The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2021; 28: 506-513. http://doi.org/10.5551/jat.57091

Serum Cystatin C Level as a Biomarker of Aortic Plaque in Patients with an Aortic Arch Aneurysm

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Aim: During surgery for an aortic arch aneurysm, aortic plaque in the descending aorta should be evaluated, but there are currently no suitable biomarkers for it. Surgeons should be especially aware of cerebral embolism from femoral perfusion and of peripheral embolism from stent graft deployment. Cystatin C is a known useful marker of renal dysfunction with a role as a biomarker for severity of coronary artery disease. In the absence of a suitable biomarker for aortic plaque in the descending aorta, we examine cystatin C as a candidate.

Methods: In all, 75 patients who underwent surgery for an aortic arch aneurysm were enrolled. They were divided into two groups, depending on whether they had chronic kidney disease or not. The serum cystatin C value and creatinine value were evaluated preoperatively. The aortic plaque volume ratio and components in the descending aorta were calculated from preoperative enhanced computed tomography.

Results: The soft plaque volume ratio was higher in patients with chronic kidney disease than in patients without it. Cystatin C positively correlated with the total aortic plaque volume ratio in all cases, and it positively correlated with the soft plaque volume ratio in both groups. Creatinine had no correlation with any type of plaque volume ratio in either group. In patients without chronic kidney disease, the soft plaque volume ratio was higher in patients with higher cystatin C levels than in patients with normal levels.

Conclusion: The preoperative serum cystatin C level could be a biomarker of aortic plaque in the descending aorta in patients with an aortic arch aneurysm.

See editorial vol. 28: 474-476

Key words: Cystatin C, Biomarker, Aortic plaque, Descending aorta, Aortic arch aneurysm

Introduction

Cerebral infarction during total arch replacement for an aortic arch aneurysm is a serious postoperative complication[1]. An important cause is retrograde embolism by aortic plaque in the descending aorta due to femoral perfusion during aortic surgery. This occurs especially in cases of a "shaggy aorta"[2]. The frozen elephant trunk procedure is a recent advance in aortic arch surgery, and it enables quick deployment of a stent graft into the descending aorta. The existence of aortic plaque at the deployment zone of the descending aorta is important in this procedure because it has been shown to potentially lead to paraplegia due to distal embolism to the Adamkiewicz artery[3].

Aortic plaque in the descending aorta is mainly diagnosed by enhanced computed tomography, however, computed tomography imagery alone cannot determine the character of aortic plaque, such as its vulnerability. Moreover, biomarkers for aortic plaque have not yet been fully investigated. If there were biomarkers for aortic plaque and its components, the preoperative evaluation of the risk of embolism caused by aortic plaque may be improved.

Cystatin C, an endogenous cysteine protease inhibitor, is known to be a useful marker of renal dysfunction[4]. It has been reported to have a role as a bio-

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Received: April 15, 2020 Accepted for publication: June 24, 2020

marker for severity of the intima–media thickness of the carotid artery and of coronary artery disease[5, 6].

In the preoperative evaluation of patients who will undergo cardiovascular surgery, cystatin C sometimes shows a high value despite normal creatinine levels. In such cases, we hypothesize that cystatin C might reflect the severity of atherosclerotic plaque of the aorta. Here, to assess whether the serum cystatin C level could be a biomarker for aortic plaque of the descending aorta in patients with an aortic arch aneurysm, we evaluated the relationship between cystatin C and aortic plaque and its components.

Patients and Methods

We retrospectively investigated 75 patients with an aortic arch aneurysm who underwent surgery at Wakayama Medical University, Japan between May 2010 and October 2019. This study was approved by the Wakayama Medical University Institutional Review Board (No. 2768), and informed consent was obtained from all the patients. Serum cystatin C and creatinine (Cr) were evaluated preoperatively. The estimated glomerular filtration rate (eGFR) was calculated by the following equation:

eGFR (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times age^{-0.287}$ × (0.739 if female). Chronic kidney disease (CKD) was defined as eGFR < 60 mL/min/1.73 m^2.

Patients were classified into two groups according to the eGFR values: eGFR <60 as the CKD group and eGFR ≥ 60 as the non-CKD group. Cystatin C is considered to be a more sensitive indicator of renal dysfunction than creatinine, and it can indicate early stages of renal dysfunction[4]. To clarify the difference between cystatin C and creatinine-based eGFR, subjects in the non-CKD group were further subdivided into two groups: group A (cystatin C ≤ 0.95 mg/L) and group B (cystatin C >0.95 mg/L) **(Fig. 1)**.

Preoperative computed tomography angiography (CTA) of the entire aorta was performed as routine clinical care and used for the evaluation of aortic plaque. Omnipaque 240 (Daiichi Sankyo Co., Ltd., Tokyo, Japan) was used as the contrast agent for CTA, and the amount used was 450 mg I/kg. Analysis of aortic plaque was performed using an Aquarius iNtuition Viewer (TeraRecon Inc., Foster, CA, USA). CTA images were reconstructed in the straightened multiplanar reformatting mode with centerline. The section of the thoracic aorta between the origin of the left subclavian artery and of the celiac artery was isolated as the region of interest (ROI). The program automatically calculates the volume of the aorta. Aortic plaque volume was classified into soft, intermediate, or hard. By Hounsfield units (HU), soft plaque was defined as −25 to 50 HU, intermediate plaque was defined as 51–120 HU, and hard plaque was defined as 501–2000 HU[7, 8]. Total aortic plaque volume was defined as the sum of the volume of soft, intermediate, and hard plaque. The volume of the descending aorta may vary from patient to patient. Therefore, to adjust for this difference, we defined the aortic plaque volume ratio as the percentage of the volume of each component in the total volume of the descending aorta. To differentiate aortic plaque from mural thrombus of the aortic arch aneurysm, if the aortic arch aneurysm involved the origin of the left subclavian artery, ROI was defined as the range from the distal endpoint of the aneurysm to the origin of the celiac artery. Patients with an aortic arch aneurysm combined with a descending aortic aneurysm, and patients with a highly tortuous aorta, were excluded from this study because of difficulty in measurement.

Statistical Analysis

The distribution of each variable was checked for normality using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± SD or, where indicated, median and interquartile range. Categorical variables were expressed as number and percentages. For continuous variables, statistical differences between the two groups were evaluated by the parametric unpaired *t*-test and the nonparametric Mann–Whitney *U* test. For categorical data, the two-group comparison was evaluated by the χ^2 test. Correlation analysis between biomarker and aortic plaque volume ratio was evaluated by Pearson's correlation for parametric variables and Spearman's correlation for nonparametric variables. Spearman's ρ was used as the correlation coefficient. Statistical results were reported as significant if $P < 0.05$. Statistical analysis was performed using Stat Mate III (ATMS Co., Ltd., Chiba, Japan).

Results

Patient characteristics, classified into the CKD group and the non-CKD group by renal function, are shown in **Table 1**. There were no significant differences in age, gender, total cholesterol value, triglyceride value, or low-density or high-density lipoprotein cholesterol value between the two groups. Combination with coronary artery disease (CAD) or carotid artery stenosis (CAS) was more common in the CKD group, but combination with peripheral artery disease, diabetes mellitus or an abdominal aortic aneurysm, and history of smoking was similar between the two groups.

Table 1. Subject Characteristics

	All ($n=75$)	CKD group ($n=48$)	non-CKD group ($n=27$)	*P* value
Age (year)	74.5 ± 6.4	74.9 ± 5.2	74.0 ± 8.1	0.610
Gender (male/female)	57/18	37/11	20/7	0.707
CAD (%)	31	40	15	0.048
PAD (%)	16	19	11	0.591
CAS (%)	16	25	0	0.012
AAA (%)	37	35	41	0.647
DM (%)	7	8	4	0.440
Smoking (%)	63	63	63	0.968
Cystatin C (mg/L)	1.21 ± 0.39	1.34 ± 0.40	0.95 ± 0.19	< 0.001
Creatinine (mg/dL)	1.04 ± 0.35	1.19 ± 0.36	0.78 ± 0.02	< 0.001
eGFR (ml/min/ 1.73m^2)	55.1 ± 14.6	46.5 ± 9.0	70.3 ± 9.0	< 0.001
Total Chol (mg/dL)	194 ± 43	192 ± 47	196 ± 34	0.714
Triglyceride (mg/dL)	143 ± 63	142 ± 67	144 ± 58	0.890
LDL Chol (mg/dL)	115 ± 36	112 ± 41	119 ± 27	0.381
HDL Chol (mg/dL)	46 ± 12	46 ± 12	47 ± 12	0.545

CAD: coronary artery disease, PAD: peripheral artery disease, CAS: carotid artery stenosis
AAA: abdom inal aortic aneurysm, DM: diabetes mellitus, Chol: cholesterol *P* value: CKD group vs non CKD group

Table 2. Total aortic plaque volume ratio and its component

	All ($n=75$)	CKD group ($n=48$)	non-CKD group ($n=27$)	*p* value
Total aortic plaque (%)	19.4 ± 5.5	30.4 ± 5.7	28.3 ± 3.4	0.066
Soft plaque (%)	9.4 ± 3.3	10.0 ± 3.7	8.2 ± 2.0	< 0.01
Intermediate plaque (%)	9.6 ± 2.6	9.7 ± 2.8	9.3 ± 2.3	0.531
Hard plaque (%)	0.13 (0.03-0.29)	0.15 (0.07-0.33)	0.10 (0.02-0.20)	0.082

p value: CKD group vs non CKD group

Table 3. Correlation between cystatin C and plaque volume ratio

	ALL ($n=75$)		CKD group ($n=48$)		non-CKD group ($n=27$)	
	Correlation Coefficient	*P* value	Correlation Coefficient	*P* value	Correlation Coefficient	*P* value
Total aortic plaque (%)	$r=0.266$	0.021	$\rho=0.226$	NS	$r=0.397$	0.040
Soft plaque (%)	$r=0.345$	0.002	$\rho=0.318$	< 0.05	$r=0.417$	0.030
Intermediate plaque (%)	$r=0.122$	0.297	$\rho=0.065$	NS	$r=0.296$	0.134
Hard plaque (%)	$\rho=0.253$	< 0.05	$\rho=0.205$	NS	$\rho=0.014$	NS

Table 2 shows the total aortic plaque volume ratio and its components in all cases and in cases with or without CKD. The soft plaque volume ratio was significantly higher in the CKD group than in the non-CKD group.

The correlation between cystatin C and plaque volume ratio is shown in **Table 3**. The cystatin C level correlated positively with the total aortic plaque volume ratio, soft plaque volume ratio, and hard plaque volume ratio in all cases. In terms of renal function, the cystatin C level correlated better with the soft plaque volume ratio in the CKD group. In the non-CKD group, the cystatin C level correlated best with the soft plaque volume ratio. Cystatin C also correlated with the total aortic plaque volume ratio in the non-CKD group.

The correlation between creatinine and the plaque volume ratio is shown in **Table 4**. The creati-

Table 4. Correlation between creatinine and plaque volume ratio

	ALL ($n=75$)		CKD group ($n=48$)		non-CKD group ($n=27$)	
	Correlation Coefficient	*P* value	Correlation Coefficient	*P* value	Correlation Coefficient	*P* value
Total aortic plaque (%)	$r=0.242$	0.036	$\rho=0.235$	NS	$r=0.006$	0.976
Soft plaque (%)	$r=0.359$	0.001	$r=0.278$	0.056	$r=0.137$	0.494
Intermediate plaque (%)	$r=0.024$	0.837	$r=1.04E-06$	1.0	$r=-0.131$	0.516
Hard plaque (%)	$\rho=0.151$	NS	$\rho=0.008$	NS	$\rho=0.0006$	NS

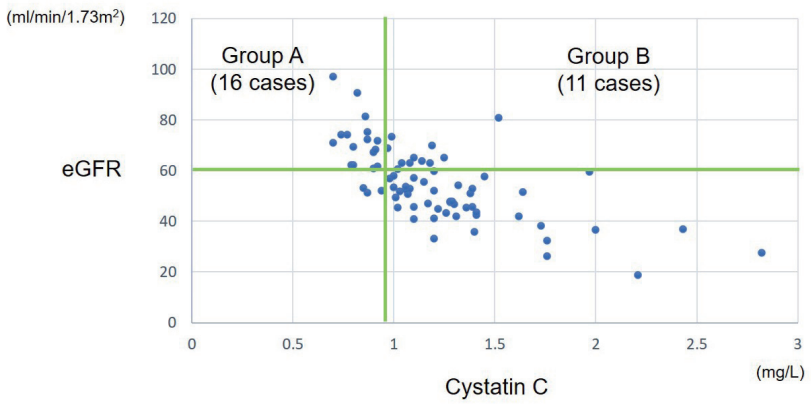

Fig. 1. Higher cystatin level in the non-CKD group

Group B showed a higher level of cystatin C among groups in which eGFR was maintained at 60 mL/min/1.73 m^2 or more.

Table 5. High cystatin C level despite normal renal function

	Group A ($n=16$)	Group B ($n=11$)	*P* value
Total aortic plaque (%)	16.6 ± 0.8	19.5 ± 1.3	0.080
Soft plaque (%)	7.5 ± 1.9	9.2 ± 2.2	0.034
Intermediate plaque (%)	8.9 ± 1.9	10.0 ± 2.7	0.241
Hard plaque (%)	0.09 (0.02-0.27)	0.10 (0.01-0.16)	NS

Group A: Cystatin C < 0.95, eGFR > 60
Group B: Cystatin C > 0.95, eGFR > 60

nine level correlated positively with the total aortic plaque volume and soft plaque in all cases. There were no significant correlations, however, with the total aortic plaque volume ratio or its components in either the CKD group or the non-CKD group.

As mentioned in the patients and methods section, to clarify the difference between cystatin C and creatinine-based eGFR, subjects in the non-CKD group were further subdivided into two groups: group A (cystatin C ≤ 0.95 mg/L) and group B (cystatin C > 0.95 mg/L) **(Fig. 1)**. **Table 5** shows the total aortic plaque volume ratio and its components in groups A and B; the soft plaque volume ratio was higher in group B than in group A.

Preoperative laboratory data, including total cholesterol, triglyceride, and high-density/low-density lipoprotein cholesterol, did not positively correlate with the total aortic plaque volume ratio or its components.

In relation to cystatin C and atherosclerosis, CAD and CAS as co-morbidities have been reported to be associated with higher serum cystatin C levels[9]. In addition, CAD and CAS were significantly different between the CKD group and the non-CKD group among the subjects **(Table 1)**. We therefore considered that CAD and CAS could be confounding factors in the association between cystatin C and aortic plaque, and conducted the same study in 47 cases

Table 6. Correlation between cystatin C and plaque volume ratio in patients without coronary artery disease and carotid artery stenosis

	Patient without CAD and CAS ($n=47$)		CKD group ($n=24$)		non-CKD group ($n=23$)	
	Correlation Coefficient	*P* value	Correlation Coefficient	*P* value	Correlation Coefficient	*P* value
Total aortic plaque (%)	$r=0.235$	0.112	$r=0.111$	0.604	$r=0.451$	0.031
Soft plaque (%)	$r=0.334$	0.022	$r=0.292$	0.167	$r=0.436$	0.038
Intermediate plaque (%)	$r=0.159$	0.285	$r=0.078$	0.719	$r=0.389$	0.066
Hard plaque (%)	$\rho=0.234$	NS	$\rho=0.248$	NS	$\rho=0.095$	NS

CAD: coronary artery disease, CAS: carotid artery stenosis

Table 7. Correlation between creatinine and plaque volume ratio in patients without coronary artery disease and carotid artery stenosis

	Patient without CAD and CAS ($n=47$)		CKD group ($n=24$)		non-CKD group ($n=23$)	
	Correlation Coefficient	*P* value	Correlation Coefficient	*P* value	Correlation Coefficient	*P* value
Total aortic plaque (%)	$r=0.094$	0.532	$r=0.006$	0.979	$r=-0.0004$	0.998
Soft plaque (%)	$r=0.182$	0.220	$r=0.131$	0.543	$r=0.147$	0.502
Intermediate plaque (%)	$r=-0.005$	0.976	$r=-0.040$	0.854	$r=-0.126$	0.567
Hard plaque (%)	$\rho=0.080$	NS	$\rho=-0.070$	NS	$\rho=0.024$	NS

CAD: coronary artery disease, CAS: carotid artery stenosis

Table 8. High cystatin C level despite normal renal function in patients without coronary artery disease and carotid artery stenosis

	Group A ($n=16$)	Group B ($n=7$)	*P* value
Total aortic plaque (%)	16.6 ± 3.2	20.2 ± 4.9	0.113
Soft plaque (%)	7.5 ± 1.8	9.5 ± 2.1	0.032
Intermediate plaque (%)	8.9 ± 1.9	10.6 ± 3.1	0.215
Hard plaque (%)	0.09 (0.02-0.27)	0.10 (0.06-0.14)	NS

Group A: Cystatin C < 0.95, eGFR > 60
Group B: Cystatin C > 0.95, eGFR > 60

after the exclusion of subjects with CAD and CAS (Tables 6–8). Cystatin C significantly correlated with the soft plaque volume ratio in patients without CAD and CAS. In the non-CKD group, cystatin C significantly correlated with the total aortic plaque volume ratio and soft plaque volume ratio (Table 6). Creatinine did not show any correlation with aortic plaque volume and its components in patients without CAD and CAS (Table 7). In patients who had higher cystatin C levels in the non-CKD group without CAD and CAS, the soft plaque volume ratio was higher than in patients who had normal cystatin C levels (Table 8).

Within this study cohort, we did not observe postoperative cerebral infarction or distal thromboembolism in clinical practice, including spinal ischemia and intestinal ischemia.

Discussion

We investigated biomarkers for aortic plaque in the descending aorta of patients with an aortic arch aneurysm. Preoperative serum cystatin C levels were found to be correlated with aortic plaque volume in the descending aorta and also with soft plaque volume by components. If patients with CAD and CAS were excluded, the preoperative cystatin C level also correlated with soft plaque volume.

To date, biomarkers for aortic plaque have not been widely investigated. Momiyama *et al.* reported

that plasma high-sensitivity C-reactive protein (hsCRP) correlates with aortic plaque using the plaque score based on aortic magnetic resonance imaging slices[10]. Agmon *et al.* reported the association between the hsCRP level and the presence of aortic plaque using three segments of images of intimal thickness by transesophageal echocardiography[11]. Regarding cystatin C as a biomarker of atherosclerosis, Sugiyama *et al.* reported that serum cystatin C levels are associated with coronary artery calcification examined by multidetector computed tomography[5]. Kaneko *et al.* reported that the serum cystatin C level was associated with carotid arterial elasticity[6]. To the best of our knowledge, however, there have been no reports on the relationship between cystatin C and aortic plaque and its components.

It can be speculated that there are two possible mechanisms by which cystatin C correlates with total aortic volume and soft plaque volume: the effect of renal dysfunction on aortic plaque, and the direct effect of cystatin C on aortic plaque aside from renal dysfunction.

Association between Atherosclerotic Plaque and Cystatin C Reflecting Renal Dysfunction

In the present study, the soft plaque volume ratio was higher in the CKD group than in the non-CKD group. Both the cystatin C level and creatinine level showed a positive correlation with the soft plaque volume ratio in all cases. These results suggest that renal dysfunction itself may promote the development of soft plaque in the descending aorta. Amann *et al.* reported that uremia may affect the wall thickness of the aorta in experimental renal failure[12]. The presence of CKD was reported by Matsumura *et al.* to be associated with complex aortic plaques detected using transesophageal echocardiography, and they suggested that this association is stronger in the descending aorta than in the proximal aorta[13]. As a possible mechanism, they suggested embolization of the plaque from the descending aorta to renal vasculature, or an association between CKD and systemic atherosclerosis.

In our cohort, however, when patients were divided into CKD and non-CKD groups, cystatin C and creatinine showed different correlations with the soft plaque volume ratio. The cystatin C level showed a positive correlation with the soft plaque volume ratio in both the CKD and non-CKD groups in all cases, but the creatinine level did not. These results suggest that cystatin C and creatinine, which are both indicators of renal function, differ as biomarkers for aortic plaque. To clarify this difference, we evaluated the cases in which serum cystatin C shows a high value despite retention of renal function (creatinine-based eGFR ≥ 60 mL/min/1.73 m^2), and we found that a higher cystatin C level in the non-CKD group was associated with a greater soft plaque volume ratio. This may be because cystatin C reflects early renal dysfunction better than creatinine-based eGFR. Similar reports have been made regarding CAD. Shlipak *et al.* reported that cystatin C, which reflects the state of preclinical kidney disease, is a prognostic biomarker of risk for cardiovascular disease among elderly persons without CKD[14]. Imai *et al.* reported that cystatin C concentrations were correlated with early-stage coronary atherosclerotic plaque among patients without established chronic kidney dysfunction. In their report, the mechanism of this association was assumed to represent early kidney disease[15].

Effect of Cystatin C on Atherosclerotic Plaque other than Renal Dysfunction

Regarding the difference between the effects of cystatin C and creatinine on aortic plaque, effects other than renal dysfunction may be a consideration. Koenig *et al.* reported that cystatin C concentrations have a strong association with secondary cardiovascular events in patients with CAD[16]. They speculated that plasma cystatin C increased to compensate for the increased activity of elastolytic cysteine protease stimulated by inflammatory cytokines during vascular injury. Batra *et al.* reported that higher plasma cystatin C levels were associated with a higher carotid intima–media thickness, and in patients with normal or near-normal renal function, higher cystatin C levels were associated with severity of CAD[17]. They postulated that the association between cystatin C and cardiovascular events may be due either to direct pathological effects or to a heightened inflammatory state and clustering with other risk factors. Regarding the direct pathological effect of cystatin C for the aorta, Shi *et al.* reported that cystatin C expression decreased in the wall of an abdominal aortic aneurysm[18]. Conversely, elastolytic cathepsin, for which cystatin C is an inhibitor, is overexpressed both in the atherosclerotic plaque and in the wall of the abdominal aortic aneurysm. Abisi *et al.* investigated the activity of cathepsin and cystatin C in the wall of the abdominal aortic aneurysm and aortic occlusive disease. They found that the cystatin C levels were significantly lower in the wall of the abdominal aortic aneurysm compared with the levels in aortic occlusive disease[19]. Salgado *et al.* reported on the discrepancy between tissue and circulating cystatin C levels. They speculated that higher serum cystatin C would result from cytokine-stimulated cells, which release cystatin C into circulation during atherosclerosis and compensate for the decreased cystatin C in the plaque[9]. They also sug-

gested that cystatin C has different roles in circulation and in the plaque.

Cystatin C and Plaque Vulnerability

In the current study, cystatin C had notable correlation with soft plaque among the plaque components. Soft plaque can be considered as unstable, vulnerable, or noncalcified. Zhao *et al.* reported that cystatin C was downregulated in the unstable plaque of the popliteal artery[20]. The interplay between cathepsin and cystatin C may underlie the progression of plaques from stable to unstable. Regarding the association between cystatin C and plaque vulnerability, Dai *et al.* reported that cystatin C-based eGFR is related to a higher prevalence of vulnerable plaque of CAD by optical coherence tomography compared with creatinine-based eGFR[21]. Serum cystatin C concentrations were reported by Imai *et al.* to be more strongly associated with noncalcified plaques in CAD detected by multidetector computed tomography[15].

Whatever the mechanism, our results suggest that in patients with an aortic arch aneurysm with near-normal renal function, higher cystatin C levels are associated with soft plaque volume in the descending aorta. Therefore, if significant plaque is detected in the descending aorta by preoperative CTA in patients with an aortic arch aneurysm, serum cystatin C may be used as a biomarker. If the serum cystatin C levels are high, it is suggested that there will be a larger quantity of soft plaques in the descending aorta. In such cases, a surgical strategy should be considered, including the site of arterial perfusion selection, with the assumption that aortic plaque in the descending aorta is vulnerable.

Study Limitation

We used the correlation coefficient as a statistical analysis in this study. There is no way to adjust the confounding factor for the correlation coefficient statistically; therefore, subgroup analyses excluding CAD and CAS were performed as an alternative method. Owing to the small number of cases, however, the effects of age and sex on cystatin C could not be adjusted. In this study, it was not possible to examine the clinical effect of the relationship between serum cystatin C levels and aortic plaque on perioperative complications during total arch replacement for an aortic arch aneurysm. Moreover, the number of cases was small, and further evaluation is needed.

Conclusion

Preoperative serum cystatin C levels could be a biomarker for aortic plaque in the descending aorta in patients with an aortic arch aneurysm. The effect of cystatin C on the progression of soft plaque volume was suggested by both the effect of renal dysfunction and the direct effect of cystatin C on atherosclerosis.

Acknowledgements

We acknowledge proofreading and editing by Benjamin Phillis at the Clinical Study Support Center, Wakayama Medical University.

Notice of Grant

This study was financially supported by research funding from KAKENHI.

Conflicts of Interest

This study was financially supported by research funding from KAKENHI. There are no other conflicts of interest to declare.

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