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Serum albumin is associated with the inherent property of acute myeloid leukemia and correlates with patient outcomes

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Abstract

An accurate prognostic model for acute myeloid leukemia (AML) can guide personalized treatment. In our prospective cohort of 591 patients newly diagnosed with AML, we evaluated the prognostic significance of serum albumin levels. We recognized baseline serum albumin as a prognostic factor by univariate Cox regression analysis (albumin-high vs albumin-low: overall survival [OS]: hazard ratio [HR]: 0.679, 95% confidence interval [CI]: 0.529–0.870, P = .002; cumulative incidence of relapse [CIR]: HR: 0.705, 95% CI: 0.530–0.938, P = .017) and multivariate Cox regression analysis (OS: HR per g/L: 0.966, 95% CI: 0.940–0.993, P = .014; CIR: HR per g/L: 0.959, 95% CI: 0.927–0.993, P = .017). In the subgroup analysis, serum albumin was prognostic significant in patients who received intermediate-dose cytarabine combined with daunorubicin and omacetaxine mepesuccinate induction (albumin-high vs albumin-low: OS: HR: 0.585, 95% CI: 0.397–0.863, P = .007; CIR: HR: 0.551, 95% CI: 0.353–0.861, P = .009) rather than those receiving conventional-dose induction regimens. In addition, the impact of baseline serum albumin level was evident in patients with intermediate European LeukemiaNet risk (albumin-high vs albumin-low: OS: HR: 0.617, 95% CI: 0.424–0.896, P = .011; CIR: HR: 0.617, 95% CI: 0.388–0.979, P = .040). Gene set enrichment analysis revealed that leukemia stem cell signatures were enriched in patients with low serum albumin levels. Our study suggested that baseline serum albumin level was associated with the inherent properties of AML and correlated with patient outcomes.

Key Words: Acute myeloid leukemia; Biomarker; Overall survival; Prognosis; Serum albumin

1. INTRODUCTION

The outcome of acute myeloid leukemia (AML) is influenced by some prognostic factors, including age, white blood cell (WBC) concentration at diagnosis, European LeukemiaNet (ELN) risk classification, induction therapy, transplantation, and measurable residual disease.[1–13] Serum albumin is a component of blood that maintains colloid osmotic pressure[14] and is a valuable biomarker of various diseases. Studies have identified that serum albumin level is a prognostic factor for myelodysplastic syndrome,[15] diffuse large B-cell lymphoma,[16] and multiple myeloma.[17] Hypoalbuminemia on day 90 after transplantation indicates worse outcomes in patients with AML or myelodysplastic syndrome.[18] Several retrospective studies on AML have demonstrated that a lower serum albumin level before treatment is associated with inferior survival in newly diagnosed AML and relapsed or refractory AML.[19–25] Serum albumin levels reflect patients' nutritional status, which is correlated with chemotherapy tolerance. Lower serum albumin levels indicate a significantly decreased CR rate and lower 60-day survival after the first chemotherapy.[21,25] It remains unclear whether the inferior outcomes of patients with lower albumin levels can be explained by the intolerability to chemotherapy or by the more aggressive status of blasts. Previous studies have been limited by small sample sizes and diverse treatment strategies. Thus, it is necessary to evaluate the prognostic significance of serum albumin levels in a prospective homogeneously treated cohort.

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Datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

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To evaluate the prognostic significance of albumin more definitively, this study analyzed the influence of baseline serum albumin levels in our prospective cohort comprising 591 patients with newly diagnosed AML who were treated homogeneously.[8,9] We studied the prognostic significance of serum albumin levels in patients with different ELN risks and in patients receiving different chemotherapy regimens. Additionally, the impact of albumin on both short- and long-term outcomes was evaluated. An albumin-related transcriptome feature in patients with AML was revealed.

2. MATERIALS AND METHODS

2.1. Participants

Patients aged 15 to 55 years with de novo newly diagnosed AML between September 1, 2010, and January 13, 2016, were enrolled in our prospective study registered at www.chictr.org.cn (identifier: ChiCTR-TRC-10001202), as detailed in our previous report.[8,9] Eligible participants were randomly assigned to receive conventional-dose (100 mg/m^2 per day on days 1–7 as a 12-hour IV infusion [standard dose cytarabine combined with daunorubicin and omacetaxine mepesuccinate {SD-HAD}]) or intermediate-dose cytarabine (100 mg/m^2 per day on days 1–4 as a 12-hour IV infusion and 1 g/m^2 every 12 hours as a 3-hour IV infusion on days 5–7 [intermediate dose cytarabine combined with daunorubicin and omacetaxine mepesuccinate {ID-HAD}]) combined with daunorubicin (40 mg/m^2 per day on days 1–3) and omacetaxine mepesuccinate (2 mg/m^2/d on days 1–7). This study was approved by the Ethics Committee of the Institute of Hematology and Blood Diseases Hospital of the Chinese Academy of Medical Sciences (approval number: NKRDP2021005-EC-2).

2.2. Statistics

The cumulative incidence of relapse (CIR) was defined as the interval between complete remission (CR) and relapse, censored at death and the last follow-up visit or contact. Overall survival (OS) was defined as the interval between randomization and death from any cause and was censored at the last follow-up visit or contact. Relapse-free survival (RFS) was defined as the interval between CR and relapse or death from any cause and was censored at the last follow-up visit or contact. Event-free survival (EFS) was defined as the interval between randomization and assessment of response after the first cycle of chemotherapy if the participant failed to achieve CR, the date of relapse in those achieving CR, or the date of death, whichever occurred first. All participants were randomly included in the EFS and OS analyses, and those who achieved CR were included in the CIR and RFS analyses. Transplantation in the first CR was treated as a time-dependent binary covariate for survival analyses. Statistical Package for Social Sciences (IBM, Singapore Pte Ltd, Changi, Singapore) version 24.0 and R software version 4.1.2 (2021; The R Foundation for Statistical Computing Platform) were used for all statistical analyses. Survival was analyzed using the Kaplan–Meier method or Cox regression model. The R package, cmprsk, was used for the competing risk model. The R package, SurvivalROC was used for landmark analyses. P values <.05 were considered significant.

2.3. Gene expression profiling

Bone marrow aspirate samples were collected from 129 patients newly diagnosed with AML at our hospital between September 2021 and August 2022. The samples were centrifuged over a Ficoll-Paque gradient to isolate mononuclear cells. All patients underwent a 3+7 induction. Total RNA was used as the input material for sequencing using the Illumina NovaSeq 6000. Differentially expressed genes (DEGs) were analyzed using the DESeq2 package in R. Gene set enrichment analysis was performed using GSEA software v.4.1.0. A 17-gene leukemia stem cell gene set (LSC17) was generated as described previously.[26]

3. RESULTS

3.1. Characteristics of the prospective cohort

Our prospective cohort included 591 participants (Table 1) with a median age of 36 (quartile interval: 24–44) years and median baseline serum albumin of 41.8 (quartile interval: 38.9–44.3) g/L. Of the 591 patients, 538 had normal albumin levels (>35 g/L) and 53 had hypoalbuminemia (<35 g/L). Among them, 320 were male, 271 were female; furthermore, 280 patients belonged to the ELN favorable risk group, 220 to the ELN intermediate-risk group, and 91 to the ELN adverse risk group. In the cohort, 295 received ID-HAD and 296 received SD-HAD.

3.2. Baseline serum albumin correlated with survival

To evaluate the impact of serum albumin level, the 591 participants were divided into albumin-high (N = 299) and albumin-low (N = 292) groups according to the median baseline serum albumin (41.7 g/L). Participants in the albumin-low group were of older age (38 vs 34y, P = .001), exhibited higher WBC count (15.5 vs 10.5, 10E + 9/mL, P = .010), and demonstrated a higher rate of treatment with ID-HAD (54.5% vs 45.5%, P = .032; Table 1). Analysis of the correlation between serum albumin levels and common genetic lesions revealed that the albumin-low group had a higher proportion of NPM1 (20.9% vs 9.4%, P < .001) and RUNX1 mutations (5.9% vs 0.7%, P < .001; Supplementary Table 1, http://links.lww.com/BS/A95).

In univariate analysis, the albumin-high group had more favorable outcomes than the albumin-low group (albumin-high vs albumin-low: OS: hazard ratio [HR]: 0.679, 95% confidence interval [CI]: 0.529–0.870, P = .002; RFS: HR: 0.688, 95% CI: 0.524–0.905, P = .007; EFS: HR: 0.797, 95% CI: 0.638–0.995, P = .045; Table 2, **Fig. 1**). The CIR of the albumin-high group was significantly lower than that of the albumin-low group (albumin-high vs albumin-low: HR: 0.705, 95% CI: 0.530–0.938, P = .017), whereas the non-relapse mortality of the 2 groups showed no significant difference (P = .472, Table 2, Supplementary Table 2, http://links.lww.com/BS/A95, **Fig. 1**). Based on the patients' OS, we identified 38.6 g/L as the best cut-off value for serum albumin (low vs high: HR: 1.762, 95% CI: 1.352–2.296, P < .001).

Table 1

Baseline characteristics for patients with different baseline serum albumin levels.

Variate	Low (n = 292)	High (n = 299)	*P* value
Baseline serum albumin (g/L)			
Median (range)	38.9 (14.9, 41.7)	44.3 (41.8, 55.4)	
Age (y)			
Median (range)	38 (15, 54)	34 (15, 54)	.001
Baseline WBC (10E + 9/mL)			
Median (range)	15.5 (0.7, 370.9)	10.5 (0.8, 265.2)	.010
Gender			
Male	146 (50.0%)	174 (58.2%)	.048
Female	146 (50.0%)	125 (41.8%)	
Induction			
SD-HAD	133 (45.5%)	163 (54.5%)	.032
ID-HAD	159 (54.5%)	136 (45.5%)	
ELN risk group			
Favorable	127 (43.5%)	153 (51.2%)	.063
Intermediate	111 (38.0%)	109 (36.5%)	
Adverse	54 (18.5%)	37 (12.4%)	
Transplantation	54 (18.5%)	53 (17.7%)	.831
Complete remission rate	242 (82.9%)	243 (81.3%)	.668
30-d mortality	7 (2.4%)	3 (1.0%)	.218

ELN = European LeukemiaNet, ID-HAD = intermediate dose cytarabine combined with daunorubicin and omacetaxine mepesuccinate, SD-HAD = standard dose cytarabine combined with daunorubicin and omacetaxine mepesuccinate, WBC = white blood cell.

Table 2

Univariate Cox regression of serum albumin levels for OS, RFS, EFS, and cumulative incidence of relapse of AML patients.

		OS				RFS			
Group	**Variate**	***P* value**	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P* value**	**HR**	**Lower 95% CI**	**Upper 95% CI**
Total	Baseline serum albumin (per g/L)	<.001	0.947	0.922	0.972	<.001	0.946	0.919	0.975
	Baseline serum albumin subgroup (high vs low)	.002	0.679	0.529	0.870	.007	0.688	0.524	0.905
SD-HAD	Baseline serum albumin (per g/L)	.031	0.961	0.926	0.996	.052	0.960	0.922	1.000
	Baseline serum albumin subgroup (high vs low)	.053	0.722	0.520	1.004	.145	0.762	0.528	1.098
ID-HAD	Baseline serum albumin (per g/L)	<.001	0.925	0.890	0.962	.001	0.928	0.888	0.969
	Baseline serum albumin subgroup (high vs low)	.007	0.585	0.397	0.863	.009	0.571	0.375	0.870
ELN favorable	Baseline serum albumin (per g/L)	.367	0.977	0.930	1.027	.589	0.987	0.942	1.035
	Baseline serum albumin subgroup (high vs low)	.047	0.629	0.398	0.995	.162	0.744	0.492	1.125
ELN intermediate	Baseline serum albumin (per g/L)	<.001	0.918	0.883	0.955	<.001	0.889	0.846	0.933
	Baseline serum albumin subgroup (high vs low)	.011	0.617	0.424	0.896	.013	0.563	0.357	0.886
ELN adverse	Baseline serum albumin (per g/L)	.364	1.028	0.969	1.090	.282	1.043	0.966	1.126
	Baseline serum albumin subgroup (high vs low)	.151	1.441	0.875	2.373	.087	1.756	0.922	3.345
		EFS				**CIR**			
Group	**Variate**	***P* value**	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P* value**	**HR**	**Lower 95% CI**	**Upper 95% CI**
Total	Baseline serum albumin (per g/L)	.001	0.961	0.938	0.984	<.001	0.944	0.913	0.976
	Baseline serum albumin subgroup (high vs low)	.045	0.797	0.638	0.995	.017	0.705	0.530	0.938
SD-HAD	Baseline serum albumin (per g/L)	.200	0.979	0.948	1.011	.086	0.959	0.915	1.010
	Baseline serum albumin subgroup (high vs low)	.271	0.849	0.634	1.137	.260	0.804	0.552	1.170
ID-HAD	Baseline serum albumin (per g/L)	<.001	0.931	0.898	0.966	<.001	0.922	0.882	0.965
	Baseline serum albumin subgroup (high vs low)	.025	0.672	0.474	0.952	.009	0.551	0.353	0.861
ELN favorable	Baseline serum albumin (per g/L)	.457	0.983	0.941	1.028	.380	0.978	0.930	1.030
	Baseline serum albumin subgroup (high vs low)	.103	0.722	0.487	1.068	.210	0.755	0.488	1.170
ELN intermediate	Baseline serum albumin (per g/L)	.001	0.946	0.915	0.979	<.001	0.900	0.856	0.947
	Baseline serum albumin subgroup (high vs low)	.173	0.793	0.568	1.107	.040	0.617	0.388	0.979
ELN adverse	Baseline serum albumin (per g/L)	.048	1.058	1.000	1.118	.400	1.030	0.957	1.120
	Baseline serum albumin subgroup (high vs low)	.012	1.802	1.136	2.860	.190	1.560	0.806	3.030

AML = acute myeloid leukemia, CI = confidence interval, CIR = cumulative incidence of relapse, EFS = ELN = European LeukemiaNet, HR = hazard ratio, ID-HAD = intermediate dose cytarabine combined with daunorubicin and omacetaxine mepesuccinate, OS = overall survival, RFS = relapse-free survival, SD-HAD = standard dose cytarabine combined with daunorubicin and omacetaxine mepesuccinate.

Two multivariate Cox regression analyses were performed. Baseline serum albumin level was treated as a continuous variate in model 1, and categorized as low or high in mode l2 according to the median value (41.7 g/L). After adjusting for age, baseline WBC concentration, ELN risk, regimens of first course of chemotherapy, and transplantation, baseline serum albumin was prognostically significant for OS, RFS, and CIR in model 1 (OS: HR per g/L: 0.966, 95% CI: 0.940–0.993, P = .014; RFS: HR per g/L: 0.960, 95% CI: 0.931–0.991, P = .010; CIR: HR per g/L: 0.959, 95% CI: 0.927–0.993, P = .017; Table 3) and was boundary significant for OS, RFS, and CIR in model 2 (albumin-high vs albumin-low: OS: HR: 0.777, 95% CI: 0.602–1.001, P = .051; RFS: HR: 0.766, 95% CI: 0.578–1.014, P = .063; CIR: HR: 0.770, 95% CI: 0.573–1.036, P = .084; Table 3). P value for EFS was not significant in both models (model 1: HR per g/L: 0.982, 95% CI: 0.958–1.006, P = .147; model 2: albumin-high vs albumin-low HR: 0.911, 95% CI: 0.726–1.145, P = .425; Table 3).

3.3. Prognostic significance of baseline serum albumin in subgroup analysis

To further evaluate the prognostic impact of baseline serum albumin levels, we performed a subtype analysis in patients receiving different induction regimens.

Univariate analysis revealed that the albumin-low group had poorer outcomes in patients undergoing ID-HAD induction (albumin-high vs. albumin-low: OS: HR: 0.585, 95% CI 0.397–0.863, P = .007; RFS: HR: 0.571, 95% CI: 0.375–0.870, P = .009; EFS: HR: 0.672, 95% CI: 0.474–0.952, P = .025; CIR: HR: 0.551, 95% CI: 0.353–0.861, P = .009; Table 2, **Fig. 2**). In SD-HAD subgroup, the albumin-low group tended to have poor OS, but not RFS, EFS, or CIR (albumin-high vs albumin-low: OS: HR: 0.722, 95% CI: 0.520–1.004, P = .053; RFS: HR: 0.762, 95% CI: 0.528–1.098, P = .145; EFS: HR: 0.849, 95% CI: 0.634–1.137, P = .271; CIR: HR: 0.804, 95% CI: 0.552–1.170, P = .260; Table 2, **Fig. 2**). Similar to univariate analysis, multivariate analysis demonstrated that patients with lower albumin levels had poorer OS, RFS, EFS, and higher CIR in the ID-HAD induction group (OS: HR per g/L: 0.945, 95% CI: 0.906–0.985, P = .008; RFS: HR per g/L: 0.944, 95% CI: 0.900–0.990, P = .017; EFS: HR per g/L: 0.952, 95% CI: 0.914–0.991, P = .015; CIR: HR per g/L: 0.931, 95% CI: 0.889–0.974, P = .002; Supplementary Table 3, http://links.lww.com/BS/A95). The multivariate analysis revealed that the prognostic influence of albumin was not statistically significant in participants undergoing SD-HAD induction (OS: HR per g/L: 0.982, 95% CI: 0.946–1.020, P = .342; RFS: HR per g/L: 0.974, 95% CI: 0.934–1.015, P = .212; EFS: HR per g/L: 1.003, 95%

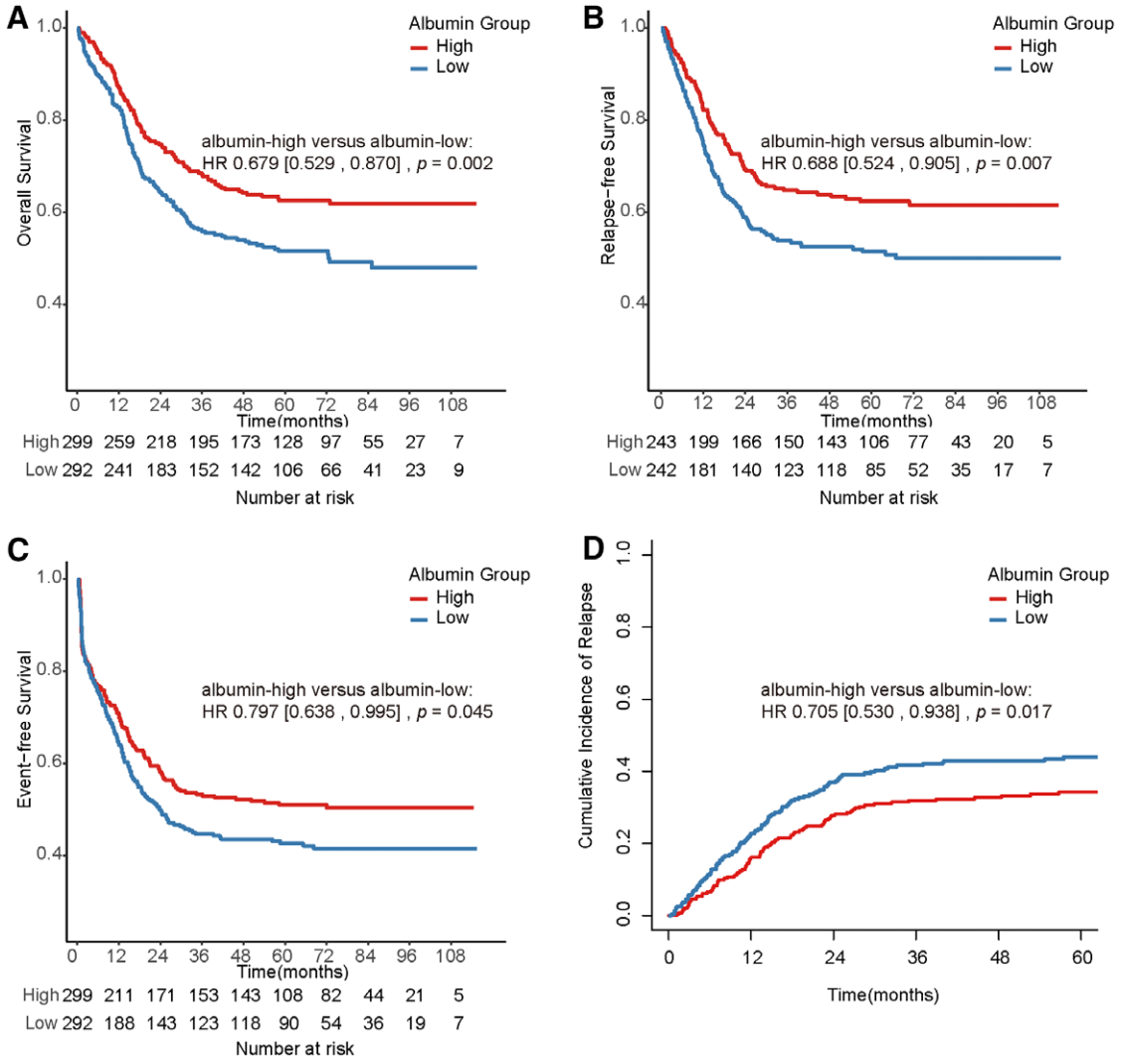

Figure 1. Overall survival (A), relapse-free survival (B), event-free survival (C), and cumulative incidence of relapse (D) of patients with high or low baseline serum albumin levels. HR = hazard ratio.

Table 3

Multivariate Cox regression model for OS, RFS, EFS, and cumulative incidence of relapse of AML patients.

Model 1	OS				RFS			
Variate	***P* value**	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P* value**	**HR**	**Lower 95% CI**	**Upper 95% CI**
Baseline serum albumin (per g/L)	.014	0.966	0.940	0.993	.010	0.960	0.931	0.991
Age (per year)	.012	1.015	1.003	1.028	.354	1.006	0.993	1.019
Baseline WBC concentration	<.001	1.005	1.003	1.007	<.001	1.004	1.002	1.007
Induction								
ID-HAD vs SD-HAD	.004	0.690	0.537	0.888	.001	0.638	0.485	0.840
ELN risk group								
Favorable	<.001				<.001			
Intermediate	<.001	2.727	2.030	3.665	<.001	1.881	1.388	2.550
Adverse	<.001	5.131	3.597	7.320	<.001	3.841	2.551	5.781
Transplantation	<.001	0.355	0.234	0.539	<.001	0.368	0.230	0.588
Model 2	**OS**				**RFS**			
Variate	***P* value**	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P* value**	**HR**	**Lower 95% CI**	**Upper 95% CI**
Baseline serum albumin subgroup								
High vs low	.051	0.777	0.602	1.001	.063	0.766	0.578	1.014
Age (per year)	.009	1.016	1.004	1.028	.264	1.007	0.995	1.020
Baseline WBC concentration	<.001	1.005	1.003	1.007	.001	1.004	1.002	1.007
Induction								
ID-HAD vs SD-HAD	.004	0.691	0.538	0.889	.001	0.634	0.481	0.834
ELN risk group								
Favorable	<.001				<.001			
Intermediate	<.001	2.747	2.045	3.691	<.001	1.890	1.394	2.562
Adverse	<.001	5.250	3.687	7.477	<.001	3.976	2.647	5.972
Transplantation	<.001	0.350	0.230	0.531	<.001	0.366	0.229	0.586
Model 1	**EFS**				**CIR**			
Variate	***P* value**	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P* value**	**HR**	**Lower 95% CI**	**Upper 95%CI**
Baseline serum albumin (per g/L)	.147	0.982	0.958	1.006	.017	0.959	0.927	0.993
Age (per year)	.110	1.009	0.998	1.019	.740	1.002	0.990	1.015
Baseline WBC (per 10E + 9/mL)	<.001	1.004	1.002	1.006	.002	1.006	1.002	1.009
Induction								
ID-HAD vs SD-HAD	<.001	0.610	0.487	0.764	.003	0.639	0.476	0.858
ELN risk group								
Favorable	<.001				<.001			
Intermediate	<.001	2.644	2.039	3.427	<.001	2.162	1.571	2.976
Adverse	<.001	5.137	3.721	7.092	<.001	4.584	2.950	7.126
Transplantation	<.001	0.344	0.217	0.543	<.001	0.138	0.071	0.270
Model 2	**EFS**				**CIR**			
Variate	***P* value**	**HR**	**Lower 95% CI**	**Upper 95% CI**	***P* value**	**HR**	**Lower 95% CI**	**Upper 95% CI**
Baseline serum albumin subgroup								
High vs low	.425	0.911	0.726	1.145	.084	0.770	0.573	1.036
Age (per year)	.084	1.009	0.999	1.020	.600	1.003	0.991	1.016
Baseline WBC (per 10E+9/mL)	<.001	1.004	1.002	1.006	.002	1.006	1.002	1.009
Induction								
ID-HAD vs SD-HAD	<.001	0.609	0.486	0.763	.002	0.632	0.472	0.847
ELN risk group								
Favorable	<.001				<.001			
Intermediate	<.001	2.661	2.054	3.449	<.001	2.170	1.572	2.996
Adverse	<.001	5.256	3.814	7.245	<.001	4.796	3.119	7.377
Transplantation	<.001	0.350	0.230	0.531	<.001	0.366	0.229	0.586

AML = acute myeloid leukemia, CI = confidence interval, CIR = cumulative incidence of relapse, EFS = ELN = European LeukemiaNet, HR = hazard ratio, ID-HAD = intermediate dose cytarabine combined with daunorubicin and omacetaxine mepesuccinate, OS = overall survival, RFS = relapse-free survival, SD-HAD = standard dose cytarabine combined with daunorubicin and omacetaxine mepesuccinate, WBC = white blood cell.

CI: 0.970–1.036, *P* = .873; CIR: HR per g/L: 0.980, 95% CI: 0.934–1.028, *P* = .400; Supplementary Table 3, http://links.lww.com/BS/A95).

We also performed subtype analyses of the different ELN risk groups. The prognostic significance of the albumin level was distinct in the ELN intermediate-risk group. Univariate analysis showed that the albumin-high group had better OS, RFS, and lower CIR in ELN intermediate group (albumin-high vs albumin-low: OS: HR: 0.617, 95% CI: 0.424–0.896, *P* = .011; RFS: HR: 0.563, 95% CI: 0.357–0.886, *P* = .013; EFS: HR: 0.793, 95% CI: 0.568–1.107, *P* = .173; CIR: HR: 0.617, 95% CI: 0.388–0.979, *P* = .040; Table 2, **Fig. 3**). In patients with ELN favorable risk, the albumin-high group demonstrated better OS than the albumin-low group (albumin-high vs albumin-low: OS: HR: 0.629, 95% CI: 0.398–0.995, *P* = .047) while RFS, EFS, and CIR of 2 groups were similar (RFS: HR: 0.744, 95% CI: 0.492–1.125, *P* = .162; EFS: HR: 0.722, 95% CI: 0.487–1.068, *P* = .103; CIR: HR: 0.755, 95% CI: 0.488–1.170, *P* = .210; Table 2, **Fig. 3**). In the ELN adverse group, poorer EFS was observed in albumin-high group (albumin-high vs albumin-low: EFS: HR: 1.802, 95% CI: 1.136–2.860, *P* = .012; Table 2, **Fig. 3**) while OS, RFS, and CIR of the 2 groups were similar (OS: HR: 1.441, 95%

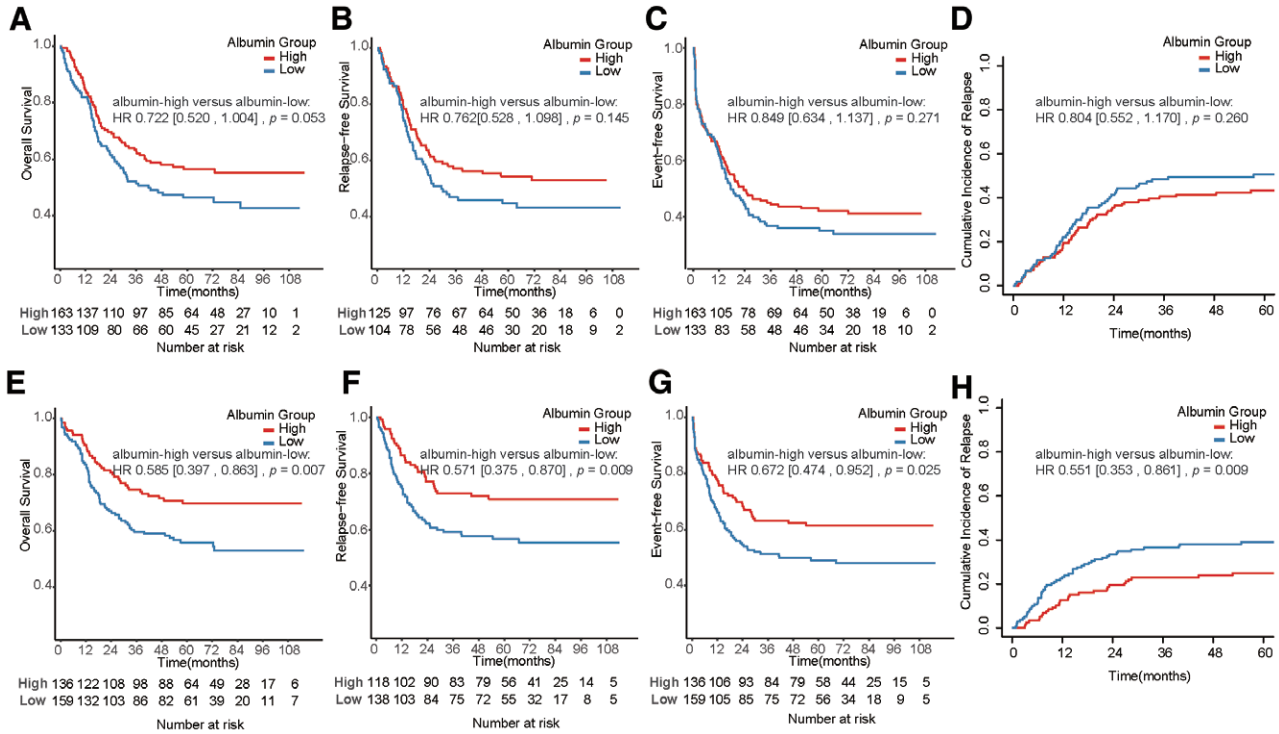

Figure 2. Overall survival, relapse-free survival, event-free survival, and cumulative incidence of relapse of patients with high or low baseline serum albumin levels in patients undergoing SD-HAD (A–D) or ID-HAD (E–H) induction. HR = hazard ratio, ID-HAD = intermediate dose cytarabine combined with daunorubicin and omacetaxine mepesuccinate, SD-HAD = standard dose cytarabine combined with daunorubicin and omacetaxine mepesuccinate.

CI: 0.875–2.373, *P* = .151; RFS: HR: 1.756, 95% CI: 0.922–3.345, *P* = .087; CIR: HR: 1.560, 95% CI: 0.806–3.030, *P* = .190; Table 2, **Fig. 3**). Multivariate analysis confirmed that higher baseline serum albumin correlated with better OS (HR per g/L: 0.925, 95% CI: 0.891–0.961, *P* < .001), RFS (HR per g/L: 0.890, 95% CI: 0.849–0.933, *P* < .001), EFS (HR per g/L: 0.949, 95% CI: 0.918–0.981, *P* = .002), and lower CIR (HR per g/L: 0.897, 95% CI: 0.860–0.936, *P* < .001; Supplementary Table 4, http://links.lww.com/BS/A95) in patients with ELN intermediate risk. Baseline serum albumin provided no prognostic value for outcomes in those with ELN favorable (OS HR per g/L: 0.989, 95% CI: 0.938–1.043, *P* = .684; RFS HR per g/L: 1.004, 95% CI: 0.955–1.055, *P* = .882; EFS HR per g/L: 0.998, 95% CI: 0.952–1.046, *P* = .928, CIR HR per g/L: 0.999, 95% CI: 0.951–1.050, *P* = .980) or adverse risk (OS HR per g/L: 1.020, 95% CI: 0.961–1.082, *P* = .518; RFS HR per g/L: 1.023, 95% CI: 0.949–1.104, *P* = .547; EFS HR per g/L: 1.050, 95% CI: 0.993–1.111, *P* = .088; CIR HR per g/L: 1.021, 95% CI: 0.938–1.111, *P* = .630; Supplementary Table 4, http://links.lww.com/BS/A95).

3.4. Short-term influence of baseline serum albumin

To identify the short-term influence of baseline serum albumin levels, we evaluated the CR rates and 30-day mortality in participants with different albumin levels.

The CR rates were similar between the albumin-high and albumin-low groups (81.3% vs 82.9%, *P* = .668; Supplementary Table 5, http://links.lww.com/BS/A95). In patients with ID-HAD or SD-HAD induction, subgroup analysis showed that baseline serum albumin levels had no influence on CR rates. Similar CR rates in the albumin-high and albumin-low groups were found in patients with a favorable or intermediate risk of ELN (Supplementary Table 5, http://links.lww.com/BS/A95). However, among patients with ELN adverse risk, lower CR rate was observed in the albumin-high group (66.7% vs 37.8%, *P* = .006; Supplementary Table 5, http://links.lww.com/BS/A95), which may be due to the limited number of cases.

The Chi-square test revealed no significant difference in 30-day mortality between the low and high albumin groups (2.4% vs 1.0%, *P* = .218; Supplementary Table 5, http://links.lww.com/BS/A95). Subgroup analysis showed that the baseline serum albumin level had little effect on 30-day mortality in patients with different first chemotherapy regimens or ELN risk.

A longitudinal analysis was also conducted. In patients who achieved CR, the serum albumin level after the first course of chemotherapy had no prognostic significance for OS, RFS, or EFS (Supplementary Table 6, http://links.lww.com/BS/A95).

3.5. Long-term influence of baseline serum albumin

To analyze the long-term impact of baseline serum albumin levels separately, we set 12 months as the landmark for survival analysis.

In the univariate analyses, higher baseline serum albumin levels were still correlated with better OS after excluding the effect of the first follow-up year (albumin-high vs albumin-low: HR 0.663, 95% CI: 0.487–0.903, *P* = .009; Supplementary Figure 1, http://links.lww.com/BS/A96, Supplementary Table 7, http://links.lww.com/BS/A95). Although not significant, patients with higher baseline serum albumin levels tended to have better outcomes in multivariate analyses (OS HR per g/L: 0.971, 95% CI: 0.937–1.005, *P* = .092; RFS HR per g/L: 0.959, 95% CI: 0.917–1.002, *P* = .064; EFS HR per g/L: 0.969, 95% CI: 0.929–1.010, *P* = .133; Supplementary Table 8, http://links.lww.com/BS/A95).

3.6. Patients with low serum albumin level enriched for leukemia stem cell signatures

Based on bulk RNA-seq for another cohort, including 129 patients newly diagnosed with AML (Supplementary Table 9, http://links.lww.com/BS/A95), we analyzed the transcriptome profiles of patients with different serum albumin levels. Gene expression analysis identified 154 DEGs, of which 7 were

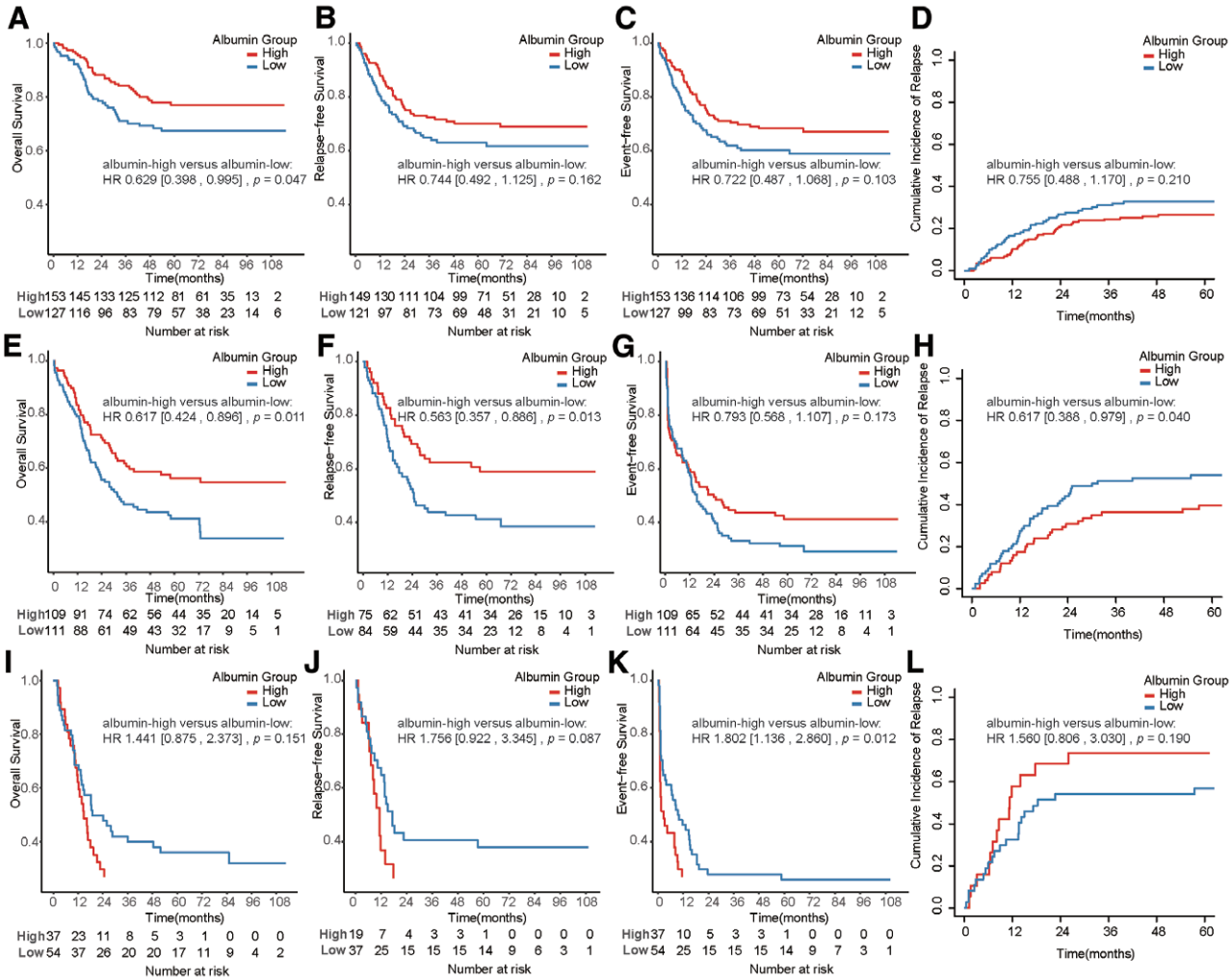

Figure 3. Overall survival, relapse-free survival, event-free survival, and cumulative incidence of relapse of patients with high or low baseline serum albumin levels in ELN favorable (A–D), intermediate (E–H), or adverse (I–L) groups. ELN = European LeukemiaNet, HR = hazard ratio.

upregulated in patients with low serum albumin levels and 147 were upregulated in patients with high serum albumin levels (Supplementary Table 10, http://links.lww.com/BS/A95). GSEA revealed that patients with low serum albumin levels were enriched in leukemia stem cell signatures[26] (Supplementary Figure 2, http://links.lww.com/BS/A96).

4. DISCUSSION

In our prospective cohort of 591 patients newly diagnosed with AML, baseline serum albumin level was found to be a prognostic factor for survival and may contribute to risk stratification, especially in patients with intermediate ELN risk. Lower baseline serum albumin levels correlated with higher CIR and inferior long-term survival, which indicated that albumin level was associated with the inherent properties of leukemia.

Previous studies have suggested that albumin levels are associated with the outcomes of patients with AML. In retrospective studies of newly diagnosed patients treated with cytarabine and anthracyclines, lower baseline serum albumin levels were associated with a higher incidence of treatment complications and may lead to early death due to intolerance to chemotherapy.[21,23] In contrast to these retrospective studies, all patients in our cohort were fit patients with AML who received HAD regimens for induction, most of whom had normal baseline serum albumin levels (>35 g/L). Since the patients in our cohort had a good nutritional status and better tolerance for intensive chemotherapy, we found no effect of albumin on CR rates or 30-day mortality. However, the 12-month landmark analysis suggested that baseline serum albumin levels correlated with inferior long-term survival. The effect of albumin on OS has been evident in multiple cohorts.[20,22,23] In a multi-center retrospective study containing 756 patients, albumin was associated with 30-day mortality, and median OS for patients with a normal albumin was significantly longer than those with hypoalbuminemia or those with marked hypoalbuminemia (1.46 vs 0.71 vs 0.37 years, log-rank $P < .01$).[24] Consistent with previous studies, univariate Cox analysis in our cohort showed that the albumin level was a significant prognostic factor for patients with AML. The baseline characteristics of patients with high or low serum albumin levels differed in our cohort. Lower serum albumin levels correlated with older age, higher WBC count, and increased adverse risk of ELN stratification, indicating that serum albumin levels were associated with the invasiveness of leukemia cells. Notably, the prognostic impact of albumin remained significant after accounting for age, WBC count, ELN risk groups, induction regimens, and transplantation in the multivariate Cox analysis. Furthermore, RNA-seq of patients with AML demonstrated that albumin levels were associated with the properties of leukemia stem cells. Taken together, our data showed that serum albumin level was associated with the inherent properties of leukemia and therefore influenced AML patient outcomes.

Serum albumin levels were significantly prognostic in patients who received ID-HAD induction compared to those who underwent SD-HAD induction. In patients who underwent SD-HAD induction, the albumin-low group showed a similar tolerance to chemotherapy and survival as the albumin-high group. In patients who underwent ID-HAD induction, an increased dose of cytarabine did not cause a difference in chemotherapy tolerance between the albumin-high and albumin-low groups, whereas survival differences between the albumin-high and albumin-low groups were significant. Although the impact of serum albumin levels on patient outcomes was not statistically significant in those who underwent SD-HAD induction, the low-albumin group showed a trend toward poor survival on the Kaplan–Meier survival curve. The different predictive effects of serum albumin between the ID-HAD and SD-HAD groups may be explained by the improved overall outcome of ID-HAD induction.

Patients in different ELN risk groups benefited from different treatment strategies.[5,13,27] However, the outcomes among ELN intermediate-risk patients vary, and further prognostic stratification may provide guidance for clinical treatment. The effect of baseline serum albumin levels was evident in patients with intermediate-risk ELNs. In patients with favorable or adverse ELN risks, patient survival is mainly determined by cytogenetic and molecular analyses, and baseline serum albumin levels do not correlate with superior or inferior outcomes. These findings suggest that baseline serum albumin level can act as a prognostic factor for further risk stratification of patients with AML and intermediate ELN risk.

Our study has some limitations. Although we performed a multivariate analysis, bias may still exist. Given the lack of other suitable cohorts, we were unable to perform external validation. Further studies are needed to validate the prognostic value of serum albumin. Albumin level has been recognized as a prognostic factor. However, we did not discover the mechanism or potential strategies for avoiding inferior outcomes in patients with low serum albumin levels. Further studies are required to address these questions.

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AUTHOR CONTRIBUTIONS

H.W. and J.W. contributed to the study design; H.W., J.W., and J.C. were involved in analyzing and interpreting the data; J.C. and H.W. wrote the report. Y.M., J.W., and H.W. provided the study materials or patients. J.C., Y.H., Y.Z., M.Y., and X.Z. were involved in the collection and assembly of clinical data. All authors reviewed the report and approved the final version.

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