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A Low Serum Albumin Level Predicts Cardiovascular Events in Hemodialysis Patients with Preserved Left Ventricular Ejection Fraction

Mizuki Komatsu[1], Masayuki Okazaki[1], Ken Tsuchiya[2], Hiroshi Kawaguchi[1], Kosaku Nitta[2*]

[1]Department of Nephrology, Jyoban Hospital, Fukushima, Japan
[2]Department of Medicine, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan
Email: [*]knitta@kc.twmu.ac.jp

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Abstract

Background: Cardiovascular (CV) diseases are the most frequent cause of death in hemodialysis (HD) patients. The aim of this study was to identify risk factors for CV events in HD patients with preserved left ventricular ejection fraction (PEF). Objectives: A total of 213 HD patients (69 years, 64.1% males) were enrolled. Demographic, laboratory test, and echocardiographic data were recorded, and CV events during the 32-month follow-up period were documented. Results: During the follow-up period, 31 patients (14.6%) died and 50 patients (23.5%) suffered a fatal or non-fatal CV event. Age and serum albumin, C-reactive protein, total cholesterol, non-HDL cholesterol, and NT-proBNP levels were associated with CV events according to a univariate analyses. A multivariate analysis identified a low serum albumin value ($p < 0.001$) as an independent predictor of CV events. A low serum albumin level was also identified as an independent predictor of all-cause mortality ($p = 0.0356$). Kaplan-Meier curves showed CV events to be more frequent in the group of subjects with the lowest tertile of serum albumin levels ($p = 0.0063$). Conclusion: A low serum albumin value is an important risk factor for death and CV events in HD patients with PEF.

Keywords

Cardiovascular Events, Albumin, Echocardiography, Hemodialysis, Mortality

[*]Corresponding author.

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1. Introduction

The high mortality of patients with end-stage renal disease (ESRD) is mainly attributable to cardiovascular (CV) diseases, which are responsible for more than 40% of the deaths in this patient population [1] [2]. Although the higher risk of CV diseases in hemodialysis (HD) patients is likely due to their severely compromised CV state, HD patients without any apparent CV diseases are also at higher risk of future CV events. Thus, identifying HD patients with an increased CV risk is of clinical importance and would enable preventive measures to be implemented.

The prognostic power of systolic function in HD patients has been investigated [3]. Systolic function may be estimated by echocardiography on the basis of the left ventricular ejection fraction (LVEF) or fractional shortening, which is the index that has been used in the great majority of studies [4]. Numerous reports have suggested that more than half of patients with congestive heart failure do not have any abnormality of systolic function. Such patients may have heart failure on the basis of diastolic dysfunction despite having preserved LVEF (PEF) [5] [6].

In recent years, circulating biomarkers, including brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), have been considered useful as a means of early detection of LV dysfunction. Tschöpe *et al*. reported finding that the median plasam NT-proBNP level of patients with normal kidney function increased with the severity of their diastolic dysfunction [7], and we have found that both NT-proBNP and the left atrial volume index are good biomarkers for predicting LV remodeling in chronic HD patients [8].

Albumin has been studied previously as a potential predictor of outcome in patients with heart failure and PEF [9] but not in HD patients with PEF. The aim of this study was to determine whether biomarkers and echocardiographic parameters, predict CV events and all-cause mortality in chronic HD patients with PEF.

2. Methods

2.1. Study Subjects

This was a prospective, observational cohort study conducted at a single center in Japan. The study was performed in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of Jyoban Hospital, Fukushima, Japan. Inclusion criteria were: 20 years of age or over; on long-term HD therapy for 6 months or more; compliance with HD treatment; and medically stable in the opinion of the investigator. All patients gave informed consent to participation in this study. The subjects were recruited from patients who had routinely undergone HD therapy through an arteriovenous fistula as previously described [10]. HD patients with malignancy, active inflammation, liver cirrhosis, gastrointestinal bleeding, cardiac valuvular disease, or severe illness were excluded from participation and were transferred to another dialysis unit for intensive care. The subjects (n = 220) underwent stable regular HD therapy with a bicarbonate dialysate and echocardiography. Since 7 of the subjects had systolic dysfunction, the data of the remaining 213 HD patients were analyzed.

Each patient underwent HD three times weekly (4 hours/day). The potassium concentration of the dialysate was 2.0 mEq/l, and its calcium concentration was 3.0 mEq/l. Blood pressure (BP) was measured with a mercury sphygmomanometer with the patient in the supine position after resting for 10 to 15 minutes, and mean values for the 1-month period preceding enrollment were used in the statistical analysis. Diabetes mellitus was diagnosed on the basis of World Health Organization (WHO) criteria [11] and presence of diabetic retinopathy or prescription of glucose-lowering agents. Hypertension was recorded as present when a patient met the WHO criteria (office BP > 140/90 mmHg and/or were being treated with an antihypertensive agents). The liver functions of all subjects were within normal range.

Medical records were carefully checked for prescriptions of antihypertensive agents, including angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers, and beta-blockers. Prescriptions were also checked for phosphate binders and active vitamin D3. All of the study subjects were treated with erythropoiesis-stimulating agents for renal anemia. In this study, CV disease was defined as electrocardiogram-documented anginal episodes and myocardial infarction, congestive heart failure, transient ischemic attacks, stroke, and peripheral artery disease. The BP data, and cardiothoratic ratio calculated from chest X-rays, and the echocardiography findings were checked after the mid-week HD session. The HD patients, who had experienced no CV evens in the 4 weeks before the serum determinations, were enrolled in this study.

2.2. Echocardiography

Echocardiography was performed on a nondialysis day before the mid-week dialysis session by an experienced senior cardiosonographer who was blinded to the clinical information and laboratory data. A Xario XG (TOSHIBA, Tokyo, Japan) ultrasound imager equipped with a 2.2/4.4 MHz (harmonics) phased-array 3S transducer during continuous electrocardiographic recording. To avoid the measurement bias, only stable patients were included in the study, with no dry weight changes > 0.5 kg, and with the same pre-dialysis blood pressure (±10%) during the 4 previous weeks. The data were saved in the device's archive (digital archive, raw data), and the images obtained were recalled for calculation of the study parameters by the same interpreter, who was unaware of the patients' clinical status. A two-dimensional guided M-mode echocardiographic study of the left ventricle (LV) was performed by using the parasternal long-axis view, and the means of measurements of LV end-systolic and end-diastolic dimension (LVDd), interventricular septum thickness (IVST), and posterior wall thickness (PWT) in five consecutive cardiac cycles were used, in accordance with the recommendations of the American Society of Echocardiography [12]. LV mass was calculated by using the formula derived by Deveraux: $1.04[(IVST + LVDd + PWT)^3 - LVDd^3] - 16.9$, and was indexed for body surface area to estimate the LV mass index (LVMI) [13]. LVEF was measured by the Quinones method on the parasternal view [14], and LV systolic dysfunction was defined as LVEF < 50%.

Each patient underwent a pulse-wave Doppler examination of mitral inflow before and during a Valsalva maneuver. Transmitral pulsed Doppler velocity recordings from three consecutive cardiac cycles were used to derive measurements for early diastole (E) and atrial (A) filling velocities, deceleration time (DT; interval between the time of the peak of the E-wave and the time when velocity declined to the baseline). Diastolic function was classified as: normal (0.75 < E/A < 1.5, DT > 140 ms); mild diastolic dysfunction (impaired relaxation pattern; E/A 0.75); moderate (pseudonormal pattern; 0.75 < E/A < 1.5, DT > 140 ms), and severe (restrictive pattern; E/A > 1.5, DT < 140 ms) [15]. The investigator who performed the echocardiography was blinded to the patient's volume status and serum NT-proBNP level.

2.3. Laboratory Measurements

Blood sampling was performed before the mid-week dialysis session at the same time echocardiography was performed. Serum urea nitrogen, creatinine, calcium, phosphorous, albumin, total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride, and C-reactive protein (CRP) levels and the hemoglobin concentration were measured with an autoanalyzer by standard laboratory methods. Total calcium was corrected by the patient's albumin level. Intact parathyroid hormone (iPTH) was measured by an immunoradiometric assay. Urea kinetics were assessed by measuring a blood-based dialysis parameter, Kt/V [16], and the mean value of the 3 measurements during each of the 3 months before the start of the study was used in the analysis. Serum NT-proBNP levels were measured by an electrochemiluminescence immunoassay on an Eclusys 2010 Analyzer (Roche Diagnostics, Tokyo, Japan). The detection limit was 5 - 35,000 pg/ml. When the NT-proBNP concentration was higher than the measurement range, 35,000 pg/ml was recorded as the final concentrations.

2.4. Outcome Evaluation

New CV events, *i.e.*, ischemic or hemorrhagic cerebrovascular accidents (diagnosed by computed tomography), myocardial infarction (diagnosed by cardiac marker elevations and electrocardiography, and diagnosis confirmed by coronary angiography), congestive heart failure (diagnosed on the basis of the presence of acute pulmonary edema and an echocardiogram with ventricular systolic dysfunction; left ventricular ejection fraction < 50%), peripheral vascular events (diagnosed on the basis of evidence of stenosis of the primary arteries or lower extremities confirmed by arteriogram and/or need for amputation), and other ischemic events, and mortality were recorded during the follow-up period. We analyzed predictors of mortality and CV events, as well as factors, including serum NT-proBNP levels.

2.5. Statistical Analysis

All data that showed a normal distribution are reported as the means ± SD and were compared by analysis of covariance. Nonparametric values are reported as median values and were compared by the Kruskal-Wallist test. Categorical values are reported in the form of percentages and were compared by the Fisher exact test. A Cox

regression analysis was used in a model to determine how independent variables predicted the occurrence of CV events and all-cause mortality. We considered some variables that possess $p < 0.1$ in a univariate logistic regression analysis as independent variables in a multivariate logistic regression analyses. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from the estimated regression coefficients and standard errors. The survival analysis was based on the Kapalan-Meier curve with subjects censored for death and with new CV events. A log-rank test was used to compare the prevalence of CV events and survival rates of 3 groups. All statistical analyses were performed with the SPSS 18.0® statistical package (SPSS, Inc., Chicago, IL, USA). p values < 0.05 were considered statistically significant. All of the statistical tests were performed by a statistician.

3. Results

The baseline characteristics of the study population are shown in **Table 1**. The underlying kidney diseases of ESRD were diabetic nephropathy (n = 96), chronic glomerulonephritis (n = 58), hypertensive nephrosclerosis (n = 50), polycystic kidney disease (n = 4), congenital anomalies (n = 3), and unknown (n = 2). The median age of the subjects was 69 years, and their mean duration of dialysis (dialysis vintage) was 54 months. There were 141 male (66.2%) of the subjects, and 96 (45.0%) had diabetes. Fifty-eight subjects (27.2%) had previous CV disease at the start of the current study. Hypertension was present in 89.5% of the study subjects.

The median M-mode and Doppler echocardiographic indices of the subjects with preserved LV systolic function are shown in **Table 2**. The median LVEF, as an index of systolic LV function, was 72%. Their median E/A ratio was 0.8, and median DT was 233.0 ms, respectively as an index of diastolic LV function. LV diastolic dysfunction was detected in 70.0%.

During the follow-up period of 32 months, 31 patients (14.6%) died. The univariate analysis (**Table 3**) revealed associations between all-cause mortality and age, and serum albumin, CRP, total cholesterol, non-HDL-cholesterol, and NT-proBNP levels. The adjusted model (**Table 3**) showed that age and serum albumin and non-HDL cholesterol levels were the only independent predictors of mortality.

A non-fatal or fatal CV event was experienced by 50 patients (23.5%) during the follow-up period. The univariate analysis (**Table 4**) showed associations between CV events and serum albumin, CRP, total cholesterol, non-HDL-cholesterol, and NT-proBNP levels. The adjusted model (**Table 4**) showed that serum albumin and non-HDL cholesterol levels were the only independent predictors of CV events.

A Kaplan-Meier survival analysis was performed to study the relationships between both the NT-proBNP levels and non-HDL cholesterol levels divided into tertiles and survival probability. There were no significant differences between the tertiles of NT-proBNP levels (**Figure 1(a)**) or non-HDL cholesterol levels (**Figure 1(b)**) and the probability of death.

According to the Kaplan-Meier curves for prevalence of CV events and the NT-proBNP levels and serum albumin levels, there were no significant differences in the prevalence of CV events according to the tertiles of NT-proBNP levels (**Figure 2(a)**), but CV events were significantly more frequent in the lowest tertile of serum albumin levels than the higher two tertiles (**Figure 2(b)**, $p = 0.0063$).

4. Discussion

The results of the present study show that a low serum albumin levels is the best long-term independent predictor of mortality in HD patients with PEF, and they identified a low serum albumin level as an independent risk factor for developing CV events. Serum NT-proBNP, usually measured to assess cardiac dysfunction, was not found to be associated with CV events or mortality in our cohort as they reflect cardiac damage.

The Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that HD patients whose serum albumin level below 3.5 g/dl were at higher risk of death [17]. A 10-year cohort study in Japan reported an increased risk of death in HD patients with a serum albumin level below 3.8 g/dl, and in that study the serum albumin level was found to be a negative inflammatory and nutritional parameter that was shown to be an independent predictor of mortality in HD patients [18]. A meta-analysis of 38 studies of a total of 265,330 HD patients showed an inverse relationship between serum albumin levels and both all-cause and CV mortality [19].

de Mutsert *et al*. investigated the effects of inflammatory and nutritional status on the association between serum albumin and mortality in dialysis patients [20] and found that a 1 g/dl decrease in serum albumin level was associated with a 47% increase in mortality risk. The increase in mortality risk was in part explained by the inflammatory pathway and was not a consequence of malnutrition. Their findings imply that the nutritional status

Table 1. Baseline characteristics of the study population.

Age, years	69	(20 - 80)
Male gender, %	66.2	
Dialysis vintage, months	54	(19 - 369)
CKD etiology, %		
Diabetes mellitus	45.0	
Glomerulonephritis	27.3	
Nephrosclerosis	23.2	
Polycystic kidney disease	1.8	
Congenital anomalies	1.4	
Unknown	0.9	
History of cardiovascular disease[1], %	27.2	
Hypertension, %	89.5	
Dry weight, kg	55.0	(32 - 96)
Mean blood pressure, mmHg	104.6	(74.9 - 142.7)
Pulse pressure, mmHg	73.8	(40.5 - 108.3)
Single pool Kt/V	1.3	(0.8 - 1.8)
Hemoglobin, g/dl	10.5	(5.9 - 13.8)
Albumin, g/dl	3.6	(2.0 - 4.4)
C-reactive protein, mg/dl	0.11	(0.01 - 15.54)
Total cholesterol, mg/dl	150	(80 - 310)
HDL-cholesterol, mg/dl	44	(15 - 103)
Non-HDL-cholesterol, mg/dl	103	(48 - 269)
Triglyceride, mg/dl	95	(31 - 507)
Calcium, mg/dl	9.0	(6.7 - 11.1)
Phosphorus, mg/dl	5.0	(2.0 - 10.0)
Intact parathyroid hormone, pg/ml	106	(10 - 1281)
NT-proBNP, pg/ml	2855	(119 - 472,084)
Antihypertensive agents		
ARBs, %	44.1	
ACEIs, %	10.5	
Beta-blockers, %	17.3	
Phosphate binders, %	43.2	
Active Vitamin D, %	50.9	

Data are expressed as median (range) or percentage. [1]History of heart disease has been defined as congestive heart failure determined by echocardiography within the 3 previous months, myocardial infarction, cerebrovascular disease and peripheral artery disease.

Table 2. Baseline echocardiographic findings.

Left atrial diameter (LAD), mm	37	(25 - 54)
Left ventricular end-diastolic diameter (LVDd), mm	47	(19 - 63)
Left ventricular end-systolic diameter (LVDs), mm	28	(12 - 48)
Intraventricular septal thickness (IVST), mm	11	(8 - 22)
Left ventricular posterior wall thickness (LVPWT), mm	11	(5 - 19)
Left ventricular ejection fraction (LVEF), %	72	(46 - 88)
Left ventricular fractional shortening (LVFS), %	41	(10 - 58)
Left ventricular mass index (LVMI), g/m^2	221	(35 - 498)
Left ventricular hypertrophy, %	97.3	
E/A	0.8	(0.38 - 4.15)
DT, ms	233.0	(14.3 - 475.0)
Diastolic dysfunction, %	70.0	

Data are expressed as median (range). E/A: ratio of mitral inflow early diastole filling velocity (E) and atrial filling velocity (A); DT: deceleration time.

Table 3. Univariate and multivariate Cox regression models for all-cause mortality.

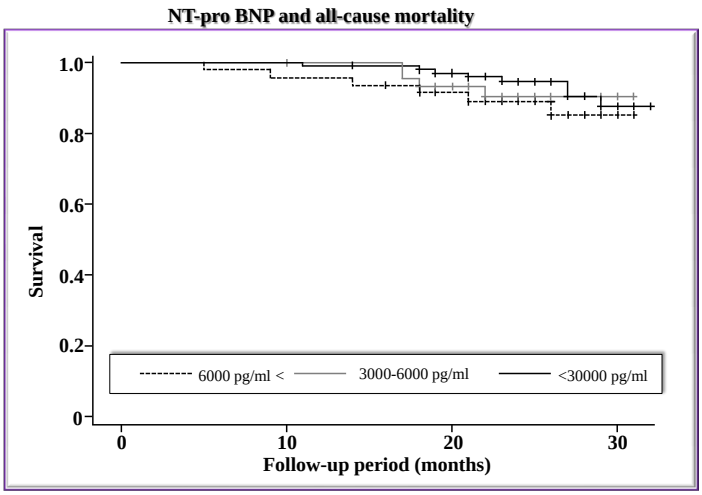
	Unadjusted model		Adjusted model*	
	HR (95% CI)	p	HR (95% CI)	p
Age, years	1.069 (1.033 - 1.107)	<0.001	1.049 (1.006 - 1.093)	0.025
Male gender[a]	1.592 (0.712 - 3.558)	0.258		
Previous heart disease	1.421 (0.538 - 3.757)	0.478		
Diabetes mellitus	1.839 (0.885 - 3.822)	0.102		
Hypertension	0.897 (0.333 - 2.418)	0.830		
Dialysis vintage, months	0.998 (0.991 - 1.004)	0.479		
Mean arterial pressure, mmHg	0.985 (0.953 - 1.018)	0.373		
Pulse pressure, mmHg	1.006 (0.978 - 1.035)	0.667		
Kt/V	0.455 (0.109 - 1.891)	0.279		
Albumin, g/dl	0.363 (0.166 - 0.792)	0.011	0.237 (0.062 - 0.909)	0.036
C-reactive protein, mg/dl (log)	1.354 (1.077 - 1.703)	0.010		
Phosphorus, mg/dl	1.099 (0.869 - 1.391)	0.431		
Total cholesterol, mg/dl	0.984 (0.971 - 0.998)	0.029		
Non-HDL-cholesterol, mg/dl	1.056 (1.024 - 1.089)	0.004	1.064 (1.026 - 1.105)	0.001
NT-proBNP, pg/ml (log)	1.390 (1.111 - 1.738)	0.004		
Left ventricular hypertrophy	0.813 (0.109 - 6.083)	0.842		
Diastolic dysfunction	0.613 (0.292 - 1.290)	0.197		
ARBs/ACEIs	0.869 (0.206 - 3.670)	0.849		
Phosphate binders	1.171 (0.536 - 2.557)	0.425		
Active vitamin D3	0.436 (0.199 - 0.956)	0.038		

Analysis performed using Cox regression. HR (95% CI) = Hazard ratio (95% confidence interval). *Model adjusted for age, albumin, C-reactive protein, total cholesterol, non-HDL cholesterol, NT-proBNP, and active vitamin D3 use. [a]Male has been codified as 0 and female as 1.

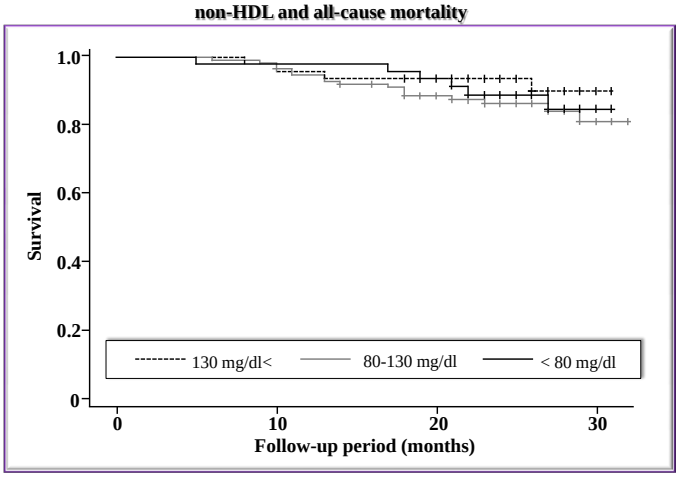
Table 4. Univariate and multivariate Cox regression models for CV events.

	Unadjusted model		Adjusted model*	
	HR (95% CI)	p	HR (95% CI)	p
Age, years	1.021 (0.998 - 1.044)	0.071		
Male gender[a]	0.973 (0.546 - 1.734)	0.927		
Previous heart disease	0.890 (0.378 - 2.094)	0.789		
Diabetes mellitus	1.325 (0.753 - 2.331)	0.329		
Hypertension	1.209 (0.471 - 3.103)	0.693		
Dialysis vintage, months	0.999 (0.994 - 1.003)	0.555		
Mean arterial pressure, mmHg	0.991 (0.967 - 1.016)	0.471		
Pulse pressure, mmHg	1.016 (0.994 - 1.039)	0.152		
Kt/V	0.651 (0.231 - 1.839)	0.418		
Albumin, g/dl	0.318 (0.182 - 0.555)	<0.001	0.216 (0.092 - 0.509)	<0.001
C-reactive protein, mg/dl (log)	1.171 (0.972 - 1.410)	0.097		
Phosphorus, mg/dl	1.064 (0.892 - 1.269)	0.493		
Total cholesterol, mg/dl	0.990 (0.980 - 1.000)	0.044		
Non-HDL-cholesterol, mg/dl	1.011 (1.011 - 1.021)	0.028	1.015 (1.004 - 1.026)	0.008
NT-proBNP, pg/ml	1.390 (1.111 - 1.738)	0.004		
Left ventricular hypertrophy	1.741 (0.239 - 12.687)	0.584		
Systolic dysfunction	2.315 (0.712 - 7.526)	0.163		
Diastolic dysfunction	0.910 (0.494 - 1.678)	0.764		
ARBs/ACEIs	1.425 (0.808 - 2.512)	0.221		
Phosphate binders	0.877 (0.477 - 1.610)	0.671		
Active vitamin D3	0.816 (0.465 - 1.431)	0.478		

Analysis performed using Cox regression. HR (95% CI) = Hazard ratio (95% confidence interval). *Model adjusted for age, albumin, C-reactive protein, total cholesterol, non-HDL cholesterol and NT-proBNP. [a]Male has been codified as 0 and female as 1.

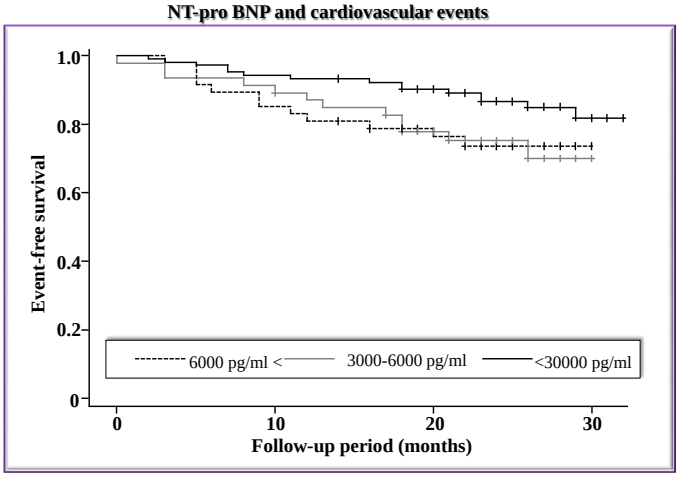


(a)

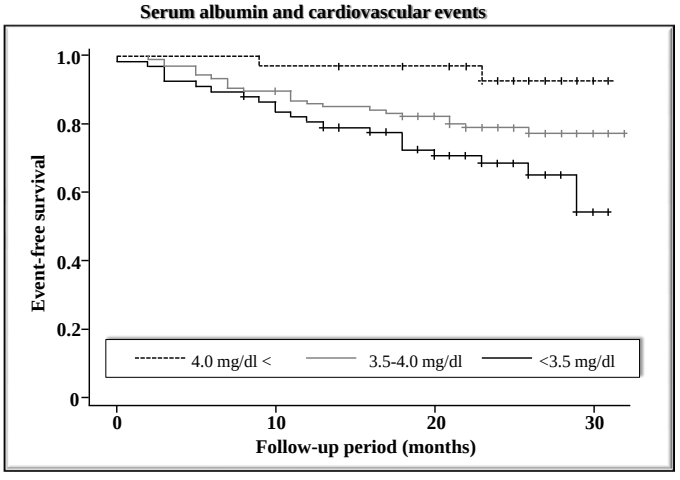


(b)

Figure 1. (a) Kaplan-Meier curves of time to death according to tertile of serum NT-proBNP levels; (b) Kaplan-Meier curves of time to death according to tertile of serum non-HDL cholesterol levels.



(a)



(b)

Figure 2. (a) Kaplan-Meier curves of time to cardiovascular events according to tertile of serum NT-proBNP levels; (b) Kaplan-Meier curves of time to cardiovascular events according to tertile of serum albumin levels.

of dialysis patients cannot be accurately assessed on the basis of serum albumin measurements in dialysis patients.

Protein-energy wasting (PEW), a condition in which there is loss of muscle and visceral protein stores that is not entirely accounted for by inadequate nutrient intake, is common in dialysis patients [21]. PEW has been found to be the strongest predictor of death in dialysis patients [22]. Hypoalbuminemia is the most commonly used surrogate for PEW in dialysis patients and is strongly associated with increased mortality [23]. Serum albumin is negative acute phase reactant, and its serum levels are profoundly affected by the presence of an inflammatory response. Low serum albumin levels may be associated with hypercoagulable states and increased blood viscosity as reviewed by Bonanni *et al*. [24] and low oncotic pressure may adversely affect the fluid shift between the intravascular space and interstitial space. Albumin also has an important role as a free-radical scavenger and is a binding agent for toxic compounds and a carrier for a wide variety of drugs and hormones. Thus, low serum albumin levels may be associated with increased mortality according to these reasons in HD patients with PEF.

Malnutrition is common, and is associated with increased mortality risk in patients with heart failure [25]. A previous study has shown that serum albumin level predicts survival in heart failure patients with reduced EF [26]. The clinical significance of nutritional risk assessment in heart failure patients with PEF [27]. Liu *et al*. [9] studied 576 consecutive heart failure patients with PEF in terms of 1year outcome after admission. Hypoalbuminemia (<3.4 g/dl) was detected in 160 (28%) at admission. Kaplan-Meier analysis showed that patients with hypoalbuminemia had a significantly lower survival rate and a higher rate of CV death when compared with those without hypoalbuminemia. Cox regression analysis revealed that hypoalbuminemia is a powerful independent predictors of all-cause mortality in heart failure patients with PEF. However, it has not been reported whether serum albumin level predicts survival in HD patients with heart failure and PEF. This is the first report showing the predictive value of serum albumin on mortality in these patients.

LV diastolic dysfunction is likely to be associated with CV events and death in HD patients with PEF [28] [29]. Quiroga *et al*. [29] reported that 94 patients in a historical cohort of 211 prevalent HD patients experienced CV events. A low serum albumin level, diastolic dysfunction, and previous history of CVD were identified as independent predictors of CV events. In our study, however, we found that the serum albumin level was an independent predictor of CV events but that diastolic dysfunction was not. While 70% of the subjects of our study had LV diastolic dysfunction, we had excluded HD patients with LV systolic dysfunction at entry. This discrepancy may be associated with the difference in the inclusion criteria of study population.

The present study had several limitations. First, it was an observational study and had the typical limitation of a small number of subjects and relatively low numbers of CV events. The second limitation was that we did not measure fluid status. Increased extracellular fluid volume may decrease serum albumin level. Third, we used the gold standard of immunonephelometry to measure serum albumin level. The previous studies reported the bromocresol purple method of albumin measurement which gives slightly lower levels [30]. Fourth, we only have one echocardiogram collected in HD patients, because our center performs once every 2 years in stable patients. In dialysis patients, echocardiography parameters change with their volume status, we avoided this bias by including only stable patients with no changes in dry weight or blood pressure values.

In conclusion, serum albumin is an emergent risk factor for death and CV events in HD patients with PEF, and conditions a poorer long-term prognosis. We should pay attention to serum albumin levels to predict CV events and death even in stable HD patients with PEF.

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Disclosure

The authors have no conflicts of interest to declare.

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