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Association of α-Klotho Levels with Clinical and Laboratory Parameters and Cardiorenal Outcomes in Patients with ACS Following PCI

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Abstract

Background: Whether plasma α-Klotho carries prognostic value in patients with acute coronary syndrome (ACS) who undergo percutaneous coronary intervention (PCI) is still unclear. Objectives: We set out to examine the links between plasma α-Klotho levels, routine clinical and laboratory findings, the occurrence of acute kidney injury (AKI), and cardiovascular mortality after PCI. **Methods:** Eighty-six patients with ACS treated by PCI were enrolled in this prospective study. Plasma α-Klotho was measured within 48 h of the procedure. Relationships were assessed by correlation analysis and logistic regression; cardiovascular mortality was tracked for 12 months. **Results:** Acute kidney injury developed in 30 patients (34.9%), and nine cardiovascular deaths (10.5%) occurred during the year of follow-up. α-Klotho showed positive correlations with platelet count, triglycerides and total protein, and inverse correlations with FIB-4, aspartate aminotransferase, creatinine, GRACE score, contrast volume and international normalized ratio. No significant link was found between α-Klotho and AKI ($p = 0.882$). Erythrocyte sedimentation rate (OR = 1.090; $p < 0.001$) and contrast volume (OR = 1.014; $p = 0.007$) remained independently associated with AKI. In univariable analysis higher α-Klotho levels were linked to lower cardiovascular mortality (OR = 0.648; $p = 0.009$). **Conclusions:** Higher plasma α-Klotho concentrations were associated with reduced odds of cardiovascular death in the univariable model. No association with AKI was detected. The mortality results should be regarded as exploratory and do not demonstrate an independent prognostic role.

Keywords: acute coronary syndrome; percutaneous coronary intervention; α-Klotho; acute kidney injury; cardiovascular mortality; biomarker; risk stratification

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1. Introduction

Despite advances in modern cardiology, cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide [1,2]. Acute coronary syndrome (ACS) comprises a spectrum of conditions caused by acute myocardial ischemia, including unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) [3]. α-Klotho is a transmembrane protein encoded by the KL gene that plays an important role in the regulation of aging. The gene was first identified in 1997, and reduced expression has been linked to premature aging phenotypes in experimental animals [4]. α-Klotho also exhibits cardioprotective and vasculoprotective properties. It has antioxidant, anti-inflammatory, and endothelial-protective effects and contributes to the maintenance of vascular homeostasis and the regulation of mineral metabolism [5]. Clinical studies have shown that lower α-Klotho levels are associated with an increased risk of cardiovascular mortality, hospitalization for heart failure, and progression of cardiovascular disease [6,7]. In both acute and chronic kidney injury, α-Klotho levels are markedly reduced in renal tissue, blood, and urine. Experimental studies have also shown that exogenous α-Klotho promotes renal tissue recovery and exerts significant renoprotective effects [8]. The 2023 European Society of Cardiology (ESC) Guidelines for the management of acute coronary syndromes highlight remaining gaps in personalized medicine, risk stratification, and the identification of novel biomarkers [3]. In this context, further investigation of α-Klotho as a potential marker of adverse outcomes appears warranted. Accordingly, we conducted a prospective, single-center study to evaluate the associations between plasma α-Klotho levels and clinical and laboratory parameters, the development of acute kidney injury, and cardiovascular mortality in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI).

2. Materials and Methods

This prospective clinical study enrolled 86 patients with acute coronary syndrome who were admitted to the Cardiology Department of the Emergency Hospital in Semey, Republic of Kazakhstan, from August 2024 to August 2025. Diagnosis of ACS followed the 2023 European Society of Cardiology (ESC) guidelines. All patients underwent percutaneous coronary intervention with stenting of the infarct-related artery. Patients were included if they had acute coronary syndrome, with or without ST-segment elevation, and hemodynamically significant coronary artery disease that required PCI according to the findings of coronary angiography. Exclusion criteria included end-stage chronic kidney disease requiring maintenance hemodialysis, malignancy, and refusal to participate.

The study adhered to the principles of the Declaration of Helsinki and received approval from the Local Bioethics Committee of Semey Medical University (Protocol No. 16 of 2 November 2023). Written informed consent was obtained from all participants before they entered the study.

Venous blood for α-Klotho measurement was taken within 48 h after PCI into EDTA vacuum tubes. Samples were centrifuged at 1000 rpm for 15 min using a CM-6M centrifuge (Sky Line, (ELMI Ltd., Riga, Latvia)). Plasma was separated and stored at −80 °C until analysis. α-Klotho levels in plasma were determined using a commercial Human KL (Klotho) ELISA Kit (Elabscience Biotechnology Inc., Houston, TX, USA; catalog No. E-EL-H5451). Each sample was analyzed in a single measurement without technical duplicates. Optical density readings were obtained at 450 nm on a Bio-Rad Model 680 microplate reader (Bio-Rad Laboratories, Inc., Hercules, CA, USA). Concentrations of α-Klotho were calculated from the calibration curve and reported in ng/mL. The manufacturer states that the assay has an analytical sensitivity of 0.19 ng/mL, a working range of 0.31–20 ng/mL, and both intra- and inter-assay coefficients of variation under 10%.

The primary endpoint was post-PCI acute kidney injury (AKI). Creatinine was measured before the procedure to set the baseline and again within 48 h afterwards. AKI was defined by the 2012 KDIGO [9] criteria as a rise in creatinine of at least 26.5 µmol/L within 48 h of PCI compared with the pre-procedural value. Renal function was also evaluated by calculating creatinine clearance with the Cockcroft–Gault formula.

Secondary endpoints comprised death during the index hospital stay and cardiovascular death within 12 months after the index PCI. Recruitment ran from August 2024 to August 2025; each patient was followed for 12 months after PCI, so follow-up of the last participant finished in August 2026. Vital status of all 86 patients was checked through the Population Attachment Register by means of the individual identification number (IIN) for the entire 12-month period after PCI.

Vital status was successfully ascertained for all 86 patients at 12 months. Vital status ascertainment included patients who had not been readmitted during follow-up. When a death was registered, the date was taken from the register and the cause, place and circumstances were later verified from the hospital records and discharge summaries. Deaths were labelled cardiovascular if that was the cause stated in the documents. In the present cohort the recorded causes were myocardial infarction and post-infarction cardiosclerosis. Deaths that occurred during the index hospitalization were counted in the 12-month cardiovascular mortality endpoint.

Statistical Analysis

Statistical analyses were carried out with IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was checked by the Kolmogorov–Smirnov test. Variables that followed a normal distribution are shown as mean ± standard deviation (M ± SD); those that did not are given as median (Me) with interquartile range (Q1–Q3). When the assumptions were satisfied, means of two independent groups were compared by Student's *t*-test; otherwise, the Mann–Whitney U test was used. Relationships between continuous variables were evaluated with Spearman's rank correlation coefficient. Univariable binary logistic regression was applied to explore links between clinical and laboratory parameters and both acute kidney injury (AKI) and cardiovascular mortality. Multivariable modelling was performed only for the AKI endpoint. Given the small number of cardiovascular deaths ($n = 9$), mortality analyses were restricted to exploratory unadjusted associations, and no multivariable mortality model was reported. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). The multivariable AKI model was built by forward stepwise selection that used the likelihood-ratio criterion. Entry and removal thresholds in the SPSS syntax were set at 0.05 and 0.10, respectively. Discriminative ability was examined with receiver-operating-characteristic (ROC) curves; areas under the curve (AUCs) and their 95% confidence intervals were calculated. Exploratory cut-off values for cardiovascular mortality were determined from the study cohort by maximising the Youden index (sensitivity + specificity − 1). Lower values of α-Klotho, total protein, and left ventricular ejection fraction were associated with cardiovascular death. These data-derived thresholds have not been validated in an independent sample. A two-sided *p*-value below 0.05 was considered statistically significant.

3. Results

The study included 86 patients with acute coronary syndrome who underwent percutaneous coronary intervention (PCI). The mean age was 63.3 ± 9.6 years, ranging from 35 to 86 years. Of these, 60 patients (69.8%) were men, with a mean age of 62.7 ± 9.2 years, and 26 (30.2%) were women, with a mean age of 64.6 ± 10.6 years. Plasma concentrations

of soluble α-Klotho ranged from 0.31 to 17.34 ng/mL. The median α-Klotho concentration was 5.18 ng/mL (interquartile range: 1.04–5.94 ng/mL).

Nine cardiovascular deaths occurred during the 12-month follow-up (10.5%). Two patients died from myocardial infarction during the index hospitalization (index-hospitalization mortality 2.3%, 2/86). Seven patients died during subsequent hospitalizations; post-infarction cardiosclerosis was the cause of death documented in their medical records and discharge summaries. The correlations between plasma α-Klotho levels and clinical and laboratory parameters are presented in Table 1.

Table 1. Correlations between plasma α-Klotho and clinical and laboratory parameters.

Variable	ϱs	*p*-Value
Platelets, $\times 10^9$/L	0.393	<0.001
FIB-4 index	−0.377	<0.001
AST, U/L	−0.216	0.045
Creatinine, μmol/L	−0.243	0.024
GRACE score	−0.312	0.003
Triglycerides, mmol/L	0.236	0.028
Contrast volume, mL	−0.266	0.013
INR	−0.239	0.026
Total protein, g/L	0.326	0.002

Values are Spearman's rank correlation coefficients. *p*-values < 0.05 are shown in bold. ϱs, Spearman's rank correlation coefficient; *p*, level of statistical significance; FIB-4, Fibrosis-4 Index (liver fibrosis index); AST, aspartate aminotransferase; GRACE, Global Registry of Acute Coronary Events risk score; INR, international normalized ratio.

The clinical and laboratory characteristics of patients with and without acute kidney injury are presented in Table 2.

Table 2. Characteristics of patients with and without acute kidney injury.

Variable	Without AKI (*n* = 56)	AKI (*n* = 30)	*p*
Clinical, demographic, and medical history characteristics			
Age, years	62.4 ± 9.2 (35–79)	64.8 ± 10.4 (46–86)	0.269 *
Sex, male/female, *n* (%)	36/20 (64.3/35.7)	24/6 (80.0/20.0)	0.130 [a]
BMI, kg/m^2	27.68 (24.68–30.35)	25.66 (24.22–29.12)	0.213 **
Smoking, *n* (%)	48 (85.7)	28 (93.3)	0.483 [b]
History of stroke, *n* (%)	1 (1.8)	4 (13.3)	0.048 [b]
Arterial hypertension, *n* (%)	54 (96.4)	30 (100)	0.540 [b]
Diabetes mellitus, *n* (%)	10 (17.9)	9 (30.0)	0.196 [a]
Chronic ischemic heart disease, *n* (%)	38 (67.9)	24 (80)	0.231 [a]
Post-infarction cardiosclerosis, *n* (%)	9 (16.1)	6 (20)	0.647 [a]
Atrial fibrillation, *n* (%)	9 (16.1)	2 (6.7)	0.315 [b]
Chronic kidney disease stage			
Stage 1, *n* (%)	18 (32.1)	2 (6.7)	0.008 [a]
Stage 2, *n* (%)	26 (46.4)	15 (50.0)	0.752 [a]
Stage 3, *n* (%)	12 (21.4)	11 (36.7)	0.128 [a]
Stage 4, *n* (%)	0 (0.0)	2 (6.7)	0.119 [b]
Hemodynamic and clinical characteristics			
SBP, mmHg	130 (112.5–140)	130 (90–142.5)	0.637 **
DBP, mmHg	80 (50–90)	80 (60–90)	0.586 **
Heart rate, beats/min	73 (67–88)	72 (68–86)	0.931 **
ST-segment elevation, *n* (%)	32 (57.1)	12 (40)	0.130 [a]

Table 2. *Cont.*

Variable	Without AKI ($n = 56$)	AKI ($n = 30$)	p
Antiplatelet therapy			
Clopidogrel, n (%)	8 (14.3)	10 (33.3)	0.039 [a]
Ticagrelor, n (%)	47 (83.9)	20 (66.7)	0.100 [b]
Complete blood count and inflammatory markers			
Hemoglobin, g/L	136 (119–146)	114 (92–135)	0.008 **
Hematocrit, %	40.6 (35.5–43.6)	36 (28.9–40)	0.009 **
Red blood cells, $\times 10^{12}$/L	4.5 ± 0.82 (1.85–6.12)	3.9 ± 0.87 (2.49–6.36)	0.002 *
WBC, $\times 10^{9}$/L	9.45 (8.13–12.44)	10.65 (7.92–15.46)	0.213 **
ESR, mm/h	13 (4–21)	33.5 (15.5–42.25)	<0.001 **
Platelets, $\times 10^{9}$/L	243.5 (198.5–277.3)	218.5 (177.5–286.5)	0.195 **
MCV, fL	89.3 (86–92.2)	90.4 (87.1–93.5)	0.184 **
MCH, pg	29.4 (28.2–30.5)	29.5 (28–30.3)	0.878 **
MCHC, g/L	327.43 ± 11.6 (293–352)	325.8 ± 10.9 (311–349)	0.321 *
Biochemical parameters			
α-Klotho, ng/mL	5.22 (2.99–5.90)	5.13 (0.69–5.98)	0.562 **
LDL-C, mmol/L	2.47 (1.78–3.36)	2.26 (1.58–2.63)	0.146 **
HDL-C, mmol/L	1.05 (0.9–1.23)	0.99 (0.82–1.06)	0.042
Total cholesterol, mmol/L	5.0 ± 1.48 (2.44–9.37)	4.53 ± 1.11 (2.64–7.23)	0.127 *
Triglycerides, mmol/L	1.48 (0.99–2.25)	1.39 (1.0–2.09)	0.786 **
C-reactive protein, mg/L	4.53 (2.1–15.12)	8.76 (3.0–36.0)	0.034 **
Glucose, mmol/L	6.18 (5.34–8.16)	6.52 (5.75–7.93)	0.362 **
ALT, U/L	27.6 (19.93–42.98)	33.2 (18.48–52.25)	0.670 **
AST, U/L	32.2 (23.7–85.73)	37.4 (23.8–80.8)	0.436 **
FIB-4	1.67 (1.05–3.94)	2.32 (1.35–4.75)	0.166 **
Potassium, mmol/L	3.9 (3.6–4.1)	3.85 (3.68–4.1)	0.564 **
Sodium, mmol/L	140 (137.25–144)	140 (138.75–142.25)	0.906 **
Calcium, mmol/L	2.2 (2.08–2.33)	2.22 (2.05–2.33)	0.942 **
Magnesium, mmol/L	0.775 (0.75–0.84)	0.83 (0.75–0.97)	0.078 **
Urea, mmol/L	6.39 (5.07–7.65)	7.15 (5.89–9.69)	0.055 **
CK-MB	19.4 (11.0–32.0)	22.0 (13.28–124.5)	0.626 **
Hemostasis and platelet function			
ADP-induced platelet aggregation, %	34.9 (29.7–63.4)	53.8 (34.3–65.6)	0.029 **
D-dimer, mg/L FEU	0.51 (0.30–0.95)	0.64 (0.39–1.47)	0.200 **
aPTT, s	26.0 (23–41.25)	26.0 (10–30)	0.422 **
Procedural characteristics			
Contrast volume, mL	200 (150–200)	200 (200–225)	0.006 **

p-values < 0.05 are shown in bold. * Student's t-test; data are presented as mean ± standard deviation (M ± SD), with minimum and maximum values indicated. ** Mann–Whitney U test; data are presented as median (Me) and interquartile range (Q1–Q3). Categorical variables are presented as absolute numbers of patients, n (%). [a] Pearson's chi-square (χ^2) test; [b] Fisher's exact test. AKI, acute kidney injury; ESR, erythrocyte sedimentation rate; ADP, adenosine diphosphate; CKD, chronic kidney disease; FIB-4, Fibrosis-4 Index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; HTN, arterial hypertension; DM, diabetes mellitus; IHD, ischemic heart disease; WBC, white blood cell count; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase-MB isoenzyme; aPTT, activated partial thromboplastin time; stroke, acute cerebrovascular event; PICS, post-infarction cardiosclerosis; AF, atrial fibrillation.

In univariable analysis, six variables were significantly associated with AKI (Table 3). In the final stepwise model, higher ESR (adjusted OR 1.090, 95% CI 1.046–1.136; $p < 0.001$) and greater contrast volume (adjusted OR 1.014, 95% CI 1.004–1.025; $p = 0.007$) remained associated with AKI. α-Klotho was not significantly associated with AKI in univariable analysis ($p = 0.882$).

Table 3. Univariable and multivariable logistic regression analyses of acute kidney injury.

Variable	Univariable OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value
α-Klotho, ng/mL	1.010 (0.890–1.146)	0.882	—	—
Hemoglobin, g/L	0.979 (0.962–0.996)	0.018	—	—
Hematocrit, %	0.931 (0.874–0.992)	0.027	—	—
Red blood cells, $\times 10^{12}$/L	0.414 (0.230–0.744)	0.003	—	—
ESR, mm/h	1.082 (1.042–1.123)	<0.001	1.090 (1.046–1.136)	<0.001
ADP-induced platelet aggregation, %	1.026 (1.001–1.051)	0.041	—	—
Contrast volume, mL	1.012 (1.003–1.021)	0.011	1.014 (1.004–1.025)	0.007

Values are odds ratios (ORs) with 95% confidence intervals (CIs). *p*-values < 0.05 are shown in bold. A dash indicates that an adjusted estimate is not reported for that variable. The final stepwise model included ESR and contrast volume. ESR, erythrocyte sedimentation rate; ADP, adenosine diphosphate.

The ROC curves for erythrocyte sedimentation rate (ESR) and contrast volume in predicting acute kidney injury are presented in Figure 1.

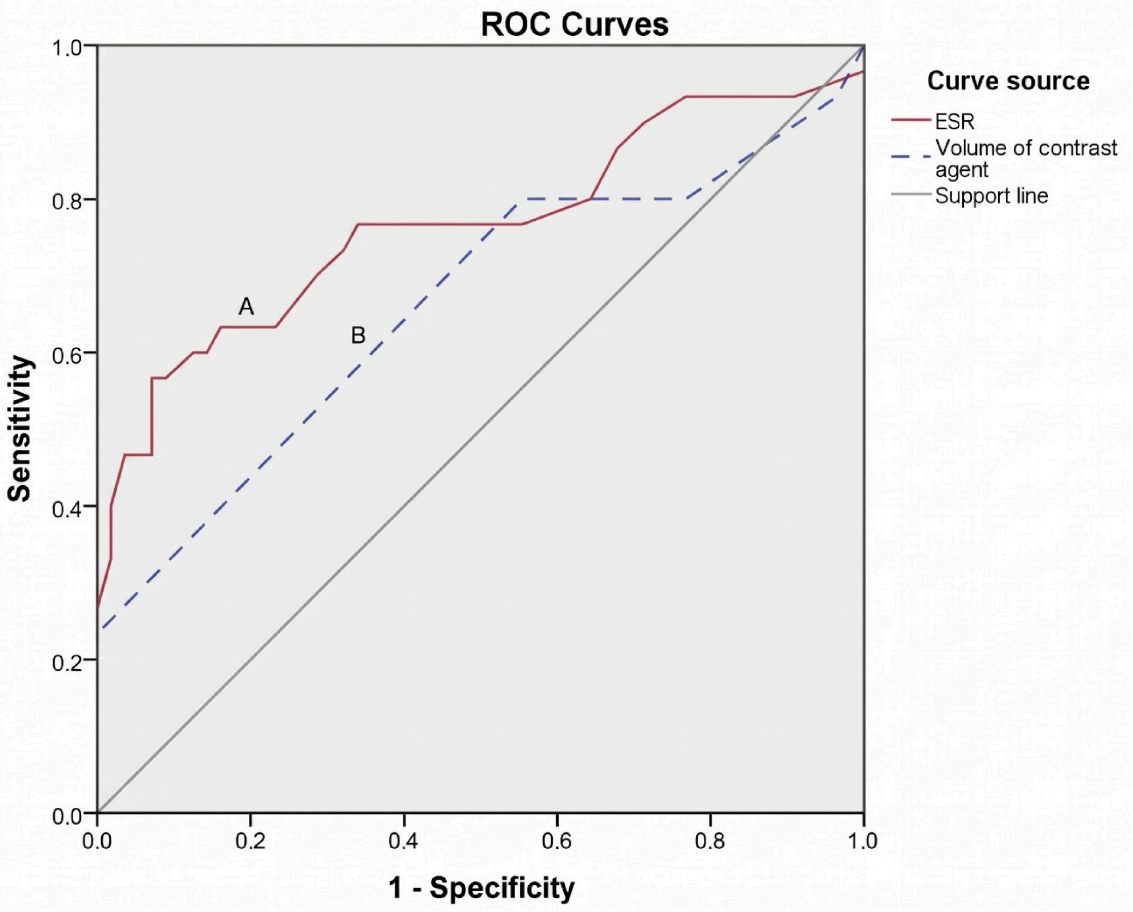

Figure 1. ROC curves of erythrocyte sedimentation rate (ESR) and contrast volume for acute kidney injury.

ROC analysis showed statistically significant discrimination for both markers. The AUC was 0.765 for ESR (95% CI: 0.646–0.884; $p < 0.001$) and 0.662 for contrast volume (95% CI: 0.532–0.792; $p = 0.014$).

No statistically significant difference in α-Klotho concentrations was observed between patients with and without AKI (Table 2), consistent with the univariable regression result in Table 3. The clinical and laboratory characteristics of patients with and without cardiovascular mortality are presented in Table 4.

Table 4. Characteristics of survivors and patients who died from cardiovascular causes.

Variable	Without Cardiovascular Mortality (n = 77)	With Cardiovascular Mortality (n = 9)	p
Age, years	63.0 ± 9.6 (35–86)	65.1 ± 10.6 (52–84)	0.589 *
Sex, male/female, n (%)	52/25 (67.5/32.5)	8/1 (88.9/11.1)	0.266 [b]
BMI, kg/m^2	27.44 (24.73–29.59)	29.03 (23.44–32.39)	0.621 **
Smoking, n (%)	67(87)	9(100)	0.590 [b]
History of stroke, n (%)	4(5.2)	1(11.1)	0.433
Arterial hypertension, n (%)	75(97.4)	9(100)	1.000 [b]
Diabetes mellitus, n (%)	16(20.8)	3 (33.3)	0.407 [b]
Chronic ischemic heart disease, n (%)	57 (74)	5 (55.6)	0.258 [b]
Post-infarction cardiosclerosis, n (%)	14 (18.2)	1(11.1)	1.000 [b]
Atrial fibrillation, n (%)	9(11.7)	2 (22.2)	0.323 [b]
Acute kidney injury, n (%)	23 (29.9)	7 (77.8)	0.008 [b]
GRACE score	122 (99.5–145.5)	158 (126.5–174)	0.009 **
Hemodynamic and clinical characteristics			
SBP, mmHg	130 (120–140)	90 (85–125)	0.013 **
DBP, mmHg	80 (80–90)	60 (50–80)	0.011 **
Heart rate, beats/min	74 (68–86)	70 (59–100)	0.955 **
Left ventricular ejection fraction, %	54 (46–58)	41 (32–46)	<0.001 **
Left ventricular mass index, g/m^2	75.7 (66.0–90.6)	88.9 (77.5–133.3)	0.041 **
ST-segment elevation, n (%)	37(48.1)	7(77.8)	0.157 [b]
Antiplatelet therapy			
Clopidogrel, n (%)	16 (20.8)	2 (22.2)	1.000 [b]
Ticagrelor, n (%)	60 (77.9)	7 (77.8)	1.000 [b]
Complete blood count and inflammatory markers			
Hemoglobin, g/L	129 (109–144.5)	116.6 (88–145)	0.306 **
Hematocrit, %	38.8 (32.3–43.0)	37 (28.4–43.2)	0.352 **
Red blood cells, ×10^{12}/L	4.3 ± 0.82 (2.49–6.12)	4.0 ± 1.32 (1.85–6.36)	0.487 *
WBC, ×10^9/L	9.58 (8.07–13.21)	12.24 (8.96–15.06)	0.225 **
ESR, mm/h	17.0 (6.5–30.5)	19.0 (3.0–40.5)	0.877 **
Platelets, ×10^9/L	240 (194–287)	190 (121.2–267.0)	0.187 **
MCV, fL	89.8 (86.9–92.2)	91.4 (86.7–116.4)	0.370 **
MCH, pg	29.4 (28.4–30.5)	27.7 (26.2–30.6)	0.413 **
MCHC, g/L	326 (320–333)	319 (315–337.5)	0.296 **
Biochemical parameters			
α-Klotho, ng/mL	5.26 (3.16–6.09)	1.02 (0.31–4.05)	0.003 **
NT-proBNP, pg/mL	321.5 (98.0–795.1)	2033.2 (1401.1–14,598.5)	<0.001 **
LDL-C, mmol/L	2.39 (1.68–3.27)	2.29 (1.45–2.95)	0.558 **
HDL-C, mmol/L	1.02 (0.89–1.20)	1.02 (0.78–1.28)	0.762 **
Total cholesterol, mmol/L	4.87 ± 1.41 (2.44–9.37)	4.51 ± 1.0 (2.64–6.09)	0.353 *
Triglycerides, mmol/L	1.49 (1.0–2.33)	1.2 (0.90–1.81)	0.236 **
C-reactive protein, mg/L	5.7 (2.1–17.03)	6.0 (2.2–63.02)	0.805 **
Glucose, mmol/L	6.26 (5.46–7.88)	6.3 (5.83–9.11)	0.568 **
ALT, U/L	27.7 (18.8–43.9)	47.6 (20.9–218.2)	0.182 **
AST, U/L	34.5 (22.7–84.1)	32.8 (25.9–244.4)	0.568 **
FIB-4	1.75 (1.09–3.99)	2.43 (1.4–5.08)	0.378 **
Potassium, mmol/L	3.9 (3.6–4.1)	3.9 (3.65–4.5)	0.321 **
Sodium, mmol/L	140 (138–144)	140 (138.5–142.5)	0.843 **
Calcium, mmol/L	2.20 ± 0.19 (1.44–2.48)	2.06 ± 0.17 (1.75–2.25)	0.034 *
Magnesium, mmol/L	0.8 (0.75–0.88)	0.76 (0.72–0.86)	0.381 **
Urea, mmol/L	6.4 (5.13–7.84)	11.79 (6.62–14.52)	0.006 **
Creatinine, μmol/L	93.9 (79.35–103.7)	120 (108.25–237.1)	0.003 **
Total protein, g/L	65.76 ± 6.99 (49.4–86.4)	54.18 ± 7.79 (41.7–63.6)	0.002 *

Table 4. *Cont.*

Variable	Without Cardiovascular Mortality (n = 77)	With Cardiovascular Mortality (n = 9)	p
Hemostasis and platelet function			
ADP-induced platelet aggregation	37.6 (30.1–63.9)	60.4 (29.7–66.6)	0.719 **
D-dimer, mg/L FEU	0.54 (0.32–0.97)	0.56 (0.43–1.29)	0.558 **
aPTT, s	26.0 (23.0–35.5)	30.0 (25.5–38.5)	0.381 **
Procedural characteristics			
Contrast volume, mL	200.0 (150–200)	300.0 (200–300)	<0.001 **

p-values < 0.05 are shown in bold. * Student's t-test; data are presented as mean ± standard deviation (M ± SD), with minimum and maximum values indicated. ** Mann–Whitney U test; data are presented as median (Me) and interquartile range (Q1–Q3). Categorical variables are presented as absolute numbers of patients, n (%), and were compared using Pearson's chi-square (χ^2) test or Fisher's exact test, as appropriate. [b] Fisher's exact test. AKI, acute kidney injury; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; GRACE, Global Registry of Acute Coronary Events risk score; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, Fibrosis-4 Index; ADP, adenosine diphosphate; aPTT, activated partial thromboplastin time.

Univariable binary logistic regression analysis identified statistically significant associations between cardiovascular mortality and 13 clinical, laboratory, and instrumental parameters.

Of particular interest was α-Klotho, which showed a significant inverse association with cardiovascular mortality (OR = 0.648; 95% CI: 0.468–0.897; $p = 0.009$). Higher α-Klotho concentrations were associated with lower odds of cardiovascular death.

Higher odds of cardiovascular mortality were also associated with increasing mean corpuscular volume (MCV) (OR = 1.058; 95% CI: 1.008–1.111; $p = 0.023$), urea (OR = 1.571; 95% CI: 1.153–2.139; $p = 0.004$), creatinine (OR = 1.031; 95% CI: 1.006–1.057; $p = 0.015$), alanine aminotransferase (ALT) (OR = 1.013; 95% CI: 1.002–1.024; $p = 0.018$), GRACE score (OR = 1.024; 95% CI: 1.005–1.044; $p = 0.011$), left ventricular mass index (LVMI) (OR = 1.040; 95% CI: 1.011–1.069; $p = 0.006$), and contrast volume (OR = 1.036; 95% CI: 1.017–1.055; $p < 0.001$).

Conversely, higher diastolic blood pressure (OR = 0.939; 95% CI: 0.896–0.984; $p = 0.008$), platelet count (OR = 0.990; 95% CI: 0.980–1.000; $p = 0.043$), calcium concentration (OR = 0.030; 95% CI: 0.001–0.950; $p = 0.047$), left ventricular ejection fraction (LVEF) (OR = 0.849; 95% CI: 0.772–0.935; $p = 0.001$), and total protein concentration (OR = 0.821; 95% CI: 0.734–0.917; $p = 0.001$) were associated with lower odds of cardiovascular mortality.

Given the small number of cardiovascular deaths ($n = 9$), the mortality analysis was restricted to univariable logistic regression. These findings should be regarded as exploratory, as the absence of multivariable adjustment precludes determining whether the observed associations are independent of other clinical risk factors. Univariable binary logistic regression analysis identified statistically significant associations between cardiovascular mortality and 13 clinical, laboratory, and instrumental parameters (Table 5).

Table 5. Univariable logistic regression analysis of cardiovascular mortality.

Variable	Univariable OR (95% CI)	*p*-Value
α-Klotho, ng/mL	0.648 (0.468–0.897)	0.009
MCV, fL	1.058 (1.008–1.111)	0.023
Urea, mmol/L	1.571 (1.153–2.139)	0.004
Creatinine, μmol/L	1.031 (1.006–1.057)	0.015
ALT, U/L	1.013 (1.002–1.024)	0.018
GRACE score	1.024 (1.005–1.044)	0.011
LVMI, g/m^2	1.040 (1.011–1.069)	0.006
Contrast volume, mL	1.036 (1.017–1.055)	<0.001
DBP, mmHg	0.939 (0.896–0.984)	0.008
Platelets, ×10^9/L	0.990 (0.980–1.000)	0.043
Calcium, mmol/L	0.030 (0.001–0.950)	0.047
LVEF, %	0.849 (0.772–0.935)	0.001
Total protein, g/L	0.821 (0.734–0.917)	0.001

Values are unadjusted odds ratios (ORs) with 95% confidence intervals (CIs). *p*-values < 0.05 are shown in bold. MCV, mean corpuscular volume; ALT, alanine aminotransferase; GRACE, Global Registry of Acute Coronary Events; LVMI, left ventricular mass index; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction.

The ROC curves for mean corpuscular volume (MCV), plasma α-Klotho, left ventricular ejection fraction (LVEF), and total protein in relation to cardiovascular mortality are presented in Figure 2.

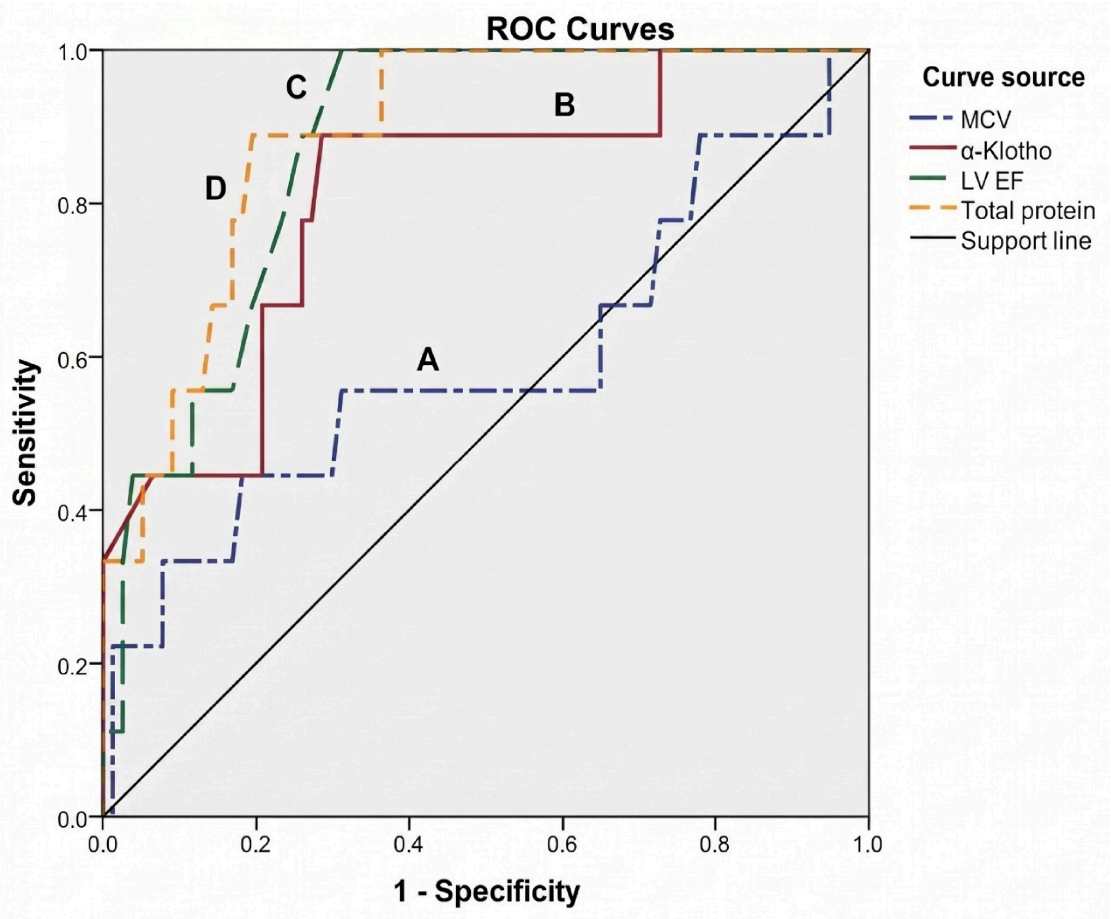

Figure 2. ROC curves of mean corpuscular volume (MCV), plasma α-Klotho, left ventricular ejection fraction (LVEF), and total protein for cardiovascular mortality.

ROC analysis using the Youden index identified exploratory cutoffs for distinguishing patients who died from cardiovascular causes from survivors during the 12-month follow-up. For plasma α-Klotho, the cutoff was 4.13 ng/mL; lower concentrations were associated with cardiovascular death (AUC = 0.799; 95% CI: 0.650–0.948; $p = 0.003$). MCV did not show statistically significant discrimination (AUC = 0.592; 95% CI: 0.360–0.823; $p = 0.370$). For total protein, the cutoff was 61.285 g/L; lower concentrations were associated with cardiovascular death (AUC = 0.889; 95% CI: 0.802–0.976; $p < 0.001$). For LVEF, the cutoff was 48.5%; lower values were associated with cardiovascular death (AUC = 0.874; 95% CI: 0.787–0.960; $p < 0.001$).

These cutoffs were derived from the study dataset and should not be interpreted as validated clinical decision thresholds. These AUC estimates reflect apparent discrimination in the study sample and do not establish incremental prognostic value.

Given the small number of cardiovascular deaths ($n = 9$), the findings should be considered preliminary and require confirmation in larger studies.

4. Discussion

In this cohort, lower plasma α-Klotho levels were linked to cardiovascular mortality in the univariable analysis. No significant association was found between α-Klotho and AKI on univariable testing. As the mortality analysis was limited to unadjusted associations, the results do not demonstrate an independent prognostic value for α-Klotho. α-Klotho concentrations were also related to a number of clinical and laboratory parameters that reflect different aspects of the patients' overall clinical condition.

Blood samples were obtained within 48 h after PCI and contrast administration. Thus, the measured α-Klotho concentrations represent postprocedural rather than baseline levels. Lower concentrations may reflect more severe systemic illness, renal dysfunction, hemodynamic disturbance, or procedure-related changes. Without preprocedural or serial measurements, these explanations cannot be distinguished. In particular, the inverse correlation with contrast volume does not establish a causal effect of contrast exposure on α-Klotho.

In the ROC analysis, plasma α-Klotho demonstrated good discrimination for cardiovascular mortality (AUC = 0.799). The observed differences in α-Klotho concentrations and its apparent discrimination in this cohort warrant further investigation but do not establish incremental prognostic value beyond established risk factors. These findings are consistent with those of the PEACE study, in which low α-Klotho concentrations in patients with stable coronary artery disease were associated with an increased risk of cardiovascular mortality and hospitalization for heart failure, independently of traditional risk factors and other biomarkers. Furthermore, the combination of low α-Klotho levels and elevated FGF23 concentrations was associated with a further increase in the risk of adverse cardiovascular outcomes [6]. Experimental studies have shown that α-Klotho attenuates oxidative stress and inflammation, helps preserve vascular endothelial function, and limits myocardial ischemia–reperfusion injury [5,10,11].

Similar findings were reported in a large population-based study involving 9871 participants, in which lower serum α-Klotho levels were independently associated with greater severity of chronic coronary insufficiency, as well as a 21% increase in all-cause mortality and a 76% increase in cardiovascular mortality [7].

Olejnik et al. showed that α-Klotho concentrations change within the first hours of acute myocardial infarction, which, according to the authors, may reflect a compensatory protective response to myocardial ischemic injury [12]. These findings are particularly relevant to the present study, as plasma α-Klotho was measured within 48 h after PCI. The reported time-dependent changes suggest that the timing of blood sampling should be

considered when interpreting associations with clinical outcomes. Reduced α-Klotho levels in chronic cardiovascular diseases, including coronary artery disease and heart failure, have been associated with an increased risk of adverse cardiovascular outcomes and mortality, consistent with the findings of the present study [6,7].

Experimental studies have also demonstrated the antifibrotic effects of α-Klotho. α-Klotho deficiency has been shown to promote myocardial fibrosis, whereas increased α-Klotho expression or administration of exogenous α-Klotho reduces extracellular matrix accumulation, suppresses myofibroblast activation, and limits pathological myocardial remodeling. One proposed mechanism is inhibition of the focal adhesion kinase (FAK) signaling pathway, which is involved in cardiac fibrosis and remodeling. These experimental findings suggest that reduced α-Klotho levels may contribute to structural myocardial changes, although their direct relationship with clinical mortality requires further investigation [13].

In the present study, the development of AKI was associated with higher erythrocyte sedimentation rate and C-reactive protein levels, lower hemoglobin and hematocrit levels and red blood cell counts, as well as greater ADP-induced platelet aggregation and a larger volume of administered contrast medium. The distribution of chronic kidney disease stages also differed between groups. In the multivariable analysis, erythrocyte sedimentation rate and contrast volume remained independently associated with AKI, highlighting the potential contribution of systemic inflammation and procedural factors to post-PCI renal dysfunction. In contrast, plasma α-Klotho concentrations were not significantly associated with AKI, suggesting that its clinical utility as a biomarker of postprocedural renal injury remains uncertain in this cohort.

Ortega-Hernandez et al. demonstrated that systemic inflammation plays a key role in the development of AKI in patients with ACS by contributing to endothelial injury, microcirculatory dysfunction, and the progression of renal dysfunction [14]. Zhang et al. also reported that chronic kidney disease and the volume of contrast medium administered are among the most important risk factors for the development of AKI following PCI [15]. Similar conclusions were reported in the systematic review by Marenzi et al., in which the development of AKI was attributed to the combined effects of pre-existing renal dysfunction, inflammation, and contrast-induced kidney injury [16].

Experimental studies have shown that α-Klotho protects against contrast-induced acute kidney injury through its antioxidant, anti-inflammatory, and anti-apoptotic properties [17]. The inverse correlation between α-Klotho levels and creatinine concentrations observed in the present study indicates an association between α-Klotho and renal function. In addition, α-Klotho has been shown to suppress NLRP3 inflammasome activation and induce autophagy, thereby reducing pyroptosis of renal tubular epithelial cells and limiting renal tissue injury following contrast administration [18]. However, the present clinical study did not demonstrate a significant association between α-Klotho and AKI, and does not establish that lower α-Klotho increases susceptibility to contrast-related injury.

An inverse correlation was observed between α-Klotho levels and the GRACE score, indicating an association between lower α-Klotho concentrations and higher estimated clinical risk in ACS. Although clinical evidence directly evaluating the relationship between α-Klotho levels and the GRACE score remains limited, these findings appear biologically plausible. Reduced α-Klotho levels are known to be associated with an increased risk of cardiovascular mortality, heart failure, and adverse cardiovascular outcomes [6,7]. Given that the GRACE score is an extensively validated tool for risk stratification in patients with ACS, this association may suggest a potential role for α-Klotho as an additional biomarker for prognostic assessment in this patient population.

An inverse correlation was also observed between α-Klotho levels and the FIB-4 liver fibrosis index. Although clinical evidence on the relationship between α-Klotho and liver fibrosis remains limited, a recently published experimental study showed that α-Klotho deficiency promotes liver fibrosis through activation of the TGF-β/Smad signaling pathway, whereas administration of an α-Klotho-derived peptide (KP1) suppresses hepatic stellate cell activation, reduces extracellular matrix accumulation, and attenuates fibrotic changes [19]. These mechanisms may partly explain the inverse association between α-Klotho levels and the FIB-4 index observed in the present study. However, given the limited clinical evidence available, this relationship warrants further investigation.

The positive correlation between α-Klotho concentrations and platelet count also merits consideration. An analysis of NHANES 2007–2016 data demonstrated a statistically significant inverse association between soluble α-Klotho levels and platelet count, which remained significant after adjustment for potential confounding factors [20]. The authors suggested that this association may be related to the anti-inflammatory properties of α-Klotho, whereas an increased platelet count may reflect a more pronounced systemic inflammatory response [20]. Our finding of a positive correlation differs from the inverse association reported in NHANES 2007–2016. Differences between the study populations may help explain this discrepancy. While NHANES 2007–2016 included participants from the general population, the present study was conducted exclusively in patients with ACS following PCI, a population characterized by pronounced inflammatory activation, endothelial dysfunction, and alterations in hemostasis. In experimental work in mice, Park et al. linked α-Klotho exposure to platelet-derived factors, including PF4 [21]. This preclinical evidence provides biological context but does not establish a mechanism for the platelet association observed in patients with ACS.

The positive correlation between α-Klotho and triglyceride concentrations warrants further investigation. Although evidence on this relationship remains limited, α-Klotho levels have been shown to be associated with lipid parameters, suggesting a potential role for this protein in the regulation of lipid metabolism [22]. This association may reflect the specific characteristics of the study cohort of patients with ACS following PCI. However, the mechanisms underlying this relationship remain poorly understood and require further investigation.

Limitations of the Study

This was a single-centre study of 86 patients in which only nine cardiovascular deaths occurred. Because of the small number of events, a multivariable mortality model was not kept, and the mortality associations that are reported remain unadjusted and exploratory. Confounding by known risk factors therefore cannot be ruled out.

The ROC estimates and the cut-offs derived from the data were generated within the same cohort and may be over-optimistic; they should not be regarded as validated tools for clinical prediction.

α-Klotho was measured in EDTA plasma after PCI and contrast administration, without preprocedural or serial measurements. Its associations with clinical severity and contrast volume may therefore reflect both underlying illness and procedure-related changes. In addition, α-Klotho sampling and AKI ascertainment occurred within the same 48-h post-procedural window, so the biomarker was not necessarily measured before the onset of AKI. Each sample was analyzed once, without duplicate measurements, limiting assessment of technical reproducibility. Manufacturer-reported assay precision does not establish the precision achieved in the patient samples analyzed in this study.

The unadjusted association of α-Klotho with cardiovascular mortality does not prove that the relationship is independent of other risk factors, nor does it show any incremental

clinical value over existing risk assessment tools. Larger prospective studies that include prespecified analyses, standardised sampling protocols and independent validation will be required.

Detailed angiographic characteristics, including the number of diseased coronary arteries and the presence of coronary calcification, as well as intraprocedural major adverse cardiac events, were not included in this analysis. This limits assessment of confounding by anatomical and procedural factors. Although all patients underwent stenting, this does not account for differences in the complexity of coronary artery disease. Cardiovascular causes of death were obtained from the treating hospitals' medical records and discharge summaries, and their accuracy depends on the underlying clinical documentation.

5. Conclusions

In patients with ACS undergoing PCI, plasma α-Klotho concentrations were associated with several clinical and laboratory parameters, including GRACE score, creatinine, and contrast volume. α-Klotho was not significantly associated with AKI in univariable analysis. ESR and contrast volume were associated with AKI in the adjusted model.

Higher α-Klotho levels were linked to lower odds of cardiovascular death in the univariable analysis. Because blood was sampled after the procedure, the number of deaths was small, and no adjustment for other risk factors was performed, these results should be viewed as exploratory. It remains unclear whether α-Klotho carries independent or incremental prognostic value beyond the risk factors already in use.

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Data Availability Statement: The data presented in this study are available from the corresponding author upon reasonable request.

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