapies ($p = .004$).

Prognostic impact of serum albumin at diagnosis

A total of 170 deaths occurred until 1 June 2018. Out of the total 170 deaths during the study period, 91 had hypoalbuminemia while 79 patients had normal albumin levels. As Supplementary Table 2 shows, patients with hypoalbuminemia had early deaths due to induction related toxic effects ($p = .018$) or lack of response ($p < .001$), whereas, patients with normal albumin exhibited delayed deaths following treatment of maintenance ($p = .002$).

The median follow-up for normal albumin group was 29 months (range: 0–99 months), while median follow-up for hypoalbuminemia group was 6 months (range: 0–58 months). Additionally, patients with hypoalbuminemia had a significantly inferior OS and LFS (Figure 2): the estimate 2-year OS was 19% (95%CI: 15–23%) and the estimate 2-year LFS was 10% (95%CI: 7–13%). In comparison, patients with normal albumin levels showed a superior OS and LFS (Figure 2): the estimated 2-year OS was 57% (95%CI: 53–61%) and the estimate 2-year LFS was 46% (95%CI: 42–50%). Furthermore, there were significant differences observed in OS ($p < .001$; Figure 2(A)) and LFS ($p < .001$; Figure 2(B)) between hypoalbuminemia and normal albumin groups by the Kaplan–Meier analysis.

Results of the univariable analyses for factors affecting OS and LFS are listed in Table 2. The univariable analysis revealed that serum albumin level at diagnosis was significantly associated with survival outcomes. Not only as a categorical variable (OS: HR = 0.346, 95%CI 0.253–0.472, $p < .001$; LFS: HR = 0.379, 95%CI 0.281–0.511, $p < .001$), but also as a continuous variable (OS: HR = 0.887, 95%CI 0.859–0.917, $p < .001$; LFS: HR = 0.903, 95%CI 0.876–0.931, $p < .001$) serum albumin demonstrated significant impact on OS and LFS. In addition, the following clinical parameters were significantly associated with OS and LFS as well: age (as categorical and continuous variables), cytogenetic characteristics, Hb level, BM response after one course of chemotherapy and HSCT treatment. Moreover, WBC count displayed correlation with LFS as well.

Multivariable analysis included all the variables with p value $<.1$ in univariable analysis, as presented in Table 3. Hypoalbuminemia was an independent predictor of shorter OS (HR = 0.343, 95%CI 0.241–0.488, $p < .001$) and LFS (HR = 0.374, 95%CI 0.265–0.526, $p < .001$). Besides, as a continuous variable, serum albumin also had significant impact on OS (HR = 0.910, 95%CI 0.878–0.943, $p < .001$) and LFS (HR = 0.924, 95%CI 0.893–0.955, $p < .001$) as well. *C*-index for multivariable Cox proportional hazards model was 0.758, and corrected *C*-index was 0.750.

However, serum albumin correlated with the strongest predictors of poor outcome (such as age and cytogenetic risk groups). Stratified multivariable analyses based on different stratifications (such as age and cytogenetic risk groups) are shown in Figure 3. Hypoalbuminemia still remained an independent adverse predictor for OS and LFS in patients with age <60 years, patients with favorable and intermediate

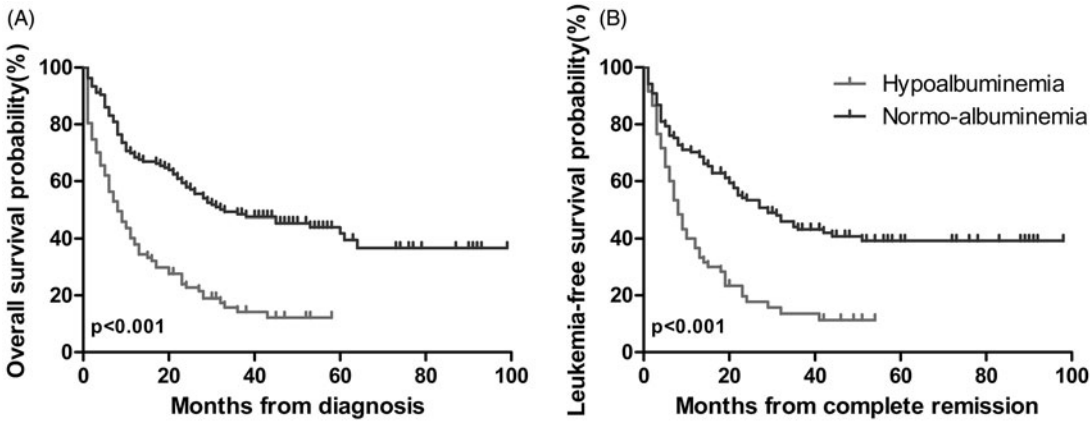


Figure 2. Kaplan–Meier's estimates of overall survival and leukemia-free survival in patients with non-M3 acute myeloid leukemia. *Notes*: Patients with hypoalbuminemia vs. patients with normo-albuminemia. (A) The estimate 2-year OS was 19% ($N = 104$, 95%CI: 15–23%) vs. 57% ($N = 139$, 95%CI: 53–61%), respectively, $p < .001$. (B) The estimate 2-year LFS was 10% ($N = 104$, 95%CI: 7–13%) vs. 46% ($N = 139$, 95%CI: 42–50%), respectively, $p < .001$. p Values were based on the log-rank test.

Table 2. Univariable analysis for leukemia-free and overall survival.

	Overall survival			Leukemia-free survival		
Variables	HR	95%CI	*p* Value	HR	95%CI	*p* Value
Albumin (g/L; continuous variable)	0.887	0.859–0.917	<.001	0.903	0.876–0.931	<.001
Albumin (g/dL; >3.5 vs. ≤3.5)	0.346	0.253–0.472	<.001	0.379	0.281–0.511	<.001
Age (years; continuous variable)	1.019	1.009–1.029	<.001	1.017	1.007–1.026	<.001
Age (years; ≥60 vs. <60)	1.921	1.365–2.703	<.001	1.854	1.332–2.580	<.001
Sex (male vs. female)	0.859	0.636–1.160	.322	0.906	0.678–1.210	.502
Cyto/molecular genetic risk group (favorable vs. other)	0.621	0.420–0.918	.017	0.691	0.480–0.996	.048
WBC count ($\times 10^9$/L)	1.002	1.000–1.004	.092	1.002	1.000–1.004	.093
Hb (g/L; ≥100 vs. <100)	0.58	0.400–0.842	.004	0.682	0.484–0.960	.028
PLT ($\times 10^9$/L; ≥20 vs. <20)	1.038	0.747–1.441	.826	1.063	0.774–1.460	.707
Blasts in PB (%; ≥60 vs. <60)	1.167	0.864–1.577	.314	1.086	0.813–1.451	.576
Blasts in BM (%; ≥90 vs. <90)	1.026	0.661–1.592	.910	0.951	0.624–1.450	.816
CR[a]	0.445	0.328–0.603	<.001	0.478	0.356–0.641	<.001
Postconsolidation treatment (HSCT vs. non-HSCT)	0.204	0.123–0.338	<.001	0.262	0.168–0.408	<.001

WBC: white blood cell; Hb: hemoglobin; PLT: platelet; PB: peripheral blood; BM: bone marrow; CR: complete remission; HSCT: hematopoietic stem cell transplantation; HR: hazard ratio; 95%CI: 95% confidence interval.
[a]Achieved CR after one course of induction therapy.

Table 3. Multivariable analysis of clinical factors for leukemia-free and overall survival.

	Overall survival			Leukemia-free survival			Overall survival			Leukemia-free survival		
Variables	HR	95%CI	*p* Value	HR	95%CI	*p* Value	HR	95%CI	*p* Value	HR	95%CI	*p* Value
Albumin[a] (g/L; continuous variable)							0.910	0.878–0.943	<.001	0.924	0.893–0.955	<.001
Albumin (g/dL; >3.5 vs. ≤3.5)	0.343	0.241–0.488	<.001	0.374	0.265–0.526	<.001						
Age (years; ≥60 vs. <60)	1.076	0.747–1.551	.693	1.074	0.753–1.532	.695	1.085	0.751–1.566	.664	1.096	0.766–1.569	.615
Cyto/molecular genetic risk group (favorable vs. other)	0.684	0.458–1.022	.064	0.768	0.528–1.118	.168	0.671	0.449–1.003	.052	0.769	0.528–1.121	.172
WBC count ($\times 10^9$/L)	1.000	0.997–1.002	.875	1.000	0.998–1.003	.817	1.001	0.998–1.003	.646	1.001	0.999–1.003	.357
Hb (g/L; ≥100 vs. <100)	0.668	0.452–0.987	.043	0.758	0.528–1.089	.135	0.699	0.470–1.039	.076	0.775	0.537–1.119	.173
Postconsolidation treatment (HSCT vs. non-HSCT)	0.193	0.115–0.326	<.001	0.246	0.155–0.390	<.001	0.233	0.139–0.392	<.001	0.290	0.184–0.458	<.001

WBC: white blood cell; Hb: hemoglobin; HSCT: hematopoietic stem cell transplantation; HR: hazard ratio; 95%CI: 95% confidence interval.
[a]This analysis was done in separate multivariate Cox regression analysis, including all patient characteristics as specified in this table besides the albumin as a categorical variable.

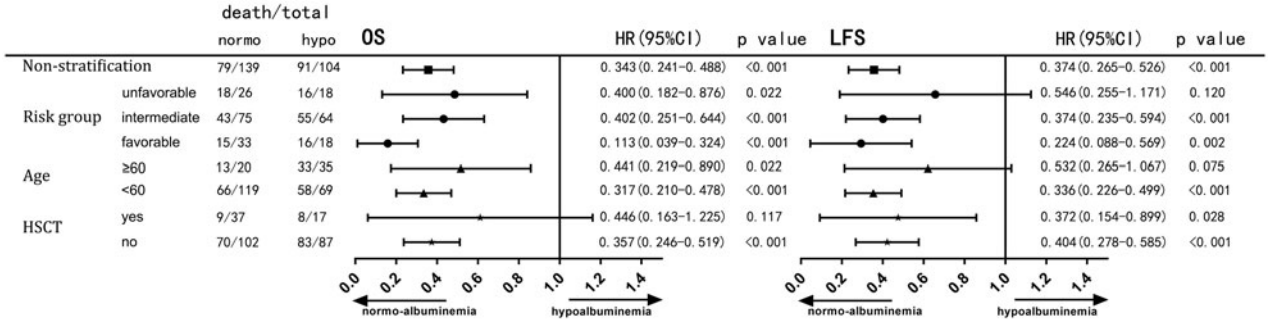


Figure 3. Stratified multivariable analyses for leukemia-free and overall survival.

cytogenetic risk groups, and patients undergoing maintenance therapy instead of HSCT. Also, hypoalbuminemia was still a prognostic factor for OS in patients with age ≥60 and patients with unfavorable cytogenetic risk group. Furthermore, in patients who underwent HSCT, hypoalbuminemia was a predictor for LFS.

Discussion

The association between serum albumin and survival outcomes has been previously reported for several malignant tumors [9,20–23]. The aim of this retrospective study was to elucidate the prognostic importance of the serum albumin level in patients with non-M3 *de novo* AMLs who have undergone at least one course of conventional '3 + 7' chemotherapy. Our study demonstrated that patients with serum albumin level ≤3.5 g/dL at the time of diagnosis have significantly increased relapses and mortality, with early deaths due to induction related toxic effects and lack of response. Serum albumin is an additional prognostication factor that may be helpful in further refining

current risk stratification for *de novo* non-M3 AML, especially for patients with age <60 years, patients undergoing maintenance therapy and patients in favorable and intermediate cytogenetic risk groups. Our findings corroborated those of Sorror et al.'s risk model, which includes hypoalbuminemia as a factor, which predicts early and 1-year mortality [10]. Filliatre-Clement et al. have proposed that AML patients with serum albumin <3.0 g/dL showed a reverse trend to relapse and death when compared with patients with body mass index <25 kg/m^2 [11]. However, serum albumin cutoff of 3.0 g/dL lacked both sensitivity and specificity. Furthermore, it did not include patients receiving allo-HSCT, which has an important effect on AML prognosis.

For several decades, advanced understandings of biology and genomic architecture have contributed significantly to the refinement of risk assessment for AML, which helps in the selection of risk-adapted regimens [24,25]. Apart from cytogenetic risk classification, there are certain confirmed factors commonly used to predict clinical outcomes (e.g. age, WBC count, coexisting comorbidities, and a history of an antecedent hematologic disorder) [10,26–29]. Our study observed a new prognostication factor at diagnosis to predict poor outcomes of AML: serum albumin.

Albumin is synthesized in the liver and is regulated by cytokines such as tumor necrosis factor α (TNFα), interleukin (IL)-1 and 6 [5]. Pivotal roles of inflammatory cytokines have been identified in the biology of AML. While cytokines such as IL-1β, IL-6, and TNFα are considered as pro-inflammatory mediators, they tend to raise the risk of AML aggressiveness [30,31]. In the context of pro-inflammatory milieu, reduced levels in serum can be a reflection of the circulating cytokine profile in patients with AMLs.

Besides, malnutrition, routinely measured through serum albumin level, is also present in patients with malignancies, which is considered to be an essential indicator of the poor non-relapse mortality [32,33]. Reduced level of serum albumin, commonly observed in hospitalized patients undergoing surgery [20–23] or chemotherapy [8,34–36], interferes with clinical responses. A potential mechanism for association between serum albumin and prognosis of AML might be that serum albumin plays a role in chemotherapy-related tolerance of patients with AMLs. The association between hypoalbuminemia and poor clinical outcomes poses a question of whether or not albumin infusion pretreatment is beneficial and shows improved survival outcomes. Further analyses are needed to determine efficacy of supplement of albumin in AML patients.

Additionally, hypoalbuminemia is a marker for concomitant sepsis [5], which may be associated with higher mortality. Thus, we consider sepsis as an unmeasured confounding. However, there were only five (2%) patients diagnosed with sepsis in our study. All of whom had hypoalbuminemia, and four of these patients died eventually. On addition of sepsis as a variable in multivariable analysis, hypoalbuminemia was still an independent predictor of shorter OS ($p < .001$, HR = 0.354, 95%HR: 0.250–0.501) and LFS ($p < .001$, HR = 0.386, 95%HR: 0.275–0.542). While sepsis was not found to be associated with survival (OS: p=.929, HR = 1.047, 95%HR: 0.381–2.881; LFS: p=.634, HR = 0.782, 95%HR: 0.285–2.147). Thus, presence of sepsis likely did not affect the results. It is necessary to validate the effect of concomitant sepsis on association between hypoalbuminemia and AML prognosis in future research based on larger survey sample.

Cytarabine is an important chemotherapeutic option in AML, which is detoxicated primarily in the liver [37]. Serum albumin is an indicator of liver function. It could be inferred that hypoalbuminemia is a signal of weakened liver based detoxication.

The limitations of our study include: (1) the retrospective nature of the study, (2) a single-center research study with inevitable selection bias, and (3) lack of incorporating comorbidities such as cirrhosis, diabetes, and kidney disease that may have impact on serum albumin. Despite the above limitations, our analyses have pivotal clinical applications for risk stratification and regimen selection.

At present, decisions about initial treatment mainly depend on age of patients and cytogenetic and molecular features. When taking account of serum albumin levels of *de novo* AML patients, clinicians might select more intensive treatment for older patients with normal albumin levels who have traditionally been offered palliative care. Conversely, younger patients with hypoalbuminemia who might hardly benefit from intensive chemotherapy due to toxic effects, could be selectively treated with palliative care. It further fuels the question whether pretreatment albumin infusions in patients with hypoalbuminemia can alter long-term outcomes and responses to therapy.

In conclusion, we found that albumin serves as a simple, objective prognostication factor in the Chinese AML cohort. Given its cost effectiveness and convenience, we hypothesize that serum albumin might further aid in selection of regimens. More detailed, larger

prospective studies are required to establish serum albumin as an important prognostic factor in progressions and outcomes of AML. Further independent prospective studies will be helpful to validate and address the position of albumin in risk stratification of AML patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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