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Combined Values of Serum Albumin, C-Reactive Protein and Body Mass Index at Dialysis Initiation Accurately Predicts Long-Term Mortality

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Key Words
Albumin · CRP · BMI · Composite · Survival · CVD mortality

Abstract
Background: Protein-energy wasting and chronic inflammation are prevalent in patients with end-stage renal disease (ESRD). We investigated the combination of serum albumin, C-reactive protein (CRP) and body mass index (BMI) at initiation of hemodialysis therapy as a predictor of all-cause and cardiovascular disease (CVD) mortality in Japanese ESRD patients. ***Methods:*** A total of 1,228 consecutive Japanese ESRD patients on hemodialysis therapy were enrolled and followed for up to 10 years. Patients were divided into quartiles according to levels of albumin, CRP and BMI. Furthermore, to clarify the joint role of these factors, albumin <3.5 g/dl, CRP >4.0 mg/l and BMI <19.6 were defined as risk factors using receiver operating characteristic analysis; thereafter, patients were divided into groups according to the positive number of these factors. ***Results:*** Adjusted hazard ratios (HRs) for lower serum albumin, elevated CRP and lower BMI for 10-year all-cause mortality were 1.97, 3.13 and 2.61, respectively. Regarding the combination of these variables, adjusted HRs for mortality were 2.31, 4.28 and 8.07, respectively, in patients having any one factor, any two factors and all three factors. The C-index for an established risk model with these three positive markers was the most accurate for predicting mortality (0.768), as compared to other models with one or two markers. Similar results were seen for CVD mortality. ***Conclusions:*** Serum albumin, CRP and BMI at the start of hemodialysis therapy were able to individually stratify the risk of long-term mortality in ESRD patients. Furthermore, a combination of these variables could more accurately predict mortality.

Introduction

As compared to the general population, patients with renal failure reportedly have a higher risk of death, particularly by cardiovascular diseases (CVDs) [1]; thus, identifying and stratifying the sickest end-stage renal disease (ESRD) patients is important for improving the prognosis and survival of this patient group. Multiple risk factors for this increased morbidity and mortality have been reported in these patients [1]. Traditional risk factors, such as diabetes mellitus and smoking, were strongly associated with all-cause and CVD mortality, while neither serum total cholesterol nor systolic blood pres-

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sure was associated with coronary heart diseases [1–3]. Protein-energy wasting and atherosclerosis are common problems in predicting morbidity and mortality in patients with ESRD [1, 3]. Systemic inflammation and nutritional indices have been shown to predict outcome in hemodialysis (HD) and peritoneal dialysis, just as they have in chronic kidney disease (CKD) in general [1, 4, 5]. Serum albumin levels [6, 7], serum C-reactive protein (CRP) concentrations [5, 8] and body mass index (BMI) [9–11] have been reported as predictors of all-cause and CVD mortality, and we have reported that increased levels of CRP can predict future events in the coronary artery and peripheral arteries after intervention [12, 13]. In contrast, other groups have reported that these factors are not associated with mortality [1, 14, 15].

A lower prevalence of inflammation has been reported in dialysis patients in Asian countries, such as Japan and Korea, and this may depend on genetic factors and cultural habits such as food intake [1, 3, 16, 17]. For BMI, baseline obesity appears to be paradoxically associated with improved survival [9, 10, 17]. It has been reported that Asian Americans have a markedly lower adjusted relative mortality rate than Caucasian dialysis patients; however, BMI is significantly lower in Asian Americans [18]. The International Society of Renal Nutrition and Metabolism proposed BMI of less than 23 as a criterion for protein-energy wasting in CKD, but they have not expanded their recommendation to Southeast Asian CKD patients or the general population [19]. Thus, it may be difficult to use these single markers to clearly predict mortality.

The aim of this study was therefore to investigate the prognostic value of serum albumin, CRP and BMI at initiation of HD therapy, both individually and in combination, for all-cause and cardiovascular mortality in ESRD Japanese patients who are considered to have lower BMI and inflammatory markers [3, 8].

Subjects and Methods

Study Population

A total of 1,228 consecutive ESRD patients who were stably inducted into HD therapy at Nagoya Kyoritsu Hospital (Nagoya, Japan), Kaikokai Central Clinic (Nagoya, Japan), Meiko Kyoritsu Clinic (Nagoya, Japan), Ama Kyoritsu Clinic (Yatomi, Japan) and Anjou Kyoritsu Clinic (Anjou, Japan) between January 1998 and December 2007 were enrolled. All patients were Japanese aged over 18 years (mean age: 60 ± 14). Diabetic nephropathy accounted for 44.4% of the primary cause of ESRD, which was similar to the rate in the Japanese total dialysis patient survey of 2008 [20]. Patients with acute cardiovascular, infectious or systemic inflammatory diseases; malignancies; or other active diseases at the initiation of HD therapy were excluded. Patients were followed for up to 10 years. The primary endpoint was all-cause death. The secondary endpoint was cardiovascular death caused by cardiac disease, stroke and peripheral arterial disease. All studies were approved by the Ethics Committee for Human Research of the Faculty of Medicine, Nagoya Kyoritsu Hospital, and were conducted in accordance with the Declaration of Helsinki. Physicians obtained written informed consent from each patient.

Serum Albumin, CRP and BMI

Serum albumin and CRP were measured using albumin kits and latex-enhanced high-sensitive CRP immunoassay, as described previously [12, 13]. Blood samples were taken before HD sessions at 2 weeks after induction of HD therapy. BMI was calculated from height and weight data at 2 weeks after induction of HD because the state of overhydration in most patients was controlled by this period. Patients were divided into quartiles based on levels of serum albumin, CRP and BMI.

Combined Setting of Variables

In order to clarify the combined predictive power for mortality, cutoff values for serum albumin, CRP and BMI were determined using receiver operating characteristic (ROC) analysis. Based on cutoff values, low albumin, high CRP and low BMI were defined as risk factors. Patients were then stratified into four groups according to the presence of risk factors, as follows: patients without any risk factors (group 0), patients with one risk factor (group 1), patients with two risk factors (group 2) and patients with all risk factors (group 3).

Statistical Analysis

Statistical analysis was performed using SAS 6.10 (SAS Institute, Cary, N.C., USA) software. A Shapiro-Wilk test was applied to test normal distributions. Variables without a normal distribution were analyzed by a nonparametric test. Variables with a normal distribution are expressed as mean values ± SD, and asymmetrically distributed data are given as medians and interquartile range (IQR). Analysis of variance (ANOVA) or a Kruskal-Wallis test was used for comparison of quantitative data, and a χ^2 test was used for comparison of categorical data among the groups. Cumulative survival rates in each group were estimated by the Kaplan-Meier method, and the differences in survival rates between groups were evaluated using the log-rank method. Hazard ratios (HRs) and 95% CI were calculated for each factor by Cox univariate analysis. Furthermore, Cox multivariate regression analysis was used to determine independent predictors for the endpoint. Factors with $p < 0.05$ on univariate analysis were entered into multivariate Cox regression analysis. In addition, to assess whether the accuracy of predicting mortality would improve after the addition of albumin, CRP and BMI, or a combination of these markers, the C-index of ROC curves for mortality were calculated as a global estimate of accuracy in a baseline model with established risk factors, including gender, age, diabetes, hypertension, smoking status, hematocrit, phosphate, total cholesterol, LDL cholesterol and HDL cholesterol, and in an enhanced model including the established risk factors plus albumin, CRP and BMI, as well as the combination of these markers. Differences were considered to be statistically significant at $p < 0.05$.

Table 1. Baseline characteristics

	All patients (n = 1,228)	Group 0 (n = 314)	Group 1 (n = 409)	Group 2 (n = 385)	Group 3 (n = 120)	p
Male, %	65.1	69.1	61.1	65.9	64.2	0.16
Age, years	60 ± 14	58 ± 13	62 ± 12	65 ± 13	68 ± 12	<0.0001
Diabetes, %	44.4	35.3	49.1	46.8	38.8	0.0010
Hypertension, %	70.9	71.1	72.3	65.9	60.6	0.056
Smoking, %	23.7	26.5	18.7	20.7	27.3	0.17
BMI	21.0 ± 3.2	22.7 ± 2.7	21.5 ± 3.3	20.1 ± 3.0	17.8 ± 1.3	<0.0001
Hematocrit, %	29.5 ± 4.4	30.8 ± 4.5	29.3 ± 4.2	28.7 ± 4.2	29.8 ± 4.5	<0.0001
Total protein, g/dl	6.3 ± 0.6	6.5 ± 0.5	6.2 ± 0.6	6.1 ± 0.6	6.3 ± 0.7	<0.0001
Albumin, g/dl	3.5 ± 0.4	3.9 ± 0.2	3.4 ± 0.4	3.2 ± 0.4	3.1 ± 0.4	<0.0001
Urea nitrogen, mg/dl	59.8 ± 19.4	62.4 ± 17.0	58.0 ± 18.8	55.5 ± 18.4	55.2 ± 16.5	0.0001
eGFR, ml/min/1.73 m^2	6.3 ± 2.4	5.4 ± 2.0	6.1 ± 2.1	6.7 ± 2.5	7.2 ± 2.9	<0.0001
Calcium, mg/dl	8.1 ± 0.9	8.5 ± 0.8	8.1 ± 0.9	8.0 ± 0.7	8.0 ± 0.9	<0.0001
Phosphate, mg/dl	5.1 ± 1.4	5.3 ± 1.5	5.0 ± 1.3	4.9 ± 1.5	4.7 ± 1.5	0.0011
TC, mg/dl	163 ± 38	162 ± 33	170 ± 41	162 ± 37	160 ± 48	0.022
LDL-C, mg/dl	93 ± 33	88 ± 27	96 ± 35	89 ± 31	86 ± 40	0.0069
HDL-C, mg/dl	41 ± 14	41 ± 14	41 ± 14	41 ± 13	43 ± 17	0.84
CRP, mg/l	2.0 (0.8–6.7)	1.0 (0.5–2.0)	1.4 (0.7-3.3)	5.6 (1.3–13.0)	11.9 (7.2–29.9)	<0.0001

Values are means ± SD or medians (IQR).

Group 0 = Patients without any risk factors; Group 1 = patients with one risk factor; Group 2 = patients with two risk factors; Group 3 = patients with all risk factors.

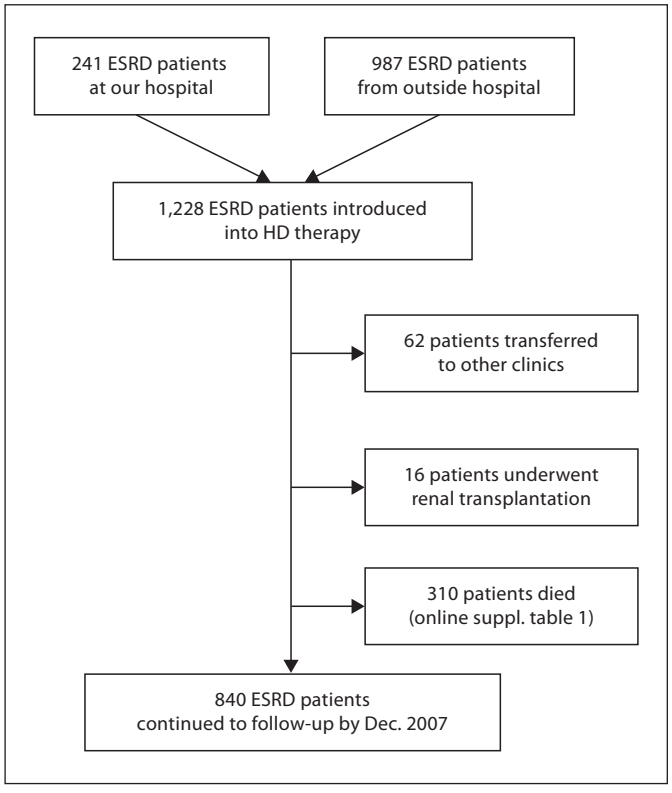

Fig. 1. Flow diagram for study population.

Results

Clinical Characteristics

The median duration of follow-up was 47 months (IQR: 23–84) from the initiation of HD. The baseline characteristics of all patients, flow diagram of the study population and causes of death are shown in table 1, figure 1 and online supplementary table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000339940). A total of 310 patients (25.2%) died during the follow-up period. Among these, 147 (12% of total patients) were cardiovascular deaths. Enrolled patients were divided into quartiles (Q) based on levels of serum albumin (Q1: <3.1 g/dl; Q2: ≥3.1 and <3.6 g/dl; Q3: ≥3.6 and <3.9 g/dl; Q4: ≥3.9 g/dl), serum CRP (Q1: <0.8 mg/l; Q2: ≥0.8 and <2.6 mg/l; Q3: ≥2.6 and <7.6 mg/l; Q4: ≥7.6 mg/l) and BMI (Q1: <19.8; Q2: ≥19.8 and <20.6; Q3: ≥20.6 and <22.8; Q4: ≥22.8). Baseline characteristics among the groups according to serum albumin concentrations, CRP levels and BMI are shown in online supplementary tables 2–4.

Prognostic Value of Albumin, CRP and BMI Alone

Clinical follow-up data were obtained from all enrolled patients. According to serum albumin levels, the

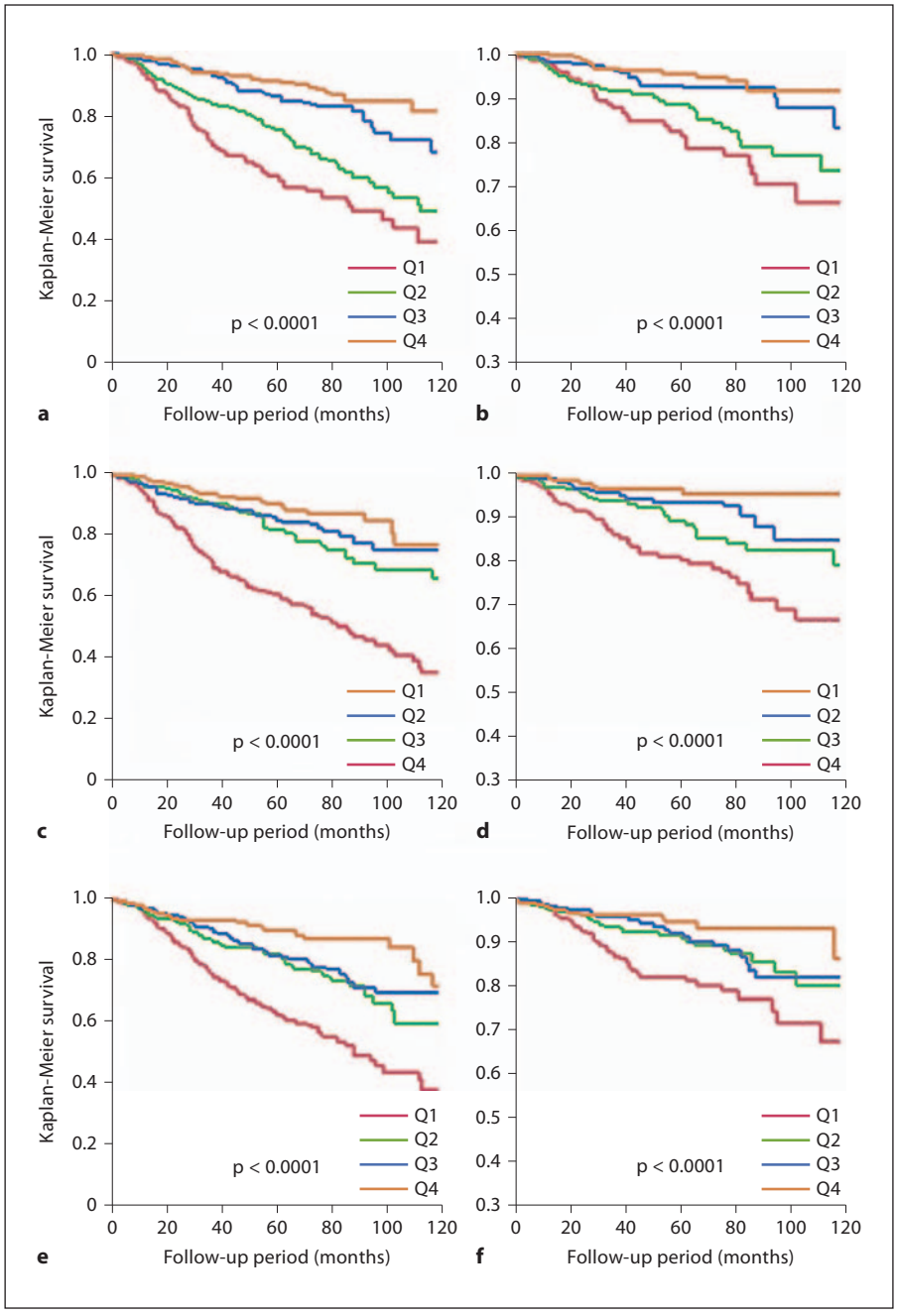

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Fig. 2. All-cause (**a**) and cardiovascular (**b**) survival among quartiles according to serum albumin levels. All-cause (**b**) and cardiovascular (**c**) survival among quartiles according to serum CRP levels. All-cause (**e**) and cardiovascular (**f**) survival among quartiles according to BMI levels.

10-year Kaplan-Meier survival rates for all-cause and cardiovascular mortality were 38.6 and 65.5% in Q1, 48.2 and 73.3% in Q2, 67.8 and 83.1% in Q3, and 81.1 and 91.6% in Q4, respectively (fig. 2a, b). According to serum CRP concentrations, the 10-year survival rates for all-cause and cardiovascular mortality were 77.0 and 95.8% in Q1, 75.3 and 85.4% in Q2, 65.8 and 79.2% in Q3, and 35.4 and 66.8% in Q4, respectively (fig. 2c, d). According to BMI levels, the 10-year survival rates for all-cause and cardiovascular mortality were 38.6 and 67.2% in Q1, 59.5 and 80.2% in Q2, 69.5 and 82.0% in Q3, and 72.5 and 86.8% in Q4, respectively (fig. 2e, f). After adjustment for other confounding factors (e.g. serum albumin, CRP and BMI), lower albumin, elevated CRP and lower BMI were independent predictors for all-cause mortality (table 2) and CVD mortality (table 2). Each risk factor alone had sig-

Table 2. Predictive value of serum albumin, serum CRP and BMI for all-cause and cardiovascular mortality by Cox analysis

	All-cause mortality		Cardiovascular mortality	
	nonadjusted	adjusted*	nonadjusted	adjusted*
Albumin (vs. Q4)				
Q3	1.48 (0.92–2.38)	1.16 (0.71–1.88)	1.48 (0.74–2.99)	1.23 (0.61–2.48)
Q2	3.19 (2.07–4.91)	1.87 (1.17–2.98)	3.25 (1.73–6.12)	2.09 (1.07–4.10)
Q1	4.87 (3.18–7.46)	1.97 (1.26–3.08)	4.32 (2.29–8.14)	2.22 (1.16–4.26)
p for trend	<0.0001	0.0033	<0.0001	0.032
CRP (vs. Q1)				
Q2	1.55 (0.94–2.56)	1.71 (1.03–2.86)	2.12 (0.92–4.93)	2.22 (0.96–5.16)
Q3	1.83 (1.13–2.97)	1.76 (1.07–2.91)	3.34 (1.52–7.33)	3.30 (1.49–7.33)
Q4	4.72 (3.06–7.30)	3.13 (1.98–4.94)	6.27 (2.96–13.3)	4.19 (1.93–9.06)
p for trend	<0.0001	<0.0001	<0.0001	0.0017
BMI (vs. Q4)				
Q3	1.61 (1.02–2.54)	1.27 (0.80–2.01)	1.62 (0.84–3.11)	1.33 (0.69–2.57)
Q2	1.99 (1.28–3.09)	1.59 (1.02–2.49)	1.80 (0.95–6.41)	1.55 (0.80–2.99)
Q1	3.80 (2.54–5.68)	2.61 (1.71–4.00)	3.33 (1.85–5.99)	2.58 (1.39–4.79)
p for trend	<0.0001	<0.0001	0.0002	0.0091

Figures in parentheses are 95% CI.
* Multivariate model includes all baseline variables with $p < 0.05$ by univariate analysis.

nificant predictive value for all-cause and CVD mortality (fig. 2; table 2). Even from analysis using continuous values, albumin, CRP and BMI were able to independently predict all-cause mortality (HR = 0.64, 95% CI: 0.47–0.87, p = 0.0044; HR = 1.01, 95% CI: 1.01–1.02, p = 0.0002; and HR = 0.89, 95% CI: 0.84–0.95, p = 0.0002, respectively) and CVD mortality (HR = 0.60, 95% CI: 0.39–0.94, p = 0.024; HR = 1.01, 95% CI: 1.00–1.02, p = 0.0073; and HR = 0.88, 95% CI: 0.80–0.96, p = 0.0051, respectively).

Combined Prognostic Value of Albumin, CRP and BMI

In order to maximize the power of each category in predicting all-cause mortality, the best probabilistic cutoff values for albumin, serum CRP and BMI were determined using ROC analysis. Based on these analyses, serum albumin <3.5 g/dl, serum CRP >4.0 mg/l and BMI <19.6 were defined as risk factors (online suppl. fig. 1). Thereafter, patients were divided into four groups based on the number of risk factors: patients without any risk factors (group 0, n = 314), patients with one risk factor (group 1, n = 409), patients with two risk factors (group 2, n = 385) and patients with all risk factors (group 3, n = 120; table 1). The respective 10-year Kaplan-Meier survival rates for all-cause and CVD mortality were 85.5 and 91.2% in group 0, 69.6 and 83.4% in group 1, 42.8 and 72.5% in group 2, and 21.7 and 52.2% in group 3 ($p < 0.0001$; fig. 3). After adjustment for other confounding factors, the presence of three risk factors (low serum albumin, high CRP and/or lower BMI) was found to strongly predict all-cause death (table 3). More granular analysis is shown in online supplementary table 5. Diabetes and age were also independent predictors for all-cause mortality (HR = 1.74, 95% CI: 1.28–2.36, p = 0.0004; and HR = 1.04, 95% CI: 1.03–1.06, $p < 0.0001$) and CVD mortality (HR = 2.24, 95% CI: 1.42–3.54, p = 0.0005; and HR = 1.03, 95% CI: 1.01–1.05, p = 0.0013), respectively. We also analyzed the accuracy of predicting mortality by adding these three risk factors into established risk factors. Adding single factors such as albumin, CRP and BMI to the established risk factors improved the prediction of all-cause mortality, as shown by the increase in C-index for ROC curves (table 4; online suppl. fig. 2). Furthermore, adding any two factors to the established risk factors further improved the prediction, and the combination of three factors to the established risk factors most accurately predicted mortality with the highest C-index being 0.768 (table 4). Similar results were seen for CVD mortality (table 4).

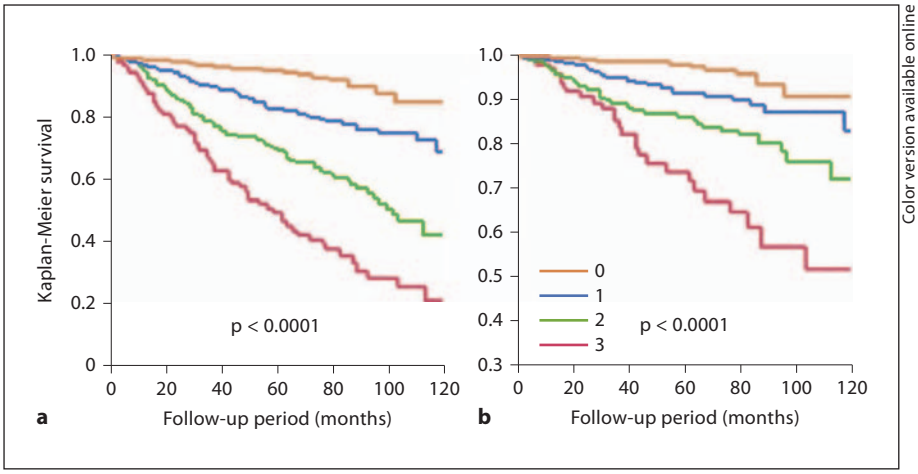

Fig. 3. All-cause (**a**) and cardiovascular (**b**) survival among groups according to number of risk factors

Table 3. Predictive value of number of risk factors for all-cause and cardiovascular mortality by Cox analysis

	All-cause mortality		Cardiovascular mortality	
	nonadjusted	adjusted*	nonadjusted	adjusted*
Number of risk (vs. 0)				
1	2.91 (1.70–5.01)	2.31 (1.34–4.00)	2.59 (1.22–5.51)	2.04 (1.01–4.36)
2	6.41 (3.84–10.71)	4.28 (2.54–7.22)	5.13 (2.50–10.51)	3.53 (1.70–7.33)
3	12.07 (7.05–20.67)	8.07 (4.65–14.02)	10.02 (4.71–21.32)	7.48 (3.46–16.21)
p for trend	<0.0001	<0.0001	<0.0001	<0.0001

Figures in parentheses are 95% CI.
* Multivariate model includes all baseline variables with $p < 0.05$ by univariate analysis.

Discussion

Serum albumin levels, CRP concentrations and BMI have been considered as predictors of mortality. In our analysis, we found that albumin, CRP and BMI were independent predictors of all-cause mortality and cardiovascular mortality after adjustment for other confounding factors (fig. 2; table 2). Albumin is now considered to be a marker for inflammation rather than nutrition [7]. Low serum albumin levels in dialysis patients are correlated with the systemic inflammation marker CRP, and early albumin changes have been shown to be negatively correlated with changes in CRP [7]. However, albumin may not always correlate well with CRP, as factors other than inflammation, such as uremia and metabolic acidosis, dental or periodontal diseases, and peripheral vascular disease, also reportedly affect CRP levels [7]. In our cohort, we did not observe strong correlations between albumin and CRP on linear regression analysis (data not shown). In addition, BMI was not correlated with CRP, as reported previously [7, 10]. These three markers, serum albumin, CRP and BMI, are considered to be related to inflammation, but are not specific markers for inflammation and are not always well correlated with one another. Thus, evaluation of these individual factors is important. However, analysis of the combination of these markers may provide additive value by involving factors other than inflammation. Indeed, these factors are partly affected by nutritional status [7, 19, 21].

Individual analyses using these markers do not always reflect mortality [14, 15]. Furthermore, most of the AUCs on ROC curves for each marker were previously reported to be less than 0.7, which suggests low accuracy when predicting mortality [22, 23]. In our study, comparison of each marker with a clinical prediction model individually or in combination by C-index on ROC curves sug-

Table 4. C-index of each predictive model for all-cause and cardiovascular mortality

	C-index	95% CI	p
All-cause mortality			
Established risk factors +	0.637	0.595–0.679	ref.
Albumin	0.674	0.634–0.713	0.010
CRP	0.718	0.681–0.756	<0.0001
BMI	0.692	0.653–0.731	0.0006
Albumin + CRP	0.747	0.712–0.782	<0.0001
Albumin + BMI	0.729	0.691–0.767	<0.0001
BMI + CRP	0.751	0.715–0.788	<0.0001
Albumin + CRP + BMI	0.768	0.733–0.802	<0.0001
Cardiovascular mortality			
Established risk factors +	0.621	0.564–0.678	ref.
Albumin	0.663	0.609–0.717	0.028
CRP	0.701	0.651–0.751	0.0011
BMI	0.699	0.649–0.749	0.0034
Albumin + CRP	0.724	0.677–0.768	0.0002
Albumin + BMI	0.725	0.676–0.772	0.0002
BMI + CRP	0.733	0.686–0.780	0.0003
Albumin + CRP + BMI	0.752	0.707–0.798	<0.0001

Established risk factors included gender, age, diabetes, hypertension, smoking status, hematocrit, urea nitrogen, eGFR, calcium, phosphate, total cholesterol, LDL cholesterol and HDL cholesterol.

gested that the individual C-indexes of the three markers with established clinical risk factors are better than those of the baseline established risk factors. Moreover, a combination of the three markers with established risk factors is more useful and accurate than other models (table 4).

BMI is the commonly used measure for assessing protein-energy wasting in CKD patients [19]. However, BMI can be heavily influenced by hydration status [19]. Therefore, we used BMI data at 2 weeks after initiation of HD. In addition, obesity in uremic patients cannot be estimated by high BMI alone, as BMI does not differentiate muscle mass from adipose tissue. Our analysis of BMI is consistent with the notion that high BMI is a potentially protective risk factor because higher BMI clearly showed better survival (table 2). In ESRD patients, overweight (BMI: 25–30) or obesity (BMI: >30) is reportedly associated with improved survival, whereas low BMI (BMI <19) is associated with increased mortality [9, 10]. In contrast, in this Japanese cohort, mean BMI for all patients was 21.0, and the range of the highest quartile for BMI was >22.8 (mean: 25.2; online supplementary table 4). BMI <23 is one of the criteria for clinical diagnosis of protein-energy wasting in CKD [19]. This suggests that our cohort with relatively low BMI differs from that in previous cohorts of US and European patients, and this Japanese cohort is likely to have less fat tissue. In contrast to the notion that fat is protective for HD patients, Kalantar-Zadeh et al. [10] showed no difference in inflammatory markers in four different BMI groups of HD patients [10, 21]. In recent studies, protein-energy wasting was present, even in high BMI ESRD patients [21, 22]. Other reports have suggested that BMI alone has limitations in predicting mortality [11, 21]. In this respect, a combination of factors and a multiple marker approach may provide a better means to predict mortality.

Awareness of long-term mortality and CVD risk stratification is important for identifying the sickest ESRD patients, as therapies with specific anti-inflammatory agents, such as IL-1β receptor antagonists, have recently been introduced to improve survival [24]. Establishment of screening methods for whole populations of ESRD patients to identify candidates for anti-inflammation therapy is therefore necessary. Because these three markers are commonly measured, analysis based on these risk factors with or without established risk factors is potentially very useful. Malnutrition inflammation score (MIS) and subjective global assessment of nutrition (SGA), which include medical history and physical examination, have been reported to be useful in assessing protein-energy wasting [25, 26]. MIS incorporating the 7 components of the SGA plus BMI, albumin and total iron-binding capacity or transferrin levels was associated with quality of life, hospitalization and mortality, and may be superior to SGA [23, 26]. Combination with medical history, physical examination and these three markers (albumin, CRP and BMI) may be a better predictor than MIS. However, due to insufficient data, we could not perform comparisons with these scores. Further studies are therefore necessary.

In this study, there were several limitations. The most important issue is that we only analyzed these predictors at the initiation of HD. We did not analyze the impact of improvements in these factors after initiation of HD therapy on mortality, and such analysis is necessary in subsequent studies. Precise medical treatment and intervention were not evaluated in this study. In addition, all patients in the study were Japanese, and Japanese patients are reported to have better prognosis than comparable patients in the United States and Europe, and subclinical atherosclerosis, coronary disease mortality and risk of coronary calcification are lower in Japanese [27]. In addition, we could not analyze the CVD history as a comorbid condition because of insufficient data. Finally, investiga-

tions into whether the combination of these markers is useful for monitoring are also required.

In summary, lower serum albumin, elevated serum CRP and lower BMI at initiation of HD therapy may independently predict all-cause death and CVD mortality in Japanese ESRD patients characterized by lower BMI and inflammatory markers. The predictive value of these combined markers is superior to individual factors, offers incremental additive value for predicting mortality and may identify the sickest ESRD patients with the worst outcomes. Further studies are necessary to determine whether these markers can also act as monitoring markers, and whether their improvement affects outcomes.

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