Original Article

Comparison of Serum Albumin, Serum C-Reactive Protein, and Pulse Wave Velocity as Predictors of the 4-Year Mortality of Chronic Hemodialysis Patients

Nobuyuki Amemiya[1], Tetsuya Ogawa[2], Kuniaki Otsuka[2], Yoshitaka Ando[3] and Kosaku Nitta[1]

[1]Kidney Center, Department of Medicine, Tokyo Women's Medical University, Tokyo Japan
[2]Medical Center East, Department of Medicine, Tokyo Women's Medical University, Tokyo Japan
[3]Hidaka Hospital, Gunma, Japan

***Aim*: Although serum albumin and C-reactive protein (CRP) levels and pulse wave velocity (PWV) are known to be associated with the clinical outcome of hemodialysis (HD) patients, it is unknown which of these parameters are more predictive of the long-term mortality of such patients.**
***Methods*: We measured biochemical parameters, including serum albumin and CRP, and the PWV of 202 patients on maintenance HD therapy and followed their course for 4 years, and 186 of the patients were enrolled in the current study analyses. We divided the 186 patients into three tertiles according to their serum albumin and CRP levels and PWV values, and conducted multivariate analyses to examine the impact of the tertiles on 4-year mortality.**
***Results*: Twenty-three (12.4%) patients died during the follow-up period, and the serum albumin of the group that died was significantly lower than in the group that survived, but the CRP levels and PWV were significantly higher in the group that died. The results of Kaplan-Meier analyses revealed a significantly higher risk of all-cause mortality in HD patients with higher CRP based on the results of Cox proportional hazards analyses; however, the serum albumin and PWV values were not associated with all-cause mortality.**
***Conclusion*: The results of this study suggest that serum CRP levels are a better mortality predictor than serum albumin or PWV values of chronic HD patients.**

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Key words; Albumin, C-reactive protein, Pulse wave velocity, All-cause mortality, Hemodialysis

Introduction

Hypoalbuminemia predicts earlier mortality in hemodialysis (HD) patients[1]. Because low serum albumin is commonly used as a marker of poor nutritional status in HD patients, the causes of mortality are thought to be underdialysis and malnutrition[2, 3]; however, serum albumin may be a poor marker of nutritional status, because it is also a negative acute-phase protein[4]. Kaysen *et al*. reported that activation of the acute-phase response as evidenced by high C-reactive protein (CRP), is a stronger predictor of hypoalbuminemia in HD patients than measures of nutritional status[5]. These findings suggest that the serum albumin reflects the presence of an acute-phase response and is not primarily a marker of poor nutrition in HD patients.

Zimmermann *et al*. reported that multivariate Cox regression analysis identified age and serum CRP level as more powerful predictors of cardiovascular mortality in HD patients than their serum albumin level[6]. Stenvinkel *et al*. observed a greater prevalence of carotid plaques and significantly greater carotid intima media area in predialysis patients with end-stage renal disease (ESRD) who had elevated CRP levels[7]. These investigators used surrogate markers for atherosclerotic disease, but they did not address the relationship between cardiovascular disease (CVD)

Address for correspondence: Kosaku Nitta, Kidney Center, Department of Medicine, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
E-mail: knitta@kc.twmu.ac.jp
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and mortality. Recently, however, low serum albumin has been found to be correlated with coronary artery disease in HD patients[8].

The aim of the present study was to compare the clinical importance of baseline serum albumin, CRP and pulse wave velocity (PWV) as predictors of 4-year mortality in chronic HD patients. We measured all three parameters and compared their clinical value as a predictor of 4-year mortality.

Patients and Methods

Subjects

This is a retrospective cohort study. The subjects of this study were 202 chronic HD patients (HD duration >6 months) under 85 years of age who gave their consent to participate in this study at the Kidney Center of Hidaka Hospital in Takasaki, Japan. No patients had an acute infection, congestive heart failure (CHF), or a malignancy at entry into the study. We measured their baseline parameters in January 2006 and then followed them up in December 2010. This study was approved by the ethics review committee of the hospital, and was conducted in compliance with the Declaration of Helsinki.

Dialysis Procedure

All patients had been on regular HD for 4 to 5 hours each time three times per week at a blood flow rate of 180 to 200 mL/min via their arteriovenous fistulas. A bicarbonate dialysate was used at a flow rate of 500 mL/min in every patient. All HD sessions were performed using a high-flux polysulfone membrane dialyzer (BS-U; Toray Medical, Tokyo, Japan or APA; Asahi Medical, Tokyo, Japan). No bacteria or pyrogens grew from the dialysate prepared from water obtained by reverse osmosis. An endotoxin removal filter was used to maintain the endotoxin concentration below 0.020 EU/mL. A blood sample was drawn at the start and end of the dialysis session after a 2-day interval. The efficiency of dialysis was assessed based on the delivered dose of dialysis (Kt/V) calculated using a single-pool urea kinetic model[9].

Measurement of PWV

PWV, as a marker of arterial stiffness, was measured with a volume-plethysmographic apparatus (Form/ABI; Omron-Colin Co., Ltd., Komaki, Aichi, Japan). Details of the methodology have been described elswhere[10]. Occlusion and monitoring cuffs were placed snugly around all four limbs with the patient in the supine position, and the pressure waveforms of the brachial and tibial arteries were recorded with an automatic waveform analyzer after 15 min of bed rest. Validation of this method has been reported previously[11]. To assess the intra-reader variability of the PWV measurements, randomly selected measurements were re-read by the same observer at different times, and the median PWV variability was less than 5%.

Biochemical Assays and Other Measurements

Blood was drawn just before the start of a dialysis session in a fasting state. Serum albumin, urea nitrogen, creatinine, calcium, phosphorus, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, and CRP were measured by routine laboratory methods. Non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol. The means of the values obtained by 3 measurements during the 3 months before PWV measurement were used in the analysis. Serum intact parathyroid hormone (PTH) was measured once at the time of PWV measurement. Diabetes mellitus (DM) was diagnosed based on the World Health Organization (WHO) criteria[12].

The clinical status of each subject was evaluated by means of a routine clinical examination before the regular HD session. Systolic and diastolic blood pressure (BP) was measured with a mercury sphygmomanometer after the patient had rested in the supine position for 10 to 15 minutes, and mean values of 1-month measurements were used in the analysis. Pulse pressure was calculated by subtracting diastolic BP from systolic BP. Information on treatment with intravenous erythropoiesis-stimulating agents and prescriptions of vitamin D3, angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and statins was collected from the medical records.

Statistical Methods

Data are expressed as the means ± standard deviation (SD). The chi-square test was used to statistically analyze categorical variables. Univariate correlations between two laboratory variables were tested by nonparametric Spearman's rank analysis. The subjects were divided into three tertiles according to their serum albumin levels: (1: ≤3.7 g/dL; 2: 3.8-4.0 g/dL; 3: ≥4.1 g/dL). We also divided the subjects into three tertiles according to their serum CRP levels: (1: <1.0 mg/L; 2: 1.0-3.0 mg/L; 3: >3.0 mg/L) and according to their PWV values: (1: <1600 cm/sec; 2: 1600-1995 cm/sec; 3: >1995 cm/sec).

Survival was estimated on the basis of the Kaplan-Meier curves, and compared using the log-rank test. The following Cox proportional hazard models were

Table 1. Baseline characteristics of hemodialysis patients who died during follow-up versus survivors

Parameter	All	Dead	Alive	*p* value
Number	186	23	163	
Age (years)	61 ± 12	66 ± 11	60 ± 12	0.0252
Dialysis vintage (months)	105 ± 94	81 ± 81	109 ± 95	0.2199
Gender (men, %)	61.8	60.9	62	0.9999
Diabetes (%)	31.7	34.8	31.3	0.9221
Body mass index (kg/m^2)	21.4 ± 3.7	21.1 ± 4.5	21.4 ± 3.6	0.4318
Kt/V	1.2 ± 0.3	1.2 ± 0.2	1.2 ± 0.4	0.9592
Albumin (g/dL)	3.8 ± 0.3	3.6 ± 0.3	3.8 ± 0.3	0.0145
Total cholesterol (mg/dL)	151 ± 34	147 ± 32	152 ± 34	0.8947
HDL cholesterol (mg/dL)	44 ± 13	40 ± 15	44 ± 13	0.1026
Non-HDL cholesterol (mg/dL)	107 ± 32	108 ± 33	107 ± 32	0.7438
Triglyceride (mg/dL)	110 ± 64	123 ± 82	108 ± 61	0.8751
Blood urea nitrogen (mg/dL)	69.5 ± 12.8	65.0 ± 11.8	70.1 ± 12.8	0.1150
Creatinine (mg/dL)	11.1 ± 3.0	10.1 ± 3.3	11.3 ± 2.9	0.1121
Calcium (mg/dL)	8.8 ± 0.9	8.6 ± 0.9	8.8 ± 0.9	0.3430
Phosphorus (mg/dL)	6.1 ± 1.2	5.9 ± 1.4	6.1 ± 1.2	0.2664
Intact-PTH (pg/mL)	227 ± 136	241 ± 211	225 ± 123	0.5120
Hemoglobin (g/dL)	10.2 ± 1.0	10.0 ± 1.0	10.2 ± 1.0	0.1985
C-reactive protein (mg/L)	3.5 ± 7.2	8.4 ± 14.2	2.8 ± 5.4	0.0051
Systolic blood pressure (mmHg)	137 ± 24	142 ± 25	137 ± 23	0.5146
Diastolic blood pressure (mmHg)	79 ± 12	78 ± 13	79 ± 12	0.6504
Pulse pressure (mmHg)	58 ± 16	64 ± 19	58 ± 16	0.1662
Pulse wave velocity (cm/s)	1870 ± 539	2031 ± 454	1847 ± 547	0.0347
Erythropoiesis stimulating agent (%)	29.6	34.8	28.8	0.7330
Vitamin D3 (%)	55.4	34.8	58.3	0.0577
ACE-I or/and ARB (%)	44.1	47.8	43.6	0.8716
Statins (%)	7.5	8.7	7.4	0.9999

HDL, high-density lipoprotein; PTH, parathyroid hormone; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

applied to calculate the hazard ratios (HRs) and adjusted survival curves for time to all-cause death: no adjustment (model 1); adjustment for classical risk factors, including age, gender, and DM (model 2); and adjustment for age, gender, presence of DM, dialysis vintage, and pulse pressure, calcium, phosphorus, intact PTH, and hemoglobin values (model 3). The results of the Cox proportional hazards analysis are reported as the HR and 95% confidence interval (CI). $P < 0.05$ was considered significant. All statistical calculations were performed using StatView 5J software (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics of the Subjects

During the 4-year follow-up period, 16 patients were censored because 12 patients had transferred to other clinics and the laboratory data of the other 4 patients were insufficient for analysis. Thus, we ultimately analyzed the data of 186 patients.

Table 1 shows the baseline characteristics of the 186 subjects. They consisted of 115 males and 71 females, and their mean age was 61 ± 12 years (range: 35-85 years). The mean duration of HD therapy was 105 ± 94 months (range: 35-400 months). The cause of their ESRD was primary renal disease in 127 patients and DM in 59 patients. Residual urine output was within 100 mL/day in 186 patients. Fourteen patients were treated with statins during the follow-up period. The median serum albumin and CRP were 3.8 ± 0.3 g/dL and 3.5 ± 7.2 mg/L, respectively. The median PWV was 1870 ± 539 cm/sec.

There was a significant correlation between age and the serum albumin level ($r = -0.416$, $p < 0.0001$), and PWV value ($r = 0.434$, $p < 0.0001$) according to Spearman's rank tests, and there was an inverse correlation between the serum albumin level and both the

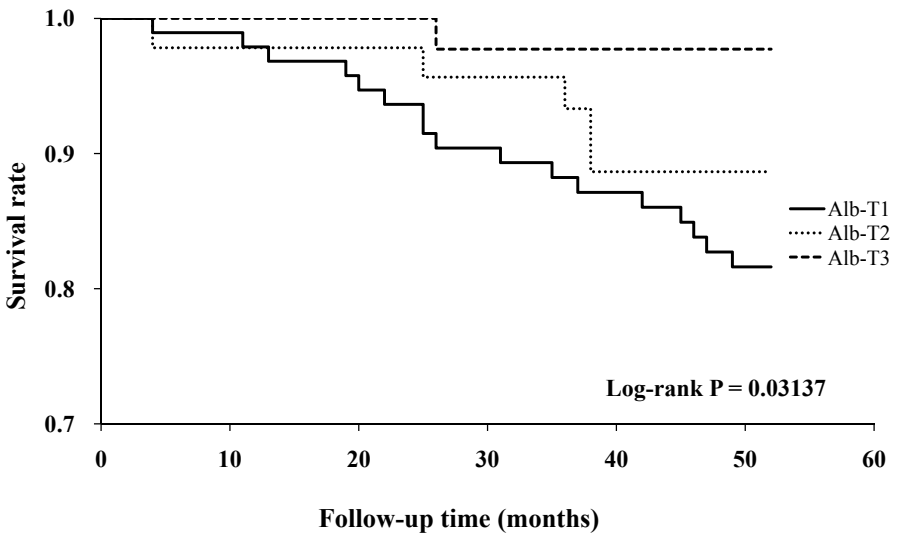

Fig. 1. Overall survival curves of hemodialysis patients according to tertile with respect to serum albumin level. Alb-T1, 1: ≤3.7 g/dL; Alb-T2, 3.8-4.0 g/dL; Alb-T3, ≥4.1 g/dL.

CRP level ($r=-0.333$, $p<0.0001$) and PWV value ($r=-0.268$, $p=0.0002$).

Clinical Parameters and Mortality

During the follow-up period, 23 patients (12.4%) died, and 14 (7.5%) of the deaths were due to CVD. The CVD was CHF in 6 patients, acute myocardial infarction in 4 patients, cerebrovascular disease in 2 patients, and others in 2 patients. The non-CVD causes of death consisted of an infection in 4 patients, malignancy in 2 patients, gastrointestinal bleeding in 2 patients, and other in 1 patient.

Table 1 shows the differences in basal characteristics between the group of patients who died and the group that survived. The patients in the group that died were significantly older than in the group that survived ($p=0.0252$). There was a significant difference between the serum albumin ($p=0.0145$) and CRP levels of the group that died and the group that survived ($p=0.0051$). PWV was significantly higher in the group that died ($p=0.0347$). There was no significant difference in serum lipid levels in the two groups.

As shown in **Fig. 1**, there were significantly differences among the Kaplan-Meier survival curves of the HD patients according to tertiles with respect to the serum albumin level ($p=0.03137$). The survival rate in the top tertile (albumin, ≥4.0 g/dL, $n=46$) was significantly higher than in the bottom tertile (albumin, ≤3.7 g/dL, $n=95$) ($p=0.0106$). **Fig. 2** shows significant differences in serum CRP levels among the three groups ($p=0.0241$). The group in the highest tertile with respect to serum CRP levels (>3.0 mg/L, $n=54$) had a significantly lower survival rate than the lowest tertile (CRP <1.0 mg/L, $n=97$) ($p=0.0112$). There was no significant difference in survival rate between the bottom tertile with respect to PWV values (PWV <1600 cm/sec, $n=61$) and the middle tertile (PWV 1600-1995 cm/sec, $n=63$) or the top tertile (PWV >1995 cm/sec, $n=62$) ($p=0.08397$) (**Fig. 3**).

Predictors of All-Cause Mortality (Table 2)

Cox regression analysis without adjustment for traditional risk factors (model 1) revealed that the group in the top tertile with respect to serum CRP levels had a significantly higher risk of all-cause mortality than the lowest tertile. A higher risk of mortality was also found in the group in the highest tertile with respect to PWV values than in the lowest tertile. The relative risk of all-cause mortality did not significantly differ between the group in the top tertile with respect to serum albumin levels and the bottom tertile. When adjusted for age, gender, and DM (model 2), with respect to serum CRP levels, the group in the top tertile had a 3.05-fold higher risk than the bottom tertile ($p=0.0174$). In addition, CRP in the group of patients who died (6.8±1.2 mg/L) was significantly higher than in the group that survived to the end of the follow-up period (2.4±2.3 mg/L) ($p<0.0001$). There was no significant difference in mortality risk among the tertiles with respect to serum albumin or PWV values. When further adjusted for dialysis vintage, pulse pressure, calcium, phosphorus, intact PTH,

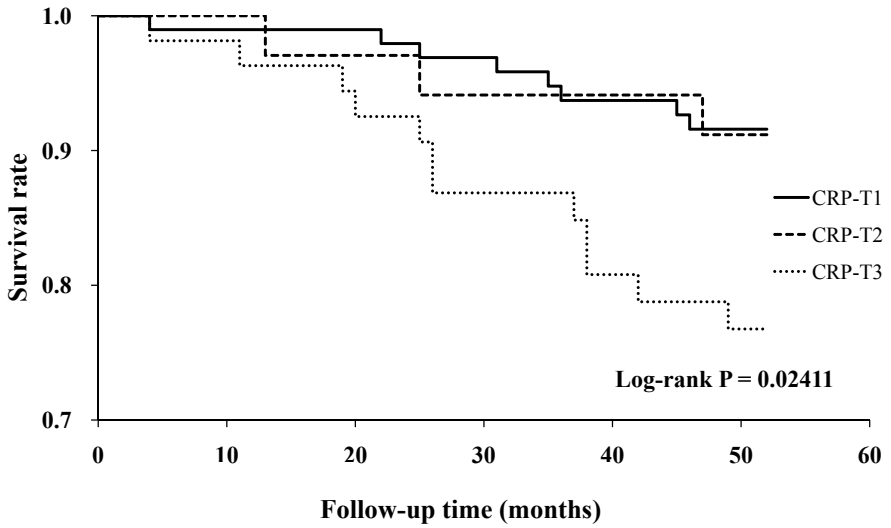

Fig. 2. Overall survival curves of hemodialysis patients according to tertile with respect to serum C-reactive protein (CRP) level. CRP-T1, <1.0 mg/L; CRP-T2, 1.0-3.0 mg/L; CRP-T3, >3.0 mg/L.

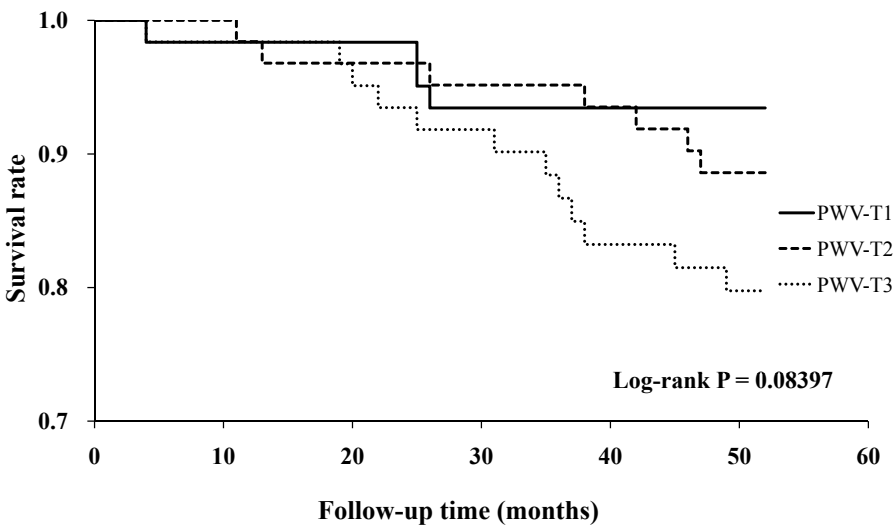

Fig. 3. Overall survival curves of hemodialysis patients according to tertile with respect to pulse wave velocity (PWV) value. PWV-T1, <1600 cm/sec; PWV-T2, 1600-1995 cm/sec; PWV-T3, >1995 cm/sec.

and hemoglobin (model 3), with respect to serum CRP levels, the group in the top tertile had a 2.8-fold higher risk of all-cause mortality than the bottom tertile during the follow-up period (p=0.0406). In contrast, the serum albumin and PWV values were not associated with 4-year all-cause mortality in model 3. By adjusted Cox regression analysis, serum lipids, including total cholesterol (HR=1.000; 95% CI=0.983-1.018; p=0.9570), HDL-cholesterol (HR=0.984; 95% CI=0.998-1.029; p=0.4793), LDL-cholesterol (HR=0.998; 95% CI=0.977-1.019; p=0.8465), non-HDL-cholesterol (HR=1.003; 95% CI=0.985-1.022; p=0.7135) and triglyceride (HR=1.006; 95% CI=0.998-1.015; p=0.1449), were not associated with all-cause mortality.

Discussion

Low serum albumin has been found to be one of the most powerful predictors of mortality in cross-sec-

Table 2. Cox hazard analysis for total deaths during the 4-year follow-up

	(N)	Model 1			Model 2			Model 3		
		HR	(95%CI)	*p* value	HR	(95%CI)	*p* value	HR	95%CI	*p* value
Albumin										
1st tertile	(95)	1.703	(0.628-4.617)	0.2953	1.183	(0.389-3.597)	0.7672	1.064	(0.311-3.641)	0.9211
2nd tertile	(45)	0.193	(0.023-1.654)	0.1333	0.177	(0.021-1.524)	0.1150	0.155	(0.017-1.380)	0.0946
3rd tertile	(46)	1.000			1.000			1.000		
CRP										
1st tertile	(97)	1.000			1.000			1.000		
2nd tertile	(35)	1.052	(0.279-3.967)	0.9401	0.946	(0.250-3.577)	0.9348	0.836	(0.212-3.300)	0.7984
3rd tertile	(54)	3.004	(1.227-7.354)	0.0160	3.050	(1.217-7.646)	0.0174	2.786	(1.045-7.429)	0.0406
PWV										
1st tertile	(61)	1.000			1.000			1.000		
2nd tertile	(63)	1.775	(0.519-6.064)	0.3601	1.390	(0.380-5.086)	0.6186	1.227	(0.320-4.715)	0.7653
3rd tertile	(62)	3.248	(1.047-10.075)	0.0413	2.111	(0.591-7.541)	0.2499	2.060	(0.523-8.113)	0.3013

Model 1 includes serum albumin, CRP, and PWV; model 2 adjusted for age, gender, and diabetes mellitus; model 3 further adjusted for HD vintage, pulse pressure, calcium, phosphorus, intact PTH, and hemoglobin.

tional studies of HD patients[13]. A previous study showed that lower albumin was associated with an adjusted risk of 4-year mortality that was 2.1-fold higher than in healthy subjects with higher serum albumin levels who did not have evidence of inflammation[14]. Danielski *et al.* found significantly higher oxidative stress in a hypoalbuminemia group of HD patients than in a normoalbuminemia group[15]. Increased oxidative stress, in turn, may accelerate the atherosclerotic process, and hypoalbuminemia has also been found to be closely associated with endothelial dysfunction in HD patients[16].

Serum albumin in HD patients decreases primarily as a consequence of increased inflammatory status and a subsequent decline in the rate of albumin synthesis coupled with the failure to downregulate albumin catabolism that occurs during protein restriction. Inadequate dietary nitrogen intake is clearly correlated with serum albumin levels, and since nutritional supplements have not been very effective in correcting hypoalbuminemia, the relationship between nitrogen intake and hypoalbuminemia in HD patients is likely to be the result of the inflammation-mediated inability of HD patients to reduce the albumin fractional catabolic rate when nitrogen intake is limited, making these patients sensitive to nitrogen restriction[17]. Cox regression analysis that was adjusted for many risk factors in the present study revealed that the serum albumin levels were not associated with all-cause mortality.

Serum CRP has been found to be more reliable than serum albumin in predicting mortality and, when compared in multiple regression models, inflammatory markers have frequently displaced albumin as a predictor of outcome in HD patients[18], suggesting that it is the inflammatory cause of hypoalbuminemia rather than other causes that dominates the link between hypoalbuminemia and poor outcome of HD patients. Qureshi *et al.* first compared the relative power of serum albumin and CRP levels as predictors of all-cause mortality in HD patients[19], and found that increased CRP was independently associated with mortality after a 36-month follow-up period, but low serum albumin (≤3.3 g/dL) was unrelated to a poor outcome. In the present study, serum CRP >3.0 mg/L emerged as a significant determinant of all-cause mortality that was independent of established adverse parameters.

Serum albumin levels have recently been shown to be associated with early mortality of incident HD patients rather than poor nutritional status. Serum albumin <3.3 g/dL has been demonstrated to predict all-cause mortality with a sensitivity of 78.6% sensitivity and 65.7% specificity during a 26-month follow-up period[20]. The Netherlands Cooperative Study on the Adequacy of Dialysis-II Study Group also recently showed that the increased mortality risk associated with low serum albumin levels in incident dialysis patients was not a consequence of malnutrition[21]. A recent meta-analysis of 38 studies (265,330 patients) demonstrated a significant inverse correlation between serum albumin levels and all-cause mortality and cardiovascular mortality, whereas the serum CRP level was weakly but significantly correlated with all-cause mortality, but not with cardiovascular mortality[22].

Based on the results of the meta-analysis it was concluded that the potential adverse effects of malnutrition and infection in relation to mortality highlight the need for continued treatment of infections and correction of malnutrition in HD patients. In the present study, we could not intervene to correct increased CRP of unknown origin, but it may be associated with the inflammatory status.

A growing body of evidence has accumulated indicating that chronic kidney disease constitutes a critical determinant of the progression of arterial stiffness and CVD. PWV is a predictor of cardiovascular outcome in HD patients[23, 24]. Washida *et al*. have recently reported that arterial stiffness constitutes a novel determinant that predicts the severity of CVD in patients with ESRD in addition to the classical risk factors, and they have shown lower serum albumin levels and higher serum CRP levels in HD patients with severe lacunes[25]. Evidence has shown that atherosclerosis reflects the vascular inflammatory process[26]. To the extent that cerebral infarction is a consequence of atherosclerosis, the association between CRP and lacunar infarction is reasonably anticipated in patients with ESRD as well as in patients on HD therapy[27]; however, PWV was not a sensitive predictor of all-cause mortality in the present study.

Several drugs have been reported to reduce inflammation as assessed by CRP and cytokine levels. Treatment with ACE-I was associated with lower serum CRP in HD patients[28], and a CRP-lowering effect of statins has previously been described in patients with renal failure[29]. All statins, including atrovastatin, simvastatin, and cerivastatin, seem to lower serum CRP. This effect appears to be dose-dependent, but lowering serum CRP was not correlated with a decrease in serum cholesterol. Thus, treatment with renin-angiotensin system blockers and statins can be used to ameliorate inflammation in HD patients. In the present study, 14 patients were being treated with statins, and 44.1% of our patients were also being treated with an ACE-I and/or ARB. These drugs may have affected the serum CRP during the follow-up period; however, targeting the inflammatory response in HD patients probably requires a multifactorial approach involving pathogenetic aspects of inflammation.

There were several limitations in this study. First, we investigated only the effect of baseline serum albumin and CRP levels at the time of entry into the study and changes in serum albumin over time have been demonstrated to predict mortality[30]. A recent study has shown that patients with ESRD have a higher inflammatory status with increased CRP associated with endothelial dysfunction and atherosclerosis[31]. Second, we did not assess different approaches to the detection of malnutrition. Clinical nutritional scores have recently been demonstrated to be superior as prognostic indicators in HD patients to laboratory markers, such as serum albumin <3.5 g/dL or CRP >10 mg/L, in a 3-year follow-up study[32]; however, the regular determination of these scores is time consuming and not practical in maintenance HD patients. Third, the mechanism by which serum albumin <3.8 g/dL contributes to the long-term outcome remains to be determined. Although low serum albumin was found to be related to all-cause mortality in this study, hypoalbuminemia may be related to infectious disease[33]. The National Kidney Foundation Kidney Disease Quality Initiative guideline has recommended prealbumin as a useful measure of nutritional status[34]; however, similar to albumin, inflammation can lead to a reduction in serum prealbumin[35]. Finally, because we conducted this study on a specific longevity group, the results may not be generally applicable.

In summary, the results of this study showed that baseline serum CRP levels are superior to serum albumin levels and PWV values as a predictor of 4-year all-cause mortality in chronic HD patients. A better understanding of the biological role of CRP is needed to corroborate its suitability as a target of therapy.

Conflicts of Interest

None.

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