Original Article

Early albumin level and mortality in hemodialysis patients: a retrospective study

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Background: Hypoalbuminemia is a significant risk factor of cardiovascular disease and all-cause death in patients undergoing conventional hemodialysis (HD). However, the albumin (ALB) level of these dialysis patients runs through the whole process of dialysis, and the prognostic value of serum ALB in the early stage of HD and the relationship between the early ALB value and death in HD patients has not been reported.

Methods: The data of 447 patients with HD were retrospectively analyzed. The patients were stratified into three ALB (g/L) groups: low, ALB ≤34.2; moderate, 34.3< ALB <40.1; high, ALB ≥40.2. Survival trends of the three groups were analyzed by the Kaplan-Meier method.

Results: Comparison of the clinical data among the three groups showed a positive correlation between Hb, RBC, K^+, Ca^{2+}, Mg^{2+}, and PHOS (P<0.05), but a negative correlation between age and high-sensitivity C-reactive protein (hsCRP) (P<0.05). The ALB level in early HD patients was an independent predictor of death [hazard ratio (HR) =0.945; 95% confidence interval (CI): 0.916–0.976; P=0.000], while age and hsCRP were protective factors (HR =1.048, 95% CI: 1.028–1.067, P=0.000; HR =1.049, 95% CI: 1.024–1.075, P=0.000). The estimated median overall survival (OS) at early HD was 56.00 months in the low ALB group, 83.00 months in the moderate ABL group, and 95.00 months in the high ALB group. The Kaplan-Meier estimate of survival showed a significant difference in OS among the three groups (log-rank P=0.000).

Conclusions: The early ALB level not only reflects the nutritional and chronic inflammation status of HD patients, but can also predict the prognosis, which has guiding significance for the management of HD patients.

Keywords: Albumin (ALB); death; hemodialysis (HD); inflammation; nutritional status

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Introduction

For patients with end-stage renal disease, hemodialysis (HD) remains the main treatment strategy. The HD patient population of China is increasing rapidly (1,2). Although therapeutic strategies developed over the past few decades have improved survival in patients with kidney disease, the prognosis still remains poor. Cardiovascular diseases, under nutrition and inflammation are predictive factors for

HD mortality. Treatment and early management of these factors are essential for reducing morbidity and mortality (3). Recently, several clinical and biochemical biomarkers, including the serum level of gut microbiota-dependent trimethylamine N-oxide, urine neutrophil gelatinase-associated lipocalin concentration and aldosterone, these factors have been identified as key to death and cardiovascular events in patients with chronic kidney disease (CKD) (4-6). However, these factors may be difficult to obtain in clinical practice, costly or unreliable to detect. Therefore, new prognostic markers need to be identified.

Albumin (ALB) and globulin (GLB), the two main constituents of serum protein, are markers of nutrition and systemic inflammation (7). Inflammation and malnutrition are common in patients with CKD (8). In well-nourished patients, inflammation can lead to malnutrition, while malnutrition can induce inflammatory responses (9). In general, the serum ALB level reflects nutritional status, and that of GLB reflects its important role in immunity and inflammation (10). Some studies have demonstrated that hypoalbuminemia is an independent risk factor for survival of several cancers, including stomach, colorectal, breast and lung cancers (11-13).

CKD is a clinical disorder characterized by a high level of malnutrition and abnormally severe inflammation (7). Hypoalbuminemia is a significant risk factor of cardiovascular disease and all-cause death in patients undergoing conventional HD (14,15). However, most studies of ALB levels have come from the average level of dialysis patients, and the prognostic value of the serum ALB level in the early stage of HD has not been reported. HD patients had the highest mortality rate in the first 6 months, with an 80% higher risk of death in the first 2 months (16). Thus, this study was conducted to assess the prognostic value of the serum ALB level in early HD patients. In addition, we compared the prognostic value between ALB and other clinical indicators. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2611).

Methods

Study population

This study included 447 HD patients from January 1, 2012 to June 30, 2020 at the Affiliated Huadu Hospital, Southern Medical University (People's Hospital of Huadu District). Inclusion criteria: at least 3 months of HD treatment and older than 18 years. Subjects were excluded if they met the following characteristics: (I) history of kidney transplantation or peritoneal dialysis (PD); (II) patients with malignant tumors; (III) patients on immunosuppressive drugs; (IV) patients with insufficient data of ALB; (V) patients who developed acute infection within 3 months of HD treatment.

Clinical and laboratory data collection

Baseline data were collected, including age, sex, dialysis age and outcomes. A retrospective method was adopted to collect laboratory results at 3 months post-dialysis, including hemoglobin (Hb), red blood cell count (RBC), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), phosphorus (PHOS), high-sensitivity C-reactive protein (hsCRP), ALB, globulin (GLB), blood urea nitrogen (BUN), ALB/CLB ratio (A/G), creatinine (CREAT), prothrombin time (PT), international normalized ratio (INR), NT-proBNP, cardiac troponin I (hs-cTnI), and total cholesterol (CHOL). Incomplete data such as GLB, A/G, PT, INR, B-type natriuretic peptide (BNP), and hs-cTnI were excluded from statistical analysis. This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board (IRB) of People's Hospital of Huadu District (No. 2020018). Due to the non-invasive and anonymous nature of this retrospective analysis, individual consent was waived by the IRB.

Statistical analysis

The study patients were assigned to three ALB groups according to the median as follows: low, ALB ≤34.2; moderate, 34.3< ALB <40.1; high, ALB ≥40.2. Descriptive statistics of the baseline characteristics of ALB patients in the three groups were mean ± standard deviation of normal distribution continuous variables, median [interquartile range (IQR)] of non-normal distribution, and the number (%) for enumeration variables. Differences in distribution of variables among the three ALB groups were compared using univariate, multivariate and Cox regression analyses to identify the factors affecting the survival and prognosis of patients. Survival trends of the three groups were analyzed by the Kaplan-Meier method and significance was determined by the log-rank test.

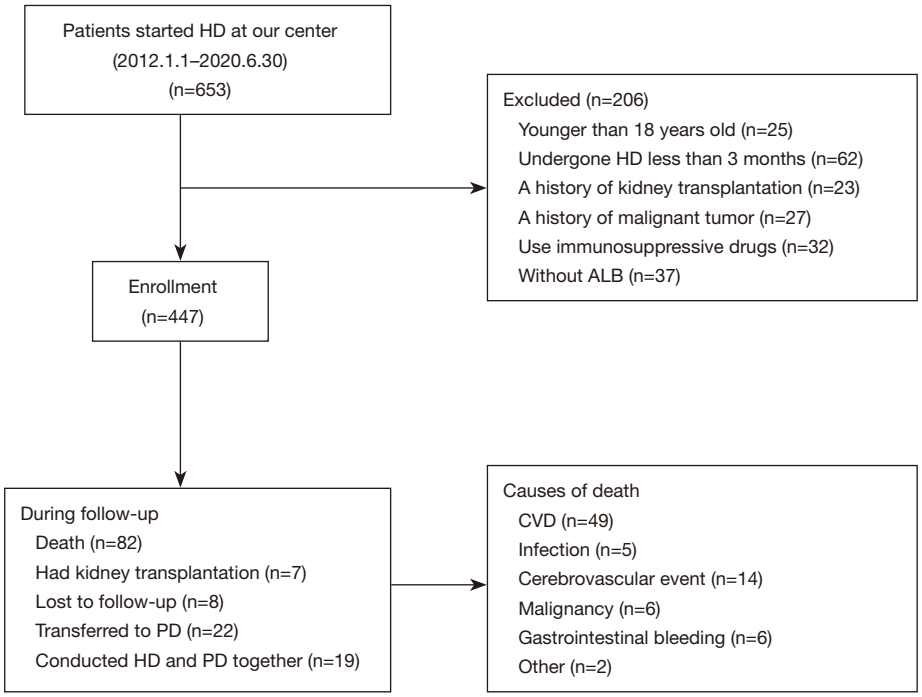

Figure 1 A flow chart of the study. HD, hemodialysis; PD, peritoneal dialysis; ALB, albumin; CVD, cardiovascular disease.

Results

Baseline characteristics of patients

A total of 447 HD patients were enrolled as the study cohort (shown in *Figure 1*). Comparison of clinical data among the three groups showed a positive correlation between Hb, RBC, K^+, Ca^{2+}, Mg^{2+}, and PHOS (P<0.05); that is, the higher the ALB, the higher the corresponding index. In contrast, there was a negative correlation between age and hsCRP (P<0.05); that is, the higher the ALB, the lower the corresponding index (*Table 1*).

Univariate and multivariate analyses showed that sex, age, hsCRP and ALB are potential predictors of OS of HD (P<0.05). We included these indicators in a Cox multivariate regression model, and the results showed that ALB in early HD patients was an independent predictor of death [hazard ratio (HR) =0.945; 95% confidence interval (CI): 0.916–0.976; P=0.000], while age and hsCRP were protective factors (HR =1.048, 95% CI: 1.028–1.067, P=0.000; and HR =1.049, 95% CI: 1.024–1.075, P=0.000) (see *Table 2*).

ALB and mortality

During a median follow-up of 6.5 years, there were 82 of 447 patients (18.34%) died. Causes of death included cardiovascular disease (49, 59.76%), infections (5, 6.10%), cerebrovascular disease (14, 17.07%), malignant tumors (6, 7.32%), gastrointestinal bleeding (6, 7.32%), and others (2, 2.44%). As shown in *Figure 2*, Kaplan-Meier survival analysis diagram showed that there were significant differences in overall survival (OS) between the three ALB groups (log-rank P=0.000). The estimated median OS at early HD according to ALB level was 56.00 months in the low ALB group, 83.00 months in the moderate ABL group, and 95.00 months in the high ALB group. In other words, the low ALB group had the worst OS, while the high ALB group had the best OS.

Discussion

With the acceleration of China's aging population, as well as the increases in obesity, type 2 diabetes, hypertension and other modern civilized diseases, the number of HD patients in China is increasing daily. Although some achievements have been made in the management of dialysis patients, the high mortality rate still needs improvement. Therefore, exploration of easy-to-evaluate and accessible prognostic indicators can help form normative decisions in the

Table 1 Comparison of ALB and baseline characteristics of patients

Variable	Low ABL group (ALB ≤35.7, n=151)	Moderate ABL group (35.7< ALB ≤38.9, n=147)	High ABL group (ALB >38.9, n=149)	Statistic	P
Age (years)	63.92±14.56	58.20±15.30	52.01±14.58	24.237[c]	0.000*
Sex, male	94 (62.3%)	90 (61.2%)	93 (62.4%)	0.052[b]	0.974
Hb (g/L)	90 (73, 106)	104 (90, 116)	107 (95, 119)	43.48[a]	0.000*
RBC (10^{12}/L)	3.33 (2.78, 3.78)	3.6 (3.14, 4.07)	3.68 (3.23, 4.23)	30.11[a]	0.000*
K^+ (mmol/L)	4.41 (3.85, 5.30)	4.81 (4.30, 5.40)	4.90 (4.32, 6.65)	16.15[a]	0.000*
Ca^{2+} (mmol/L)	2.02 (1.87, 2.15)	2.09 (1.90, 2.22)	2.12 (1.94, 2.28)	12.88[a]	0.002*
Mg^{2+} (mmol/L)	0.96 (0.84, 1.02)	1.00 (0.92, 1.08)	1.02 (0.94, 1.14)	27.63[a]	0.000*
PHOS (mmol/L)	1.72 (1.23, 2.03)	1.99 (1.59, 2.25)	2.08 (1.59, 2.64)	30.73[a]	0.000*
hsCRP (mg/L)	5.65 (5.65, 8.29)	5.65 (2.36, 5.65)	4.83 (1.46, 5.65)	30.56[a]	0.000*
BUN (mmol/L)	24.46 (16.67, 26.58)	24.46 (19.98, 27.00)	24.46 (20.14, 28.31)	4.15[a]	0.126
CREAT (μmol/L)	785.37 (528.50, 970.41)	883.39 (709.07, 1,054.41)	1,020.9 (885.01, 1,234.76)	43.53[a]	0.056
CHOL (mmol/L)	4.09 (3.41, 4.36)	4.09 (3.55, 4.29)	4.09 (3.53, 4.75)	1.37[a]	0.505

[a], nonparametric rank sum test; [b], Chi-square test; [c], analysis of variance; *, P<0.05, statistical significance. ALB, albumin; Hb, hemoglobin; RBC, red blood cell count; PHOS, phosphorus; hsCRP, high-sensitivity C-reactive protein; BUN, blood urea nitrogen; CREAT, creatinine; CHOL, total cholesterol.

Table 2 Univariate and multivariate regression analyses of overall survival

Variable	Univariate analysis		Multivariate regression analysis		Cox regression analysis	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (years)	1.039 (1.021, 1.058)	0.000*	1.035 (1.015, 1.054)	0.000*	1.048 (1.028, 1.067)	0.000*
Sex (male/female)	0.538 (0.316, 0.915)	0.022*	0.557 (0.322, 0.964)	0.037*	0.738 (0.451, 1.210)	0.229
Hb (g/L)	1.006 (0.995, 1.017)	0.293	–	–	–	–
RBC (10^{12}/L)	1.302 (0.994, 1.707)	0.056	–	–	–	–
K^+ (mmol/L)	1.111 (0.869, 1.420)	0.401	–	–	–	–
Ca^{2+} (mmol/L)	0.973 (0.748, 1.266)	0.839	–	–	–	–
Mg^{2+} (mmol/L)	1.783 (0.466, 6.820)	0.398	–	–	–	–
PHOS (mmol/L)	0.801 (0.557, 1.153)	0.233	–	–	–	–
hsCRP (mg/L)	1.112 (1.044, 1.185)	0.001*	1.090 (1.019, 1.165)	0.012*	1.049 (1.024, 1.075)	0.000*
ALB (g/L)	0.957 (0.916, 1.000)	0.045*	0.996 (0.948, 1.047)	0.026*	0.945 (0.916, 0.976)	0.000*
BUN (mmol/L)	1.011 (0.995, 1.028)	0.187	–	–	–	–
CREAT (umol/L)	1.000 (0.999, 1.000)	0.383	–	–	–	–
CHOL (mmol/L)	0.921 (0.708, 1.198)	0.539	–	–	–	–

*, P<0.05, statistical significance. Hb, hemoglobin; RBC, red blood cell count; PHOS, phosphorus; hsCRP, high-sensitivity C-reactive protein; ALB, albumin; BUN, blood urea nitrogen; CREAT, creatinine; CHOL, total cholesterol.

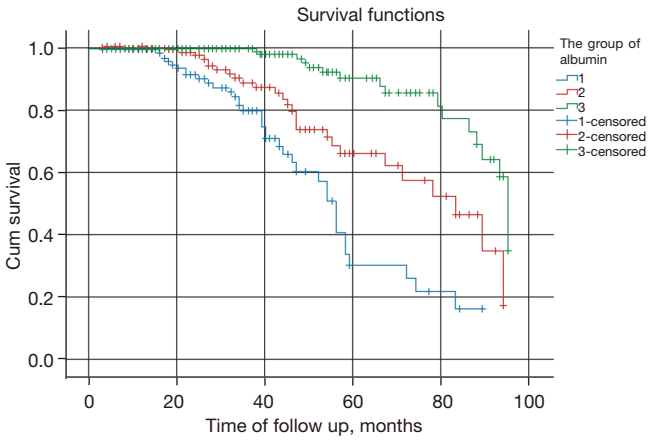

Figure 2 Survival function of different levels of serum ALB in early stage of hemodialysis. 1= low ABL group, ALB ≤34.2; 2= moderate ABL group, 34.3< ALB <40.1; 3= high ABL group. ALB, albumin.

management of dialysis patients. Laboratory indicators such as ALB, hsCRP, protein-energy wasting, and atherosclerosis have been reported to predict long-term survival in dialysis patients (9,17,18). Summary of previous experience, this is the first work to show the prognostic value of ALB in overall and cardiovascular mortality in the early stage of HD.

There is increasing evidence that nutritional status and chronic inflammation play an important role in the prognosis of dialysis patients. Nutritional disorders in dialysis patients are mainly manifested by inflammation, various metabolic changes, uremia, and loss of nutrients (19). Nutritional disorders may cause immunosuppression, reduced resistance to the disease and decrease wound healing (20). Elderly patients are more likely to show these signs. The results of this study showed that age was a protective factor for the survival of HD patients. Older people tend to reduce their dietary intake due to various factors, such as psychosomatic and social factors, as well as taste impairment and age-related loss of appetite. According to a 2016 Health and Nutrition Survey, malnutrition rates among 65 years old tend to be 17.8%, which applied to approximately one-sixth of the elderly (21). Sarcopenia occurs commonly in HD patients and correlates with the nutritional status, especially in the elderly (22).

In another hand, malnutrition is a particular factor affecting the prognosis and deterioration of patients. ALB is mainly synthesized in liver parenchyma and is the main component of serum protein, which is often used to reflect the nutritional status of the body (23). If there is a sufficient amount of ALB, polyunsaturated fatty acids (especially docosahexaenoic acid, eicosapentaenoic acid and arachidonic acid) are mobilized from the liver, and contribute to the formation of cell-bioactive lipids, such as hydrolyzed protein and the protective blood-brain barrier (24). However, a low ALB level could damage the body's natural defense mechanisms, including homeostasis of steroid hormones and calcium, anatomic barriers, and even the pharmacological activity of drugs (25). Lower ALB is related to increased rates of hospitalization and number of hospital days in incident HD patients (26).

The results of this study showed that the ALB level in early HD patients was an independent predictor of death. In terms of nutritional prediction, Stosovic *et al.*'s study (27), which analyzed random ALB levels during dialysis, detected malnutrition with a predictive value of 74% and a specificity of 88%. Their results suggested that ALB was a sensitive but highly specific assay for the assessment of malnutrition in HD. With regard to prognosis, Caraceni *et al.*'s study showed that hypoalbuminemia powerfully predicts morbidity and mortality (28). Other research has pointed out that both hypoalbuminemia (<3.2 g/dL) and undernourishment (being underweight: body mass index <23 kg/m^2) were significant predictors of death in patients in HD (29). In our study, the prognostic significance of ALB for HD patients was found in the early stage of dialysis. Therefore, nutritional intervention can be initiated in the early stage of HD to improve the ALB level.

Systemic inflammation is characteristic of various chronic diseases including CKD. Inflammation is thought to be a complex biological response of vascular tissue to various types of injury, but instead serves as a protective mechanism (30). The persistent inflammatory state is partly due to impaired renal clearance of pro-inflammatory cytokines and partly due to increased generation of cytokines (31). Uremia is a chronic inflammatory condition that has been confirmed by several studies (32,33). Even after each dialysis, HD patients remain in an inflammatory state due to elevated serum levels of pro-inflammatory cytokines such as IL-6,tumor necrosis factor-a, and interleukin-1 (IL-1) (34,35). An elevated level of CRP, an acute-phase reactant, has been found to predict the clinical outcome for a variety of cardiovascular diseases, such as myocardial infarction and stroke, in patients with CKD

and those undergoing dialysis (18). The results of our study showed that CRP was a protective factor for the survival of HD, which further verified the above studies. Therefore, we believe that it is possible to improve patients' inflammatory status in the early stage of dialysis, such as reducing catheter infection, endotoxemia, fluid overload, unhealthy lifestyle and diet, to improve patients' long-term survival outcomes. We could enhance self-care behaviours include restricted fluid intake, an appropriate diet, coping with stress and regular drug use to improve the overall survival rate of HD patients and improve the quality of life (36).

It is important to note that the effects of nutrition and inflammation are interrelated, and that the presence of malnutrition and inflammation may prevent the synthesis of ALB (20). Univariate analysis in our study showed that the lower the ALB in early dialysis patients, the higher the hsCRP level. A significant negative correlation between ALB and hsCRP levels was reported by As'habi *et al.* (37) in their research on malnutrition, inflammation and cardiovascular disease in HD patients, which further confirms our findings. In addition, hypoalbuminemia may reflect malnutrition, but other studies have reported that elevated hsCRP level is a strong and independent predictor of low ALB level, suggesting that hypoalbuminemia in HD patients may be due to inflammation rather than malnutrition (38). In conclusion, ALB is an indicator that can reflect both the nutritional status and chronic inflammation, and is closely related to the survival prognosis of HD patients.

During a median follow-up of 6.5 years, there were 82 of 447 patients (18.34%) died. Cardiovascular disease (49, 59.76%) accounted for most of the deaths. Further analysis found that the estimated median OS according to ALB level in early dialysis was 56.00 months in the low ALB group, 83.00 months in the moderate ABL group, and 95.00 months in the high ALB group. Compared with patients with reduced ALB in the early stages of dialysis, patients with higher ALB in the early stages of dialysis had a lower risk of overall death and cardiovascular death. It has been shown that increased oxidative stress caused by biological changes in the ALB level could promote the development of atherosclerosis and cardiovascular disease in HD patients (39). The ALB level in HD patients has been related to left ventricular hypertrophy and heart failure, and this can be used by doctors to determine the patient's ability and risk of cardiovascular diseases (40). In a report on the ALB trajectory in PD patients, the ALB level after PD was better than ALB level at the start of PD in predicting mortality risk. With the extension of time, the gradual increase of ALB level can improve the outcome and prognosis of PD patients (17). Although our study could not determine whether ABL had an effect on the prognosis of patients with the duration of HD, it showed it was possible to improve the survival time of patients by intervening in the ALB level in the early stage of HD.

Study limitations

First of all, all the included studies were retrospectively analyzed from a single center and all of them were from China. Prospective studies should be added to verify our findings. Second, we only studied the relationship between early ALB level and death in HD patients. We did not control how the ALB level would change over time, and this issue is an interesting topic for further research. Finally, in this study, indicators such as GLB, A/G, PT, INR, BNP and hs-cTnI were not included in the final statistical analysis because too little data was collected, which may affect the results of regression analysis. And we will try to increase the epidemiological investigation of maintenance HD patients and the correlation analysis of survival prognosis.

Conclusions

In conclusion, for HD patients, the early ALB level not only reflects the nutritional status and chronic inflammation of dialysis patients, but also predicts the prognosis of patients, which has guiding significance for the intervention and treatment of HD patients and is worthy of our attention and application.

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Footnote

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Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-2611

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2611). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board (IRB) of People's Hospital of Huadu District (No. 2020018). Due to the non-invasive and anonymous nature of this retrospective analysis, individual consent was waived by the IRB.

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