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ORIGINAL ARTICLE

Differences in association between hypoalbuminaemia and mortality among younger versus older patients on haemodialysis

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ABSTRACT

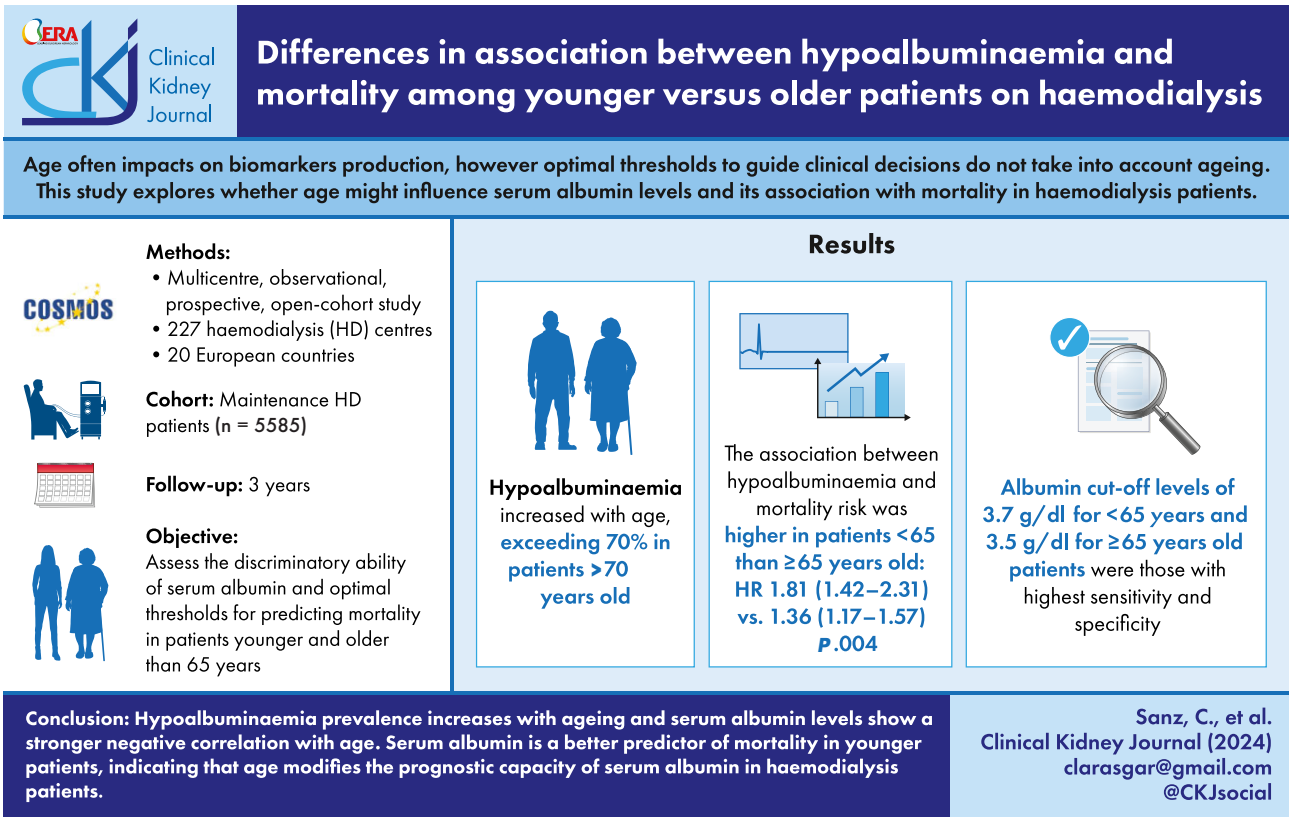
Background. Ageing often affects biomarker production. Yet, clinical/optimal thresholds to guide clinical decisions do not consider this. Serum albumin decreases with age, but hypoalbuminaemia is defined as serum albumin <4.0 g/dl. This study explores whether age might affect serum albumin levels and its association with mortality in haemodialysis patients.

Methods. COSMOS (Current Management of Secondary Hyperparathyroidism: a Multicentre Observational Study) is a prospective, open-cohort, observational study of haemodialysis patients followed for 3 years. Binary logistic and linear regression were used to analyse the association between age and hypoalbuminaemia or serum albumin (continuous). Cox proportional hazard multivariate regression was used to examine the relationship between hypoalbuminaemia and mortality in patients younger and older than 65 years. Time-dependent receiver operating characteristic (ROC) curves were used to assess the discriminatory ability of serum albumin and optimal thresholds for predicting mortality.

Results. The present analysis included 5585 patients. The odds of experiencing hypoalbuminaemia increased with age [adjusted odds ratios = 1.56(95%CI: 1.31–1.86), 1.89(95%CI: 1.59–2.24), 2.68(95%CI: 2.22–3.23) for 56–65, 66–75, and >75 years, respectively (reference ≤55 years; *P* value for trend: <0.001)]. Survival analysis showed that the association between hypoalbuminaemia and mortality was weaker in patients aged ≥65 compared to <65 years [hazard ratios: 1.36(95%CI: 1.17–1.57) and 1.81(95%CI:1.42–2.31) respectively; *P* value for interaction 0.004]. The ability of albumin levels to predict mortality was consistently higher in younger patients. Optimal albumin thresholds for predicting mortality were 3.7 g/dl in patients younger than 65 years and 3.5 g/dl in patients 65 years and older.

Conclusions. Ageing is accompanied by lower albumin levels, and the association between hypoalbuminaemia and mortality may be modified by age. Different clinical thresholds that consider age may better discriminate risks associated with hypoalbuminaemia.

GRAPHICAL ABSTRACT



Keywords: ageing, albumin, chronic kidney disease, haemodialysis, mortality

KEY LEARNING POINTS

What was known:

- Serum albumin is a well-established marker of nutritional status and a strong predictor of mortality in haemodialysis patients.
- Hypoalbuminaemia (low serum albumin levels) is associated with increased morbidity and mortality in haemodialysis patients.
- The impact of age on the association between serum albumin levels and mortality in haemodialysis patients had not been thoroughly investigated.

This study adds:

- In haemodialysis patients, the association between hypoalbuminaemia and mortality is influenced by age, being stronger in younger patients (<65 years) compared to older patients (≥65 years).
- The hypoalbuminaemia prevalence increases with age, and serum albumin levels show a stronger negative correlation with age.
- Serum albumin is a better predictor of mortality in younger patients, indicating that age modifies the prognostic capacity of serum albumin in haemodialysis patients.

Potential impact:

- These findings suggest the need to adjust current guidelines for optimal serum albumin levels in haemodialysis patients based on age.
- Clinicians should consider age-specific cut-off points for serum albumin when assessing the nutritional status and mortality risk in haemodialysis patients.
- Future prospective studies could establish evidence-based age-adjusted cut-off levels for serum albumin, improving mortality risk stratification and patient care in haemodialysis.

INTRODUCTION

Hypoalbuminaemia is a significant prognostic marker of adverse outcomes in the general population and in patients undergoing haemodialysis. Serum albumin levels are extensively used to evaluate the nutritional status of individuals, whether they have chronic kidney disease (CKD) or not. A decrease in these levels is associated with inflammation, fluid overload, frailty, and malnutrition, among others [1–4].

The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for haemodialysis patients define hypoalbuminaemia as serum values below 4.0 g/dl [5]. However, the most recent update of these guidelines did not establish a specific cut-off value for hypoalbuminemia [6].

A great proportion of patients undergoing haemodialysis are elderly, with the ageing, there are important changes in body composition, characterized by an increase in fat mass, a decrease in lean mass, reduced physical activity, and lower daily energy requirements [7]. In our clinical experience, many elderly haemodialysis patients with seemingly good health status, exhibit albumin levels lower than those recommended by guidelines.

Several studies have been published on the association between hypoalbuminaemia and increased morbidity and mortality in haemodialysis patients [8–13]. However, no studies have yet been conducted to determine whether this relationship is modified by the age of the patients.

In this study, we hypothesize that the decline in albumin levels with the ageing could influence the albumin prognostic capacity in the elderly haemodialysis patients.

MATERIALS AND METHODS

Study design

COSMOS is a multicentre, observational, prospective, open-cohort study spanning a 3-year period. It involved a total of 6797 patients from 227 haemodialysis centres across 20 European countries. Patients and centres were randomly selected from a full list of dialysis facilities in these 20 countries. Haemodialysis centres with more than 40 patients were included in the study, and each centre contributed with 20 patients. The number of patients recruited per country was proportional to the haemodialysis population in each participating country.

Patient recruitment began in February 2005 and concluded in July 2007, thus the follow-up period finished in July 2010. The study received approval by the Ethics Committee of University Hospital, Doctor Peset (Approval number 05/054, Valencia, Spain). Patients provided informed consent to participate in the study which was conducted following the principles of the Declaration of Helsinki. All study details have been previously published [14–17].

Baseline data collected from each patient included demographics [age, gender, body mass index (BMI)], medical history (smoking habits, aetiology of CKD, diabetes mellitus, cardiovascular disease), and treatments (time on haemodialysis, haemodialysis regimen including hours per week and type). Moreover, laboratory values from the previous 6 months [calcium, phosphate, parathyroid hormone (PTH), albumin, and haemoglobin] were also collected. Additional data on treatments, monthly laboratory values, and outcomes (including death) were collected every 6 months throughout the entire 3-year follow-up period. All data were obtained from medical records. At baseline and at subsequent 6-month intervals, the mean values of laboratory tests from the preceding 6 months were calculated.

Patients lost to follow-up regardless of reason were replaced with new patients undergoing haemodialysis for <1 year. From an initial cohort of 6797 patients, 4500 were randomly selected at study outset and 2297 individuals entered the study later to compensate the dropout of patients during the follow-up period.

Statistical analysis

A descriptive analysis was performed in patients with and without hypoalbuminaemia at cohort entry (referred to as baseline and defined as serum albumin <4 g/dl), in patients above or below 65 years. We also classified patients by quintiles of distribution in serum albumin. Numerical variables were described using means and standard deviations for normally distributed data, and medians and interquartile ranges for non-normally distributed data. To account for the data distribution, statistical comparisons were performed by using one-way ANOVA or Kruskal–Wallis tests accordingly. Categorical variables were presented as frequencies and percentages of patients and chi-squared test was used for comparisons.

The association between baseline serum albumin (dependent numeric variable) and various characteristics of patients (independent variables) was assessed using linear regression analysis. Crude and adjusted estimates were calculated for the following variables: age, gender, BMI, smoking habit, aetiology of CKD, presence of cardiovascular disease, time on haemodialysis, type of dialysis, serum PTH, calcium, and phosphate levels.

The relationship between age and baseline hypoalbuminaemia (yes/no) was assessed using binary logistic regression. For this analysis, age was categorized into four increasing groups: ≤55 years (reference), 55–65 years, 65–75 years, and >75 years. Crude and multivariate adjustments were performed. The multivariable model included the following covariates: gender, BMI, smoking habit, aetiology of CKD, presence of cardiovascular disease, time on haemodialysis, type of dialysis, serum PTH, calcium, and phosphate levels.

Cox proportional hazard regression was used to study the association between all-cause mortality and baseline hypoalbuminaemia in patients older and younger than 65 years. Hazard ratios were adjusted by the variables detailed previously. The potential effect modification of age on the association between hypoalbuminaemia and all-cause mortality was assessed by examining the interaction term between these two covariates. The same analysis was also conducted in different patient subgroups: men, women, those with and without diabetes, and those with and without cardiovascular disease. Additional analyses were carried out considering baseline serum albumin as a continuous variable using restricted cubic splines with three knots at fixed percentiles. Furthermore, the relative risk of mortality was examined using serum albumin as a time-dependent variable, collected every 6 months.

Time-dependent receiver operating characteristic curves (ROC) was used to assess the discrimination of baseline serum albumin in predicting all-cause mortality and identify the cut-off value with highest sensitivity and specificity.

Statistical analyses were performed using R software for windows (version 4.4.0, R Foundation for Statistical Computing, Vienna, Austria) with the RStudio interface (version 2024.04.1 Build 748).

Table 1: Clinical and demographic characteristics of 5585 HD patients from COSMOS stratified by albumin and age at cohort entry.

		Albumin (g/dl)		Age (years)	
	Overall	<4	≥4	<65	≥65
n	5585	3592	1993	2458	3127
Albumin (g/dl) [median (IQR)]	3.8 [3.5, 4.1]	3.6 [3.3, 3.8]	4.2 [4.1, 4.4]	3.9 [3.6, 4.2]	3.8 [3.4, 4.0]
Age (years) [mean (SD)]	64.1 (14.3)	66.1 (13.6)	60.3 (14.9)	51.0 (10.7)	74.3 (6.0)
Sex = male (%)	3396 (60.8)	2063 (57.4)	1333 (66.9)	1566 (63.7)	1830 (58.5)
BMI (kg/m²) [mean (SD)]	25.3 (5.1)	25.2 (5.2)	25.5 (4.9)	25.5 (5.5)	25.2 (4.7)
Smoking habits (%)					
Current	805 (14.4)	499 (13.9)	306 (15.4)	572 (23.3)	233 (7.5)
Former	1220 (21.9)	794 (22.1)	426 (21.4)	455 (18.5)	765 (24.5)
Never	3555 (63.7)	2298 (64.0)	1257 (63.2)	1427 (58.1)	2128 (68.1)
Primary kidney disease (%)					
Diabetic nephropathy	1208 (21.6)	844 (23.5)	364 (18.3)	479 (19.5)	729 (23.3)
Hypertension/nephroangiosclerosis	1136 (20.4)	749 (20.9)	387 (19.4)	324 (13.2)	812 (26.0)
Glomerulonephritis	953 (17.1)	550 (15.3)	403 (20.3)	570 (23.2)	383 (12.2)
Obstructive/interstitial nephropathy	655 (11.7)	413 (11.5)	242 (12.2)	307 (12.5)	348 (11.1)
PKD	451 (8.1)	274 (7.6)	177 (8.9)	249 (10.1)	202 (6.5)
Tumours	90 (1.6)	56 (1.6)	34 (1.7)	44 (1.8)	46 (1.5)
Unknown aetiology	636 (11.4)	410 (11.4)	226 (11.4)	247 (10.1)	389 (12.4)
Other	452 (8.1)	295 (8.2)	157 (7.9)	234 (9.5)	218 (7.0)
Diabetes mellitus = yes (%)	1723 (30.9)	1199 (33.4)	524 (26.3)	623 (25.3)	1100 (35.2)
CV history = yes (%)	4032 (72.2)	2650 (73.8)	1382 (69.5)	1520 (61.9)	2512 (80.4)
Dialysis vintage (months) [median (IQR)]	20.0 [8.0, 51.0]	17.0 [7.0, 48.0]	26.0 [10.0, 58.0]	20.0 [8.0, 51.0]	21.0 [8.0, 51.0]
Dialysis technique (%)					
Low-flux	3007 (53.8)	2037 (56.7)	970 (48.7)	1204 (49.0)	1803 (57.7)
High-flux	2075 (37.2)	1268 (35.3)	807 (40.5)	986 (40.1)	1089 (34.8)
Others	503 (9.0)	287 (8.0)	216 (10.8)	268 (10.9)	235 (7.5)
PTH (pg/ml) [median (IQR)]	209.2 [108.0, 370.0]	200.0 [103.0, 355.6]	227.5 [121.5, 401.5]	236.3 [116.0, 428.4]	193.2 [103.5, 334.8]
Calcium (mg/dl) [median (IQR)]	9.1 [8.6, 9.5]	9.0 [8.6, 9.5]	9.2 [8.8, 9.7]	9.1 [8.6, 9.5]	9.1 [8.7, 9.5]
Phosphate (mg/dl) [median (IQR)]	5.2 [4.4, 6.2]	5.1 [4.3, 6.1]	5.4 [4.5, 6.3]	5.6 [4.7, 6.6]	4.9 [4.1, 5.8]
Haemoglobin (g/dl) [median (IQR)]	11.5 [10.7, 12.3]	11.4 [10.5, 12.2]	11.7 [11.0, 12.4]	11.5 [10.6, 12.2]	11.5 [10.8, 12.3]

PKD: polycystic kidney disease, CV: cardiovascular.

RESULTS

A total of 5585 patients (82.2% of the initial cohort) were included in the present analysis of the COSMOS cohort after excluding individuals with missing follow-up data ($n = 490$) or lacking serum albumin at baseline ($n = 722$). During follow-up, 1470 patients died, 582 received a kidney transplant, 215 were transferred to other haemodialysis centres, 21 switched to peritoneal dialysis, and 46 were lost to follow-up for other reasons.

Table 1 shows the baseline characteristics of the entire cohort and stratified by the presence/absence of hypoalbuminaemia at baseline (<4 g/dl) and by age (<65 or ≥65 years). The full cohort had a mean age of 64.1 years and a haemodialysis vintage of 20.0 months. Men comprised a higher proportion of participants (60.8%). Diabetic nephropathy and hypertension/nephroangiosclerosis were the two most frequent primary causes of kidney disease. Diabetes mellitus and cardiovascular disease were frequent comorbidities in this cohort (30.9% and 72.2%, respectively). The median serum albumin was 3.8 and interquartile range 3.5–4.1 g/dl.

A total of 3592 (64.3%) patients met the criterion for hypoalbuminaemia, (serum albumin below 4 g/dl). These patients were 5.8 years older, and less often males, had lower dialysis vintage, higher prevalence of diabetes and cardiovascular disease and lower levels of serum PTH, calcium, phosphate, and haemoglobin. To provide a more detailed understanding of the relationships between serum albumin levels and patient characteristics, Supplementary Table S1 categorizes the full cohort into quintiles of serum albumin concentration.

A total of 3127 patients (56.0%) were 65 years or older. Compared to younger patients, the elderly population had a lower proportion of males, a higher prevalence of diabetes and cardiovascular disease, and lower serum levels of PTH and phosphate (Table 1).

The prevalence of hypoalbuminaemia increased linearly with age, exceeding 70% in patients over 70 years old (Fig. 1). This association between serum albumin and age was confirmed by both crude and adjusted linear regression analyses, demonstrating a strong negative correlation (β standardized coefficients of −0.204 and -0.187, respectively; $P < .001$) (Supplementary Table S2). Crude and adjusted binary logistic regression also confirmed increased odds for clinical hypoalbuminaemia with older age (P for trend $\leq .001$, Table 2).

The association between all-cause mortality and serum albumin, modelled as a continuous variable, differed graphically between patients younger and equal or older than 65 years. Patients younger than 65 years exhibited a more pronounced increase in the relative risk of mortality with lower serum albumin levels (e.g. HR = 3.71 at 2.5 g/dl) compared to older patients (HR = 2.36), although the 95% confidence interval was wider, probably due to the smaller number of cases in this group (Fig. 2).

Additional analyses revealed that hypoalbuminaemia was associated with an increased hazard ratio of mortality in both, younger and older patients. However, the hazard ratio was higher in magnitude in the younger patients [1.81 (95% CI: 1.42–2.31)] compared to older ones [1.36 (95% CI: 1.17–1.57)]. The interaction term age × serum albumin in the Cox regression

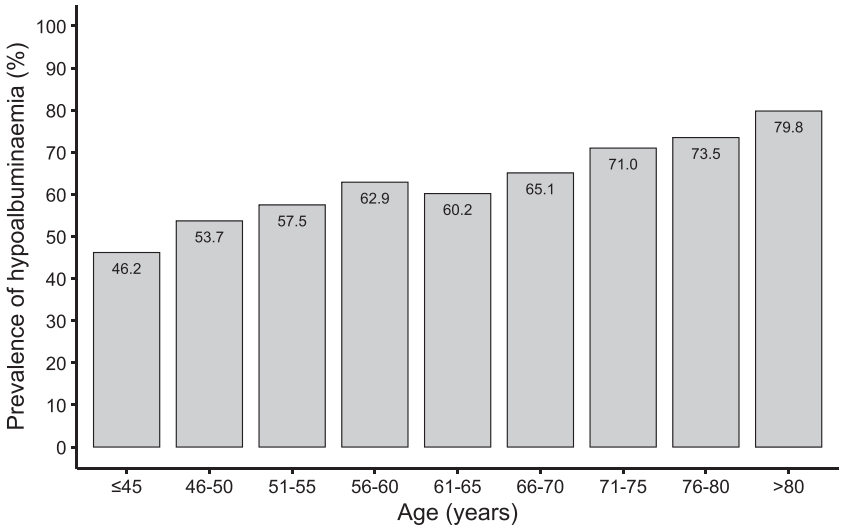


Figure 1: Prevalence of hypoalbuminaemia (serum albumin <4.0 g/dl) across age groups.

Table 2: Crude and adjusted logistic regression analysis showing odds for clinical hypoalbuminaemia (<4.0 g/dl) across increasing age categories.

	Odds-ratio[95%CI]				
Age (years)	**≤55**	**55–65**	**65–75**	**>75**	**P trend**
Crude	Reference	1.57[1.34–1.85]	2.05[1.77–2.38]	3.00[2.55–3.53]	<.001
Adjusted*		1.56[1.31–1.86]	1.89[1.59–2.24]	2.68[2.22–3.23]	<.001

*Estimates were adjusted by age, sex, smoking habits, aetiology of CKD, BMI, diabetes, cardiovascular disease, type of haemodialysis, dialysis vintage, PTH, serum calcium, and phosphorous.

model was statistically significant ($P = .004$) (Fig. 3). Hazard ratios were consistently higher in patients younger than 65 years compared to those aged 65 and older across all subgroups of patients. This pattern was observed in men [1.85 (95%CI: 1.39–2.47) vs. 1.42 (95%CI: 1.18–1.71)], women [1.71 (95%CI: 1.07–2.71) vs. 1.29 (95%CI: 1.02–1.63)], patients with diabetes [1.76 (95%CI: 1.18–2.63) vs. 1.15 (95%CI: 0.92–1.44)], patients without diabetes [1.85 (95%CI: 1.36–2.51) vs. 1.49 (95%CI: 1.23–1.81)], patients with cardiovascular disease [1.73 (95%CI: 1.32–2.28) vs. 1.36 (95%CI: 1.16–1.59)], and patients without [1.98 (95%CI: 1.16–3.37) vs. 1.46 (95%CI: 0.98–2.19)]. Cox regression analysis using serum albumin as a time-dependent variable further demonstrated significantly higher hazard ratio in patients younger than 65 years [4.05 (95%CI: 2.81–5.84) vs. 2.79 (95%CI: 2.24–3.49), *P* for interaction = .001].

Time-dependent ROC curves identified the cut-offs of 3.7 g/d; for patients younger and 3.5 g/d; for patients aged 65 years and older as those with highest sensitivity and specificity (Fig. 4).

DISCUSSION

In haemodialysis patients, hypoalbuminaemia is an indicator of nutritional status/inflammation and a strong predictor of mortality. The present study suggests that the ageing is accompanied by lower albumin levels, and that age may influence the association between serum albumin and mortality. Conceptually, our study proposes to use in clinical practice different cut-offs for laboratory biomarkers by age (when indicated). In our study, the association between albumin and mortality was stronger in younger patients, and the thresholds to discriminate risk were slightly higher than those older than 65 years.

Serum albumin levels are important indicators of nutritional status, particularly in clinically stable people [18]. In these cases, low albumin levels reflect overall malnutrition [19], making it a reliable tool for identifying individuals at risk of adverse health outcomes. Several studies have demonstrated that maintaining adequate serum albumin levels has been associated with improved clinical outcomes in patients on maintenance haemodialysis [20]. Levels below 4 g/dl are considered clinically low by KDOQI [5], although other guidelines such as those of the International Society of Renal Nutrition and Metabolism consider 3.8 g/dl [21].

The present study found that the prevalence of hypoalbuminaemia increased with age despite multiple adjustments for identified confounders. A negative correlation between serum albumin and age has been previously described in both the general population [22] and haemodialysis patients [23]. However, age itself may not be the sole cause of the decrease in serum albumin in the elderly [18]. Age may encompass other conditions of ageing, including loss of appetite, changes in body composition, lower energy needs, lower physical activity etc… [24, 25]. In haemodialysis patients, despite the technological advances in the filters used, and their adaptation to different clinical situations, there may be a (small) loss of serum albumin during the session, which confers an additional risk of hypoalbuminaemia [26–28].

Our study identified an independent association between baseline hypoalbuminaemia and increased mortality risk,

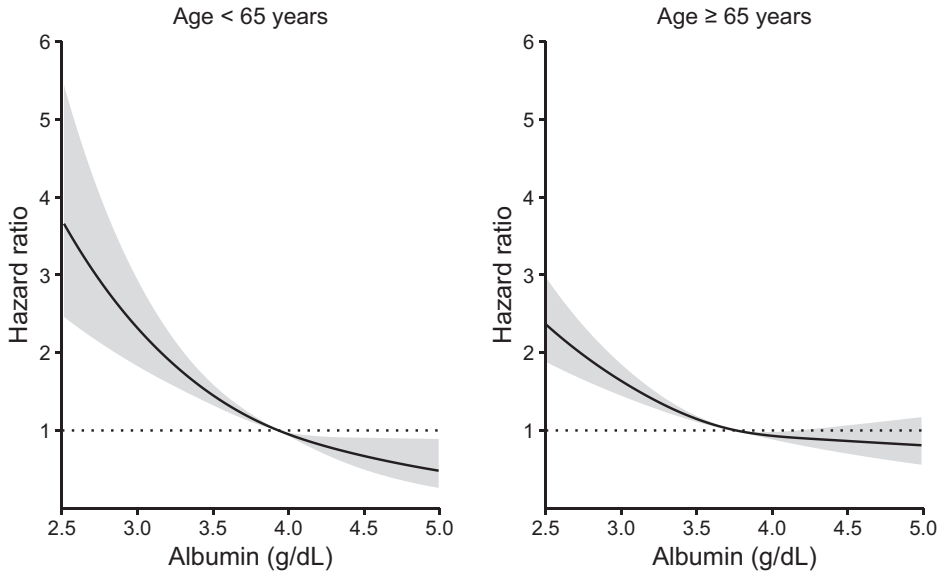


Figure 2: Impact of serum albumin on mortality risk in haemodialysis patients: a restricted cubic spline analysis with age stratification. Hazard ratios and 95% confidence intervals (shaded area) are depicted in the elderly (≥65 years old, $n = 3127$) and non-elderly (<65 years old, $n = 2458$) haemodialysis patients. Estimates were adjusted for age, sex, smoke, aetiology of CKD, BMI, diabetes, cardiovascular disease, type of haemodialysis, vintage, PTH, calcium, and phosphate.

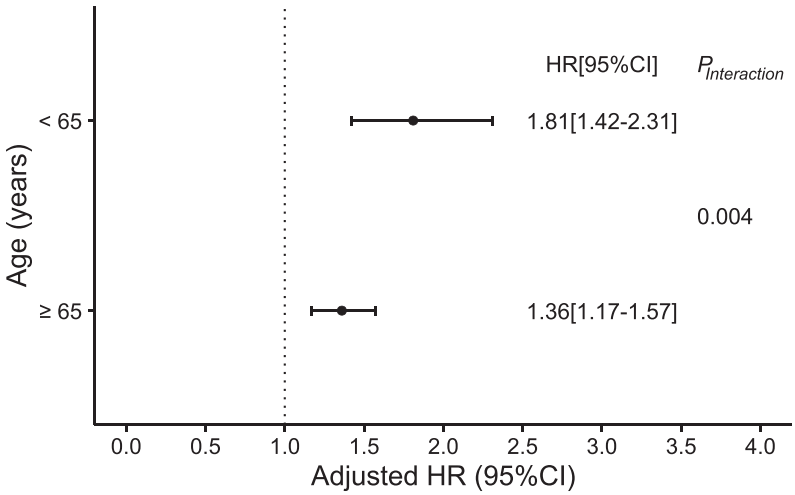


Figure 3: Differential association between hypoalbuminaemia and 3-year mortality risk in non-elderly (<65 years) vs. elderly (≥65 years) haemodialysis patients. Hazard ratios were adjusted for age, sex, smoke, aetiology of CKD, BMI, diabetes, cardiovascular disease, type of haemodialysis, vintage, PTH, calcium, and phosphate.

aligning it with previous reports [20, 29]. Previous research suggests that inflammation contributes to this association [25]. Building on this, a recent DOPPS study proposed a combined measure of malnutrition (serum albumin) and inflammation (C-reactive protein) as a strong predictor of mortality in haemodialysis patients [11]. Unfortunately, the COSMOS study focused on CKD-Mineral and Bone Disorder, and inflammatory markers such as C-reactive protein or other surrogate markers of inflammation, were not collected, which would have allowed a better analysis of the multivariate models and a better assessment of the association between relative mortality risk and serum albumin.

Interestingly, the present study revealed a stronger association between hypoalbuminaemia and mortality risk in patients younger than 65 compared to those older than this age. This finding was consistent across the full cohort and various patient subgroups including men, women, and patients with or without diabetes or cardiovascular disease. The modifying effect of age on the association between serum albumin and mortality was also independent of whether baseline (representing long-term effects) or time-dependent serum albumin (representing short-term effects [30]) were used. Serum albumin had a better mortality predictive capacity in the younger patients, as evidenced by time-dependent ROC curves. In line with the present results, a previous study, which developed a nutritional risk index to screen haemodialysis patients for mortality risk, identified distinct age-dependent cut-off points for serum albumin to best predicted death: 3.7 g/dl for patients younger than 65 years

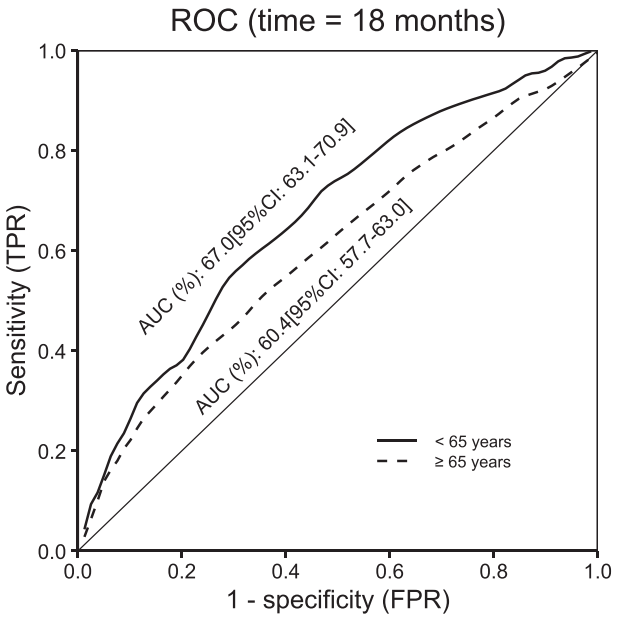


Figure 4: Age-dependent predictive ability of baseline serum albumin for mortality at 18 months in haemodialysis patients using time-dependent ROC. The area under the curve (AUC) of the time-dependent ROC curve was consistently higher in patients younger than 65 years throughout all follow-up periods (data not shown). As an example, the ROC curve at 18 months demonstrated that the AUC for predicting 18-month mortality risk using baseline serum albumin levels was significantly higher in patients younger than 65 years (95% confidence intervals do not overlap). Serum albumin levels with the maximum sensitivity and specificity were 3.7 g/dl for patients younger than 65 years and 3.5 g/dl for those aged 65 years and older. TPR: true positive rate, FPR: false positive rate.

and 3.5 g/dl for those equal or older than 65 years, identical to the cut-off values found in the present study [31].

Albumin has traditionally been used as a marker of poor nutritional status, but serum albumin is a negative acute-phase reactant that decreases during acute and chronic illness and inflammation [22, 32]. Consequently, relying solely on serum albumin as an indicator of nutritional status in inflammatory contexts can be misleading, underscoring the need for comprehensive assessments that account for both nutritional intake and inflammatory markers [33].

The reason for the potentially greater impact of hypoalbuminaemia on mortality in younger patients remains unclear. Despite extensive literature searches, we have not identified scientific evidence supporting this finding. As previously mentioned, it is possible to speculate that, as patients age, albumin levels may decline 'physiologically' due to physical and nutritional changes associated with ageing, without necessarily implying pathological conditions. These changes could include the progressive loss of muscle mass and the increase in fat mass that occur with age, as well as reduced protein-caloric intake due to decreased physical activity and energy requirements in these patients. Furthermore, hypoalbuminemia in older patients often reflects chronic inflammation and frailty. By contrast, in younger patients, hypoalbuminemia may be more closely associated with acute and severe comorbidities such as infections, acute inflammation, or neoplastic conditions, thereby contributing to the potential increase in mortality in this group of patients.

One limitation of the COSMOS study is its observational design, which precludes establishing causality. Also, the data vintage may not fully reflect the current practices and outcomes of haemodialysis patients. As discussed earlier, the absence of inflammatory markers and other surrogate markers of inflammation limited our ability to adjust for them in the relative risk of mortality analysis and go further in the search of possible explanations.

In conclusion, this study in a large cohort of haemodialysis patients confirms that the prevalence of hypoalbuminaemia increases with age, but adds the novel perspective that albumin exhibits stronger associations with mortality in younger vs. older patients. Therefore, optimal thresholds varied and may be considered differently in routine practice to inform clinical decisions. Future prospective studies with more contemporary and diverse patient populations are needed to confirm our observations and help establish evidence-based cut-off levels for serum albumin in younger and older haemodialysis patients.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

Conception and study design: J.L.G.-T., J.F., F.L., C.Z., A.F., C.A.-M., J.B.C.-A., J.L.F.-M., and J.J.C. Analysis design: C.S.-G., M.R.-G., J.L.G.-T., E.S.-A., C.G.-A., A.F., C.A.-M., J.B.C.-A., J.L.F.-M., and J.J.C. Statistical analysis: C.S.-G., M.R.-G., B.M.-C., F.L., J.L.F.-M., and J.J.C. Interpretation of results: C.S.-G., M.R.-G., J.L.G.-T., C.P.-A., E.S.-A., C.G.-A., J.F.-G., J.F., B.D.-L., M.A.H.-S., J.F.N.-G., M.D.A., F.L., C.Z., A.F., C.A.-M., J.B.C.-A., J.L.F.-M., and J.J.C. Draft writing: C.S.-G., M.R.-G., C.P.-A., C.A.-M., J.B.C.-A., J.L.F.-M., and J.J.C. Manuscript revision: All authors. Acquisition of funding: J.L.G.-T., C.A.-M., J.B.C.-A., and J.L.F.-M.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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