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CLINICAL RESEARCH REPORT

Clinical Usefulness of the Serum Cystatin C Levels in Patients with Transient Ischemic Attack

Xiaoyu Dong [1] · Jianfei Nao [1]

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Introduction

Transient ischemic attack (TIA) is characterized by sudden onset neurological impairment lasting < 24 h and is associated with brain or optic nerve ischemia (Dennis et al. 1990). It is a premeditated event that usually indicates a subsequent stroke (Johnston et al. 2000). A number of efforts have been made to predict the risk of eventual acute ischemic stroke (AIS), including the ABCD2 and ABCD3-I scores (the latter combined with brain and carotid imaging results and the ABCCD2 standard score) (Merwick et al. 2010). In addition to these well-defined traditional means of prediction, some serum biomarkers are also associated with a poor prognosis in patients with TIA and may help to detect patients who require urgent treatment at an early stage.

Some serum biomarkers play a pivotal role in the initiation and progression of atherosclerosis, which is the underlying lesion of TIA. Serum uric acid may promote atherosclerosis in carotid arteries in patients with ischemic stroke (Arevalo-Lorido et al. 2018). It has been demonstrated that high uric acid levels are an independent, indicative risk factor for large-artery disease in patients with AIS (Acar et al. 2018). High homocysteine level appears to be associated with intracranial strong plaque enhancement, and elevated plasma homocysteine is an independent risk factor for ischemic stroke (Lu et al. 2018). Recent studies also show the association between cystatin C and stroke; cystatin C level increases in the hippocampus after ischemic injury in different animal models (Ishimaru et al. 1996; Palm et al. 1995; Pirttila and Pitkanen 2006). High serum cystatin C is found in stroke patients and is associated with a larger infarct size and hemorrhage volume (Ni et al. 2007; Xiao et al. 2012). Serum cystatin C is also associated with the risk of ischemic stroke and may predict death after AIS onset (Zhu et al. 2018a). It has been reported that cystatin C is independently associated with shorter survival after ischemic stroke (Winovich et al. 2017). Previous research has also demonstrated that a high level of serum cystatin C is associated with the total burden of cerebral small vessel disease in patients with acute lacunar stroke independent of conventional risk factors (Yang et al. 2017b). Moreover, Yang et al. suggested that cystatin C could also be an independent risk factor and therapeutic target for AIS (Yang et al. 2015).

Although these associations between cystatin C and AIS have been investigated in previous studies (Kanhai et al. 2013; Zhu et al. 2018b), no study has evaluated the association between cystatin C and TIA. As one kind of ischemic stroke, whether there is an elevation of serum cystatin C in patients with TIA, is there any predictive value of cystatin C level in the prognosis of TIA patients? In this study, we investigated the clinical association between serum cystatin C levels and TIA and we further evaluated the prognostic value of cystatin C for predicting the risk of eventual AIS in 90-day follow-ups of these patients.

Materials and Methods

Study Population

We retrospectively identified 232 newly diagnosed patients with TIA admitted to the Department of Neurology, Shengjing Hospital of China Medical University from January 2016 to September 2017; 182 age- and gender-matched healthy individuals were enrolled during the same period. TIA was defined as acute onset focal neurological impairment of brain function lasting < 24 h due to cerebral ischemia, with or without diffusion-weighted imaging (DWI) support (Dennis et al. 1990). The diagnosis of TIA

✉ Jianfei Nao
18940256567@163.com

[1] Department of Neurology, Shengjing Hospital of China Medical University, 36 Sanhao Street, Heping District, Shenyang 110004, Liaoning, People's Republic of China

was made jointly by at least two neurologists. Other inclusion criteria for our study including magnetic resonance imaging (MRI) applied to all patients within 48 h of symptom onset. Age ≥ 18 years and sex were unlimited. The exclusion criteria were the following: (1) TIAs attributable to arteritis, cerebral compression, or other rare etiology; (2) organic brain disease producing neurologic dysfunction; (3) concomitant acute or chronic inflammation, a recent acute coronary syndrome, renal diseases, such as glomerulonephritis, renal dysfunction, serious liver disease, blood system diseases, or heart failure that may affect serum cystatin C levels; and (4) loss to follow-up or failure to comply with regular examinations and treatment.

Clinical Data

Demographic data, cerebrovascular risk factors, and medical history were collected upon admission. Hypertension was considered in subjects previously diagnosed according to the hypertension guidelines of the World Health Organization and the International Society of Hypertension or in those routinely receiving antihypertensive therapy. Diabetes mellitus (DM) was diagnosed as fasting serum glucose ≥ 7 mmol/L, non-fasting glucose of ≥ 11.1 mmol/L, routine use of an antidiabetic treatment, or a previously established diagnosis. Atrial fibrillation (AF) was defined as AF recorded at the time of electrocardiography or any previously known episode of AF.

MRI Acquisition and Analysis

MRI was performed with a 3.0 T scanner (Philips Healthcare, Amsterdam, the Netherlands) using an eight-channel phased array coil. The scanning protocol included DWI with 4-mm sections. Time-of-flight magnetic resonance angiography (MRA) was also performed to evaluate intracranial arterial stenosis. A 22-color ultrasonography unit (Philips Healthcare) was used to detect the degree of stenosis in the main and internal branches of the carotid artery.

Focal signal loss on MRA was interpreted as severe stenosis with recovery of the distal arterial signals, and no blood flow signal intensity at all, including distal branches, was considered occlusion (Lam et al. 2004). Ultrasound was used to assess stenosis of the internal carotid artery in accordance with the North American symptomatic carotid endarterectomy trial criteria. Greater than 50% stenosis was considered a serious luminal complication (Oates et al. 2009).

Laboratory Methods

Venous blood samples were taken from the patients within 24 h after admission and after a 12-h overnight fast. Biochemical tests, such as fasting blood glucose, total cholesterol, triglycerides, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, uric acid, and glycated hemoglobin were measured spectrophotometrically. The reference range for the serum cystatin C level was 0.59–1.03 mg/L.

Medications and Follow-Up

Treatment and prevention of AIS or TIA included statins and platelet aggregation inhibitors (100 mg aspirin or 75 mg clopidogrel). Warfarin was administered to prevent AF. The hospital's electronic record system was used to evaluate in-hospital and 90-day outcomes after TIA, and patients were contacted by telephone or WeChat instant messaging for the follow-up survey.

Statistical Analysis

Continuous variables were compared using the *t* test for independent samples or the Mann–Whitney *U* test. Categorical variables were compared using Fisher's exact test or the chi-square test. Binary logistic regression analyses were performed to identify the factors that affected 90-day outcomes in patients with TIA. Spearman's correlation analysis was used to determine the correlation between cystatin C and other factors. The optimal cutoff value for continuous serum cystatin C levels was calculated by applying a receiver operating characteristics (ROC) curve analysis to test all possible cutoffs to discriminate AIS and no AIS. Based on the cutoff values, the survival curves for cystatin C were plotted by the Kaplan–Meier method, with differences assessed by the log-rank test. A p value < 0.05 was considered significant. All statistical analyses were performed using IBM SPSS 17.0 software (IBM, Chicago, IL, USA).

Results

Sample Characteristics

A total of 232 patients with TIA and 182 healthy controls were enrolled in our study. Serum cystatin C levels were 1.09 ± 0.52 mg/L vs. 0.95 ± 0.02 mg/L in the TIA and control groups, respectively ($p = 0.001$) (Fig. 1a), indicating that the serum cystatin C level in the TIA group was significantly higher than that in the healthy control group (Table 1).

Factors Associated with AIS

All 232 patients with TIA (male, 143; mean age, 62.56 ± 11.34 years) completed the 90-day follow-up regimen, and 38 patients (16.37%) had AIS. The baseline characteristics and laboratory parameters of the study groups are shown in Table 2. AIS-positive (vs. AIS-negative) patients were significantly older than those without AIS ($p = 0.001$). Furthermore, a history of

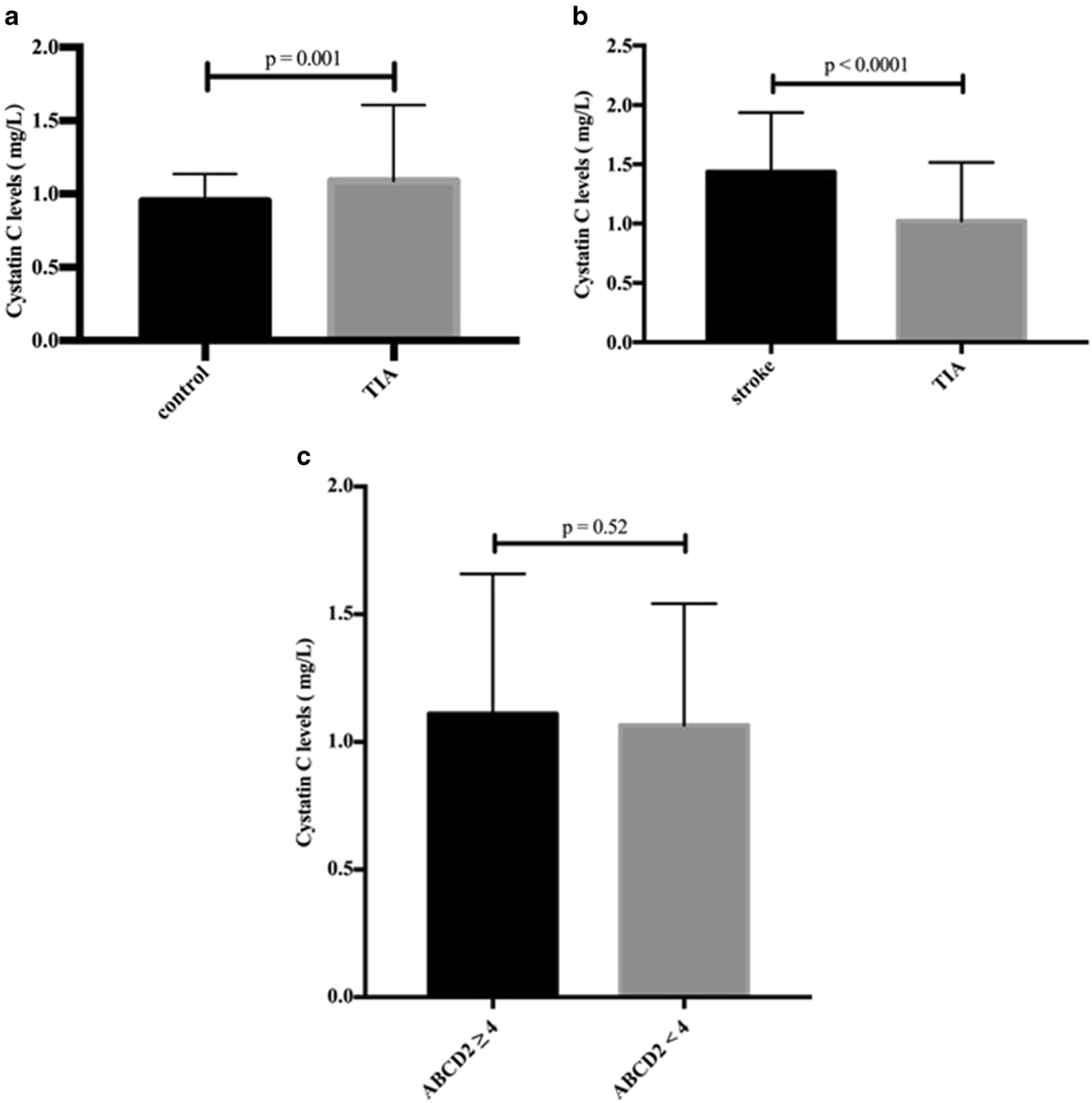

Fig. 1 **a** Cystatin C levels in patients with a transient ischemic attack (TIA) were significantly higher than those in the control group. **b** No differences in cystatin C levels were observed between the ABCD2 score ≥ 4 and ABCD2 score < 4 groups. **c** The cystatin C level in patients with acute ischemic stroke (AIS) was significantly higher than that of patients with a TIA

hypertension ($p = 0.045$), DM ($p = 0.004$), and AF ($p = 0.008$) was more common in AIS-positive (vs. AIS-negative) patients. Serum cystatin level in AIS-positive patients was significantly higher than that of AIS-negative patients (1.44 ± 0.50 vs. 1.02 ± 0.49 mg/L, $p < 0.001$) (Fig. 1b). No difference in the ABCD2 score was observed between the two groups (Fig. 1c).

Table 1 Comparison of cystatin C between TIA and control groups

	TIA ($n = 232$)	Control ($n = 182$)	*P* value
Cystatin C (mg/L), mean ± SD	1.09 ± 0.52	0.95 ± 0.02	0.001

TIA transient ischemic attack

Table 2 Baseline characteristics of TIA with or without AIS

	All subjects ($n = 232$)	AIS-negative ($n = 194$)	AIS-positive ($n = 38$)	*P* value
Age (years), mean ± SD	62.56 ± 11.34	61.5 ± 11.31	67.9 ± 10.02	0.001*
Gender, male, *n* (%)	143 (61.64)	119/75	24/14	0.833
History of hypertension, *n* (%)	130 (56.03)	103 (53.37%)	27 (71.05%)	0.045*
History of DM, *n* (%)	60 (25.86)	43 (22.16%)	17 (44.74%)	0.004*
History of coronary, *n* (%)	19 (8.19)	16 (8.29%)	3 (7.89%)	0.935
History of smoking, *n* (%)	97 (41.81)	82 (42.27%)	15 (39.47%)	0.749
History of alcohol, *n* (%)	76 (32.76)	65 (33.85%)	11 (28.95%)	0.557
History of atrial fibrillation, *n* (%)	5 (2.16)	2 (1.03%)	3 (7.89%)	0.008*
Intracranial vascular stenosis, *n* (%)	41 (17.7)	32 (16.49)	9 (23.68)	0.288
Carotid artery stenosis, *n* (%)	15 (6.47)	12 (6.19)	3 (7.89)	0.695
ABCD2 score	3.58 ± 1.55	3.53 ± 1.55	3.87 ± 1.56	0.221
FBG (mmol/L)	5.78 ± 1.96	5.77 ± 2.03	5.79 ± 1.54	0.943
Cholesterol (mmol/L)	4.75 ± 1.11	4.78 ± 1.13	4.63 ± 1.03	0.437
Triglycerides (mmol/L)	1.73 ± 1.53	1.73 ± 1.55	1.72 ± 1.43	0.981
LDL (mmol/L)	3.00 ± 0.93	3.03 ± 0.93	2.88 ± 0.89	0.349
HDL (mmol/L)	1.12 ± 0.30	1.12 ± 0.29	1.11 ± 0.31	0.788
HCY (mmol/L)	15.00 ± 6.85	14.95 ± 6.88	15.29 ± 6.86	0.781
Uric acid (μmol/L)	331.09 ± 88.36	334.20 ± 88.27	315.21 ± 88.14	0.230
Vitamin B_{12} (pg/mL)	350.20 ± 233.68	356.19 ± 245.11	319.63 ± 162.47	0.252
Cystatin C (mg/L)	1.09 ± 0.52	1.02 ± 0.49	1.44 ± 0.50	< 0.001*
Folic acid (ng/mL)	8.12 ± 4.17	8.05 ± 3.97	8.50 ± 5.12	0.608
HbA1c (%)	6.10 ± 1.16	6.08 ± 1.15	6.22 ± 1.23	0.511

Data are presented as number (percentage) or mean ± standard deviation, unless otherwise indicated

AIS acute ischemic stroke, *DM* diabetes mellitus, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *HCY* homocysteine, *FBG* fasting blood glucose, *TIA* transient ischemic attack

**P* is less than 0.05 when compared with the study group

Multivariate Predictors of AIS After TIA

A multiple logistic regression analysis showed that age (odds ratio [OR] = 1.044, 95% confidence interval [CI] 1.004–1.084, $p = 0.030$), DM (OR = 2.678, 95% CI 1.212–5.913, $p = 0.015$), and serum cystatin C (OR = 3.107, 95% CI 1.177–8.206, $p = 0.022$) were independently associated with AIS (Table 3).

Table 3 Multiple logistic regression analysis of AIS in TIA patients

Variables	Odd ratio (95% confidence interval)	*P* value
Age	1.044 (1.004–1.084)	0.030*
Hypertension	2.314 (0.989–5.418)	0.053
Diabetes	2.678 (1.212–5.913)	0.015*
Atrial fibrillation	5.506 (0.821–36.924)	0.079
Cystatin C	3.107 (1.177–8.206)	0.022*

AIS acute ischemic stroke, *TIA* transient ischemic attack

Relationship Between Cystatin C and Other Factors

Spearman's correlation analysis showed that cystatin C was positively correlated with age ($r = 0.269$, $p < 0.001$), levels of homocysteine ($r = 0.325$, $p < 0.001$), uric acid ($r = 0.204$, $p = 0.002$), and intracranial vascular stenosis ($r = 0.150$, $p = 0.022$) in patients with TIA and was positively correlated with age ($r = 0.323$, $p = 0.048$) and the level of homocysteine ($r = 0.526$, $p = 0.001$) in patients with AIS (Table 4).

ROC Curve and Kaplan–Meier Analyses

A ROC curve analysis was used to detect the sensitivity and specificity of serum cystatin C for predicting 90-day AIS (Fig. 2). Serum cystatin C > 1.055 predicted 90-day AIS attacks with specificity of 73.7% and sensitivity of 70.6%, respectively (c-statistic 0.813, 95% CI 0.740–0.886, $p < 0.001$).

The Kaplan–Meier analysis showed that patients with a high serum cystatin C level had significantly higher 90-day AIS than those with a low serum cystatin C level (log-rank test, $p < 0.001$; Fig. 3).

Table 4 Spearman correlation coefficient of serum cystatin C levels with other factors among TIA and AIS patients

Variables	TIA patients		Stroke patients	
	Cystatin C	*P* value	Cystatin C	*P* value
Age	0.269	< 0.001*	0.323	0.048*
Gender	− 0.217	0.001*	− 0.375	0.020*
History of hypertension	0.067	0.311	− 0.249	0.131
History of DM	0.108	0.101	0.000	0.999
History of coronary	− 0.026	0.690	− 0.069	0.680
History of smoking	0.113	0.085	− 0.023	0.889
History of alcohol	0.043	0.519	0.152	0.363
History of atrial fibrillation	0.080	0.222	− 0.059	0.724
FBG	− 0.002	0.979	0.217	0.190
Cholesterol	− 0.019	0.775	0.002	0.989
Triglycerides	− 0.058	0.375	− 0.204	0.218
LDL	0.003	0.962	0.087	0.602
HDL	− 0.016	0.809	0.081	0.628
HCY	0.325	< 0.001*	0.526	0.001*
Uric acid	0.204	0.002*	0.314	0.055
VB_{12}	− 0.117	0.075	− 0.327	0.045*
Folic acid	− 0.113	0.085	− 0.206	0.214
HbA1c	0.033	0.614	− 0.018	0.915
ABCD2 score	0.056	0.321	0.129	0.439
Intracranial vascular stenosis	0.150	0.022*	− 0.099	0.555
Carotid artery stenosis	0.017	0.792	0.200	0.229

AIS acute ischemic stroke, *DM* diabetes mellitus, *FBG* fasting blood glucose, *TIA* transient ischemic attack, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *HCY* homocysteine

Discussion

This study revealed that serum cystatin C was significantly related to patients with TIA, and a higher serum cystatin C level was associated with AIS at the 90-day follow-up in patients with TIA. Our results indicate that a serum cystatin C level > 1.055 mg/L can be used to predict the development of AIS after TIA.

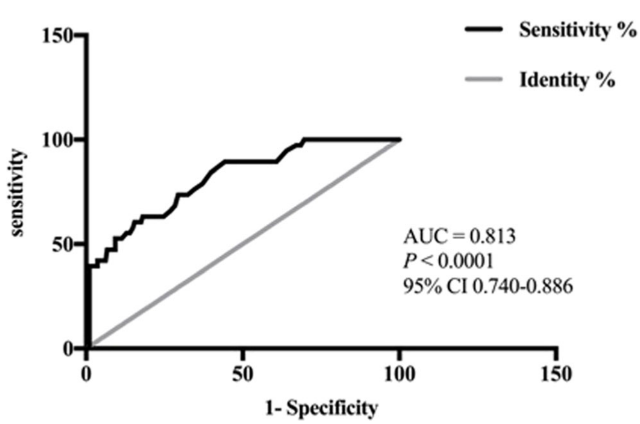

Fig. 2 Receiver operating characteristic curve of cystatin C > 1.055 mg/L for predicting a 90-day AIS attack. AUC area under the curve, CI confidence interval

It has been well recognized that cystatin C is involved in the pathophysiology of atherosclerosis and is closely related to vascular disease (Kaneko et al. 2018). Chung et al. also determined that serum cystatin C level is significantly associated with subclinical atherosclerosis, and an increase in cystatin C level could be a valuable surrogate marker for the risk of cardiovascular disease in patients with DM (Chung et al. 2018). High cystatin C levels are associated with AIS. Huang et al. suggested that

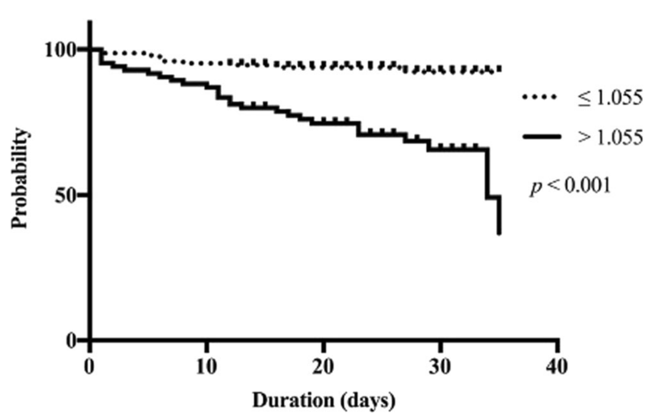

Fig. 3 Kaplan–Meier curves for cystatin C in patients with transient ischemic attack (TIA) by levels ≤ 1.055 mg/L vs. > 1.055 mg/L.

there is a close relationship between cystatin C and AIS, independent of conventional risk factors (Huang et al. 2016). Zeng et al. concluded that cystatin C is an independent risk factor for AIS, particularly in patients with large artery atherosclerosis. Furthermore, cystatin C levels predict the risk of recurrent AIS (Zeng et al. 2015). Yang concluded that an elevated level of serum cystatin C is associated with the total burden of cerebral small vessel disease in patients with acute lacunar stroke independent of conventional risk factors (Yang et al. 2017b). Cystatin C is associated not only with ischemic stroke but also with hemorrhagic cerebrovascular disease. Yoon et al. inferred that cystatin C may be the most sensitive indicator of cerebral microbleed severity among the renal disease markers, and high cystatin C is associated with an increased risk of mortality in patients with acute intracerebral hemorrhage (Oh et al. 2014).

In summary, high cystatin C levels were associated with AIS severity, recurrence and mortality, cerebral microbleeds, and cerebral hemorrhage. However, few previous studies have focused on the relationship between cystatin C level and TIA. Our results strongly suggest that serum level of cystatin C was significantly related to patients with TIA and that cystatin C could be a predictor of AIS within 90 days after TIA. The mechanism by which serum cystatin C levels increase in patients with TIA has not been fully elucidated and may be due to the following factors: (1) Cystatin C, as an inhibitor of cysteine proteases, plays an important role in the pathogenesis of atherosclerosis (Tejera-Segura et al. 2016). Intracranial arterial stenosis affects cerebral blood flow, may increase the risk of stroke, and is highly prevalent in Asia (Gonzalez et al. 2013). (2) Serum cystatin C has been considered a marker for endothelial dysfunction in the glomerulus and throughout the vascular tree (Yang et al. 2017a), so elevated cystatin C may reflect a greater degree of cerebral vessel damage during the acute phase of ischemic stroke and increase the risk of a poor prognosis (Zhu et al. 2018b). (3) Serum cystatin C concentrations are associated with higher levels of cyclic adhesion molecules (Davis et al. 2008). By expressing these adhesion molecules on endothelial cells, circulating platelets adhere to the vascular wall, thereby promoting thrombosis and increasing the probability that a TIA patient would progress to AIS (Kanhai et al. 2013). (4) Cystatin C may have direct toxic effects that contribute to its association with the risk of stroke and other cardiovascular events (Ni et al. 2007).

In addition to cystatin C, age and DM are also associated with the 90-day prognosis of TIA, consistent with previous studies. Appelros et al. reported that age and DM were the most significant risk factors for stroke after TIA (Appelros et al. 2017). Chen et al. noted that DM is associated with an increased risk of recurrent stroke in patients with minor stroke and TIA (Chen et al. 2017).

Cystatin C has been reported to be a novel marker of renal function that is not affected by gender, muscle mass, or other factors (Coll et al. 2000). However, in our study, serum cystatin C was correlated with age, levels of homocysteine and uric acid, as well as intracranial vascular stenosis in patients with TIA and AIS, respectively. This was not entirely consistent with previous studies. It has been reported that cystatin C can increase homocysteine, resulting in vascular injury and leading to the formation of thrombosis by interacting with homocysteine and cathepsin (Tobin et al. 2009). The PREVEND study found that older age, male gender, and uric acid are related to higher levels of serum cystatin C (Knight et al. 2004). Umemura et al. suggested that higher levels of cystatin C are independently associated with symptomatic extracranial internal carotid artery stenosis in patients with non-cardioembolic stroke (Umemura et al. 2016). Therefore, factors influencing cystatin C level should be considered in further studies.

Much effort has been made to predict the risk of final AIS, including ABCD2 and ABCD3-I scores (Merwick et al. 2010), and the ABCD2 risk prediction scoring system predicts who is likely to be at a higher risk of recurrent early stroke after the initial stroke or TIA, regardless of the mechanism of the acute stroke or TIA (Saedon et al. 2017). Although several major clinical guidelines recommend ABCD2 as an important prognostic tool for TIA patients (Chandratheva et al. 2010), applying the ABCD2 score alone does not meet clinical needs, and a new biomarker needs to be validated and applied in clinical practice. In this study, the ABCD2 score did not play a predictive role, but many factors affect its predictive effectiveness. However, our results show a significant correlation between increased cystatin C levels and TIA. In addition, we also showed that cystatin C was an independent predictor of 90-day outcome in TIA patients and that cystatin C level > 1.055 predicted AIS at the 90-day follow-up with specificity of 73.7% and sensitivity of 70.6%. This is the first study to investigate the association between cystatin C and TIA and the predictive value of AIS in patients with TIA with a 90-day follow-up. However, our results need to be validated in larger prospective studies.

Our study had several limitations. First, this study was conducted with limited time and a relatively small sample size, and the single-center construct was a possible source of selection bias and statistical error. A long-term prognostic follow-up study with a larger sample size in patients with TIA would be interesting. Second, although we excluded patients with renal disease and other factors that may affect cystatin C levels, some diseases and conditions that may have affected cystatin C levels may not have been considered. Future studies are required to better elucidate the predictive value of cystatin C in patients with TIA.

Conclusions

Serum cystatin C was significantly correlated with TIA. In addition, high serum cystatin C (> 1.055) was an independent predictor for the development of AIS after TIA in a 90-day follow-up. Further studies are needed to investigate the pathophysiological mechanism of cystatin C in affecting AIS in TIA patients and to confirm the value of serum cystatin C as a potential biomarker.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Conduct All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Formal consent is not required for this type of study.

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