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Original Article

Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction

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Abstract

Background. Hypoalbuminaemia is a marker of malnutrition–inflammation complex syndrome (MICS) and a strong predictor of cardiovascular (CV) death in maintenance haemodialysis (MHD) patients. However, serum albumin may change over time. Hence, its time-varying associations with outcome may be different.

Methods. Associations between 3-month averaged serum albumin levels, measured in a single laboratory using bromocresol green, and CV mortality were studied longitudinally in a 2-year cohort of 58 058 MHD patients. Mortality predictability of fixed baseline and trimonthly-varying serum albumin concentrations were compared.

Results. Hazard ratios (HRs) of CV death strictly increased across decrements of baseline serum albumin, whereas the HR for time-varying serum albumin decrements below 3.8 g/dl did not differ. A drop in serum albumin in the first 6 months was associated with increasing all-cause and CV death risks in the subsequent 18 months, while a rise in serum albumin was a predictor of better survival independent of baseline serum albumin. The multivariate adjusted population-attributable fraction of death due to baseline serum albumin <3.8 g/dl was 19%.

Conclusions. Time-varying hypoalbuminaemia predicts all-cause and CV death differently from fixed measures of serum albumin in MHD patients. An increase in serum albumin over time is associated with better survival independent of baseline serum albumin or other MICS surrogates. If this association is causal, an intervention that could increase serum albumin >3.8 g/dl might reduce the number of MHD deaths in the USA by ~10 000 annually. Nutritional interventions examining benefits of increasing serum albumin in MHD patients are urgently needed.

Keywords: albumin; cardiovascular death; haemodialysis; malnutrition–inflammation complex syndrome; population-attributable fraction; time-dependent Cox model

Introduction

Approximately two-thirds of all maintenance haemodialysis (MHD) patients in the USA die within 5 years of initiation of chronic dialysis treatment, mostly due to cardiovascular (CV) disease [1]. The annual mortality rate among MHD patients has remained at ~20% for many years [1]. Hence, out of 300 000 individuals currently undergoing MHD treatment in the USA, at least 60 000 will die within the next 12 months. A recent multi-centre clinical trial known as the HEMO Study [2] failed to show any survival advantage of increasing dialysis dose or use of different dialysis membranes in MHD patients. Moreover, despite ongoing efforts at treating conventional CV risk factors in MHD patients including obesity, hypertension, hypercholesterolaemia and hyperhomocysteinaemia, survival has not improved substantially in these individuals. A recent randomized, double-blind controlled clinical trial known as the 4D Study (Die Deutsche Diabetes Dialyse Studie) in 1255 patients from 178 dialysis centres throughout Germany (1998–2002) testing atorvastatin 20 mg *vs* placebo

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failed to show any improvement in survival or CV events [3]. A clinical trial testing usual to higher doses of folic acid supplement to improve hyperhomocysteinaemia and survival in MHD patients was also reported negative [4]. Indeed, epidemiological studies have indicated paradoxically inverse associations between classical CV risk factors and death in MHD patients, a phenomenon that has been referred to as 'reverse epidemiology' [5]. Protein-energy malnutrition and inflammation, together also known as the malnutrition–inflammation complex syndrome (MICS), have been implicated as the most powerful death indicators in MHD patients and a main cause of the reverse epidemiology [5].

Among markers of MICS, hypoalbuminaemia has been studied extensively, especially because it is common and correlates strongly with poor outcome including CV death in MHD patients [6]. However, most investigators have studied only the effect of the initial or baseline serum albumin, obtained at the start of the cohort, on subsequent mortality. We are unaware of other studies that have examined the effect of changes in serum albumin over time on all-cause or CV mortality with or without multivariate adjustment for other elements of MICS. It is not clear whether a drop or rise in serum albumin over time will change the subsequent death risk accordingly. We studied time-dependent multivariate models and examined whether serum albumin changes over time are predictors of changes in survival in MHD patients independent of baseline serum albumin and other covariates. Moreover, the population-attributable fraction (PAF) of hypoalbuminaemia-associated deaths was explored to ascertain how many deaths can theoretically be prevented if serum albumin increases over time.

Methods

National MHD database

The national database of DaVita, Inc., the second largest dialysis care provider in the USA, includes information on ~40 000 maintenance dialysis patients at any given time. Database creation has been described elsewhere [7]. In brief, a 2-year cohort consisting of eight longitudinal quarters was created using data collected between July 1, 2001 and June 30, 2003. All repeated measures for each patient within a given quarter (13 week interval) were averaged to obtain quarterly mean values. The study was approved by the Institutional Review Committees of Harbor-UCLA and DaVita, Inc.

Clinical and demographic data

Patient's post-dialysis weight was averaged over each 13 week quarter, and body mass index (BMI) was calculated from the equation $\mathrm{BMI} = \mathrm{weight(kg)}/\mathrm{height}^2(\mathrm{m}^2)$. Age was calculated using date of birth and the first day of the entry quarter. Five race/ethnic groups were defined: (i) Caucasians (including non-Hispanic whites and Middle Easterners); (ii) self-described Blacks (including African Americans and other sub-Saharan Africans); (iii) Asians (including Pacific Islanders); (iv) American Indians; and (vi) others.

Cohort time, dialysis vintage and mortality

Cohort time included the number of days that a patient participated in the cohort and was a number between 1 and 731 days. Dialysis vintage was defined as the duration of time between the first day of dialysis treatment and the first day that the patient entered the cohort. Four categories of vintage were formed: (i) first 6 months; (ii) between 6 and 24 months; (iii) between 2 and 5 years; and (iv) >5 years. The entry quarter was defined as the first quarter in which a patient's dialysis vintage was >3 months for at least half the duration of the quarter. By implementing this criterion, any patient who did not remain in the cohort beyond the first 3 months of MHD was excluded. The computerized causes of death, reflecting the reported information in the Cause of Death form (Form 2746), were obtained and summarized into six main categories: CV, infectious, gastrointestinal, cancer-related, others and unspecified/unknown. CV death included death due to myocardial infarction, cardiac arrest, heart failure, cerebrovascular accident and other cardiac.

Laboratory data and indicators of MICS

Most blood samples were collected pre-dialysis, with the exception of the post-dialysis serum urea nitrogen to calculate urea kinetics. Blood samples were drawn using uniform techniques in all DaVita dialysis clinics across the nation and were transported to the DaVita Laboratory in Deland, Florida, usually within 24 h. All laboratory values were measured via automated and standardized methods in the DaVita Laboratory. Most laboratory values, including complete blood cell counts and serum levels of urea nitrogen, albumin, creatinine, ferritin and total iron binding capacity (TIBC), were measured monthly. Serum ferritin was measured quarterly. Haemoglobin was measured weekly to bi-weekly in most patients. Kt/V used to estimate dialysis dose and normalized protein equivalent of total nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR), an estimation of daily protein intake, were measured monthly.

Serum albumin was measured monthly via the bromocresol green method [8]. Nine categories of serum albumin were created: <3.0 g/dl, ≥4.4 g/dl and seven 0.2 g/dl incremental categories in between. Patients with missing serum albumin values in all eight quarters or with values below the 0.25th or above the 99.75th percentile levels of serum albumin were excluded because of increased likelihood of errors of such outliers. Seven additional laboratory variables were also selected as available surrogates of the nutritional state and/or inflammation, together also known as MICS, with known mortality predictability: (i) nPNA as an indicator of daily protein intake; (ii) serum TIBC, which has a strong association with subjective global assessment of nutrition [9]; (iii) serum ferritin, a possible inflammatory marker [10]; (iv) serum creatinine, an indicator of muscle mass; (v) peripheral white blood cell count (WBC), which correlates with serum C-reactive protein (CRP) and survival

in MHD patients [11]; (vi) lymphocyte percentage, a known nutritional marker which can decrease with protein-energy malnutrition [12]; and (vii) blood haematocrit.

Epidemiologic and statistical methods

A non-concurrent cohort was formed to include all existing MHD patients of the first quarter (q1) and all new MHD patients of the subsequent quarters (q2–q8). Eight quarterly data sets were linked using unique patient identifiers. For patients who were not matched initially, additional merging methods using the initial letters of the patient's last and first names combined with his/her date of birth were performed. In addition to eight quarterly values for every variable, a baseline value was also created for each measure by left-truncating the first available value of the entry quarter for each patient.

Because of the very large numbers involved, most associations described have low *P*-values. Therefore, caution must be exercised in interpretation of low *P*-values. In addition to standard descriptive statistics, multiple linear regression models were fitted to construct partial correlations, and regular and time-dependent Cox proportional hazard regression analyses for truncated and censored data [13] were examined and compared with each other to determine whether the baseline serum albumin associated differently with 2-year mortality when compared with the mortality predictability of time-varying serum albumin. The reference serum albumin category for all analyses was the 3.6–3.8 g/dl range. This category was chosen because it included the median and mean serum albumin, it was adjacent to the modal category and had almost the same sample size, it had the highest number of death cases, and it produced the most precise comparison with higher and lower serum albumin categories.

For each analysis, three models were examined based on the level of multivariate adjustment: (i) an unadjusted model included only serum albumin categories and mortality data; (ii) case mix-adjusted models included age, gender, race and ethnicity, diabetes mellitus, vintage categories, entry quarter, primary insurance (Medicare, Medicaid, private and others), marital status (married, single, divorced, widowed and other), standardized mortality ratio of the dialysis clinic during entry quarter, Kt/V (single pool), and residual renal function during the entry quarter, i.e. urinary urea clearance; and (iii) case mix- and MICS-adjusted models included all of the above-mentioned covariates as well as eight surrogates of nutritional status and inflammation including BMI and the seven above-mentioned laboratory values. In time-dependent models, in addition to time-varying quarterly serum albumin categories, eight surrogates of MICS and Kt/V were also entered as quarterly time-varying variables.

The PAF of death due to hypoalbuminemia was calculated according to the following equation: $PAF = P_e \times (RR - 1)/RR$ where P_e is the prevalence of hypoalbuminaemia among all who died, and RR is the relative risk of death; for the purpose of setting confidence limits, PAF was transformed into $\ln(1 - PAF)$ [14]. Missing covariate data (<5%) were imputed by the mean or median of the existing values, whichever was most appropriate. All descriptive and multivariate statistics were carried out with the SAS, version 8.02 (SAS Institute, Inc., Cary, NC).

Results

The original 2-year national database of all MHD patients included 69 819 subjects. After implementing the above-mentioned selection criteria including deleting MHD patients who did not remain in the cohort beyond 3 months of MHD or who had inadequate or overtly missing data, the resulting cohort included 58 058 MHD patients, of which 37 049 patients (64%) originated from the first quarter data set (q1) and the rest from the subsequent quarters (q2–q8). Table 1 shows baseline demographic, clinical and laboratory characteristics of the cohort categorized into two groups based on a serum albumin cut-off level of 3.8 g/dl at baseline. Hypoalbuminaemic patients were 5.7 years older and included more diabetic, Caucasian and incident (newly started) MHD patients. CV death was less prevalent, but infectious death was slightly more prevalent among hypoalbuminaemic patients, who also had a lower BMI and protein intake and most of whose laboratory measures were also significantly different from the other group,

Table 1. Baseline data of the non-concurrent (left truncated) cohort of 58 058 MHD patients, divided into two groups according to the serum albumin cut-off level of 3.8 g/dl

Variable (mean ± SD or %)	Albumin ≥3.8 ($n = 27\,757$)	Albumin <3.8 ($n = 30\,244$)
Age (years)	57.6 ± 16.0	63.3 ± 14.6
>65 years old (%)	37	50
Diabetes mellitus (%)	38	51
Race and ethnicity		
Caucasians (%)	35	39
Blacks (%)	33	31
Asians (%)	5	4
Hispanics (%)*	17	17
Vintage (time on dialysis)		
3–6 months (%)	32	48
6–24 months (%)	24	20
2–5 years (%)	28	30
>5 years (%)	16	11
Primary insurance		
Medicare (%)	62	58
Medicaid (%)	6	5
Causes of death		
Cardiovascular (%)	56	49
Infectious (%)	11	14
Cancer (%)	3	4
Gastrointestinal (%)**	2	2
Others/unknown (%)	28	31
Standardized mortality ratio	0.80 ± 0.29	0.82 ± 0.32
Post-HD weight (kg)	75.2 ± 19.5	72.4 ± 20.0
Body mass index (kg/m^2)	26.3 ± 5.9	25.9 ± 6.5
Kt/V (single pool)	1.54 ± 0.30	1.53 ± 0.33
NPCR or nPNA (g/kg/day)	1.04 ± 0.23	0.96 ± 0.24
Serum albumin (g/dl)	4.06 ± 0.19	3.46 ± 0.35
Creatinine (mg/dl)	10.1 ± 2.3	8.0 ± 2.9
Ferritin (ng/ml)**	617 ± 429	609 ± 520
TIBC (mg/dl)	211 ± 39	193 ± 43
Blood haemoglobin (g/dl)	12.1 ± 1.4	11.7 ± 1.4
WBC (per fl)	6.9 ± 2.0	7.6 ± 2.6
Lymphocyte (% of total WBC)	22.1 ± 7.4	19.8 ± 7.5

*$P = 0.51$; **$P = 0.04$; all other *P*-values are <0.001.

including a lower serum creatinine and TIBC, a lower blood haemoglobin and lymphocyte percentage and a higher WBC count.

Table 2 shows the bivariate (unadjusted) and multivariate adjusted correlation coefficients between serum albumin and some clinically relevant variables in the baseline quarter of the non-concurrent cohort. Serum TIBC and creatinine had the highest correlations. Table 3 shows the nine serum albumin categories among 58 058 MHD patients. Both all-cause and CV mortality exhibited almost strictly increasing rates across decreasing serum albumin categories.

Figure 1 compares the hazard ratios of all-cause death for time-varying serum albumin with up to eight quarterly serum albumin values per patient with those derived from non-time-dependent Cox models based on one single serum albumin value at the baseline of the cohort. The observed relationship between death and baseline serum albumin was similar to what was reported previously [15]. However, with adjustment for case mix and MICS, the magnitude of the association was partially mitigated, indicating that much of the mortality was related to underlying characteristics. This difference was particularly dramatic with time-dependent modelling, in that decrements of serum albumin below 3.8 g/dl did not have a differential association with death. Figure 2 shows that the differences between the two models were even more prominent for CV mortality. Hazard ratios for time-varying albumin were similar across categories below 3.8 g/dl, whereas in non-time-dependent models, lower serum albumin categories exhibited increasing hazard ratios (Figure 2). As evident from both Figures 1 and 2, the addition of MICS surrogates did not change the case mix-adjusted associations substantially.

Of 37 049 MHD patients originally in q1, who formed the longest concurrent cohort, 30 827 patients survived and remained in the cohort through the entire first 6 months. This allowed the estimation of the rate of change in their serum albumin over the first 6 month interval. Table 4 shows the rate of serum albumin change in seven distinct categories. The stable category included 14 514 MHD patients (47%), whose serum albumin had only a minimal change, i.e. within the range +0.1 and −0.1 g/dl over the 6 month interval. Those whose serum albumin decreased by at least 0.1 g/dl or more were subdivided further into three categories based on decrements of 0.1 g/dl. The gain in serum albumin was also subcategorized into three groups in a similar fashion. As shown in Table 4, those whose serum albumin increased the most (≥0.3 g/dl over 6 months) had the lowest baseline serum albumin (3.4 ± 0.4 g/dl) to start with.

Figures 3 and 4 show hazard ratios of death in the subsequent 18 months for changes in serum albumin during the first 6 months of the cohort. The stable (reference) group had the lowest unadjusted mortality hazard ratio. Both unadjusted and adjusted hazard ratios for death across decreasing serum albumin groups were strictly increasing, whereas a tendency towards a better survival and reduced CV death was observed across increasing serum albumin gain groups after multivariate adjustment, which included controlling for the baseline serum albumin. Those patients whose serum albumin increased by ≥0.3 g/dl within the 6 month interval had 22% lower all-cause mortality risk compared with patients with stable serum albumin [hazard ratio, 0.78; 95% confidence interval (CI), 0.71–0.86]. Among relevant interactions examined,

Table 2. Bivariate (unadjusted) and multivariate correlation coefficients between serum albumin and some relevant variables at baseline in 58 058 MHD patients

Variable	Pearson correlation *r*	Multivariate correlation[a]
Age	−0.19	−0.02
Kt/V	+0.05	+0.05
BMI	+0.07	+0.01*
nPNA (nPCR)	+0.24	+0.09
Serum ferritin	−0.01**	+0.07
TIBC	+0.34	+0.32
Creatinine	+0.39	+0.20
Blood haematocrit	+0.12	+0.15
WBC	−0.19	−0.11
Lymphocyte	+0.19	+0.07

[a]The multiple regression model includes all case mix and MICS covariates (see text).
*$P = 0.02$; **$P = 0.002$; all other P-values are <0.001.

Table 3. Categories of 3 month averaged serum albumin at baseline (first quarter) of the cohort in 58 058 MHD patients

Albumin range(g/dl)	Group size (% of all patients)	No. of deceased cases (2 year mortality rate %)	
		All-cause death	Cardiovascular death
≥4.4	1800 (3)	141 (8)	80 (4)
≥4.2 and <4.4	4631 (8)	609 (13)	304 (7)
≥4.0 and <4.2	9900 (17)	1614 (16)	749 (8)
≥3.8 and <4.0	14 032 (24)	2976 (21)	1395 (10)
≥3.6 and <3.8 (reference)	11 617 (20)	3047 (26)	1322 (12)
≥3.4 and <3.6	7107 (12)	2312 (33)	967 (14)
≥3.2 and 3.4	3954 (7)	1483 (38)	587 (15)
≥3.0 and <3.2	2166 (4)	919 (42)	362 (17)
<3.0	2851 (5)	1432 (50)	478 (17)

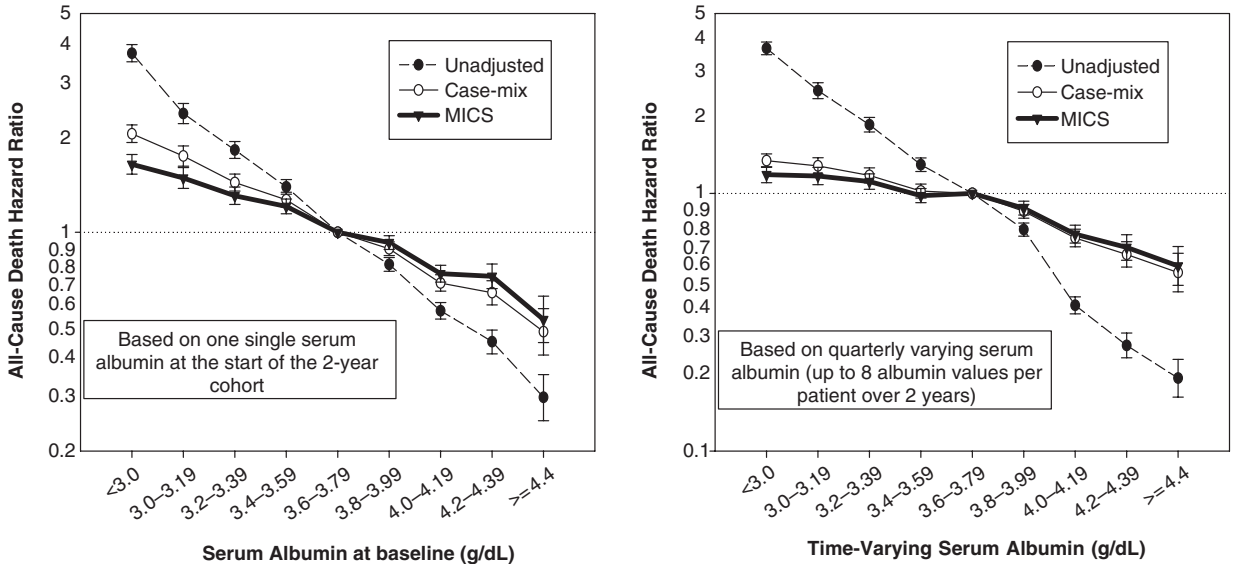

Fig. 1. Hazard ratio of all-cause mortality over 2 years (July 2001–June 2003). Left panel: conventional Cox analysis based on the baseline serum albumin at the beginning of the cohort. Right panel: time-dependent Cox analysis based on time-varying serum albumin with up to eight serum albumin concentrations for eight calendar quarters for each patient. Note that all laboratory values, Kt/V, nPNA and BMI, are also quarterly varying in the time-dependent model.

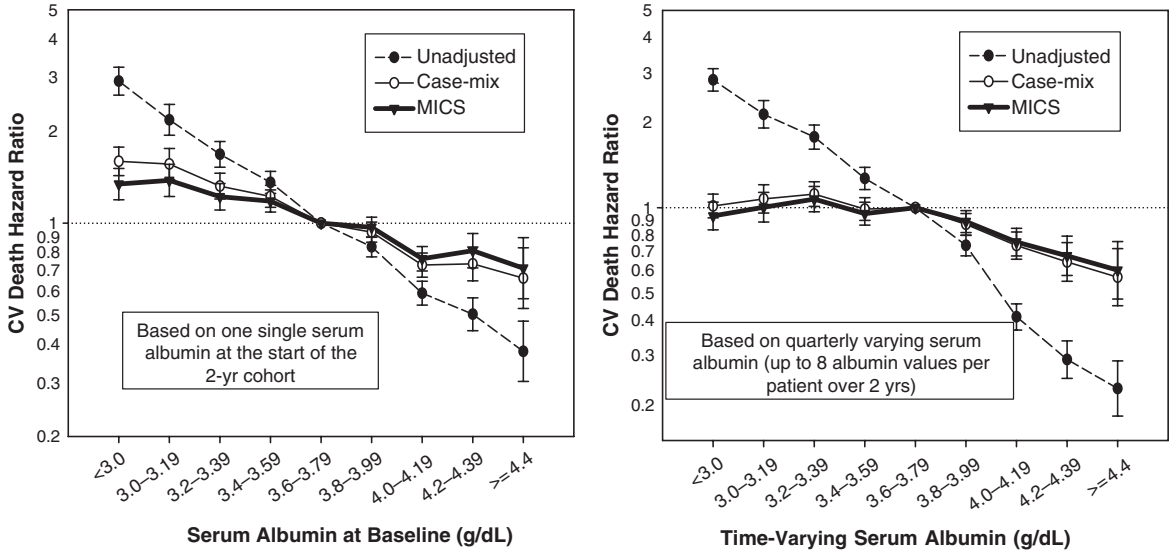

Fig. 2. Hazard ratio of cardiovascular mortality over 2 years (July 2001–June 2003). Left panel: conventional Cox analysis based on the baseline serum albumin at the beginning of the cohort. Right panel: time-dependent Cox analysis based on time-varying serum albumin with up to eight serum albumin concentrations for eight calendar quarters for each patient. Note that all laboratory values, Kt/V, nPNA and BMI, are also quarterly varying in the time-dependent model.

Table 4. Categories of changes in serum albumin during the first 6 months in 30 827 MHD patients who survived and remained in the cohort through the first 6 months of the 2 year cohort

Direction of change	Categories of albumin change	Group size	Percentage of total	Baseline serum albumin (mean ± SD)
Decrease	≤−0.3 g/dl	1876	6%	3.8 ± 0.4
	>−0.3 and ≤−0.02 g/dl	2284	7%	3.9 ± 0.4
	>−0.2 and ≤−0.1 g/dl	3926	13%	3.9 ± 0.3
No change (stable)	>−0.1 and <+0.1 g/dl	14 514	47%	3.9 ± 0.3
Increase	≤+0.1 and <0.2 g/dl	4209	14%	3.8 ± 0.3
	≤+0.2 and <0.3 g/dl	2378	8%	3.7 ± 0.3
	≤+0.3 g/dl	1640	5%	3.4 ± 0.4

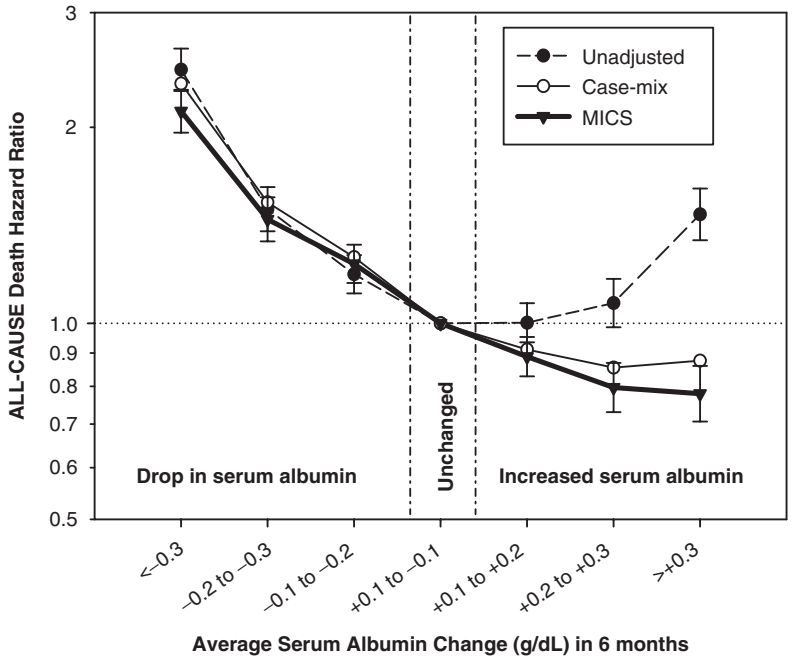

Fig. 3. Association between serum albumin changes in the first 6 months and risk of all-cause mortality in the subsequent 18 months in 30 827 MHD patients across the USA.

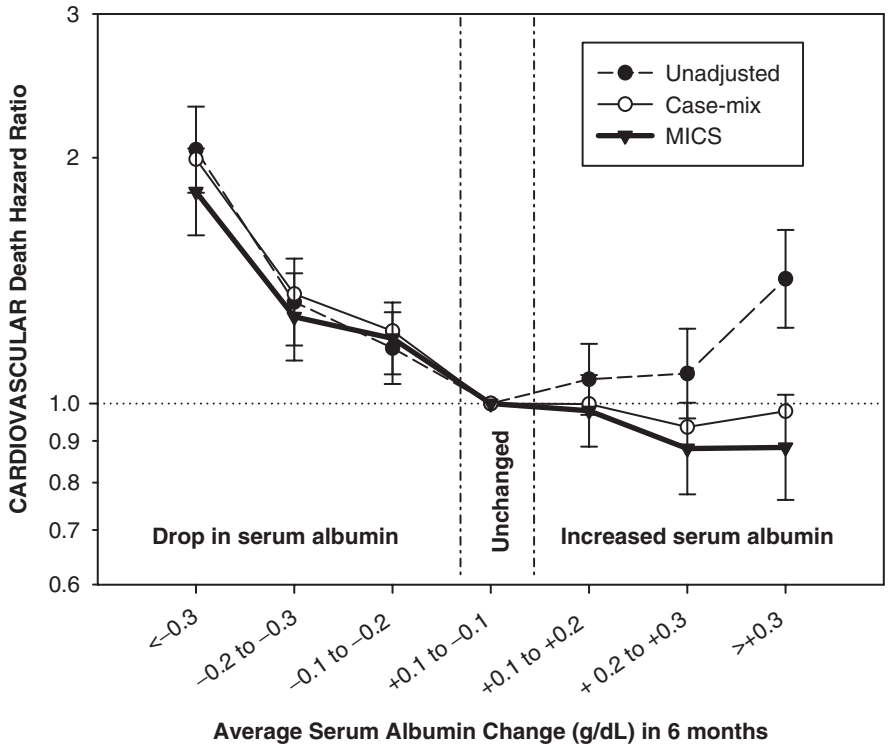

Fig. 4. Association between serum albumin changes in the first 6 months and risk of cardiovascular mortality in the subsequent 18 months in 30 827 MHD patients across the USA.

some interaction terms that were the product of the baseline serum albumin and serum albumin change groups had a significant effect on CV mortality (data not shown here).

To explore the impact of several relevant cut-off levels of serum albumin on survival and to estimate the PAF of death due to hypoalbuminaemia, serum albumin data were dichotomized at several levels.

The multivariate adjusted hazard ratio of death was between 1.40 and 1.60 for a hypoalbuminaemia below most of the serum albumin cut-off levels. However, the prevalence of hypoalbuminaemia differed substantially according to the selected cut-off level. Over 50% of MHD patients were hypoalbuminaemic, defined as a serum albumin <3.8 g/dl. The PAF of death for this level of hypoalbuminaemia was 19% (95% CI 16–22). If this estimate reflects the true effect of hypoalbuminaemia, hypothetically 19% of MHD patient deaths could be prevented if serum albumin <3.8 g/dl would be corrected to levels >3.8 g/dl. Because almost 60 000 of the 300 000 MHD patients in the USA die each year (a 20% annual mortality rate), this would mean ~10 000 deaths could be prevented hypothetically by interventions that would correct the underlying conditions associated with hypoalbuminaemia in these individuals.

Discussion

Using a large national database that is representative of the US dialysis population, we have shown that longitudinal associations between quarterly-varying serum albumin and death are somewhat different from the well-known associations between the baseline serum albumin and mortality in MHD patients. This finding has important clinical implications, since physicians usually evaluate MHD patients using current serum albumin levels without considering previous serum albumin concentrations measured in the past at the baseline of some observational cohort. Moreover, we showed that changes in serum albumin over a 6 month period are predictive of prospective mortality independent of baseline serum albumin. An increase in serum albumin was associated with improved survival, whereas decreased serum albumin over time correlated with increased CV death independent of demographic, clinical or other laboratory characteristics. We have found that once the current serum albumin is below 3.8 g/dl, its time-dependent association with increased CV death is somewhat uniform for the entire hypoalbuminaemic range, whereas the survival advantages conferred by serum albumin levels <3.8 g/dl are strictly incremental, so that a serum albumin of ≥4.4 g/dl is associated with 48% higher survival and 40% lower CV death than a serum albumin <3.8 g/dl.

These findings were derived from a national database cohort that included virtually all MHD patients of a major dialysis care provider with uniform patient management practices and standardized laboratory values, all measured in one laboratory. Hence, the internal and external validity of our findings is substantial. Based on these data, we have shown that if an intervention could correct conditions associated with hypoalbuminaemia in all MHD patients with serum albumin <3.8 g/dl, ~10 000 lives could hypothetically be saved each year. However, caution must be exercised in interpreting epidemiological inferences as long as clinical trials have not verified these findings.

Many epidemiological studies have shown a strong association between serum albumin and prospective mortality, including CV death, in MHD patients [6]. Hypoalbuminaemia is considered to be a reliable indicator of the presence of MICS in MHD patients. Kaysen *et al.* [6] showed that the serum albumin concentration in MHD patients changes with inflammation and nutritional status through their effects on albumin catabolism and synthesis, respectively. They showed that nutritional variables primarily affected albumin synthesis, whereas inflammation caused hypoalbuminaemia by increasing the albumin fractional catabolic rate [6]. In another study, Kaysen *et al.* showed that proxies of inflammation and dietary protein intake exerted competing effects on serum albumin in MHD patients [16]. In our study, multivariate adjustment included case mix and available surrogates of MICS, including nPNA as a measure of protein intake and indicator of clinical outcome. Since progressively increasing serum albumin values over time continued to have a strong association with improved outcome in our study, the effect of serum albumin may be beyond its function as a sole MICS surrogate. Similar to lipoprotein, serum albumin may bind to endotoxins and hence mitigate cytokine cascade activation that would otherwise occur in hypoalbuminaemic patients [17,18]. Consistent with this hypothesis, in our study the prevalence of death due to infection was higher in hypoalbuminaemic MHD patients (see Table 1). Hence, the protective role of high serum albumin in MHD patients may have a causal component. Furthermore, our study indicated the survival advantages of serum albumin >3.8 g/dl and its incremental association with decreasing CV death up to a serum albumin of ≥4.4 g/dl.

Our study lacked data on history of CV co-morbidity. However, data concerning diabetes mellitus were available and adjusted for in all multivariate models. Moreover, many other covariates that were included in the models are known to have strong associations with co-morbid conditions. Hence, we suspect that the associations would not have been very different if additional adjustments had been made for other co-morbidities. Our adjustments are not too different from past studies, as the limited co-morbidity data used in those studies usually originated from the dialysis initiation form (Form 2728), in which co-morbid conditions are significantly under-reported [19] and which is outdated for prevalent patients with higher vintage periods. Another limitation of our study is lack of explicit laboratory markers of inflammation such as CRP. However, we did use data on serum ferritin and TIBC, and blood WBC, lymphocyte percentage and haematocrit, which have significant association with inflammation [9–11,20].

Another limitation of our study is that we did not examine the causes of hypoalbuminaemia in MHD patients. In addition to MICS, several other conditions may contribute to hypoalbuminaemia including the

residual urine output with proteinuria, especially in incident dialysis patients. Goldwasser *et al*. [21] showed an increase in serum albumin in the months after initiation of dialysis, related presumably to a reduction in proteinuria rather than an improved nutritional status. In line with this hypothesis, in our study incident patients with a dialysis vintage <6 months were over-represented among hypoalbuminaemic patients (see Table 1). Other conditions which may also lead to hypoalbuminaemia include overhydration and liver disease. However, our study showed that changes in serum albumin over time may modify survival risk stratification regardless of the causes of hypoalbuminaemia.

Among the strengths of our study is the use of time-dependent models to examine the time-varying effect of serum albumin groups on CV mortality while controlling for the time-varying effect of other nutritional and inflammatory indices and the dialysis dose. A limitation of our time-dependent analysis is that it is based on a 2 year period of the cohort, rather than complete longitudinal follow-up over many years, and so may not apply to long-term survival of individuals. Nonetheless, the narrow time window of our study ensures that confounding by changes in practice or technology is minimal. Our time-dependent findings are supported by the observed relationships of different rates of serum albumin gain and loss over time to survival. The data originate from one dialysis care provider that has uniform patient management practices; all laboratory measurements are performed in one facility, and most data are means of several measures. Hence, measurement variability is minimized.

We recognize that our effect estimates are subject to various potential biases, not all of which are addressable with the observational database available to us. Nonetheless, if causal, the time-dependent association of serum albumin and its changes over time with survival would have major clinical and public health implications. Hence, it may be time for clinical trials of albumin-increasing interventions in MHD patients including nutritional supplements with or without anti-inflammatory or anti-oxidant properties. Such interventions may also include appetite-stimulating arms, since a poor appetite is associated with MICS and poor outcome [22]. Although these interventions might lead to obesity, hypercholesterolaemia or hyperhomocysteinaemia, which are known CV risk factors in the general population, these conditions have been shown to be paradoxically associated with improved survival in MHD patients, i.e. the reverse epidemiology. Currently >60% of MHD patients die within 5 years of commencing dialysis treatment; hence, long-term consequences of nutritional interventions may be of secondary concern. Nevertheless, utmost caution must be exercised when dealing with such deleterious consequences. Initial trials should target MHD patients with a serum albumin <3.8 g/dl (which are approximately half of all MHD patients in the USA), and enrol patients in lower BMI levels, for whom weight gain would probably have the least serious CV impact and who experience the highest mortality among dialysis patients.

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