BMJ Open

Non-linear relationship between basal serum albumin concentration and cardiac arrest in critically ill patients with end-stage renal disease: a cross-sectional study

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ABSTRACT

Objectives The aim of our study was to investigate the association between serum albumin concentration and the risk of cardiac arrest in critically ill patients with end-stage renal disease in the intensive care unit (ICU).

Design This was a secondary analysis.

Setting The Phillip electronic-ICU collaborative database from 2014 to 2015.

Participants This study included 4990 critically ill patients diagnosed with end-stage renal disease.

Primary and secondary outcome measures The exposure of interest was serum albumin concentration. The outcome variable was cardiac arrest.

Results A non-linear relationship was observed between serum albumin concentration and risk of cardiac arrest, with an inflection point of 3.26 g/dL after adjusting for potential confounders. The effect sizes and the CIs on the left and right sides of the inflection point were 0.88 (0.65 to 1.19) and 0.32 (0.16 to 0.64), respectively.

Conclusions Within an albumin range of 3.26–5.6 g/dL, each 1 g/dL increase in serum levels is associated with a 68% decrease of the risk of cardiac arrest in critically ill patients with end-stage renal disease.

Strengths and limitations of this study

► This study explores the the non-linear relationship between serum albumin and risk of cardiac arrest.
► This study is a secondary analysis of electronic-intensive care unit data, limited by the quality of the database, some variables could not be adjusted.
► The design of this study was cross-sectional study, we cannot infer causal relationship.
► We only studied critically ill patients with end-stage renal disease, therefore, our results cannot be extrapolated to other populations.

carries high morbidity and mortality,[8 9] especially in the intensive care unit (ICU).[10] Although CA is mostly attributed to coronary artery disease in the general population, ESRD-related CA may be mediated by additional mechanism,[11 12] which have not yet been clearly defined. Thus, primary prevention of CA in the ESRD population is still unattainable.

Previous studies have shown that lower serum albumin levels seem to mediate a higher risk of death, through cardiovascular events, in patients with non-dialysis-dependent CKD and patients with ESRD.[13–15] Therefore, we aimed to explore the relationship between serum albumin concentration and CA in critically ill patients with ESRD. To this end, we used an electronic ICU (eICU) database to design a cross-sectional study that would address this question and provide pilot data for future or ongoing cohorts studies.

BACKGROUND

Low serum albumin concentration is a marker of malnutrition and inflammation and has been demonstrated to be a strong predictor of mortality in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). A retrospective cohort analysis in 2011 suggested that serum albumin concentration levels were an essential component of a multivariable predictor of mortality in patients with ESRD.[1] Other studies have found that declining albumin levels in ESRD are associated with higher mortality, whereas increasing levels reduc this risk.[2–6]

Previous studies have shown that among patients with ESRD, cardiovascular disease is a major cause of morbidity and mortality.[7] Cardiac arrest (CA) is common among these patients and

PARTICIPANTS AND METHODS
Data source

This study used data stored in the Phillip eICU collaborative research database, which is a multi-centre ICU database including over 200 000
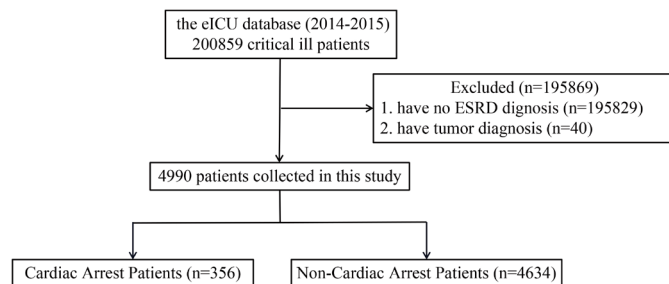
Figure 1 Flow chart of study population. eICU, electronic-intensive care unit; ESRD, end-stage renal disease.

admissions between 2014 and 2015. The specific information on the database can be found in the official website (https://eicu-crd.mit.edu/) and previous literature.[16]

Study design

This is a post hoc analysis of data from critically ill patients with ESRD admitted to the ICUs of 208 hospitals participating in the eICU programme. The study design was a cross-sectional study, and the target independent and outcome variables were serum albumin concentration and CA status. ESRD was defined as a glomerular filtration rate of less than 15 mL/min/1.73 m^2,[17] and CA was defined as the cessation of cardiac activity associated with unresponsiveness, apnoea and no signs of circulation.[18]

Study population

All patients in the eICU collabrotive research databases were eligible for inclusion in the present investigation (n=200 859). Patients diagnosed with ESRD were collected (n=5030). After exclusion of patients who had a diagnosis of malignancy (n=40), a total of 4990 participants were included in data analysis (figure 1).

Variables
Serum albumin concentration
The serum albumin concentration was the independent variable in this study. We performed the analysis using albumin concentration both as a continuous variable and a categorical variable (tertile).

Cardiac arrest

CA data were extracted from the eICU diagnosis form. CA was the outcome variable of this study and was analysed as a binary variable (without CA=0, with CA=1).

Covariates

Covariates included sociodemographic factors (age, sex and race), body mass index (BMI), comorbid conditions (diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), hypertension and acute respiratory failure (ARF)), other cardiovascular events (acute coronary syndrome (ACS), acute myocardial infarction (AMI), rapid ventricular response (RVR), atrial fibrillation (AF), congestive heart failure (CHF)) and laboratory data (creatinine, haemoglobin, platelet count (PLT), pH, serum calcium and serum potassium). The above

covariates were determined to affect CA based on review of the literature[19 20] and clinical experience.

Statistical analysis

Continuous variables are presented as medians with their IQRs, and categorical variables as total numbers and percentages. Proportions were compared using the χ^2, and continuous variables were compared using Wilcoxon rank-sum test. Patients were categorised into two groups according to the outcome variable: the CA group and the non-CA group. Multivariate logistic regression was used to test the association between serum albumin concentration and CA using a series of models. In the first model the covariates was not adjusted, in the second model adjustments were made only for the demographic characteristics, and in the third model all covariates were adjusted, as shown in table 1. To account for the non-linear relationship between serum albumin concentration and CA, we also used the smooth curve fitting (penalised spline method) to address non-linearity. In addition, two-piecewise function was used to further explain the non-linearity.

All analyses were performed using the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Boston, Massachusetts, USA). P values less than 0.05 (two sided) were considered statistically significant.

Patient and public involvement

Patients and the public were not directly involved in the design and conduct of this study.

RESULTS

A total of 4990 patients were included in this study, with a median age of 63 (53, 73) years, 51.58% and 29.56% were Caucasian and African-American, respectively, and 55.31% were male. The prevalence of CA was 7.13%. All the participants were categorised into two groups according to whether CA occurred, and their demographic and clinical characteristics are detailed in table 1. Compared with the non-CA group, patients in the CA group had higher BMI (p=0.022) and greater probability of DM (p=0.039), ARF (p<0.001) and ACS (p=0.005), but a lower probability of COPD (p=0.013), hypertension (p<0.001) and CHF (p<0.001). Most laboratory data, including creatinine, haemoglobin, albumin and pH, were lower in the CA group. Age, sex, ethnicity, dialysis status, etc showed no differences between the two groups (p>0.05).

Lower serum albumin concentrations were associated with a higher risk of CA (table 2). This association remained statistically significant and was minimally attenuated when adjusted for demographic variables and other covariates. Each 1 g/dL increase in serum albumin concentration was associated with a 36% decrease in CA risk in an unadjusted model (OR (OR): 0.64; 95% CI

Table 1 Characteristics of patients in the analysis

Characteristics	Cardiac arrest patients, n=356	Non-cardiac arrest patients, n=4634	P value
Demographics			
Age, years	63.00 (51.00–71.25)	63.00 (53.00–73.00)	0.280
Gender, male	184 (51.83%)	2576 (55.59%)	0.170
Ethnicity			0.082
Caucasian	113 (32.01%)	2461 (53.50%)	
African-American	113 (32.01%)	1362 (29.61%)	
Hispanic	37 (10.48%)	313 (6.80%)	
Asian	6 (1.70%)	105 (2.28%)	
Native American	3 (0.85%)	69 (1.50%)	
Other/unknown	22 (6.23%)	290 (6.30%)	
BMI, kg/m^2	27.81 (23.11–32.94)	27.01 (22.44–31.95)	0.022
Comorbidities			
DM	132 (37.08%)	1472 (31.77%)	0.039
COPD	17 (4.78%)	395 (8.52%)	0.013
Hypertension	70 (19.66%)	1308 (28.23%)	<0.001
ARF	156 (43.82%)	907 (19.57%)	<0.001
Cardiovascular events			
ACS	45 (12.64%)	386 (8.33%)	0.005
AMI	24 (6.74%)	233 (5.03%)	0.159
RVR	18 (5.57%)	194 (4.55%)	0.494
AF	51 (14.33%)	565 (12.19%)	0.238
CHF	45 (12.64%)	917 (19.79%)	<0.001
Dialysis	261 (73.31%)	3365 (72.62%)	0.775
Laboratory data			
Creatinine, mg/dL	5.66 (3.81–7.80)	5.89 (4.10–8.46)	0.036
Haemoglobin, g/L	97.00 (84.00–111.75)	100.00 (87.00–114.00)	0.017
PLT, 10^9/L	191.00 (136.25–257.00)	190.00 (141.00–253.00)	0.908
Albumin, g/dL	2.90 (2.30–3.20)	3.00 (2.50–3.50)	<0.001
pH	7.33 (7.23–7.41)	7.37 (7.29–7.43)	<0.001
Serum potassium, mg/dL	4.40 (3.80–5.20)	4.50 (3.90–5.20)	0.228
Serum calcium, mg/dL	8.78±1.62	8.69±0.94	0.294

Continuous data presented as median (IQR) and categorical data were reported as n (%).
ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; ARF, acute respiratory failure; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; PH, potential of hydrogen; PLT, platelet; RVR, rapid ventricular response.

0.54 to 0.75), and a similar OR value was obtained in the fully adjusted model (OR: 0.69; 95% CI 0.55 to 0.86). In a sensitivity analysis, we converted serum albumin from a continuous variable to a categorical variable (tertile). In each model, the results were still roughly the same as when albumin was used as a continuous variable (table 2).

Given that serum albumin concentration was a continuous variable, we considered the possibility of a non-linear correlation with CA. Indeed (figure 2), we found that the relationship between serum albumin and risk of CA was non-linear (after adjusting for age, sex, race, BMI, DM, COPD, hypertension, ARF, ACS, AMI, RVR, AF, CHF,

creatinine, haemoglobin, PLT, serum albumin, PH and serum calcium, serum potassium). Using a two-piecewise linear regression model, we calculated the inflection point to be 3.26 g/dL. On the right of the inflection point, the effect size, 95% CI and p value were 0.32, 0.16 to 0.64 and 0.0013, respectively. However, no relationship was detected between serum albumin and risk of CA on the left of the inflection point (0.88, 0.65 to 1.19, 0.4180) (table 3).

DISCUSSION

Numerous studies conducted over the past decades have suggested that cardiovascular events play a key role in

Table 2 The associations between serum albumin concentrations and cardiac arrest

	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Albumin	0.64 (0.54 to 0.75)***	0.63 (0.54 to 0.74)***	0.69 (0.55 to 0.86)**
Albumin (tertile)			
T1	1.0	1.0	1.0
T2	0.83 (0.64 to 1.08)	0.82 (0.63 to 1.06)	0.82 (0.58 to 1.14)
T3	0.46 (0.34 to 0.61)***	0.44 (0.33 to 0.59)***	0.54 (0.37 to 0.79)*

Model 1: model adjusted for age, gender, ethnicity.
Model 2: model further adjusted for BMI, comorbidities including DM, COPD, hypertension and ARF, cardiovascular events including ACS, AMI, RVR, AF and CHF, dialysis, creatinine, haemoglobin, PLT, albumin, PH, serum calcium concentration, serum potassium concentration.
*P<0.01, **p<0.001, ***p<0.0001.
ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; ARF, acute respiratory failure; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; PH, potential of hydrogen; PLT, platelet; RVR, rapid ventricular response.

the mortality of patients with ESRD.[7 21] For the critical ill patients with ESRD, CA is a common terminal event.[22] However, few studies have focused on the factors predisposing this population to CA. Some studies have already shown an association between low serum albumin concentration and higher risk of mortality in patients with ESRD; this association seems to be related to cardiovascular events.[13–15] Therefore, we used data from 4990 critically ill patients with ESRD to determine if there is a relationship between serum albumin concentration and risk of CA. This cross-sectional study provided several novel results. First, a stable association between higher serum albumin concentration and a decreased risk of CA, after adjustment for potential confounders, was revealed. Second, a non-linear relationship between serum albumin and risk of CA was seen, such as for serum albumin concentration in the range of 3.26–5.6 g/dL, each 1 g/dL increase in

serum albumin concentration was associated with a 68% decrease in CA risk.

Several processes are associated with serum albumin concentration, including the absolute rate of albumin synthesis, the fractional catabolic rate, albumin distribution between the vascular and extravascular compartments, and exogenous loss of albumin. It is well known thay the majority of patients with ESRD have low serum albumin concentration. In our study, up to 2705 patients (54.21%) had low serum albumin concentrations (<3.26 g/dL). There are many reasons for the low serum albumin concentrations in these patients. First, the rate of albumin synthesis is reduced due to the chronic inflammatory state associated with ESRD and malnutrition, often compounded by a commonly prescribed protein-restricted diet.[23] Second, a large amount of serum albumin is lost in the urine due to the destruction of the nephron. Third, most patients with ESRD require dialysis, which can cause protein loss.[24] Furthermore, fever, hospital stay, bacteraemia, age, sex and DM are associated with low serum albumin (<3.8 g/dL).[25] There are multiple potential mechanisms by which low serum
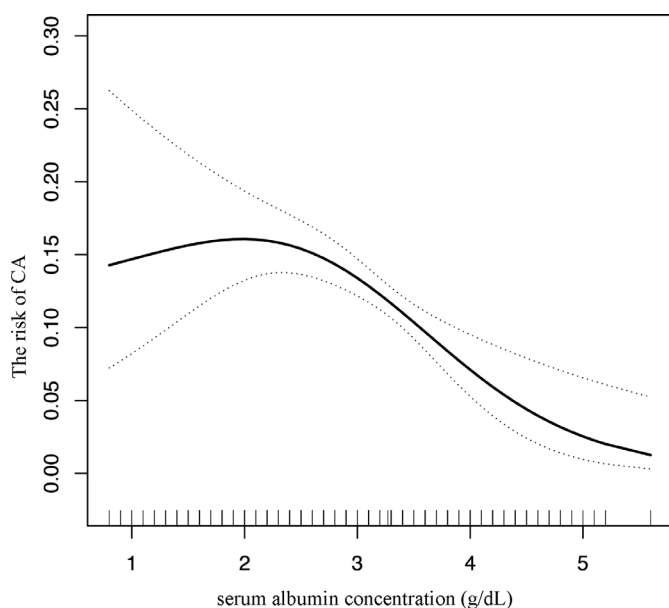
Figure 2 The non-linear relationship between serum albumin concentration and risk of CA. CA, cardiac arrest.

Table 3 The results of two-piecewise linear model

Inflection point of serum albumin	Effect size (OR)	95% CI	P value
<3.26 g/dL	0.88	(0.65 to 1.19)	0.4180
>3.26 g/dL	0.32	(0.16 to 0.64)	0.0013
P for loglikely ratio test	0.013		

Adjusted: BMI, DM, COPD, hypertension, ARF, ACS, AMI, RVR, AF, CHF, dialysis, creatinine, heamoglobin, PLT, albumin, PH, serum calcium concentration, serum potassium concentration.
ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; ARF, acute respiratory failure; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; PH, potential of hydrogen; PLT, platelet; RVR, rapid ventricular response.

albumin concentration may result in adverse clinical outcomes. As a major source of sulfhydryl groups, serum albumin binds some toxic lipid moieties and contributes, to some extent, to the removal of uraemic toxins. Meanwhile, serum albumin has the anticoagulant and antithrombotic effects, which may be due to the binding of nitric oxide (NO) free radicals.[26] Furthermore, studies have suggested that albumin may act as a reservoir for NO.[27] Therefore, low serum albumin concentration may reduce NO-induced vasodilatation, thereby increasing cardiovascular mortality in patients with ESRD. However, additional studies are required to understand the biological mechanisms linking low serum albumin concentration with the risk of CA.

Although we have discovered a relationship between low serum albumin and the risk of CA, we should realise that there are still many challenges. First, it is still not clear whether the correction of serum albumin concentrations improves outcomes. There is no clinical evidence that interventions targeting an increase of serum albumin above a pre-specified threshold can lead to better clinical outcomes in the ESRD population. Second, it is possible that the interventions to increase serum albumin concentrations may be associated with adverse patient outcomes.[28] Additionally, in patients with ESRD, serum albumin concentrations may reflect a complex interplay between variables. Therefore, further clinical studies are needed to explore the effective method of albumin supplementation and evaluate its effectiveness in improving patient outcomes. Notwithstanding these caveats, our study provides evidence that serum albumin concentration may be a useful clinical tool for clinicians in risk-stratifying patients for the occurrence of CA.

The strengths of this study are obvious. First, this is the first study to analyse the relationship between serum albumin concentration and the risk of CA in critically ill patients with ESRD with a large sample size. Second, The results were robust when we determined the effect of serum albumin concentration analysed both as a continuous and categorical variable. Third, this study provided a novel perspective that low serum albumin concentration is associated with a common terminal event—CA in the ICU, which may be the underlying mechanism leading to poor prognosis of patients in patients with ESRD in the ICU. There are some limitations to our study. First, this study only adjusted for measured confounders. It is, therefore, possible that the association between serum albumin concentration and CA could be affected by unmeasured confounders. Second, given this study focuses on the relationship between albumin and CA, other possible factors that may be related to CA such as different comorbidities need to be further discussed in the future.

CONCLUSION

Previous studies have shown that serum albumin concentration is associated with mortality of patients with ESRD, which seems to be related to cardiovascular events. Our study demonstrated the presence of a definite relationship between low serum albumin concentration and risk of CA in an ESRD population very prone to cardiovascular morbidity and mortality. Given that serum albumin concentration levels can be modified in this population, further studies are urgently needed to determine whether such modification is worthwhile undertaking.

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