In maintenance hemodialysis patients, there were “U-shaped” relationships between serum albumin level and mortality or hospitalization, negative linear relationship between serum albumin level and hospitalization for infection.

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Abstract

Background: Few studies are available on the non-linear association between serum albumin (S-Alb) level and prognosis in maintenance hemodialysis (MHD) patients. Methods: All stable MHD patients treated in our center from 2007 to 2011 were enrolled into this study. Demographics, laboratory data, hospitalization and mortality were collected; Cox regressive models were fitted to investigate predicting outcomes, restricted cubic splines (RCS) were allowing for non-linear association between S-Alb and prognosis. Results: S-Alb was independent protective factor for mortality, all-cause hospitalization, hospitalization for cardiovascular or cerebrovascular disease and hospitalization for infection. The relationships between S-Alb and mortality, all-cause hospitalization, hospitalization for cardiovascular or cerebrovascular disease were U-shaped; relationships between S-Alb and hospitalization for infection were negative linear relationships both in univariable Cox regression models and in multivariable Cox regression. Conclusions: In MHD population, there were “U-shaped” relationships between serum albumin level and mortality or hospitalization; the potential risks associated with excessive S-Alb should been taken into consideration. There was negative linear relationship between S-Alb and hospitalization for infection, S-Alb may be even more important in preventing infection in MHD population.

Background

S-Alb has mainly been considered a biomarker of visceral protein and nutrition status. In patients with end-stage renal disease (ESRD), hypoalbuminemia is a frequently and independently predictor for mortality and systemic inflammation[1, 2]; in dialysis patients, it is the strongest biomarker affect the patient’s prognosis among Ca-P-iPTH, acidosis, Kt/V and so on[3-5]. For the above reasons, S-Alb has been included in monthly blood testing in most dialysis centers. In 2000, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines for nutrition in chronic renal failure recommend that “patients on dialysis achieve a serum albumin level equal to or greater than the lower limit of the normal range (4.0 g/dl for the bromcresol green laboratory method) to ensure optimal nutrition and decrease risks of protein-energy wasting”[6]; since then, the S-Alb target of more than 4.0 g/dl is still being used today for MHD patients, few studies have discussed whether the upper limit should be set for S-Alb in MHD patients, few data are available on the non-linear association between serum albumin (S-Alb) level and prognosis in MHD patients.

Methods

Study Population and Data Source

All stable adult MHD patients in our center during the period January 1, 2007 through December 31, 2011, were included in this retrospective study. Inclusion criteria were age > 18 years and underwent MHD for at least 3 months, exclusion criteria were hospitalization within 3 months before the study, combined with uncured malignant tumor or active liver disease. The study was approved by the Ethics Committee of Qianfoshan Hospital, and all subjects gave their informed consent.
Demographic and biochemical data

Base-line and follow-up data were collected from medical records. The following data were collected at base-line: demographic factors (age, sex, and vintage); whether comorbid diabetes; physical constitution (systolic blood pressure(SBP) and diastolic blood pressure(DBP) before single dialysis); hemoglobin(Hb) and serum biochemical data (albumin(Alb), creatinine(Cr), blood urea nitrogen(BUN), calcium(Ca), phosphorus(P), magnesium(Mg), intact parathyroid hormone(iPTH), triglyceride(TG), cholesterol(CH), low density lipoprotein(LDL).

Blood samples were drawn from dialysis pipeline immediately after initiation of single hemodialysis treatment and shipped to our central laboratory, where measurements were made using automated and standardized methods. The S-Alb level was determined with the BCG method; the normal reference range in this study was 4.0-5.5g/dl. The corrected total serum calcium (S-Ca) and serum magnesium (S-Mg) was calculated according to the following formula: corrected S-Ca (mmol/L) = measured S-Ca (mmol/L) + (40 – S-Alb [g/L]) × 0.02, S-Mg (mmol/L) = measured S-Mg (mmol/L) + (40 – S-Alb [g/L]) × 0.005.

Follow-up and study endpoints

All patients were followed up to the study endpoint, administrative censoring (including renal transplantation, switch to peritoneal dialysis, transfer to another HD center, loss to follow-up or withdrawal from treatment) or the end of the study follow-up period (31 July 2018). The primary study endpoint was mortality, the secondary endpoint was hospitalization. Causes of death and hospitalization were collected, for subgroup analysis. If a death or hospitalization had two or more potential causes, we generally ascribed to the initial presenting condition.

Statistical Analyses

Categorical data are presented as frequencies and percentages. Continuous variables are expressed as mean ± standard deviation (SD) for normally distributed variables and as median and interquartile range (IQR, 25th–75th percentile) for variables with skewed distribution.

All these above demographic and biochemical data were assessed as potential predictors of hospitalization and mortality outcomes by univariable and multivariable Cox regression. If there were 2 or more hospitalizations, the first hospitalization was taken into Cox regression analyses. The adjustments were as follows: Model 1 (case mix): sex, age and all parameters that were significant in univariable analysis comorbidities; Model 2 (bone mineral metabolism factors): sex, age, comorbid diabetes, S-Alb, corrected S-Ca, S-P, corrected S-Mg, iPTH; Model 3(classic cardiovascular and cerebrovascular risk factors) : sex, age, comorbid diabetes, SBP, DBP, S-Alb, TG, CH, LDL.

The non-liner relationships of base-line S-Alb levels and outcomes were evaluated by restricted cubic spline(RCS) fitting univariable or multivariable Cox model; 6 knots were set and percentiles were P5, P23, P41, P59, P77, P95, respectively. For RCS fitting multivariable Cox model, only model 1 was used respectively.
All statistical analyses were two-tailed and P value <0.05 was considered significant. RCS were conducted in Stata/IC 14 (StataCorp, College Station, TX), other analyses were performed using the SPSS version 13.0 (SPSS, Chicago, IL).

Results

Demographic and biochemical data

Demographic and clinical characteristics of the total 230 MHD patients are depicted in Table 1. The median age was 56 years (range, 19-89 years). Male to female ratio was 1:1.1. Median time on hemodialysis was 3 months (range, 3-159 months). Sixty-nine (30%) patients combined diabetes mellitus. SBP pressure was 134.0(126, 142.25) mmHg, DBP was 74(68, 87) mmHg. Hb was 97.7±21.33 g/L, S-Alb was 38.25(33.78, 42) g/L, serum Cr was 755.3(510.55, 947.33) μmol/L, serum BUN was 27.15(20.18, 32.85) mmol/L, S-Ca was 2.23(2.11, 2.34) mmol/L, serum P was 1.84±0.59 mmol/L, S-Mg was 1.15(1.02, 1.27) mmol/L, serum iPTH was 211(115.1, 369.2) pg/mL, serum TG was 1.14(0.88, 1.56) mmol/L, serum CH was 4.28(3.34, 4.98) mmol/L, serum LDL was 2.47(1.96, 3.09) mmol/L.

Predictors of mortality

Median follow-up times were 51.9 months (range, 3-112.9 months).

During follow-up, 74 deaths occurred median survival time was 43.3 months (range, 3.6-68.1 months); causes of death were: 33 (44.6%) cardiovascular or cerebrovascular disease, 15 (20.3%) infections, 8 (10.8%) carcinomas, 1 (1.4%) gastrointestinal bleedings, and 17 (23%) unknown causes. Table 2 shows age (years; HR, 1.04; 95% CI, 1.02-1.06; P<0.000) was independent risk factor for mortality, S-Alb (g/L; HR, 0.94; 95% CI, 0.9-0.99; P=0.011) was independent protective factors for mortality.

Predictors of hospitalization

There were all together 865 hospitalizations occurred, the median number of hospitalizations per patient-year was 0.72 (interquartile range: 0.23–1.60). The first four causes of hospitalization were: 278 (32.1%) infections, 221 (25.5%) cardiovascular or cerebrovascular disease, 28 (3.2%) gastrointestinal bleedings, and 18 (2.1%) fractures. We created Cox regression models separately according to the first all-cause hospitalization, the first hospitalization for infection, and the first hospitalization for cardiovascular or cerebrovascular disease.

Table 3 shows S-Alb was independent protective factor for all-cause hospitalization. Table 4 shows S-Alb was independent protective factor of hospitalization for infection. Table 5 shows S-Alb were both independent protective factors of hospitalization for cardiovascular or cerebrovascular disease, except adjustment for bone mineral metabolism factors in model 2.

Association between S-Alb and prognosis
Figure 1 shows the association between S-Alb and prognosis.

Relationships between S-Alb and mortality (Figure 1a, b), all-cause hospitalization (Figure 1c, d), hospitalization for cardiovascular or cerebrovascular disease (Figure 1g, h) were U-shaped, lowest points of HR corresponds to S-Alb values of about 42g/L.

Either in univariable Cox regression models, or in multivariable Cox regression, relationships between S-Alb and hospitalization for infection were both negative linear relationships (Figure 1e, f).

**Discussion**

To our knowledge, the current retrospective study is the first single-center report discusses the potential upper limit of S-Alb in MHD patients. There were U-shaped relationships between S-Alb and mortality, all-cause hospitalization, hospitalization for cardiovascular or cerebrovascular disease.

Former studies and this study have confirmed that low S-Alb is associates with poor clinical outcome in MHD [7, 8]; this phenomenon may due to better nutrition and decreased inflammatory status [1, 9, 10]. However, there was no research on the reason why MHD patients with relatively higher S-Alb level had worse prognosis. In our view, there may be several reasons. First, to achieve higher S-Alb levels, higher protein diets are often required; which result in excessive metabolites (such as P, BUN and so on) that cannot be completely eliminated. The second, because of the Gibbs-Donnan effect, protein-bound uremic toxins are difficult to remove during hemodialysis [11-14].

Different from those above prognosis outcomes, a negative linear relationship between S-Alb and hospitalization for infection has been found in this study; which hints S-Alb may be even more important in preventing infection in MHD population. In 2009, de Mutsert R et al [10] described “association between serum albumin and mortality in dialysis patients is partly explained by inflammation, not by malnutrition, as measured with SGA and nPNA”. Mukai H et al [15] had also reported that “the mortality risk was increased in ESRD patients with low S-Alb and high CRP at baseline, but the risk was not increased in patients with low S-Alb and normal CRP, suggesting that the higher mortality associated with low S-Alb in ESRD to a large extent is dependent on concomitant presence of systemic inflammation”. Inflammation can cause low S-Alb though insufficient food intake and protein's consumption increases [16-18]; low S-Alb can cause inflammation though oxidative stress and decreased immune function. That is, low S-Alb and infection interact as both cause and effect in MHD population [19, 20].

In addition, more attentions have been paid to relationships between serum Mg levels and prognosis in MHD patients. Most studies have reported that lower Mg levels were associated with increased all-cause and cardiovascular mortality [21-24]. A rencent study [25] showed “hypomagnesaemia is not an independent risk factor for mortality in Japanese maintenance hemodialysis patients”. In our present cohort, S-Mg level was neither independent risk factor for mortality nor for hospitalization.
The limitation of this study is that neither indicator of inflammation (C-reactive protein) nor subjective global assessment was recorded for further analysis.

**Conclusions**

In our MHD retrospective cohort, S-Alb is the most important prognostic factor for patient's mortality or hospitalization. There were “U-shaped” relationships between S-Alb level and mortality or hospitalization; the potential risks associated with excessive S-Alb level should been taken into consideration. There was negative linear relationship between S-Alb and hospitalization for infection, S-Alb may be even more important in preventing infection in MHD population.

**Abbreviations**

| Abbreviation | Description                     |
|--------------|---------------------------------|
| Alb          | Albumin                         |
| BUN          | Blood urea nitrogen             |
| Ca           | Calcium                         |
| CH           | Cholesterol                     |
| Cr           | Creatinine                      |
| DBP          | Diastolic blood pressure        |
| ESRD         | End-stage renal disease         |
| Hb           | Hemoglobin                      |
| iPTH         | intact parathyroid hormone      |
| LDL          | Low density lipoprotein         |
| MHD          | Maintenance hemodialysis        |
| Mg           | Magnesium                       |
| P            | Phosphorus                      |
| RCS          | Restricted cubic splines        |
| S-Alb        | Serum albumin                   |
| SDP          | Systolic blood pressure         |
| TG           | Triglyceride                    |

**Declarations**

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**Authors’ contributions**

XYJ and DMX participated in the study design. XYJ, XW, ZSW, NZ, YZ and PC acquired the data. XYJ, JC, XLK and YPL analysed the data. XYJ, YW and LW participated in the manuscript preparation. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

The local independent ethics committee approved the study protocol. Need for consent was waived, as data was de-identified.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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### Tables

**Table 1.** Demographic and Clinical Characteristics of MHD Patients
| Characteristic                          | Total (N=230)                  |
|----------------------------------------|-------------------------------|
| Male/female                            | 121/109                       |
| Age (years)                            | 56 (42, 70)                   |
| Vintage (months)                       | 3 (3, 5)                      |
| Comorbid diabetes, n(%)                | 69 (30%)                      |
| Systolic blood pressure (mmHg)         | 134.0 (126, 142.25)           |
| Diastolic blood pressure (mmHg)        | 74 (68, 87)                   |
| Hemoglobin (g/L)                       | 97.7 ± 21.33                  |
| Serum albumin (g/L)                    | 38.25 (33.78, 42)             |
| Serum creatinine (µmol/L)              | 755.3 (510.55, 947.33)        |
| Serum urea nitrogen (mmol/L)           | 27.15 (20.18, 32.85)          |
| Serum calcium (mmol/L)                 | 2.23 (2.11, 2.34)             |
| Serum phosphorus (mmol/L)              | 1.84 ± 0.59                   |
| Serum magnesium (mmol/L)               | 1.15 (1.02, 1.27)             |
| Serum iPTH (pg/mL)                     | 211 (115.1, 369.2)            |
| Serum triglyceride (mmol/L)            | 1.14 (0.88, 1.56)             |
| Serum cholesterol (mmol/L)             | 4.28 (3.34, 4.98)             |
| Serum low density lipoprotein (mmol/L) | 2.47 (1.96, 3.09)             |
| Follow-up time (months)                | 51.9 (range, 3-112.9)         |
| Death                                  | 74                            |
| survival time (months)                 | 43.3 (range, 3.6-68.1)        |
| Hospitalizations                       | 865                           |
| number of hospitalizations per patient-year | 0.72 (0.23, 1.60)           |

**Table 2.** Prognostic significance on patient survival
| Variable                                      | Univariable Analysis | Multivariable Analysis (Model 1) | Multivariable Analysis (Model 2) | Multivariable Analysis (Model 3) |
|------------------------------------------------|----------------------|---------------------------------|---------------------------------|---------------------------------|
|                                                | HR (95% CI)          | P Value                         | HR (95% CI)                      | P Value                         | HR (95% CI)                      | P Value |
| Sex (male)                                     | 0.56 (0.35-0.88)     | .013                             | 0.84 (0.51-1.38)                 | .488                             | 0.81 (0.48-1.35)                 | .415     | 0.73 (0.42-1.28) | .276     |
| Age (years)                                    | 1.05 (1.03-1.07)     | <.001                            | 1.04 (1.02-1.06)                 | <.000                            | 1.05 (1.03-1.06)                 | <.001    | 1.04 (1.01-1.06) | .002     |
| Vintage (months)                               | 1 (0.99-1.01)        | .534                             |                                 |                                  |                                 |          |                |          |
| Comorbid diabetes, n(%)                        | 1.92 (1.21-3.06)     | .006                             | 0.98 (0.59-1.63)                 | .935                             | 1.18 (0.71-1.96)                 | .533     | 1.03 (0.59-1.79) | .931     |
| Systolic blood pressure (mmHg)                 | 1.01 (0.99-1.02)     | .320                             |                                 |                                  |                                 |          |                |          |
| Diastolic blood pressure (mmHg)                | 0.97 (0.96-0.99)     | .005                             | 1 (0.98-1.02)                    | .799                             |                                 |          |                |          |
| Hemoglobin (g/L)                               | 0.99 (0.98-1.01)     | .208                             |                                 |                                  |                                 |          |                |          |
| Serum albumin (g/L)                            | 0.93 (0.89-0.96)     | <.001                            | 0.94 (0.9-0.99)                  | .011                             | 0.95 (0.9-0.99)                  | .013     | 0.94 (0.89-0.99) | .013     |
| Serum creatinine (μmol/L)                      | 1 (1-1)              | <.001                            | 1 (1-1)                         | .181                             |                                 |          |                |          |
| Serum urea nitrogen (mmol/L)                   | 0.97 (0.94-0.99)     | .009                             | 0.99 (0.95-1.02)                 | .422                             |                                 |          |                |          |
| Serum calcium (mmol/L)                         | 2.43 (0.76-7.72)     | .132                             |                                 |                                  | 1.35 (0.39-4.69)                 | .641     |                                 |          |
| Serum phosphorus (mmol/L)                      | 0.6 (0.4-0.91)       | .016                             | 1.37 (0.79-2.38)                 | .259                             | 1.04 (0.64-1.7)                  | .880     |                                 |          |
| Serum magnesium (mmol/L)                       | 0.35 (0.1-1.29)      | .115                             |                                 |                                  | 0.73 (0.16-3.29)                 | .683     |                                 |          |
| Serum iPTH (pg/mL)                             | 1 (1-1)              | .457                             |                                 |                                  | 1 (1-1)                         | .319     |                                 |          |
| Serum triglyceride (mmol/L)                    | 1.01 (1-1.02)        | .129                             |                                 |                                  | 1 (0.99-1.02)                    | .521     |                                 |          |
| Serum cholesterol (mmol/L)                     | 0.96 (0.8-1.16)      | .675                             |                                 |                                  | 0.94 (0.66-1.34)                 | .729     |                                 |          |
| Serum low density lipoprotein (mmol/L)         | 0.81 (0.6-1.08)      | .155                             |                                 |                                  | 0.82 (0.46-1.45)                 | .492     |                                 |          |

Model 1 (case mix): sex, age and all parameters that were significant in univariable analysis comorbidities; Model 2 (bone mineral metabolism factors): sex, age, comorbid diabetes, S-Alb, corrected S-Ca, S-P, corrected S-Mg, iPTH; Model 3 (classic cardiovascular and cerebrovascular risk factors): sex, age, comorbid diabetes, SBP, DBP, S-Alb, TG, CH, LDL.

Table 3. Prognostic significance on all-cause hospitalization
| Variable                      | Univariable Analysis | Multivariable Analysis (Model 1) | Multivariable Analysis (Model 2) | Multivariable Analysis (Model 3) |
|-------------------------------|----------------------|----------------------------------|----------------------------------|----------------------------------|
|                               | HR (95% CI) P Value  | HR (95% CI) P Value              | HR (95% CI) P Value              | HR (95% CI) P Value              |
| Sex (male)                    | 0.95(0.71-1.27) .722 | 1.07(0.78-1.47) .688             | 1.01(0.74-1.39) .945             | 0.96(0.68-1.35) .810             |
| Age (years)                   | 1.02(1.01-1.03) <.001| 1.01(1.01-1.02) .224             | 1.01(1.01-1.02) .023             | 1.01(1.01-1.03) .045             |
| Vintage (months)              | 1(0.99-1) .325       |                                  |                                  |                                  |
| Comorbid diabetes, n(%)       | 1.71(1.26-2.33) .001 | 1.23(0.87-1.74) .249             | 1.26(0.89-1.79) .196             | 1.23(0.86-1.75) .259             |
| Systolic blood pressure (mmHg)| 1(0.99-1.01) .858    |                                  |                                  |                                  |
| Diastolic blood pressure (mmHg)| 0.99(0.98-1) .029    | 0.99(0.98-1.01) .377             |                                  |                                  |
| Hemoglobin(g/L)               | 1(0.99-1) .522       |                                  |                                  |                                  |
| Serum albumin(g/L)            | 0.95(0.93-0.97) <.001| 0.96(0.93-0.98) .001             | 0.95(0.93-0.98) <.001           | 0.95(0.92-0.98) <.001           |
| Serum creatinine(μmol/L)      | 1(1-1) .641          |                                  |                                  |                                  |
| Serum urea nitrogen (mmol/L)  | 1(0.99-1.02)         |                                  |                                  |                                  |
| Serum calcium (mmol/L)        | 1.2(0.61-2.36) .594  |                                  | 0.92(0.46-1.84) .807            |                                  |
| Serum phosphorus (mmol/L)     | 0.84(0.65-1.08) .168 |                                  | 1.17(0.87-1.56) .302            |                                  |
| Serum magnesium (mmol/L)      | 0.75(0.35-1.61) .455 |                                  | 0.99(0.43-2.3) .988             |                                  |
| Serum iPTH (pg/mL)            | 1(1-1) .013          | 1(1-1) .281                      | 1(1-1) .190                     |                                  |
| Serum triglyceride (mmol/L)   | 1(0.99-1.01) .740    |                                  |                                  | 1(0.99-1.01) .775               |
| Serum cholesterol (mmol/L)    | 1.02(0.91-1.15) .676 |                                  | 0.94(0.73-1.23) .668            |                                  |
| Serum low density lipoprotein (mmol/L) | 1.04(0.87-1.24) .677 |                                  | 1.13(0.77-1.65) .537            |                                  |

**Table 4.** Prognostic significance on hospitalization for infection
| Variable                          | Univariable Analysis | Multivariable Analysis (Model 1) | Multivariable Analysis (Model 2) | Multivariable Analysis (Model 3) |
|----------------------------------|----------------------|----------------------------------|----------------------------------|----------------------------------|
|                                  | HR (95% CI)          | P Value                          | HR (95% CI)                      | P Value                          | HR (95% CI)                      | P Value                          |
| Sex (male)                       | 0.92 (0.61-1.37)     | .668                             | 1.2 (0.77-1.86)                  | .428                             | 1.01 (0.74-1.39)                | .945                             | 0.91 (0.56-1.49)                | .705                             |
| Age (years)                      | 1.02 (1.01-1.03)     | .005                             | 1.01 (0.98-1.02)                 | .862                             | 1.01 (1-1.02)                   | .023                             | 1.01 (0.98-1.03)                | .560                             |
| Vintage (months)                 | 1 (0.99-1.01)        | .832                             |                                 |                                  |                                 |                                  |                                  |                                  |
| Comorbid diabetes, n(%)          | 1.03 (0.67-1.57)     | .900                             | 1.26 (0.89-1.79)                 | .196                             | 0.9 (0.53-1.51)                 | .684                             | 0.99 (0.96-1.01)                | .256                             |
| Systolic blood pressure(mmHg)    | 0.99 (0.98-1)        | .066                             | 0.98 (0.97-1)                    | .085                             | 0.99 (0.96-1.02)                | .495                             |                                  |                                  |
| Diastolic blood pressure(mmHg)   | 0.98 (0.96-1)        | .014                             | 0.98 (0.97-1)                    | .085                             | 0.99 (0.96-1.02)                | .495                             |                                  |                                  |
| Hemoglobin(g/L)                  | 0.99 (0.98-1)        | .116                             |                                 |                                  |                                 |                                  |                                  |                                  |
| Serum albumin(g/L)               | 0.92 (0.89-0.96)     | <.001                            | 0.93 (0.9-0.97)                  | <.001                            | 0.95 (0.93-0.98)                | <.001                            | 0.92 (0.89-0.96)                | <.001                            |
| Serum creatinine(μmol/L)         | 1 (1-1)              | .004                             | 1 (1-1)                          | .105                             |                                  |                                  |                                  |                                  |
| Serum urea nitrogen(mmol/L)      | 0.99 (0.96-1.01)     | .224                             |                                 |                                  |                                  |                                  |                                  |                                  |
| Serum calcium(mmol/L)            | 0.86 (0.29-2.54)     | .781                             | 0.92 (0.46-1.84)                 | .807                             |                                  |                                  |                                  |                                  |
| Serum phosphorus(mmol/L)         | 0.76 (0.53-1.09)     | .138                             | 1.17 (0.87-1.56)                 | .302                             |                                  |                                  |                                  |                                  |
| Serum magnesium(mmol/L)          | 0.39 (0.13-2.3)      | .090                             | 0.99 (0.43-2.3)                  | .988                             |                                  |                                  |                                  |                                  |
| Serum iPTH(pg/mL)                | 1 (1-1)              | .003                             | 1 (1-1)                          | .075                             | 1 (1-1)                         | .190                             |                                  |                                  |
| Serum triglyceride(mmol/L)       | 1.12 (0.9-1.39)      | .305                             | 1.02 (0.76-1.38)                 | .894                             |                                  |                                  |                                  |                                  |
| Serum cholesterol(mmol/L)        | 1.03 (0.85-1.26)     | .755                             | 0.87 (0.54-1.4)                  | .557                             |                                  |                                  |                                  |                                  |
| Serum low density lipoprotein(mmol/L) | 1.08 (0.83-1.41) | .563                             | 1.35 (0.72-2.53)                 | .355                             |                                  |                                  |                                  |                                  |

Table 5. Prognostic significance on hospitalization for cardiovascular or cerebrovascular disease
| Variable                        | Univariable Analysis | Multivariable Analysis (Model 1) | Multivariable Analysis (Model 2) | Multivariable Analysis (Model 3) |
|--------------------------------|----------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | HR (95% CI)          | P Value                         | HR (95% CI)                      | P Value                         | HR (95% CI)                      | P Value                         |
| Sex (male)                     | 1.05(0.71-1.55)      | .817                            | 1.28(0.84-1.96)                  | .257                            | 1.36(0.87-2.12)                  | .179                            | 1.18(0.74-1.89)                  | .482                            |
| Age (years)                    | 1.01(1-1.02)         | .093                            | 1(0.98-1.02)                     | .959                            | 1.01(0.99-1.03)                  | .342                            | 0.99(0.97-1.01)                  | .448                            |
| Vintage (months)               | 1(0.99-1.01)         | .381                            |                                 |                                 |                                 |                                 |                                 |                                 |
| Comorbid diabetes, n(%)        | 1.52(1.01-2.28)      | .044                            | 1.72(1.1-2.68)                   | .017                            | 1.59(0.99-2.57)                  | .056                            | 1.81(1.13-2.9)                   | .013                            |
| Systolic blood pressure(mmHg)  | 0.99(0.98-1)         | .095                            |                                 |                                 |                                 |                                 |                                 |                                 |
| Diastolic blood pressure(mmHg) | 0.98(0.96-0.99)      | .111                            | 0.97(0.96-0.99)                  | .004                            |                                 |                                 |                                 |                                 |
| Hemoglobin(g/L)                | 1(0.99-1.01)         | .626                            |                                 |                                 |                                 |                                 |                                 |                                 |
| Serum albumin(g/L)             | 0.96(0.93-1)         | .028                            | 0.96(0.92-1)                     | .043                            | 0.97(0.94-1.01)                  | .150                            | 0.95(0.91-1)                     | .029                            |
| Serum creatinine(μmol/L)       | 1(1-1)               | .086                            |                                 |                                 |                                 |                                 |                                 |                                 |
| Serum urea nitrogen(mmol/L)    | 0.99(0.97-1.01)      | .300                            |                                 |                                 |                                 |                                 |                                 |                                 |
| Serum calcium(mmol/L)          | 1.4(0.57-3.43)       | .467                            |                                 |                                 |                                 |                                 |                                 |                                 |
| Serum phosphorus(mmol/L)       | 0.82(0.59-1.15)      | .258                            |                                 |                                 |                                 |                                 |                                 |                                 |
| Serum magnesium(mmol/L)        | 0.99(0.34-2.85)      | .985                            |                                 |                                 |                                 |                                 |                                 |                                 |
| Serum iPTH(pg/mL)              | 1(1-1)               | .466                            |                                 |                                 |                                 |                                 |                                 |                                 |
| Serum triglyceride(mmol/L)     | 1(0.8-1.26)          | .967                            |                                 |                                 |                                 |                                 |                                 |                                 |
| Serum cholesterol(mmol/L)      | 0.99(0.83-1.19)      | .954                            |                                 |                                 |                                 |                                 |                                 |                                 |
| Serum low density lipoprotein(mmol/L) | 0.93(0.73-1.19)       | .569                            |                                 |                                 |                                 |                                 |                                 |                                 |

Figures
Figure 1

Association between S-Alb and prognosis, allowing for non-linear effects, with 95% CIs. Six nodes were set, and percentiles were P5, P23, P41, P59, P77, P95, respectively; the reference S-Alb for these plots (with HR fixed as 1.0) was 40g/L; in the subgroup of hospitalization for infection, none of these patients had a S-Alb level of 40g/L, the closest value to 40g/L, which is 39.7g/L was fitted as reference. a. Association between S-Alb and mortality, RCS fitting univariable Cox regression model. b. Association between S-Alb and mortality, RCS fitting multivariable Cox regression model, adjusted for sex, age and all parameters that were significant in univariable analysis (comorbid diabetes, DBP (mmHg), Cr (μmol/L), BUN (mmol/L), P (mmol/L)). c. Association between S-Alb and all-cause hospitalization, RCS fitting univariable Cox regression model. d. Association between S-Alb and all-cause hospitalization, RCS fitting multivariable Cox regression model, adjusted for sex, age and all parameters that were significant in univariable analysis (comorbid diabetes, DBP (mmHg), Cr (μmol/L), iPTH(pg/mL)). e. Association between S-Alb and hospitalization for infection, RCS fitting univariable Cox regression model. f. Association between S-Alb and hospitalization for infection, RCS fitting multivariable Cox regression model, adjusted for sex, age and all parameters that were significant in univariable analysis (DBP (mmHg), Cr (μmol/L), iPTH(pg/mL)). g. Association between S-Alb and hospitalization for cardiovascular or cerebrovascular disease, RCS fitting univariable Cox regression model. h. Association between S-Alb and hospitalization for cardiovascular or cerebrovascular disease, RCS fitting multivariable Cox regression model, adjusted for sex, age and all parameters that were significant in univariable analysis (comorbid diabetes, DBP (mmHg)).