Soluble α-Klotho as a potential predictor of all-cause mortality in Chinese maintenance hemodialysis patients

Type
Research paper

Keywords
Mortality, maintenance hemodialysis, α-klotho, Overall survival, Cox regression

Abstract

Introduction
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Material and methods
The present study is a single-center prospective cohort study. It comprised 134 MHD patients which were divided into two groups according to the median level of serum α-klotho: 68 patients representing the low soluble α-klotho group (< 1.15 ng/ml and equivalent to 1.15 ng/ml) and 66 patients representing the high soluble α-klotho group (>1.15 ng/ml). These patients were followed up for 36 months. The three-year all-cause mortality rate, overall survival (OS) and cardio-cerebrovascular mortality were observed. The potential risk factors of all-cause mortality in MHD patients were investigated by Cox regression models.

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The 3-year all-cause mortality rates in low soluble α-klotho group were significantly higher than those in high soluble α-klotho group (33.82% vs. 16.67%, P=0.039). The difference of the 3-year cardio-cerebrovascular mortality rates between the two groups was non-significant (26.47% vs. 15.15%, P=0.107). The Kaplan-Meier analysis showed that the differences in the rates of OS and cardio-cerebrovascular death free survival between the two groups were significantly different (all P<0.05). The Cox regression analyses revealed that low soluble α-klotho level was an independent predictor of all-cause mortality in MHD patients after adjusting for potential confounding factors.

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Low serum soluble α-klotho levels was associated with increased risk of all-cause mortality in Chinese MHD patients.
Soluble $\alpha$-Klotho as a potential predictor of all-cause mortality in Chinese maintenance hemodialysis patients

Running Title: $\alpha$-Klotho as a potential predictor in MHD patients

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**Keywords:** α-klotho; maintenance hemodialysis; Mortality; Overall survival; Cox regression

1. Introduction

α-Klotho is a novel protein mainly expressed in kidney, brain and parathyroid\[^1\]. It was first found by Kuro-M et al. in 1997 as an anti-ageing protein due to the fact that α-Klotho deficient mice resembled human premature-aging syndrome\[^2\]. But it was demonstrated that the anti-ageing effect of α-Klotho was associated with its protective role in avoiding excess dietary phosphate intake\[^3, 4\]. There are 2 forms of Klotho protein: a soluble form and a membrane form. The membrane α-Klotho is the specific receptor of fibroblast growth factor 23 (FGF23), a hormone mainly produced by osteoblasts and osteocytes\[^3\]. The FGF23-Klotho endocrine system plays an important role to regulate phosphate absorption, maintain mineral homeostasis, inhibit 1,25-dihydroxy vitamin D \([1,25(OH)\_2D\_3]\) activity and suppress synthesis of parathyroid hormone\[^1, 3, 6\]. The proteolytic release of the transmembrane α-Klotho generates the soluble form of α-Klotho. It has been found that soluble α-Klotho, which could be detected in plasma, urine, and cerebrospinal fluid, is a humoral factor to regulate glycoproteins on the cell surface independently of FGF-23\[^7\]. Soluble α-Klotho has multiple functions including regulating ion channels and reducing oxidative stress\[^1, 5\].
The kidney has been thought to be the main source of α-klotho[8]. The genetic studies demonstrated that klotho gene deficiency resulted in phenotypes prone to the development of kidney disease including acute kidney injury (AKI) and chronic kidney disease (CKD)[9]. In addition, the development of kidney disease could also lead to the decreased expression of α-klotho[10,11]. The animal models of CKD had lower α-klotho levels in kidney tissue and lower circulating soluble α-klotho in serum than normal animals[8]. Thus, soluble α-Klotho was regarded as a protective factor against kidney disease and its complications[5, 7].

Maintenance hemodialysis (MHD) is currently the main treatment for end-stage renal disease (ESRD). Patients’ maintenance dialysis was affected by body mass decomposition and hydration state imbalances, and it is closely related to depressive symptoms[12-13]. Compared with CKD patients not undergoing dialysis, MHD patients had highly decreased soluble α-klotho levels[14]. Cardiovascular disease and cerebrovascular disease are common hemodialysis-associated complications. In previous studies, soluble α-klotho was demonstrated to be associated with cardiovascular events and cerebrovascular disease during MHD[14-16]. In 2015, Naoko et al. found that serum soluble α-klotho levels below 309 pg/mL had significantly higher all-cause and cardiovascular mortality rates in Japanese patients on MHD[17]. However, information regarding the impact of soluble α-klotho levels on all-cause mortality rates in Chineses MHD patients still remains scarce. Thus, in the present study, we conducted this prospective study to evaluate the predictive value of soluble α-klotho levels on mortality in Chinese MHD patients.
2. Materials and Methods

2.1 Patients

The present study was a single-center prospective cohort study which was approved by the Institutional Review Board of our hospital in accordance with the provisions of the Declaration of Helsinki. From January 2017 to January 2018, a total of 150 patients from the Dialysis Center of our hospital were screened in this study. The inclusion criteria were as follows: (1) patients whose age was 18 years or older; (2) patients who received MHD for at least 3 months; (3) patients who voluntarily participated in the study. Patients were excluded if they had an active malignancy, had an active psychiatric disorder, had acute inflammation or autoimmune disease, or underwent peritoneal dialysis. Informed consents were obtained from all patients included in this study.

2.2 Data collection

The baseline parameters, including sex, age, height, weight and primary diseases, were recorded. The body mass index (BMI) was calculated from the weight and height. The fasting blood samples were obtained in the morning and pre-dialysis at the first day the patients enrolled in this study. The blood pressure (BP) was measured in a sitting position in the non-fistula arm before dialysis. All patients were followed up for 36 months (The first patient was enrolled in January 2017 and the last patient was enrolled in January 2018, after 36 months of follow-up, the last patient ended the study in January 2021.) or until the date of death or lost follow-up. The outcomes of
this study included: (1) the 3-year all-cause mortality rate; (2) overall survival (OS), which was defined as the time from the day the patients enrolled to the date of death for any reason; (3) cardio-cerebrovascular mortality, which was defined as death from any cardio-cerebrovascular event.

2.3 Laboratory analyses

Hemoglobin (Hb) was measured by an automatic blood analyzer (Mindray, Shenzhen, China). Albumin, calcium, phosphate and alkaline phosphatase (ALP) were measured by an automatic laboratory analyzer (Olympus AU560, Hamburg, Germany). Radioimmunoassay (Beckman Coulter, California, USA) was used to detect serum parathyroid hormone (PTH) levels. The enzyme-linked immunosorbent assay (ELISA) was used to detect serum soluble α-klotho and FGF23 levels in MHD patients. The antibodies against soluble α-klotho and FGF23 were purchased from Xinfan Bio technology company (Shanghai, China).

2.4 Groups

The present study is a single-center prospective cohort study. It comprised 134 MHD patients which were divided into two groups according to the median level of serum α-klotho: 68 patients representing the low soluble α-klotho group (< 1.15 ng/ml and equivalent to 1.15 ng/ml) and 66 patients representing the high soluble α-klotho group (> 1.15 ng/ml).

2.5 Statistical Analysis

SPSS 22.0 software was used in this study to analyze the data. Quantitative data were described as mean ± standard deviation (SD) for normal distribution or median
with interquartile range for non-normal distribution. Categorical data were described as numbers and percentages. The groups were compared using the Student’s t test or the Kruskal-Wallis rank test for quantitative data. The chi-square test was used to evaluate the proportional differences in categorical data. For time-to-event variables, Kaplan-Meier curves were used and compared by Log-rank tests. Cox regression models were used to investigate potential risk factors for all-cause mortality. The results of Cox regression were presented as hazard ratio (HR) with 95% confidence interval (CI). $P < 0.05$ was considered as statistical significance.

3 Results

3.1 Patients characteristics

In the present study, a total of 150 patients were screened. 6 patients received MHD less than 3 months, 5 patients had active malignancy or acute inflammation, and 5 patients underwent peritoneal dialysis. They were excluded from this study. Finally, the data of 134 patients were available to do the analysis. The median level of soluble α-klotho was 1.15 ng/mL (range: 0.34-2.45 ng/mL). Thus, 68 patients were divided into the low soluble α-klotho group (soluble α-klotho ≤ 1.15 ng/mL), and 66 patients were divided into the high soluble α-klotho group (soluble α-klotho > 1.15 ng/mL). The baseline characteristic parameters of the two groups are shown in Table 1.

3.2 The effect of soluble α-klotho on patients’ mortality

During the follow-up of three years, 34 (23.89%) patients died. Among them, 28
(20.90%) patients died of cardio-cerebrovascular events (18 in the low soluble α-klotho group and 10 in the high soluble α-klotho group), and 6 (4.48%) patients died from non-cardio-cerebrovascular causes including infectious disease, gastrointestinal hemorrhage and carcinoma (5 in the low soluble α-klotho group and 1 in the high soluble α-klotho group). Thus, the 3-year all-cause mortality rates were 33.82% in low soluble α-klotho group and 16.67% in high soluble α-klotho group. The difference of 3-year all-cause mortality rates between the two groups was statistically significant ($\chi^2=4.25, P=0.039$). The 3-year cardio-cerebrovascular mortality rates were 26.47% in low soluble α-klotho group and 15.15% in high soluble α-klotho group. The difference of 3-year cardio-cerebrovascular mortality rates between the two groups was non significant ($\chi^2=2.59, P=0.107$).

The Kaplan-Meier analysis showed that the difference in the rates of OS between the two groups was significantly different (log-rank $P=0.019$, Fig.1A). Cumulative survival was lower in the low soluble α-klotho group than in the high soluble α-klotho group [HR=2.244, 95%CI (1.414-4.415), $P=0.019$]. In addition, the cardio-cerebrovascular death free survival in the low soluble α-klotho group was also significantly lower than that in the high soluble α-klotho group [HR=2.046, 95%CI (0.974-4.299), $P=0.046$, Fig. 1B].

### 3.3 The potential risk factors for all-cause mortality

The potential risk factors for all-cause mortality in MHD patients were analyzed by Cox regression. The results showed that patients with low soluble α-klotho levels had a significantly higher risk for all-cause mortality [HR=2.324, 95%CI...
Serum calcium levels, serum phosphate levels and PTH levels also significantly affected all-cause mortality (table 2). After adjusting for serum calcium, serum phosphate and PTH, a low soluble α-klotho level remained an independent predictor of all-cause mortality \([\text{HR}=2.421, \ 95\%\text{CI} \ (1.082-5.417), \ P=0.031]\).

4. Discussion

Animal studies showed that the kidney is the main organ to produce soluble α-klotho\(^8,^{11}\). In living donors, the serum soluble α-klotho levels decreased by 30% to 50% after nephrectomy\(^{18}\). Previous studies showed that serum soluble α-klotho levels in MHD patients were significantly lower than those in healthy subjects\(^{16,19,20}\). The lower serum soluble α-klotho levels were associated with more advanced CKD conditions\(^{21, 22}\). Vascular tissue is another source of soluble α-klotho\(^{23}\). In Klotho-deficiency mice, severe calcification in vascular tissues was observed\(^{24}\). Low serum soluble α-klotho levels resulted in the increased risk of vascular calcification in dialysis patients \(^{25, 26}\). Thus, serum soluble α-klotho was regarded as an inhibitory factor for vascular calcification, which is a high risk factor to affect the survival of MHD patients\(^{27}\). Furthermore, inflammatory response and oxidative stress are linked to poor survival in MHD patients. Serum soluble α-klotho was reported to inhibit inflammation and oxidative stress via several mechanisms\(^{28, 29}\). These studies suggest that α-klotho may be closely related to mortality in MHD patients.

In 2015, Naoko et al. first found that lower serum soluble α-klotho was...
associated with all-cause mortality and cardiovascular mortality in MHD patients\textsuperscript{17}. Memmos et al. reported a study which showed that after a median follow up of 5.5 years, patients with low soluble \(\alpha\)-klotho level \((\leq 0.745\ \text{ng/ml})\) were associated with increased risk of cardiovascular events and cardiovascular death\textsuperscript{15}. Furthermore, in a cohort of 769 hemodialysis patients, patients with a soluble \(\alpha\)-klotho above 0.28 ng/mL had a significantly reduced cardiovascular events and cardiovascular death comparing to patients with soluble \(\alpha\)-klotho \(< 2.8 \times 10^5\ \text{ng/mL}\)\textsuperscript{14}. In China, Yu et al. analyzed the data from 211 patients on MHD and found that soluble \(\alpha\)-klotho level was an independent predictive factor of adverse outcomes including cardiovascular morbidity and mortality\textsuperscript{27}. Comparing with patients with soluble \(\alpha\)-klotho \(\geq 1.34\ \text{ng/mL}\), patients with soluble \(\alpha\)-klotho \(< 1.34\ \text{ng/mL}\) had more cardiovascular events and mortality\textsuperscript{27}. The results of above studies strongly supported the use of soluble \(\alpha\)-klotho as a prognostic factor in MHD patients.

In the present study, we found that MHD patients with lower serum soluble \(\alpha\)-klotho levels \((\leq 1.15\ \text{ng/mL})\) had significantly higher 3-year all-cause mortality rates and shorter overall survival. Low soluble \(\alpha\)-klotho level was an independent predictor of all-cause mortality in MHD patients after adjusting for potential confounding factors. Patients with low soluble \(\alpha\)-klotho had significantly higher 3-year all-cause mortality rates compared with patients with high soluble \(\alpha\)-klotho.

Cardio-cerebrovascular mortality is the main component of all-cause mortality in MHD patients, followed by infectious diseases and malignancies\textsuperscript{30}. In this study, the 3-year cardio-cerebrovascular mortality rates between the two groups was not
significant. However, the Kaplan-Meier analysis showed cardio-cerebrovascular event-free survival as well as OS in the low soluble α-klotho group was significantly lower than that in the high soluble α-klotho group. The reason causing this difference may be related to the insufficient cardio-cerebrovascular events we have collected. The Cox regression analyses revealed that soluble α-klotho, serum calcium, serum phosphate and PTH levels could significantly affect all-cause mortality in MHD patients. After adjusting for serum calcium, serum phosphate and PTH, a low soluble α-klotho level remained an independent predictor of all-cause mortality. Previous studies showed that increased levels FGF23 was associated with poor survival of CKD patients[^31,^32]. However, in this study, we did not find any correlation between FGF23 levels and all-cause mortality in MHD patients, consistent with the findings reported in Naoko’s study[^17].

Another issue of concern is that the cut-off value to distinguish low and high soluble α-klotho is not uniform between our study and previous studies. Naoko and colleagues considered a klotho level of >449 pg/ml (equivalent to 0.449 ng/ml) as high[^17]. Yu et al. reported that high soluble α-klotho level should exceed 1.34 ng/mL[^27]. In this study, we found the cut-off value to distinguish low and high soluble α-klotho was 1.15 ng/mL. The difference of detection method for soluble α-klotho may contribute to this phenomenon. The difference in race and characteristics of enrolled patients may also result in this phenomenon.

There are several limitations to this study. First, the follow-up period of this study was not long enough. Thus, we did not collect sufficient events of all-cause
death and cardio-cerebrovascular death. Second, the sample size of this study was relatively small and all patients were from a single center. Third, vascular and soft tissue calcification was not evaluated in MHD patients in this study. Thus, the correlation between soluble α-klotho and vascular calcification is not clear. Furthermore, repeated blood samples were not taken in this study. Thus, we can not exclude the possible intraindividual variations of soluble α-klotho levels.

5. Conclusions

In conclusion, we found that soluble α-klotho, serum calcium, serum phosphate and PTH levels could significantly affect all-cause mortality in MHD patients. After adjusting for serum calcium, serum phosphate and PTH, a low soluble α-klotho level remained an independent predictor of all-cause mortality. Thus, serum soluble α-klotho level could be a potential predictive factor for prognosis of patients with MHD. In this study, we found the cut-off value to distinguish low and high soluble α-klotho was 1.15 ng/mL, but we did not find any correlation between FGF23 levels and all-cause mortality in MHD patients.

References


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360 584-592.

Figure legends:

Figure 1:

(A) Kaplan-Meier curves of overall survival according to median soluble $\alpha$-klotho level;

(B) Kaplan-Meier curves of cardio-cerebrovascular death free survival according to median soluble $\alpha$-klotho level.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble α-klotho (low/high)</td>
<td>2.324 (1.070-5.047)</td>
<td>0.029</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>1.076 (0.509-2.276)</td>
<td>0.848</td>
</tr>
<tr>
<td>Age</td>
<td>0.995 (0.967-1.023)</td>
<td>0.706</td>
</tr>
<tr>
<td>BMI</td>
<td>0.957 (0.834-1.098)</td>
<td>0.533</td>
</tr>
<tr>
<td>SBP</td>
<td>1.010 (0.995-1.025)</td>
<td>0.196</td>
</tr>
<tr>
<td>DBP</td>
<td>1.018 (0.998-1.038)</td>
<td>0.077</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1.004 (0.975-1.034)</td>
<td>0.790</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.951 (0.870-1.039)</td>
<td>0.268</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>0.316 (0.153-0.654)</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>4.958 (1.470-16.730)</td>
<td>0.010</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>1.010 (1.003-1.016)</td>
<td>0.002</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>1.006 (0.998-1.013)</td>
<td>0.134</td>
</tr>
<tr>
<td>FGF23</td>
<td>0.822 (0.595-1.135)</td>
<td>0.234</td>
</tr>
<tr>
<td>Primary diseases</td>
<td>1.143 (0.897-1.457)</td>
<td>0.281</td>
</tr>
</tbody>
</table>

Note: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PTH, parathyroid hormone; ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23.
<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total (n=134)</th>
<th>Low soluble α-klotho group (n=68)</th>
<th>High soluble α-klotho group (n=66)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>62 (46.27)</td>
<td>32 (47.06)</td>
<td>30 (45.45)</td>
<td>0.852</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.12 ± 14.75</td>
<td>45.97 ± 14.19</td>
<td>50.33 ± 15.21</td>
<td>0.088</td>
</tr>
<tr>
<td>BMI (mg/m²)</td>
<td>22.97 ± 2.68</td>
<td>22.95 ± 2.39</td>
<td>23.00 ± 2.87</td>
<td>0.921</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>158.03 ± 22.71</td>
<td>161.44 ± 26.14</td>
<td>154.52 ± 18.53</td>
<td>0.080</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>90.10 ± 14.83</td>
<td>92.00 ± 17.80</td>
<td>88.15 ± 11.10</td>
<td>0.137</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>113±17.34</td>
<td>108±18.63</td>
<td>110±13.51</td>
<td>0.124</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>83.52 ± 12.54</td>
<td>83.18 ± 12.42</td>
<td>83.88 ± 13.22</td>
<td>0.753</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>38.11 ± 4.32</td>
<td>38.58 ± 4.80</td>
<td>37.62 ± 3.71</td>
<td>0.198</td>
</tr>
<tr>
<td>Serum calcium (mmol/L)</td>
<td>2.07 ± 0.28</td>
<td>2.02 ± 0.26</td>
<td>2.11 ± 0.29</td>
<td>0.060</td>
</tr>
<tr>
<td>Serum phosphate (mmol/L)</td>
<td>1.89 ± 0.32</td>
<td>1.89 ± 0.35</td>
<td>1.88 ± 0.27</td>
<td>0.846</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>297.54 ± 60.18</td>
<td>298.74 ± 61.68</td>
<td>296.32 ± 59.10</td>
<td>0.817</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>96.90 ± 39.01</td>
<td>98.21 ± 32.77</td>
<td>95.55 ± 50.56</td>
<td>0.718</td>
</tr>
<tr>
<td>Primary diseases, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.603</td>
</tr>
<tr>
<td>Untrolled BP n (%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP&gt;160/90</td>
<td>80(60)</td>
<td>43(63.2)</td>
<td>37(56.1)</td>
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</tr>
<tr>
<td>140/90≤BP≤160/90</td>
<td>27(20)</td>
<td>15(22.1)</td>
<td>12(18.2)</td>
<td></td>
</tr>
<tr>
<td>130/90≤BP&lt;140/90</td>
<td>20(15)</td>
<td>7(10.3)</td>
<td>13(19.6)</td>
<td></td>
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<tr>
<td>BP&lt;110/60</td>
<td>7(5)</td>
<td>3(4.4)</td>
<td>4(6.1)</td>
<td></td>
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<tr>
<td>Hypertensive kidney lesions</td>
<td>56 (41.79)</td>
<td>26 (38.24)</td>
<td>30 (45.45)</td>
<td></td>
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<tr>
<td>Diabetic nephropathy</td>
<td>12 (8.96)</td>
<td>8 (11.76)</td>
<td>4 (6.06)</td>
<td></td>
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<tr>
<td>Glomerulonephritis</td>
<td>44 (32.84)</td>
<td>24 (35.29)</td>
<td>20 (30.30)</td>
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</tr>
<tr>
<td></td>
<td>Polycystic kidney</td>
<td></td>
<td>Others</td>
<td>FGF23 (pg/mL)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-------------------</td>
<td>----------------------------------------</td>
<td>--------</td>
<td>---------------</td>
</tr>
<tr>
<td>History of cardiovascular events</td>
<td>12 (8.96)</td>
<td>6 (8.82)</td>
<td>10 (7.46)</td>
<td>521.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(424.34, 692.13)</td>
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<td></td>
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<td></td>
<td></td>
<td>(454.56, 698.52)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(413.75, 571.45)</td>
</tr>
</tbody>
</table>

Note: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PTH, parathyroid hormone; ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23.
A

Overall survival (%)

Logrank p=0.019

B

Cardio-cerebrovascular death-free survival

Logrank p=0.046

Soluble α-klotho > 1.15 ng/mL

Soluble α-klotho ≤ 1.15 ng/mL