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Circulating Klotho is linked to prognosis of acute intracerebral hemorrhage

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ABSTRACT

Background: Klotho is an anti-aging protein and its increased plasma concentrations were related to good functional outcome of acute ischemic stroke. This study was designed to ascertain the prognostic significance of plasma Klotho in intracerebral hemorrhage.

Methods: Plasma Klotho concentrations in 96 intracerebral hemorrhage patients and 96 healthy controls were quantified. Poor prognosis was defined as modified Rankin scale scores > 2 at 90 days. The association of plasma Klotho concentrations with stroke prognosis was assessed using regression model.

Results: Patients showed a substantially lower concentration of Klotho than healthy controls ($P < .01$). Klotho concentrations were highly correlated with National Institutes of Health Stroke Scale scores, Glasgow coma scale scores, intracerebral hemorrhage scores and hematoma volumes ($r = -0.426$, 0.382, -0.334 and -0.432). Patients with the highest plasma Klotho concentration were less prone to have poor prognosis at 90 days compared with the lowest quartile (odds ratio, 0.092; 95% confidence interval, 0.015–0.562). Its optimal cutoff value for distinguishing patients at risk of poor prognosis was 345 pg/ml, which yielded a sensitivity value of 0.86 and a specificity value of 0.62.

Conclusions: Decreased plasma Klotho concentrations were associated with increasing severity and poor prognosis significantly, indicating the prognostic role of plasma Klotho in intracerebral hemorrhage.

1. Introduction

Intracerebral hemorrhage (ICH) is a major cause of global disease burden with limited therapies [1–3]. National Institutes of Health Stroke Scale (NIHSS) score, hematoma volume, GCS score and ICH score are conventionally used to assess the severity and predict the prognosis of ICH, as well as thereby aid in risk stratification [4–7]. Biochemical markers can present us with some useful information regarding the pathogenesis and underlying mechanisms of stroke-induced brain injury, so this aspect of study has been emphasized gradually in recent decades [8–10].

Klotho, a type 1 transmembrane protein, has been recognized as an antiaging protein predominantly expressed in the distal convoluted tubules in the kidneys and in the choroid plexus of the brain [11–13]. Several studies have confirmed that Klotho exerted antioxidative, anti-inflammatory and neuroprotective effects [14–16]. Klotho is shed and circulates in blood, cerebrospinal fluid and urine of human and mouse [17–20]. Some previous epidemiological investigations have revealed decreased plasma or serum Klotho concentrations in patients with obstructive sleep apnoea, systemic sclerosis and chronic kidney disease [21–23]. Moreover, serum Klotho was negatively associated with metabolic syndrome in chronic kidney disease [24] and declined plasma Klotho independently predicted mortality and cardiovascular events in hemodialysis patients [25]. Of note, a more recent study showed that increased plasma Klotho concentrations were associated with good functional outcome in patients with acute ischemic stroke [26]. Hence, it is postulated that lower plasma Klotho concentrations might be related to worse prognosis in ICH.

2. Materials and methods

2.1. Subjects

Subjects were recruited with their written informed consents after approval for the study was obtained from the Ethics Committee at our hospital. This was a prospective and observational study consecutively

Abbreviations: CT, computerized tomography; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; O GCS, Glasgow coma scale

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enrolling patients with first-ever ICH admitted within 24 h after stroke confirmed by brain computed tomography (CT) from our hospital between January 2014 and December 2017. We excluded patients aged below 18 years, those with bleedings resulting from other causes (such as underlying vascular lesions, traumatic force, venous sinus thrombosis, impaired coagulation, infarction and tumors), those undergoing a surgical procedure, and those coexisting with autoimmune diseases, severe infection, pregnancy or known malignancy. In the same period, the equal number of healthy volunteers were selected from the healthy examination center of our hospital.

2.2. Data collection

Demographics, vascular risk factors and time from symptom onset to hospitalization were collected at the enrollment. Demographics included age, gender and body mass index. Vascular risk factors comprised hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, current smoking, moderate-heavy alcohol consumption, coronary artery disease, chronic kidney disease and statin pretreatment. Clinical and radiological severity was assessed with National Institutes of Health Stroke Scale (NIHSS) scores, Glasgow coma scale (GCS) scores, ICH score and hematoma volume. Hematoma volume was measured based on ABC/2 method (length × width × number of layers × thickness of layer/2) [27]. Other radiological parameters contained ICH location (deep or lobar), the presence of intraventricular bleeding and subarachnoidal extension of hematoma. Patients were followed up until 90 days after stroke onset. Physical function was assessed by the Modified Rankin Scale (mRS) score and subsequently was divided into good outcome (mRS score of 0 to 2) and poor outcome (mRS score $>$ 2).

2.3. Measurements

Blood samples, which were used to gauge plasma Klotho concentrations, were collected in tubes containing ethylenediamine tetraacetic acid as an anticoagulant agent from patients immediately after hospitalization and from controls at study entrance. Plasma was acquired by centrifugation for 15 min at 1900 $\times g$ and preserved at −80 °C until analysis. An enzyme-linked immunosorbent assay (Immuno-Biological Laboratories) was utilized for the determination of plasma Klotho concentrations.

2.4. Statistical analysis

The patients were stratified into quartiles of plasma Klotho concentrations. Data were presented as median (interquartile range) for continuous variables and as number (percentage) for categorical variables. Comparison was performed using the Kruskal-Wallis H test, Mann-Whitney U test, x^2 test or Fisher exact test where appropriate. For investigating correlations between plasma Klotho concentrations and NIHSS scores, ICH scores, GCS scores and hematoma volumes, Spearman correlation coefficients were done. The association of plasma Klotho concentrations with stroke prognosis was analyzed by a logistic model. We compared baseline characteristics between the two groups (good prognosis and poor prognosis), and the variables with $P < .05$ in univariate analysis were incorporated in the logistic model. Odds ratio values (ORs) and 95% confidence interval values (CIs) were reported. Receiver operating characteristic curve of plasma Klotho concentrations for prognostic prediction were drawn. Predictive ability was expressed as area under curve (AUC) and 95% CI. All statistical analyses were 2 tailed. A $P < .05$ was considered statistically significant. The Statistical Package for the Social Sciences version 20.0 was used for all analyses.

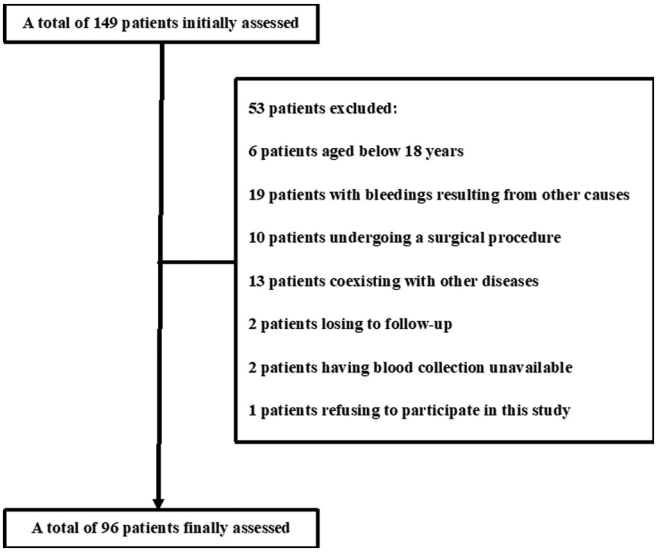

Fig. 1. Flow chart screening for patients with intracerebral hemorrhage.

3. Results

3.1. Baseline demographic, clinical and laboratory findings

Initially, a total of 149 patients were assessed. According to the exclusion criteria, we excluded fifty-three patients (Fig. 1). Finally 96 patients were available for analysis. Their baseline characteristics are presented in Table 1. In addition, a total of 96 controls were selected. Those controls were aged at median value of 62 (interquartile range,

Table 1
Baseline characteristics of patients.

Factors	All patients
Gender (male/female)	54/42
Age (y)	65 (57–76)
Body mass index (kg/m^2)	24.7 (23.3–26.4)
Smoking	47 (49.0%)
Alcohol drinking	37 (38.5%)
Hypertension	83 (86.5%)
Diabetes mellitus	29 (30.2%)
Hyperlipidemia	33 (34.4%)
Congestive heart failure	7 (7.3%)
Coronary artery disease	9 (9.4%)
Chronic kidney disease	7 (7.3%)
Statin usage	26 (27.1%)
Admission time (h)	9.1 (5.1–13.8)
Blood-collection time (h)	12.5 (7.8–17.2)
GCS score	14 (12–15)
NIHSS score	9 (6–13)
ICH score	0 (0–2)
Hematoma volume (ml)	14 (7–23)
Lobar hemorrhage	23 (24.0%)
Infratentorial hemorrhage	14 (14.6%)
Subarachnoidal extension of hematoma	6 (6.3%)
Intraventricular hemorrhage	25 (26.0%)
Systolic arterial pressure (mmHg)	167 (159–188)
Diastolic arterial pressure (mmHg)	103 (98–108)
Blood glucose level (mmol/l)	12.8 (11.3–17.1)
Serum C-reactive protein level (mg/l)	13.7 (11.7–15.9)
Blood white blood cell count ($\times 10^9$/l)	9.7 (7.3–12.5)
Blood platelet count ($\times 10^9$/l)	178 (149–219)
Serum D-dimer levels (mg/l)	2.5 (2.2–3.0)
90-day poor outcome	49 (51.0%)

Continuous variables were presented as medians with interquartile ranges. Categorical variables were presented as counts (percentages). NIHSS indicates National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; GCS, Glasgow coma scale.

Table 2
Baseline characteristics of patients according to plasma Klotho quartiles.

Components	Plasma Klotho quartiles (pg/ml)				
	≤ 224	229–298	299–379	≥ 393	*P* value
Gender (male/female)	11/13	16/8	15/9	12/12	NS
Age (y)	64 (56–77)	65 (59–74)	69 (64–76)	68 (56–76)	NS
Body mass index (kg/m^2)	24.8 (23.5–26.1)	24.5 (23.6–26.1)	24.7 (23.3–26.5)	24.1 (21.3–26.5)	NS
Smoking	14 (58.3%)	11 (45.8%)	8 (33.3%)	14 (58.3%)	NS
Alcohol drinking	10 (41.7%)	10 (41.7%)	9 (37.5%)	8 (33.3%)	NS
Hypertension	21 (87.5%)	18 (75.0%)	23 (95.8%)	21 (87.5%)	NS
Diabetes mellitus	8 (33.3%)	10 (41.7%)	4 (16.7%)	7 (29.2%)	NS
Hyperlipidemia	7 (29.2%)	11 (45.8%)	8 (33.3%)	7 (29.2%)	NS
Congestive heart failure	2 (8.3%)	2 (8.3%)	1 (4.2%)	2 (8.3%)	NS
Coronary artery disease	4 (16.7%)	0 (0%)	2 (8.3%)	3 (12.5%)	NS
Chronic kidney disease	3 (12.5%)	0 (0%)	2 (8.3%)	2 (8.3%)	NS
Statin usage	6 (25.0%)	9 (37.5%)	4 (16.7%)	7 (29.2%)	NS
Admission time (h)	6.8 (2.0–14.5)	8.3 (5.0–10.8)	11.5 (8.5–22.2)	9.7 (5.7–17.8)	NS
Blood-collection time (h)	9.8 (3.4–17.6)	12.2 (8.8–14.1)	14.7 (11.4–23.6)	12.7 (7.7–21.6)	NS
GCS score	13 (12–15)	13 (12–15)	14 (13–15)	15 (14–15)	0.013
NIHSS score	12 (7–15)	12 (8–14)	9 (7–11)	5 (5–9)	0.001
ICH score	1 (0–2)	1 (0–2)	0 (0–2)	0 (0–1)	0.054
Hematoma volume (ml)	16 (10 − 32)	21 (13–25)	12 (7–20)	7 (5–12)	0.001
Lobar hemorrhage	4 (16.7%)	9 (37.5%)	3 (12.5%)	7 (29.2%)	NS
Infratentorial hemorrhage	3 (12.5%)	5 (20.8%)	5 (20.8%)	1 (4.2%)	NS
Subarachnoidal extension of hematoma	2 (8.3%)	2 (8.3%)	0 (0)	2 (8.3%)	NS
Intraventricular hemorrhage	9 (37.5%)	6 (25.0%)	6 (25.0%)	4 (16.7%)	NS
Systolic arterial pressure (mmHg)	182 (160–196)	173 (161–187)	173 (151–184)	165 (160–174)	NS
Diastolic arterial pressure (mmHg)	107 (96–111)	101 (99–108)	104 (97–109)	102 (98–108)	NS
Blood glucose level (mmol/l)	16.8 (12.9–21.6)	13.6 (11.3–16.9)	12.6 (11.9–15.6)	12.4 (11.0–15.2)	0.016
Serum C-reactive protein (mg/l)	14.9 (13.3–19.7)	14.6 (12.0–16.8)	13.2 (10.9–14.1)	13.4 (7.8–14.5)	0.002
Blood white blood cell count ($\times 10^9$/l)	8.5 (7.0–10.1)	11.2 (9.5–12.8)	10.0 (7.0–12.8)	9.1 (7.5–12.7)	NS
Blood platelet count ($\times 10^9$/l)	225 (144–275)	184 (157–216)	173 (140–194)	163 (146–181)	NS
Serum D-dimer levels (mg/l)	2.7 (1.8–3.1)	2.4 (2.2.-3.1)	2.4 (2.0–2.6)	2.8 (2.5–3.0)	NS
90-day poor outcome	17 (70.8%)	17 (70.8%)	12 (50.0%)	3 (12.5%)	< 0.001

Continuous variables were summarized as medians with interquartile ranges. Categorical variables were presented as counts (percentages). Intergroup comparison was made using the chi-square test or Kruskal-Wallis H test as appropriate. NIHSS indicates National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; GCS, Glasgow coma scale.

58–78) y, had 51 males and 45 females, as well as exhibited the median body mass index of 24.1 (interquartile range, 23.1–26.9) kg/m^2. There were not significant differences between age, gender percentage and body mass index of patients and controls (all $P > .05$). Circulating Klotho concentrations were significantly lower in patients than in healthy controls (median 299 pg/ml, interquartile range 227–386 pg/ml, range 144–446 pg/ml vs. median 784 pg/ml, interquartile range 519–1430 pg/ml, range 411–1726 pg/ml; $P < .001$).

3.2. Baseline demographic, clinical and laboratory parameters by plasma Klotho concentrations

Patients were stratified into 4 groups according to the quartiles of plasma Klotho concentrations (≤224, 229–298, 299–379 or ≥ 393 pg/ml). And then, the demographic, clinical, and laboratory parameters were compared among the 4 groups (Table 2). The GCS score, NIHSS score, hematoma volume, blood glucose concentration and serum C-reactive protein concentration were significantly different according to quartiles of the plasma Klotho concentrations. There was a significant trend for ICH score ($P = .054$). Alternatively, with increasing quartiles of the plasma Klotho concentrations, the percentages of 90-day poor outcome were substantially declined. No significant differences were observed among the 4 groups in term of age, gender, body mass index and other variables in Table 2. Moreover, Fig. 2 displays the intimate correlations between plasma Klotho concentrations and ICH scores, NIHSS scores, GCS scores and hematoma volumes.

3.3. Components associated with poor prognosis

Circulating Klotho concentrations were significantly lower in patients who suffered from a poor outcome than in those who presented with a good outcome (260 (195–322) vs. 372.4 (287–421) pg/ml, $P < .001$). In Table 3, compared with the patients with good prognosis, the patients with poor prognosis were more likely to be older, have higher NIHSS scores and ICH scores, lower GCS scores and larger hematoma volumes; there were more patients with a history of diabetes mellitus in poor prognosis group; more intraventricular hemorrhage were shown in patients with poor prognosis; blood glucose concentrations and serum C-reactive protein concentrations of patients experiencing poor prognosis were significantly higher than those of patients developing good prognosis. Moreover, patients with poor prognosis exhibited the higher proportion of low plasma Klotho quartiles than those with good prognosis. When the preceding significant variables were included in the Logistic regression model, we found that NIHSS score, GCS score and hematoma volume remained as the independent predictors for 90-day poor outcome. In addition, compared with the lowest plasma Klotho quartile in the multivariate analysis, only the highest plasma Klotho quartile was independently and inversely associated with poor outcome (Table 4).

3.4. Analysis with respect to prognostic capability

Fig. 3 shows that plasma Klotho concentrations significantly discriminated patients at risk of 90-day poor outcome. Meanwhile, an optimal cutoff point of plasma Klotho concentrations for predicting poor prognosis was selected from Youden index, which generated the corresponding specificity, sensitivity, likelihood ratio and predictive value. We also assessed prognostic predictive ability of the other three independent prognostic predictors (NIHSS score, GCS score and hematoma volume) and their AUCs were 0.847 (95%CI, 0.759–0.912), 0.826 (95%CI, 0.735–0.896) and 0.845 (95%CI, 0.757–0.911) respectively. Of note, AUC of plasma Klotho concentrations was in the range

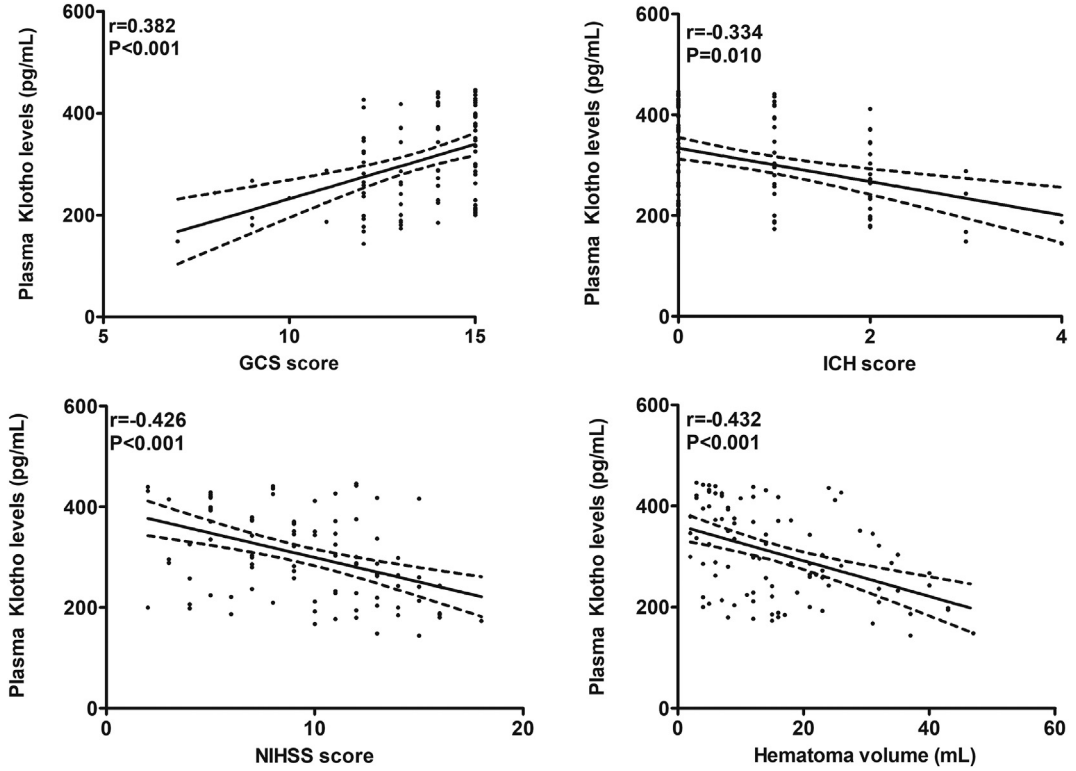

Fig. 2. Correlation between plasma Klotho concentrations and other variables among patients with intracerebral hemorrhage. Plasma Klotho concentrations were inversely correlated with NIHSS score, ICH score and hematoma volume, but was positively correlated to GCS score. NIHSS means National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; GCS, Glasgow Coma scale.

of their AUCs (all $P > .05$).

4. Discussion

In this study, we measured Klotho concentrations in the peripheral blood from ICH patients and further to determine the relationship between circulating Klotho concentrations and hemorrhagic severity in addition to prognosis in ICH patients. We showed that circulating Klotho concentrations were substantially lower in patients with ICH than in healthy controls and were negatively correlated with hemorrhagic severity indicated by NIHSS scores, GCS scores, ICH scores and hematoma volume. Importantly, plasma Klotho exhibited a significant and independent association with 90-day poor outcome, suggesting a potential link between lower Klotho concentrations and poor prognosis in patients with hemorrhagic stroke.

Klotho is recently discovered and acts as an anti-aging gene [11–13]. A growing body of data has demonstrated that Klotho exerts a protective function on many tissues or organs [14–16]. However, its exact mechanisms remain unclear. Up to now, there are three kinds of hypotheses, which may explain its protective effects. First, Klotho protects against endothelial dysfunction [28,29]. Second, Klotho shows a protective effect via anti-oxidative stress and anti-inflammation [14–16]. Third, Klotho is implicated in preservation of arterial wall integrity and pathogenesis of arterial stiffness or vascular calcification [30]. Our study found that plasma Klotho concentrations were remarkably lower in ICH patients, as compared to healthy controls. Such data hints that Klotho might be a protective factor in ICH. An explanation for this effect is that Klotho might exert a protective effect via anti-inflammation and anti-oxidative stress, because ICH-related brain injury is acute process, which is relevant to acute inflammatory response and oxidative stress [31–33], but not endothelial dysfunction and arterial stiffness.

Previously, some studies reported that increased plasma Klotho concentrations were an independently associated risk for cardiovascular disease [25], and variation of the Klotho gene was associated with chance of early- onset ischemic stroke [34]. Also, the serum Klotho concentration was a potential predictor of cerebrovascular disease in hemodialysis patients [35]. Moreover, plasma Klotho concentrations were measured in a group of patients with acute ischemic stroke. Subsequently, it was revealed that lower plasma Klotho concentrations were significantly correlated with higher NIHSS scores and larger cerebral infarction volumes. Moreover, those patients were followed up until three months after onset of stroke and low plasma Klotho concentrations were found to be independently associated with good functional outcome [26]. Thus, it is possible that plasma Klotho concentrations could aid in the assessment of severity and prognosis and facilitate risk stratification in acute ischemic stroke. Furthermore, it is postulated that circulating Klotho might be a useful prognostic biomarker for ICH.

To the best of my knowledge, this is the first series exploring the relationship between Klotho concentrations in peripheral blood and severity in ICH. In order to demonstrate the close correlation of plasma Klotho concentrations with hemorrhagic severity in ICH, we identified plasma Klotho as the continuous or categorical variable. On the one hand, plasma Klotho concentrations were divided into 4 groups according to its quartiles. And we found that, with decreasing quartiles, hemorrhagic severity was raised substantially, which was reflected by ICH scores, NIHSS scores, hematoma volumes and GCS scores. On the other hand, bivariate correlative analysis confirmed that plasma Klotho concentrations were highly and inversely correlated with hemorrhagic severity, which was also assessed by ICH scores, NIHSS scores, hematoma volumes and GCS scores. Overall, in ICH, plasma Klotho might have the potential to serve as a useful biomarker for evaluating disease severity.

Up to now, there is a paucity of data available with respect to the relation of plasma Klotho concentrations to prognosis of ICH. This

Table 3
Factors associated with 90-day poor outcome of patients.

Parameters	Poor outcome (n = 49)	Good outcome (n = 47)	P value
Gender (male/female)	28/21	26/21	NS
Age (y)	71 (62–76)	65 (57–74)	0.046
Body mass index (kg/m^2)	24.9 (23.5–26.3)	24.1 (22.7–26.3)	NS
Smoking	24 (49.0%)	23 (48.9%)	NS
Alcohol drinking	22 (44.9%)	15 (31.9%)	NS
Hypertension	41(83.7%)	42 (89.4%)	NS
Diabetes mellitus	20 (40.8%)	9 (19.2%)	0.021
Hyperlipidemia	17 (34.7%)	16 (34.0%)	NS
Congestive heart failure	6 (12.2%)	1 (2.1%)	NS
Coronary artery disease	6 (12.2%)	3 (6.4%)	NS
Chronic kidney disease	5 (10.2%)	2 (4.3%)	NS
Statin usage	15 (30.6%)	11 (23.4%)	NS
Admission time (h)	9.0 (5.6–12.6)	9.5 (4.7–20.5)	NS
Blood-collection time (h)	12.4 (8.2–14.8)	12.5 (7.6–22.5)	NS
GCS score	13 (12–14)	15 (14–15)	< 0.001
NIHSS score	12 (10–14)	7 (5–9)	< 0.001
ICH score	1 (0–2)	0 (0–1)	< 0.001
Hematoma volume (ml)	21 (14–29)	7 (5–12)	< 0.001
Lobar hemorrhage	13 (26.5%)	10 (21.3%)	NS
Infratentorial hemorrhage	9 (18.4%)	5 (10.6%)	NS
Subarachnoidal extension of hematoma	4 (8.2%)	2 (4.3%)	NS
Intraventricular hemorrhage	17 (34.7%)	8 (17.0%)	0.049
Systolic arterial pressure (mmHg)	172 (155–187)	168 (161–187)	NS
Diastolic arterial pressure (mmHg)	105 (98–109)	101 (95–108)	NS
Blood glucose level (mmol/l)	15.5 (11.6–20.1)	12.4 (11.3–14.8)	0.016
Serum C-reactive protein (mg/l)	14.6 (12.3–17.3)	13.4 (10.3–14.7)	0.007
Blood white blood cell count ($\times 10^9$/l)	9.8 (8.0–12.0)	9.7 (7.0–12.5)	NS
Blood platelet count ($\times 10^9$/l)	177 (140–273)	179 (158–204)	NS
Serum D-dimer (mg/l)	2.5 (2.3–3.0)	2.4 (1.9–2.9)	NS
Plasma Klotho quartiles (pg/ml)			< 0.001
≤224	17	7	
229–298	17	7	
299–379	12	12	
≥393	3	21	

Continuous variables were reported as medians with interquartile ranges. Categorical variables were showed as counts (percentages). Intergroup comparison was made using the chi-square test, Fisher exact test or Mann-Whitney U test where appropriate. NIHSS indicates National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; GCS, Glasgow coma scale.

Table 4
Factors associated with 90-day poor outcome in patients using multivariate analysis.

Characteristics	Odds ratio	95% confidence interval	P value
Age (y)	1.066	0.975–1.164	NS
Diabetes mellitus	7.197	0.770–67.279	NS
GCS score	0.298	0.093–0.954	0.042
NIHSS score	1.622	1.296–2.030	0.001
ICH score	1.151	0.281–4.716	NS
Hematoma volume (ml)	1.150	1.077–1.228	0.006
Intraventricular hemorrhage	1.330	0.114–15.535	NS
Blood glucose level (mmol/l)	1.046	0.813–1.346	NS
Serum C-reactive protein (mg/l)	1.196	0.984–1.454	NS
Plasma Klotho quartiles (pg/ml)			
≤224	Reference		
229–298	0.770	0.187–3.172	NS
299–379	0.607	0.144–2.559	NS
≥393	0.092	0.015–0.562	0.010

NIHSS indicates National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; GCS, Glasgow coma scale.

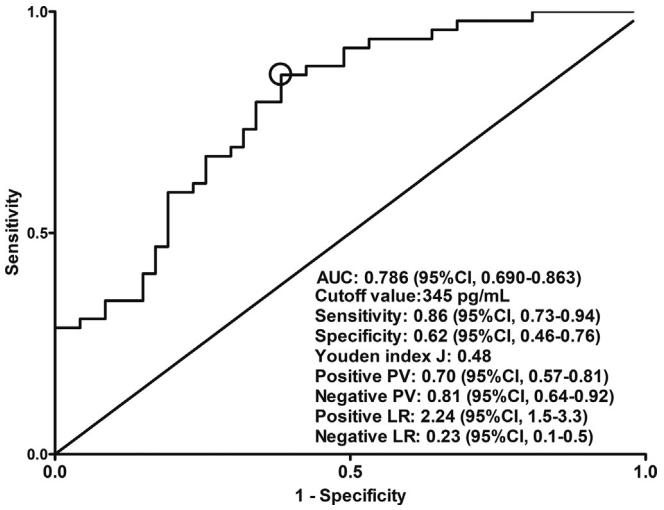

Fig. 3. Receiver-operating characteristic curve using plasma Klotho concentrations for investigating poor functional outcome at 90 days after hemorrhagic stroke. Circle indicates the optimal cut-off point of plasma Klotho concentrations by Youden method. AUC denotes area under curve; 95% CI, 95% confidence interval; PV, predictive value; LR, likelihood ratio.

group of ICH patients were followed up until 90 days post stroke. Poor outcome was designated as mRS score above 2 at 90 days after stroke. First, a multivariate logistic regression model was conFig.d, which discerned 90-day poor outcome as an independent factor, and included the significant variables in univariate analyses as the dependent parameters. It was verified that, besides NIHSS scores, GCS scores and hematoma volumes, plasma Klotho retained as an independent predictor for 90-day poor outcome. Second, we constructed a ROC curve to assess the discriminatory capability. Actually, this biomarker could be able to significantly differentiate between good outcome and poor outcome. Furthermore, we compared the predictive ability reflect by AUC between plasma Klotho concentrations and other determinants, namely, NIHSS scores, GCS scores and hematoma volumes. Interestingly, the AUC was equivalent to those of the preceding prognostic determinants. In summary, plasma Klotho might represent a promising prognostic biomarker for assessing long-term clinical outcome of hemorrhagic stroke.

5. Conclusions

Decreased Klotho concentrations are significantly associated with worse prognosis and increased severity in patients with ICH. Plasma Klotho could be an independent prognostic biomarker for ICH.

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