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ORIGINAL RESEARCH

Skin autofluorescence and malnutrition as predictors of mortality in persons receiving dialysis: a prospective cohort study

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Keywords

advanced glycation end-products, dialysis, malnutrition, mortality, skin autofluorescence.

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Abstract

Background: Skin autofluorescence (SAF), which is a measure of accumulation of advanced glycation end-products (AGE), and malnutrition are each associated with higher mortality in dialysis populations, although no studies have investigated these potentially related associations together. We simultaneously assessed SAF and malnutrition as risk factors for mortality in persons receiving dialysis.

Methods: SAF was measured in 120 haemodialysis and 31 peritoneal dialysis patients using an AGE Reader (DiagnOptics, Groningen, The Netherlands). Dietary AGE, energy, protein and fat intake, handgrip strength, anthropometry, biochemistry and Subjective Global Assessment were also evaluated. Time to event was days from baseline to death, kidney transplantation or 30 September 2018.

Results: Median observation time was 576 days, during which 33 (21.9%) patients died. Those who died had higher baseline SAF levels [3.8 ± 1.0 versus 3.3 ± 0.8 arbitrary units (AU); $P = 0.001$] and were more likely to be malnourished (58% versus 31%; $P = 0.006$). Malnourished persons who died had higher SAF values than those who died but were well-nourished (4.2 ± 1.1 versus 3.3 ± 0.7 AU; $P = 0.007$). Survival was significantly better in participants with baseline SAF below the median and in those well-nourished than those with baseline SAF above the median and in those malnourished, respectively. Multivariable analysis identified SAF [hazards ratio (HR) = 1.44; 95% confidence interval (CI) = 1.05–1.97; $P = 0.02$], malnutrition (HR = 2.35; 95% CI = 1.16–4.78; $P = 0.02$) and chronological age (HR = 1.60; 95% CI = 1.10–2.33; $P = 0.01$) as independent predictors of mortality.

Conclusions: Although higher SAF and malnutrition are potentially interrelated, they were both independently associated with increased mortality in this population. Interventions to improve outcomes by reducing SAF through correction of malnutrition or dietary AGE restriction require testing in prospective studies.

Introduction

Dialysis is a life-prolonging therapy for persons with end-stage kidney disease (ESKD), although it is associated with a high mortality rate in large part due to increased cardiovascular disease [1,2]. Malnutrition, systemic inflammation and oxidative stress have been proposed as non-traditional cardiovascular risk factors that contribute to

the increased cardiovascular mortality risk observed in the ESKD population [3], although the manner in which these factors interact and their relative importance remains to be elucidated.

Advanced glycation end-products (AGEs) are uremic toxins that accumulate in persons receiving dialysis as a result of reduced renal clearance and increased formation [4,5]. Endogenous sources of AGEs include oxidative and carbonyl stress, as well as hyperglycaemia [4]. AGEs can also be formed exogenously, either by cigarette smoking or through the ingestion of foods cooked under dry heat and high temperatures (e.g. grilling, roasting, frying) [6]. Taking advantage of the fluorescence properties of some AGEs, the accumulation of these toxins in the skin can be assessed non-invasively using skin autofluorescence (SAF), which has proven to be an independent predictor of all-cause and cardiovascular mortality in the dialysis population [7–9]; however, the mechanisms underlying this association are not completely understood.

AGEs are markers of oxidative stress, which is linked with systemic inflammation. Oxidative and inflammatory processes act synergistically with respect to promoting protein catabolism, muscle wasting and reduced hepatic albumin synthesis, which together lead to the development of malnutrition in the setting of ESKD [10,11]. Malnutrition, an independent predictor of mortality in the dialysis population [12–15], exacerbates the deleterious effects of systemic inflammation and oxidative stress by increasing the susceptibility to infections and cardiovascular disease risk [16,17]. It therefore appears reasonable to suggest that a vicious cycle between inflammation, oxidative stress and malnutrition may contribute to the poor survival rates observed in persons on dialysis [18]. Malnutrition and SAF have previously been reported in separate studies to independently predict worse survival on dialysis but, to our knowledge, no studies have simultaneously investigated the association of SAF and malnutrition with mortality. This is particularly important because it has been previously reported that higher SAF and several markers of malnutrition are independently associated in persons on haemodialysis (HD) [19], raising the possibility that the association between higher SAF and poorer survival may be explained by an association with malnutrition, which was not assessed in previous studies [7,9]. We therefore aimed to investigate the prognostic significance of SAF and malnutrition when evaluated together in persons receiving dialysis.

Materials and methods

Study population

This was a single centre prospective observational study conducted in the Department of Renal Medicine, Royal Derby Hospital. Persons receiving HD and performing peritoneal dialysis (PD) who were ≥18 years of age and had an expected survival more than 1 year were eligible. We enrolled 120 HD and 31 PD patients from September 2016 to August 2017. Participants on HD were dialysed three or four times per week for 3–4 h using high-flux polysulphone, polyarylethersulfone or polyvinylpyrrolidone dialyzers. Persons performing PD dialysed using lactate/bicarbonate-buffered 1.36% and 3.86% glucose (Physioneal; Baxter Healthcare Corporation, Deerfield, IL, USA), 7.5% icodextrin (Extraneal; Baxter Healthcare Corporation) and/or 1.1% aminoacid-containing solutions (Nutrineal; Baxter Healthcare Corporation). The exclusion criteria used were: pregnancy or intending pregnancy, breastfeeding and having dark skin colour. Written informed consent was obtained from all patients. The study was approved by the local Research Ethics Committee (East Midlands – Nottingham 1. REC reference: 16/EM/0243).

Data collection

Electronic medical records were used to collect participant characteristics, including: age, sex, ethnicity, dialysis vintage (i.e. time subsequent to first dialysis treatment), dialysis adequacy, blood results, presence of diabetes (defined by clinical diagnosis) and obesity [defined as having a body mass index (BMI), ≥30 kg m^{-2}] [20], as well as history of cardiovascular disease. Information regarding educational level, occupation and smoking status was obtained from direct interview.

Dates and causes of death were obtained from electronic medical records. Causes of death were classified into specific groups [21]: cardiovascular, infection, malignancy, treatment withdrawal and other cause of death. The classification was performed independently by two consultant nephrologists (NMS and MWT) and any disagreements were resolved by discussion. Survival time was defined as the number of days between the baseline assessment and the date of death, censoring as a result of kidney transplantation or 30 September 2018.

Skin autofluorescence measurement

SAF was measured using a validated Autofluorescence Reader, version 2.4.3 (AGE Reader; DiagnOptics, Groningen, The Netherlands) as described in more detail elsewhere [7,19]. In brief, the AGE Reader directs an ultraviolet excitation light (intensity 300–420 nm) through an illumination window of approximately 1 cm^2 on a skin area (free of visible vessels, scars, tattoos or any other skin irregularities) of the volar surface of the forearm at approximately 10 cm below the elbow. The AGE Reader then measures

the amount of emitted light that is reflected back from the skin (intensity 300–600 nm) using a spectrometer (AVS-USB2000; Avantes Inc., Eerbeek, The Netherlands) and a 200-μm glass fibre. SAF is calculated by dividing the average emitted light intensity in the range between 420–600 nm by the average excitation light intensity in the range between 300–420 nm, and expressed as arbitrary units (AU). Three SAF readings were conducted on the nonfistula arm or the dominant arm if this did not have a fistula, and within the first hour of HD treatment. The mean value of three SAF readings was used for statistical analyses. SAF readings may be affected by dark skin colour and pigmentation as a result of a higher proportion of the excitation light being absorbed. The AGE Reader has not yet been validated in persons with darker skin colour and skin reflectivity <6% (i.e. Fitzpatrick skin colour types 5–6) [22]. Consequently, SAF might not be reliable in this population and persons with dark skin were therefore excluded. It has been previously reported that SAF readings have good reproducibility and repeatability (i.e. coefficient of variation of 7–8%) [23].

Nutritional assessments

Information regarding energy, protein and fat intake was obtained from three 24-h dietary recalls. Participants were asked to recall all foods and drinks they had the day before. Dietary recalls were analysed with DIETPLAN, version 7 (Forestfield Software Limited, Broadbridge Heath, UK) to calculate the average energy, protein and fat intake. Average daily intake of energy and protein was then calculated (kJ and g, respectively) and expressed per kg of ideal body weight. Dietary AGE intake (reported in kilounits per day) was estimated with a food frequency questionnaire previously validated in persons with diabetes [24]. For further analysis, dietary AGE intake was corrected for total average energy intake and for post-dialysis body weight.

Anthropometric measurements were conducted in line with international standard methods of assessment [25]. Post-dialysis weight and height were measured to calculate BMI (kg m^{-2}), whereas measurement of mid-arm circumference (MAC) and triceps skinfold thickness (TSF) (both in cm) was conducted to calculate mid-arm muscle circumference (MAMC) using the equation: MAMC (cm^2) = MAC – (3.14 × TSF). Handgrip strength (HGS) measurement was conducted within the first hour of HD treatment or during PD clinic visits using the Takei 5401 handgrip digital dynamometer (Takei Scientific Instruments Co., Ltd, Tokyo, Japan). HGS was measured in the nonfistula arm or the dominant arm if this did not have a fistula as described elsewhere [19].

The seven-point scale Subjective Global Assessment (SGA) [26] was performed to evaluate the nutritional status. Based on the ratings of six individual core components (i.e. history of weight loss, dietary intake, gastrointestinal symptoms, functional status, metabolic stress and subjective physical examination of loss of subcutaneous fat and muscle mass, and presence of oedema), nutritional status can be classified into normal nutritional status (scores of 6 or 7), mild-moderate malnutrition (scores of 3–5) or severe malnutrition (scores of 1 or 2). For statistical analysis, participants were placed in two groups: well-nourished (SGA scores 6–7) or malnourished (SGA scores 1–5).

Statistical analysis

All statistical analyses were performed using SPSS, version 24.0 (IBM Corp., Armonk, NY, USA). Data are expressed as the mean (SD), median [interquartile range (IQR)], percentages or hazard ratios [HR, 95% confidence interval (CI)], as appropriate. Missing data were omitted: C-reactive protein (CRP), $n = 7$; HGS, $n = 6$; MAC, MAMC and TSF, $n = 1$. Comparisons of continuous variables between two independent groups were performed using Student's t test or a Mann–Whitney U test, whereas intergroup comparisons for categorical variables were conducted with a chi-squared test or Fisher's exact test. Kaplan–Meier survival curves were computed according to baseline SAF levels above or below the median value and nutritional status at baseline.

Cox proportional hazards models were used to investigate the prognostic value of SAF and malnutrition for predicting mortality. As a result of the limited number of events (deaths), only the three variables of greatest interest that were associated with mortality in the univariable analyses were included in the model. A product term (i.e. two-way interaction term) was included in the regression model to test for an interaction between SAF and malnutrition. $P < 0.05$ was considered statistically significant.

Sample size determination with mortality as the primary outcome showed that with a sample size of 150 participants split in two groups (group 1: SAF below the median, $n = 75$; group 2: SAF above the median, $n = 75$), the analysis would have more than 80% power to detect a HR of 2.7, assuming that the total number of events (i.e. deaths) achieved was 34 and the average probability of the event was 0.1 in group 1 and 0.35 in group 2 (NQUERY ADVANCED, version 8.0; Statistical Solutions Limited, Boston, MA, USA).

RESULTS

Baseline participant characteristics

The demographic, clinical, biochemical and nutritional characteristics of 120 HD and 31 PD participants are

shown in Table 1. The mean (SD) age of the whole cohort was 64 (14) years. Sixty-four percent of the population were male and 88% were of white ethnicity. Mean (SD) SAF was high at 3.4 (0.9) AU compared to the reference value of 2.5 (0.6) AU for the age group of 60–70 years [27]. Participants had low calorie and protein intake compared to the estimated nutritional requirements for persons receiving dialysis [28].

SGA identified 56 participants (37%) as malnourished and 95 as well-nourished (63%). SAF was significantly higher in malnourished participants compared to those who were well-nourished. Serum albumin, total dietary AGE, energy, protein and fat intake, HGS, and all anthropometric variables were significantly lower in malnourished participants compared to those with a well-nourished status. Dietary AGE intake corrected for post-dialysis body weight and for total energy intake was not significantly different between malnourished and well-nourished participants. Females, current smokers and those who were unemployed were more likely to be malnourished than males, nonsmokers and employed participants, respectively. Coronary heart disease was more evident in malnourished participants (Table 1).

Follow-up results

Median observation time was 576 days (IQR = 395–684 days) during which 33 (21.9%) participants died and 22 (14.6%) received a kidney transplant. The most common cause of death was infection (33.3%) followed by cardiovascular (30.3%), treatment withdrawal (15.1%), other cause of death (12.1%) and cancer (9.2%).

Table 2 shows baseline participant characteristics according to survival status. Participants who died had

Table 1 Baseline participant characteristics by nutritional status classification

Variable	Overall (*n* = 151)	Malnourished (*n* = 56)	Well-nourished (*n* = 95)	*P* value[†]
Age (years)	64 (14)	62 (16)	65 (13)	0.5
Female, *n* (%)	54 (36)	30 (54)	24 (25)	<0.0001
White ethnicity, *n* (%)	133 (88)	47 (84)	86 (91)	0.2
Educational qualifications, *n* (%)	85 (56)	28 (50)	57 (60)	0.2
Unemployed, *n* (%)	114 (76)	48 (86)	66 (70)	0.03
Current smoking, *n* (%)	23 (15)	16 (29)	7 (7)	<0.0001
Diabetes, *n* (%)	62 (41)	21 (38)	41 (43)	0.5
Coronary heart disease, *n* (%)	60 (40)	29 (52)	31 (33)	0.02
Peripheral vascular disease, *n* (%)	11 (7)	5 (9)	6 (6)	0.6
Obesity, *n* (%)	55 (36)	11 (20)	44 (46)	0.001
Dialysis vintage (months)	29 (10–69)	31 (11–61)	26 (10–67)	0.4
Dialysis adequacy (Kt V^{-1})*	1.45 (0.59)	1.54 (0.62)	1.40 (0.56)	0.1
Serum albumin (g L^{-1})	31.5 (4.6)	30.1 (5.4)	32.4 (3.8)	0.02
C reactive protein (mg L^{-1})	8 (4 to 17)	9 (3 to 23)	8 (4 to 14)	0.6
Total cholesterol (mmol L^{-1})	4.1 (1.2)	4.2 (1.3)	4.1 (1.1)	0.9
Serum creatinine (μmol L^{-1})	646 (214)	607 (211)	669 (214)	0.06
Serum phosphate (mmol L^{-1})	1.56 (0.51)	1.64 (0.56)	1.51 (0.47)	0.2
Serum potassium (mmol L^{-1})	4.6 (0.7)	4.5 (0.7)	4.7 (0.7)	0.2
Skin autofluorescence (AU)	3.4 (0.9)	3.6 (1.0)	3.2 (0.7)	0.009
Dietary AGE intake (kU day^{-1})	14545 (781)	12763 (6580)	15595 (8315)	0.02
Dietary AGE intake/body weight (kU kg^{-1})	168 (120–237)	168 (122–237)	168 (115–237)	1.0
Dietary AGE intake/energy intake (kU kJ^{-1})	2.2 (1.7–3.1)	2.3 (1.7–3.4)	2.2 (1.7–3.1)	0.6
Energy intake (kJ kg^{-1} day^{-1})[‡]	87.5 (31.8)	77.9 (31.8)	92.9 (30.6)	0.001
Protein intake (g kg^{-1} day^{-1})	0.88 (0.29)	0.79 (0.32)	0.94 (0.25)	<0.0001
Fat intake (g day^{-1})	57.9 (29.7)	47.9 (24.2)	63.8 (31.2)	<0.0001
Post-dialysis weight (kg)	79.3 (20.8)	69.7 (17.8)	85.0 (20.4)	<0.0001
Body mass index (kg m^{-2})	27.7 (6.3)	25.1 (5.1)	29.2 (6.4)	<0.0001
Handgrip strength (kg)	23.0 (11.5)	19.1 (10.9)	25.1 (11.3)	0.001
Mid-arm muscle circumference (cm^2)	25.6 (3.7)	23.9 (3.6)	26.6 (3.5)	<0.0001
Triceps skinfold thickness (mm)	17.2 (7.2)	15.1 (6.3)	18.4 (7.5)	0.02

Data are expressed as the mean (SD), median (interquartile range) or percentages, as appropriate
AGE, advanced glycation end-product; AU, arbitrary units; kU, kilounits.
*Kt V^{-1} is weekly in peritoneal dialysis and per session in haemodialysis;
[†]Malnourished versus Well-nourished.
[‡]kcal kg^{-1} day^{-1}: overall, 20.9 (7.6); malnourished, 18.6 (7.6); well-nourished, 22.2 (7.3).

Table 2 Comparison of baseline participant characteristics between survivors and non-survivors

Variable	Non-survivors (n = 33)	Survivors (n = 118)	P value*
Age (years)	69 (12)	62 (14)	0.004
Female, *n* (%)	13 (39)	41 (35)	0.6
Educational qualifications, *n* (%)	20 (61)	46 (39)	0.03
Unemployed, *n* (%)	30 (91)	84 (71)	0.02
Current smoking, *n* (%)	6 (18)	17 (14)	0.6
Diabetes, *n* (%)	15 (46)	47 (40)	0.6
Coronary heart disease, *n* (%)	17 (52)	43 (36)	0.1
Malnutrition, *n* (%)	19 (58)	37 (31)	0.006
Dialysis vintage (months)	43 (20–71)	25 (8–68)	0.1
Serum albumin (g L^{-1})	29.5 (6.1)	32.1 (3.9)	0.02
C reactive protein (mg L^{-1})	11 (5 to 29)	7 (3 to 14)	0.04
Total cholesterol (mmol L^{-1})	4.0 (1.2)	4.1 (1.2)	0.6
Serum creatinine (μmol L^{-1})	657 (206)	643 (217)	0.8
Skin autofluorescence (AU)	3.8 (1.0)	3.3 (0.8)	0.002
Dietary AGE intake (kU day^{-1})	13381 (7032)	14870 (8019)	0.4
Energy intake (kJ kg^{-1} day^{-1})†	75.4 (26.0)	90.8 (32.7)	0.01
Protein intake (g kg^{-1} day^{-1})	0.75 (0.25)	0.92 (0.29)	0.003
Fat intake (g day^{-1})	48.6 (24.7)	60.5 (30.6)	0.02
Body mass index (kg m^{-2})	28.3 (6.5)	27.5 (6.2)	0.6
Handgrip strength (kg)	18.6 (10.7)	24.1 (11.5)	0.008
Mid-arm muscle circumference (cm^2)	25.7 (4.5)	25.6 (3.5)	0.7
Triceps skinfold thickness (mm)	18.5 (6.7)	16.9 (7.4)	0.2

Data are expressed as the mean (SD), median (interquartile range) or percentages, as appropriate.

AGE, advanced glycation end-product; AU, arbitrary units; kU, kilo-units.

*Nonsurvivors versus Survivors.

†kcal kg^{-1} day^{-1}: non-survivors, 18.0 (6.2); survivors, 21.7 (7.8).

significantly higher baseline SAF and CRP levels compared to those who did not die. Nonsurvivors were more likely to be malnourished in comparison to survivors. Participants who died also had significantly lower serum albumin, HGS, and energy, protein and fat intake compared to those who did not die. Older age, lack of educational qualifications and unemployment were more evident among nonsurvivors than in survivors.

Participants who died and were malnourished (n = 19) had significantly higher SAF levels and lower serum albumin, serum creatinine, total dietary AGE, energy, protein and fat intake, BMI, HGS, MAMC, and TSF compared to those who died but were well-nourished (n = 14) (see Supporting information, Table S1). No significant differences were observed in dietary AGE intake corrected for body weight and for total energy intake between survivors and nonsurvivors, nor between those who died and were malnourished and those who died but were well-nourished.

Kaplan–Meier analysis showed that survival was significantly better in those participants with a baseline SAF level below the median value of 3.3 AU and in those who were well-nourished at baseline in comparison to those with baseline SAF level above the median value and in those malnourished at baseline, respectively (Figures 1 and 2). Univariable analysis identified malnutrition, no educational qualifications, higher SAF, chronological age and lower serum albumin, HGS, and energy, protein and fat intake as significant determinants of higher mortality, although total dietary AGE intake, as well as AGE intake corrected for body weight and for total energy intake, were not. Multivariable Cox proportional hazards analysis identified SAF (HR = 1.44; 95% CI = 1.05–1.97 per SD; P = 0.02), malnutrition (HR = 2.35; 95% CI = 1.16−4.78; P = 0.02) and chronological age (HR = 1.60; 95% CI = 1.10–2.33 per SD; P = 0.01) as independent predictors of mortality (Table 3). Inclusion of a product term in the model showed no interaction between SAF and malnutrition.

Discussion

In this prospective observational study, we found that higher SAF and malnutrition were both significant and independent predictors of increased mortality in persons receiving dialysis. We also identified that several markers of malnutrition such as serum albumin, HGS, and energy, protein and fat intake were important determinants of higher mortality, and that SAF was significantly increased among those dialysis patients who died and were malnourished.

The association between SAF and increased mortality in persons receiving dialysis has been investigated previously in several studies. In one of the first prospective studies carried out in this area [7], higher SAF was independently associated with a four-fold increased mortality risk over 3 years, with cardiovascular disease being the main cause of death. We observed a 44% higher risk of all-cause mortality for each SD increase in SAF. Similarly, Mukai *et al.* [8] reported that each one SD increase in SAF was independently associated with a 56% higher risk of death. Several other observational studies have also reported that increased SAF independently predicts higher rates of all-cause and cardiovascular mortality in persons

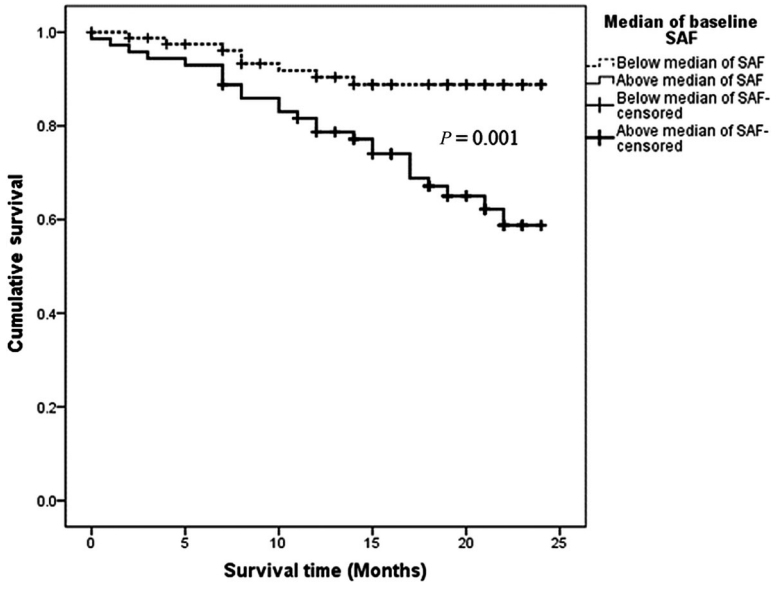

Figure 1 Kaplan–Meier plot of survival according to baseline skin autofluorescence (SAF) above or below the median value.

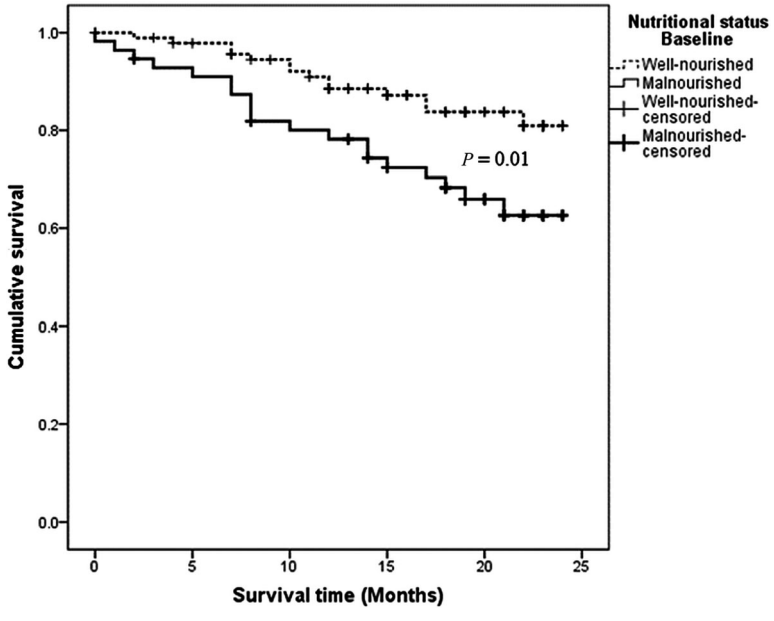

Figure 2 Kaplan–Meier plot of survival according to nutritional status at baseline.

receiving dialysis [9,29–32]. Multiple mechanisms may explain the association between increased SAF and mortality. AGEs cross-link proteins of the extracellular matrix (e.g. collagen and elastin), altering their structural and functional properties, which translates into increased arterial stiffness and endothelial dysfunction [33], both of which contribute to the pathogenesis of cardiovascular disease. In addition, AGEs exacerbate vascular tissue damage by binding to specific AGE receptors that induce oxidative stress and systemic inflammation [34]. Systemic inflammation in turn promotes endothelial dysfunction and vascular calcification [35]. Oxidative stress, alongside inflammation, also causes endothelial dysfunction, which leads to the development and progression of atherosclerosis [10,36–38]. Additionally, the association may be explained, at least in part, by an association between increased SAF and malnutrition [19], which is a well-described risk factor for reduced survival on dialysis, although, unfortunately none of the aforementioned prospective studies included an assessment of nutritional

Table 3 Cox proportional hazards analysis showing predictors of overall mortality in persons receiving dialysis

	Univariable analysis		Multivariable analysis	
Predictor	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	1.53 (1.04–2.24)	0.03	1.60 (1.10–2.33)	0.01
Sex (Female versus Male)	1.18 (0.59–2.37)	0.7		
Educational qualifications (No versus Yes)	2.09 (1.04–4.12)	0.04		
Current smoking (Yes versus No)	1.15 (0.48–2.79)	0.8		
Diabetes (Yes versus No)	1.12 (0.57–2.23)	0.7		
Coronary heart disease (Yes versus No)	1.59 (0.80–3.15)	0.2		
Nutritional status (Malnourished versus Well-nourished)	2.30 (1.15–4.59)	0.02	2.35 (1.16–4.78)	0.02
Dialysis vintage (months)	1.00 (0.99–1.00)	0.7		
Serum albumin (g L^{-1})	0.89 (0.84–0.96)	0.001		
C reactive protein (mg L^{-1})	1.01 (1.00–1.03)	0.06		
Total cholesterol (mmol L^{-1})	0.92 (0.67–1.25)	0.6		
Serum creatinine (μmol L^{-1})	1.00 (0.99–1.00)	0.6		
Skin autofluorescence (AU)	1.55 (1.16–2.07)	0.003	1.44 (1.05–1.97)	0.02
Dietary AGE intake (kU day^{-1})	1.00 (1.00–1.00)	0.4		
Dietary AGE intake/body weight (kU kg^{-1})	1.00 (0.99–1.00)	0.2		
Dietary AGE intake/energy intake (kU kJ^{-1})	1.01 (0.98–1.06)	0.3		
Energy intake (kJ kg^{-1} day^{-1})	0.93 (0.88–0.99)	0.02		
Protein intake (g kg^{-1} day^{-1})	0.16 (0.04–0.61)	0.008		
Fat intake (g day^{-1})	0.98 (0.97–0.99)	0.03		
Body mass index (kg m^{-2})	1.02 (0.97–1.07)	0.5		
Handgrip strength (kg)	0.96 (0.92–0.99)	0.04		
Mid-arm muscle circumference (cm^2)	1.01 (0.92–1.11)	0.8		
Triceps skinfold thickness (mm)	1.03 (0.98–1.07)	0.2		

AGE, advanced glycation end-product; AU, arbitrary units; CI, confidence interval; kU, kilounits; HR, hazards ratio.

status. We have now filled this knowledge gap by showing that SAF and malnutrition are independent predictors of higher mortality on dialysis. Thus, elevated SAF does not appear to be simply a surrogate marker of malnutrition.

Malnutrition is one of the major and most prevalent complications in persons receiving dialysis[39,40]. In the present study, we found that malnutrition, as assessed by the seven-point scale SGA, was a significant and independent determinant of increased mortality. Several prospective studies have also reported that malnutrition, as evaluated by the original and modified versions of the SGA, is independently and strongly associated with overall and cardiovascular mortality in the dialysis population [12–15]. This association might be partially explained by interactions between multiple risk factors related to malnutrition that are also associated with increased mortality, including inadequate dietary intake [41–44], presence of cardiovascular disease [2], metabolic acidosis [45] and, most importantly, systemic inflammation [46] and oxidative stress [36]. Although the accuracy of the seven-point scale SGA to assess nutritional status relies on the dietitian's experience and training to interpret the data collected [40], it continues to be the recommended nutritional assessment tool by national and international nutrition guidelines in the dialysis population [28,47].

It has been reported previously in a cross-sectional analysis that SAF was significantly higher among malnourished persons on HD and that markers of malnutrition such as lower serum albumin, lower protein intake and lower HGS, as well as longer dialysis vintage, presence of diabetes and history of smoking, were independent determinants of increased SAF [19]. The present study extends these observations by showing that higher SAF and malnutrition were independent risk factors for higher mortality, although no interaction was found on statistical testing. Additionally, SAF was significantly higher in nonsurvivors who were malnourished compared to those who died but were well-nourished. Furthermore, lower serum albumin, HGS, and energy, protein and fat intake were significant determinants of higher mortality in univariable analyses. The association between higher SAF and malnutrition may be explained by overlapping mechanisms that likely contribute to both. AGEs are rapidly formed during oxidative stress. Oxidative stress in turn promotes systemic inflammation and vice versa. Chronic inflammation and oxidative stress together induce a number of mechanisms including increased muscle proteolysis, decreased appetite and hypoalbuminemia, which ultimately lead to the development of malnutrition [10,11,48]. Malnutrition may also contribute to AGE

formation through its interaction with oxidative and inflammatory processes. Thus, a vicious cycle likely exists between chronic inflammation, oxidative stress and malnutrition to explain the association between SAF, malnutrition and increased mortality.

Our findings highlight the importance of dietetic monitoring and support to help patients cope with the nutritional challenges associated with ESKD [39]. Malnutrition should be detected early by means of comprehensive screening and assessment using different objective and subjective nutritional markers [40], followed by implementation of an individualised dietetic intervention to treat it. One recent proof of principle study has reported that an improvement of nutritional intake and markers of nutritional status was associated with the stabilisation of SAF levels in malnourished persons receiving dialysis [49]. On the other hand, restriction of dietary AGE intake has been found to reduce serum AGE levels in some patient groups [50,51] but risks provoking or exacerbating malnutrition in patients requiring dialysis [19,52] and would therefore require close dietetic supervision. Large prospective trials are now warranted to investigate the role of dietary interventions with respect to reducing SAF and improving outcomes in persons receiving dialysis.

There are some limitations that need to be considered when interpreting our findings. First, we included subjects from a single centre and the sample size was relatively small, which prevented us from including more variables in the multivariable Cox proportional hazards model, and may have resulted in a failure to detect weaker associations between some baseline variables and outcomes. Second, the follow-up period was relatively short, and a longer observation period may have revealed more evidence of interaction between higher SAF, malnutrition and mortality. Third, we limited our analysis to consideration of baseline variables, whereas a larger study would have allowed inclusion of change in SAF and change in nutritional status as time-varying factors. Nevertheless, unlike previous cohorts, the present study is the first to prospectively and simultaneously assess SAF and malnutrition as risk factors for increased mortality. The observational design of the present study did not allow us to assess causality; however, our results suggest that the risk of death is considerably higher among those subjects with increased SAF and malnutrition. Finally, valid SAF readings cannot be obtained when the skin reflectivity is lower than 6% [22]; therefore, persons with dark skin colour (i.e. Fitzpatrick skin colour types 5–6), who have an ultraviolet reflectance of less than 6%, were excluded from the study, and our findings may be applicable only to persons with Fitzpatrick skin types 1–4.

In conclusion, although higher SAF and malnutrition are potentially inter-related, we have found that they were independently associated with increased mortality in this dialysis population. Our observations strengthen the role of SAF as an independent risk factor in the dialysis population and suggest that interventions to reduce SAF may result in improved survival, although this should now be tested in prospective trials. Such interventions may include correction of malnutrition and dietary AGE restriction, although care should be taken in the latter case to avoid exacerbating malnutrition.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted (East Midlands – Nottingham 1. REC reference: 16/EM/0243) and that any discrepancies from the study as planned have been explained.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest. The results presented in this paper have not been published previously in whole or part, except in abstract form.
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DVH designed and conducted the study, analysed the data and wrote the manuscript. MWT assisted with the study design, the interpretation of the data and the writing of the manuscript. NMS assisted with the interpretation of data and the writing of the manuscript. All authors approved the final version of the manuscript submitted for publication.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparison of nonsurvivor characteristics according to nutritional status at baseline.