**Correlation Between Plasma Matrix Metalloproteinase-28 Levels and Severity of Calcific Aortic Valve Stenosis**

**Background:** Calcific aortic valve disease is a common cardiovascular disorder worldwide. This study aimed to investigate the correlation between plasma matrix metalloproteinase-28 (MMP-28) levels and the severity of calcific aortic valve stenosis.

**Material/Methods:** Calcific aortic valve stenosis patients who were admitted to the heart center of our hospital between January 2016 and January 2019 to undergo surgery were successively enrolled in this study (55 males and 24 females with an average age of 58.5±9.6). Information on echocardiography, plasma MMP-28 levels, and other clinical data of the patients was retrospectively collected.

**Results:** The average plasma MMP-28 level was 2.43±2.22 ng/mL (range, 0.22–8.27 ng/mL). Plasma MMP-28 levels in patients with mild (n=24), moderate (n=31), or severe (n=24) aortic valve stenosis were 0.74 (0.25–2.23), 1.46 (0.50–3.22), and 4.13 (1.54–6.18) ng/mL, respectively, indicating that the patients with severe aortic valve stenosis had significantly higher MMP-28 levels than the patients with moderate or mild aortic valve stenosis (both \( P < 0.01 \)). Regression analysis using the general linear model further revealed that plasma MMP-28 level was correlated with the peak blood flow velocity and mean pressure gradient of the transaortic valve, and the correlations were statistically significant (both \( P < 0.01 \)).

**Conclusions:** MMP-28 level is significantly elevated in severe cases of calcific aortic valve stenosis. Moreover, plasma MMP-28 levels are positively correlated with the mean pressure gradients and peak blood flow velocity of the transaortic valve.

**MeSH Keywords:** Aortic Valve Stenosis • Extracellular Matrix Proteins • Heart Valves

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Calcific aortic valve disease (CAVD) is a common cardiovascular disorder worldwide. Aortic valve stenosis (AVS) is the most frequent type of CAVD in adults, and its prevalence surpasses those of congenital bicuspid and degenerative tricuspid aortic valve diseases as well as immune factor-related rheumatic heart disease. If left untreated, AVS can have dire consequences on patient health [1,2]. With the improvement in the quality of life and life expectancy of societies, degenerative aortic valve diseases have replaced rheumatic aortic valve disease as the most common CAVD disorders [3]. Once stenosis develops, transcatheter aortic valve replacement becomes the best treatment option [4,5]. Valve stenosis grading, cardiac function evaluation, and prognostic assessment of patients serve as important indicators of surgery and its potential benefits prior to transcatheter aortic valve replacement [6].

Matrix metalloproteinases (MMPs) are a group of zinc-dependent proteolytic enzymes that can degrade collagen and proteoglycans and play key roles in coronary and degenerative heart diseases [7–9]. For example, the human MMP, MMP-28, although only recently identified, has already been reported to be associated with cardiovascular diseases [10]. Nevertheless, there are very limited independent correlation studies regarding MMP-28 and AVS among AVS patients. Thus, it is necessary to determine the risk factors for CAVD and understand the correlation between MMP-28 and the disease. Hence, this study assessed the correlation between MMP-28 and the severity of AVS, with the aim of providing a reference for the development of effective interventions in the future.

**Material and Methods**

**Subjects**

From January 2016 to January 2019, 79 CAVS patients were successively enrolled in the study after being admitted to our heart center for surgery. Since this was a retrospective study, the patients received no human intervention. All demographic and clinical information was retrospectively collected; the study flowchart is shown in Figure 1. The project was reviewed and approved by the ethics committee of the hospital, and all of the enrolled patients signed an informed consent form for the study.

**Enrollment criteria**

Patients had to meet the diagnostic criteria for AVS set forth by the American Society of Echocardiography and the European Association of Echocardiography [11,12]. The diagnosis of CAVS was confirmed based on the clinical manifestations and echocardiography results.

**Exclusion criteria**

Patients were excluded from the study if they exhibited any of the following conditions: (1) large-scale pulmonary embolism; (2) complications of severe infectious diseases; (3) malignant tumors; (4) pericardial diseases with combinatorial cardiomyopathy; (5) severe liver or kidney dysfunctions or coagulopathy; (6) severe anemia; (7) pregnancy; or (8) any other condition the researchers considered unsuitable for inclusion of the patient into the study.

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**Figure 1.** Flowchart of patient enrollment. Overall, 79 patients participated in this study.
Methods

The clinical data of all the patients were collected and included age, gender, systolic and diastolic blood pressures, and any history of hypertension, diabetes, coronary heart disease, and cholesterol-lowering treatments. Fasting venous blood samples (5 mL) were obtained from the patients within 24 h of admission. The blood samples were kept at room temperature for 2 h before being centrifuged at 1000 rpm. The supernatant was collected and stored at –80°C. Before the experiment, the samples were completely thawed at room temperature and mixed well. Other related biochemical markers in the blood samples were also examined.

Plasma MMP-28 levels were measured using an ELISA kit (ELISA Genie, Dublin, Ireland), following the manufacturer's instructions.

Echocardiography

Echocardiography was performed using a GE Vivid E9 ultrasound system at the frequency of 1.7–3.4 MHz with an M4S probe. The data were collected under both the left lateral and supine body positions. The selected image sections were the parasternal long axial view of the left ventricle, main short-axial section of the aortic root, and apical 5-chamber view. The inner diameters of the ascending aorta, left atrium, as well as the left ventricular end-diastolic diameter, left ventricular ejection fraction, supra-aortic flow velocity, mean pressure gradient of the transaortic valve, and thickness of the inter-ventricular basal septum, were measured using M-mode and 2-dimensional ultrasound imaging in addition to color flow and spectral doppler echocardiography. The degrees of stenosis were determined primarily through the mean pressure gradients (pressure differences) of the transaortic valves, aortic valve area, and stroke volume index [11,12]. Patients with <10 mmHg of mean pressure differences were not included even if they had thickened or calcified valves.

Statistical analyses

Statistical analyses were performed using SPSS 17.0 software. All measurement data were expressed as (mean±standard deviation) or median and interquartile range. Normally distributed data were compared using the t-test, whereas data following a non-normal distribution were analyzed using a nonparametric test. Count data were analyzed using the Chi-squared test or Fisher’s test. Linear regression was used for correlation analysis, and differences were considered statistically significant when P<0.05.

Results

Baseline information

A total of 79 patients with an average age of 58.5±9.6 years were included in this study. Of these, 55 were males, and 24 were females. Additional patient data including body mass index, EuroSCORE and EuroSCOREII, New York Heart Association classification, status of hypertension, diabetes, dyslipidemia, or peripheral vascular disease, as well as history of strokes, dyskinesia, recent myocardial infarction, atrial fibrillation, left ventricular ejection fraction, or pulmonary hypertension were collected (Table 1).

CAVS was diagnosed in all patients based on their clinical data, combined with results of echocardiography examination. The results showed that 12 (15.2%) patients had rheumatic heart disease, 13 (16.5%) had congenital aortic valve disease, 43 (54.4%) had degenerative changes in their aortic valves, and 11 (13.9%) had other types of AVS (Figure 2). After clinical evaluation and preparation, 46 patients received surgical treatment, 12 patients underwent transcatheter aortic valve replacement, and 21 patients received conservative medical treatment.

Results of echocardiography

Transthoracic and/or transesophageal echocardiography were performed on every patient, and the following parameters were evaluated: left ventricular end-diastolic diameter, interventricular septal thickness, left ventricular posterior wall thickness, left ventricular ejection fraction, presence or absence of aortic valve reflux, maximum pressure gradient, peak flow velocity, and mean pressure gradient of the transaortic valve (Table 2).

Measurement of plasma MMP-28 levels

The average plasma MMP-28 level of the patients was 2.43±2.22 ng/mL (range, 0.22–8.27 ng/mL). Based on the results of echocardiography, the 79 patients were divided into 3 groups of mild (n=24), moderate (n=31), and severe (n=24) cases of aortic stenosis. The median and interquartile range plasma levels of MMP-28 in these 3 groups were 0.74 (0.25–2.23), 1.46 (0.50–3.22), and 4.13 (1.54–6.18) ng/mL, respectively. It is quite evident that the average MMP-28 level of the patients with severe aortic stenosis was significantly higher than those of the moderate or mild groups (both P<0.01; Figure 3).

Correlation analysis

Linear regression analysis results demonstrated that the plasma MMP-28 level was positively correlated with the peak blood flow velocity (R²=0.388), mean pressure gradient (R²=0.343) of
### Table 1. Baseline characteristics of the study population.

| Variables                              | AVA (cm²) | Mean gradient (mmHg) | SVI (mL/m²) |
|----------------------------------------|-----------|----------------------|-------------|
|                                        | >1.5      | 1.0–1.5              | <1.0        |
|                                        | n         |                      |             |
|                                        | 25        | 33                   | 21          |
|                                        | 24        | 31                   | 24          |
|                                        | 47        | 32                   | 79          |
| Age (years), mean±SD                   | 57.7±9.9  | 59.2±9.4             | 58.2±9.8    |
|                                        | 58.7±8.5  | 58.8±10.5            | 57.8±9.8    |
|                                        | 59.5±8.8  | 56.9±10.6            | 58.5±9.6    |
| Gender (M/F)                           | 19/6      | 21/12                | 15/6        |
|                                        | 19/5      | 19/12                | 17/7        |
|                                        | 55/24     |                      |             |
| Body mass index (kg/m²), mean±SD      | 24.2±1.9  | 24.2±2.6             | 24.9±2.9    |
|                                        | 23.6±2.0  | 24.7±2.3             | 24.7±2.9    |
|                                        | 24.5±2.2  | 24.1±2.8             | 24.4±2.5    |
| Hypertension, n (%)                    | 16 (20.2) | 17 (21.5)            | 11 (13.9)   |
|                                        | 17 (21.5) | 14 (17.7)            | 13 (16.5)   |
|                                        | 28 (35.4) | 16 (20.2)            | 44 (55.7)   |
| Diabetes, n (%)                        | 12 (15.2) | 15 (18.9)            | 8 (10.1)    |
|                                        | 11 (13.9) | 14 (17.7)            | 10 (12.7)   |
|                                        | 18 (22.8) | 17 (21.5)            | 35 (44.3)   |
| Dyslipidemia, n (%)                    | 18 (22.8) | 23 (29.1)            | 11 (13.9)   |
|                                        | 18 (22.8) | 21 (26.6)            | 13 (16.5)   |
|                                        | 29 (36.7) | 23 (29.1)            | 52 (65.8)   |
| Extracardiac arteriopathy, n (%)      | 2 (2.5)   | 2 (2.5)              | 2 (2.5)     |
|                                        | 1 (1.2)   | 4 (5.1)              | 1 (1.2)     |
|                                        | 4 (5.1)   | 1 (2.5)              | 6 (7.6)     |
| Chronic lung disease, n (%)            | 1 (1.2)   | 6 (7.6)              | 2 (2.5)     |
|                                        | 1 (1.2)   | 5 (6.3)              | 3 (3.8)     |
|                                        | 5 (6.3)   | 4 (5.1)              | 9 (11.4)    |
| Previous stroke, n (%)                 | 11 (13.9) | 10 (12.7)            | 4 (5.1)     |
|                                        | 13 (16.5) | 6 (7.6)              | 6 (7.6)     |
|                                        | 15 (12.2) | 13 (16.5)            | 25 (31.6)   |
| Poor mobility, n (%)                   | 2 (2.5)   | 5 (6.3)              | 3 (3.8)     |
|                                        | 3 (3.8)   | 5 (6.3)              | 2 (2.5)     |
|                                        | 5 (6.3)   | 5 (6.3)              | 10 (12.7)   |
| Concomitant coronary disease, n (%)    | 3 (3.8)   | 7 (8.9)              | 6 (7.6)     |
|                                        | 4 (5.1)   | 4 (5.1)              | 8 (10.1)    |
|                                        | 8 (10.1)  | 8 (10.1)             | 16 (20.3)   |
| Recent acute myocardial infarction (within 90 days), n (%) | 3 (3.8) | 6 (7.6) | 2 (2.5) | 7 (8.9) | 7 (8.9) | 10 (12.7) | 6 (7.6) | 16 (20.3) |
| NYHA functional class, n (%)           | 1 (1.2)   | 5 (6.3)              | 7 (8.9)     |
|                                        | 11 (13.9) | 6 (7.6)              | 9 (11.4)    |
|                                        | 2 (2.5)   | 8 (10.1)             | 9 (11.4)    |
|                                        | 10 (12.7) | 10 (12.7)            | 17 (21.5)   |
| LVEF (%), n (%)                        | 6 (7.6)   | 4 (5.1)              | 0 (0)       |
|                                        | 7 (8.9)   | 10 (12.7)            | 0 (0)       |
|                                        | 3 (3.8)   | 7 (8.9)              | 10 (12.7)   |
| NYHA II                                | 6 (7.6)   | 4 (5.1)              | 0 (0)       |
|                                        | 7 (8.9)   | 10 (12.7)            | 0 (0)       |
|                                        | 3 (3.8)   | 7 (8.9)              | 10 (12.7)   |
| Recent acute myocardial infarction (within 90 days), n (%) | 6 (7.6) | 4 (5.1) | 0 (0) | 2 (2.5) | 2 (2.5) | 3 (3.8) | 1 (1.2) | 4 (5.1) |
| NYHA III                               | 6 (7.6)   | 4 (5.1)              | 0 (0)       |
|                                        | 7 (8.9)   | 10 (12.7)            | 0 (0)       |
|                                        | 3 (3.8)   | 7 (8.9)              | 10 (12.7)   |
| Pulmonary hypertension, n (%)          | 1 (1.2)   | 3 (3.8)              | 1 (1.2)     |
|                                        | 1 (1.2)   | 4 (5.1)              | 3 (3.8)     |
|                                        | 2 (2.5)   | 3 (3.8)              | 5 (6.3)     |
| Normal                                 | 15 (18.9) | 19 (24.1)            | 13 (16.5)   |
| Moderate (31±55 mmHg)                  | 9 (11.4)  | 11 (13.9)            | 7 (8.9)     |
|                                        | 7 (8.9)   | 12 (15.2)            | 8 (10.1)    |
|                                        | 16 (20.2) | 11 (13.9)            | 27 (34.2)   |
| Severe (>55 mmHg)                      | 1 (1.2)   | 3 (3.8)              | 1 (1.2)     |
|                                        | 1 (1.2)   | 1 (1.2)              | 3 (3.8)     |
|                                        | 2 (2.5)   | 3 (3.8)              | 5 (6.3)     |
| EuroSCORE, mean±SD                     | 12.4±3.2  | 12.8±3.5             | 12.7±2.7    |
|                                        | 12.1±3.1  | 13.0±3.5             | 12.6±2.8    |
|                                        | 12.6±3.0  | 12.7±3.4             | 12.6±3.2    |
| EuroSCORE II, mean±SD                  | 2.2±1.1   | 2.4±1.4              | 2.3±1.6     |
|                                        | 2.3±1.3   | 2.5±1.3              | 2.1±1.5     |
|                                        | 2.4±1.3   | 2.2±1.4              | 2.3±1.4     |

AVA – aortic valve area; SVI – stroke volume index; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association; SD – standard deviation.
Total=79

| N=11 (13.9%) | N=12 (15.2%) | N=43 (54.4%) |

Rheumatic valvular disease
Congenital aortic valvular malformation
Degenerative valvular disease
Other causes

**Figure 2.** The contributors of the calcific aortic valve stenosis.

**Figure 3.** Plasma MMP-28 levels in groups with different severity of calcific aortic valve stenosis. The levels of MMP-28 in mild, moderate, and severe stenosis groups were 1.33±1.47, 2.04±1.85, and 4.02±2.44 ng/mL, respectively. The level of MMP-28 was significantly higher in the severe stenosis group than in the other groups (P<0.05).

**Table 2.** Echocardiographic parameters.

| Variables | AVA (cm²) | Mean gradient (mmHg) | SVi (mL/m²) | Total |
|-----------|-----------|-----------------------|-------------|-------|
|           | >1.5      | 1.0–1.5 | <1.0 | <20 | 20–40 | >40 | <35 | >35 |
| n         |           |          |       |     |       |     |     |     |
| LVEDD (mm), mean±SD | 48.0±4.6 | 49.1±4.9 | 48.8±4.9 | 46.7±4.2 | 50.3±5.1 | 48.6±4.5 | 49.3±4.9 | 47.8±4.7 | 48.7±4.8 |
| IVST (mm), mean±SD    | 13.2±1.8 | 12.8±2.1 | 13.1±1.9 | 13.3±1.8 | 12.7±2.2 | 13.1±1.8 | 13.4±1.9 | 12.5±1.9 | 13.0±1.9 |
| LVPWT (mm), mean±SD   | 13.6±2.1 | 12.6±1.9 | 13.1±2.1 | 13.5±2.0 | 12.8±2.0 | 13.0±1.9 | 13.3±1.9 | 12.6±2.0 | 13.1±2.0 |
| Peak transaortic valve flow velocity (m/s), mean±SD | 2.9±0.3 | 3.4±0.4 | 5.3±1.1 | 2.8±0.1 | 3.4±0.3 | 5.2±1.1 | 3.7±1.1 | 3.9±1.3 | 3.8±1.2 |
| Mean transaortic pressure gradient (mmHg), mean±SD | 25.3±2.0 | 31.4±2.9 | 50.1±10.0 | 34.3±1.3 | 34.3±1.3 | 34.3±1.3 | 33.6±10.4 | 35.6±12.6 | 34.3±1.3 |
| LVEF (%), mean±SD | 51.9±10.0 | 52.6±13.2 | 53.5±11.1 | 53.8±10.6 | 53.7±12.4 | 50.0±11.7 | 50.6±10.0 | 54.2±12.5 | 52.6±11.6 |
| Associated aortic regurgitation >II/IV, n (%) | 10 | 18 | 16 | 11 | 16 | 17 | 24 | 20 | 44 |
| AVA (cm²), mean±SD | 1.9±0.2 | 1.4±0.3 | 0.8±0.2 | 1.9±0.2 | 1.4±0.3 | 0.8±0.2 | 1.4±0.4 | 1.3±0.5 | 1.4±0.5 |
| SVi (mL/m²), mean±SD | 34.6±7.7 | 32.9±6.7 | 28.9±6.2 | 34.7±7.5 | 32.8±6.9 | 29.3±8.1 | 28.6±4.2 | 37.9±8.2 | 32.4±7.7 |

LVEDD – left ventricular end-diastolic dimension; IVST – interventricular septal thickness; LVPWT – left ventricular posterior wall thickness; LVEF – left ventricular ejection fraction; AVA – aortic valve area; SVi – stroke volume index; SD – standard deviation.
the transaortic valve, and aortic valve area values ($R^2=0.107$), and the correlations were statistically significant (both $P<0.01$; Figure 4).

**Discussion**

CAVD is a progressive disease, and its most frequent clinical manifestation is AVS. The incidence of CAVD exponentially increases with age [13], and CAVD was previously considered as a primary outcome of aging. However, recent studies have discovered that CAVD is actually an active pathophysiological process caused by progressive inflammation, lipid deposition, and calcification of the valve, although the exact pathogenesis of the disease is not clearly understood [14]. Early clinical research has revealed that some risk factors that promote the development of atherosclerosis, including male sex, history of hypertension, diabetes, or abnormal lipoprotein (Lp) (a) or LDL-C levels, increase the risk of CAVD [15]. Through research and analysis, the correlation between plasma levels of MMP-28 and the severity of AVS in CAVD was confirmed and proven to be valuable.

Present studies on the roles of biomarkers in CAVD focus mostly on Lp (a) [16]. In a large-scale clinical study in Europe involving 11 years of follow-up, researchers discovered that mutations in the LPA gene could lead to AVS through regulating the levels of Lp (a) [17]. Nonetheless, there are still many conflicting results from correlation studies regarding Lp (a) and AVS. Mahabadi et al. [18] found that Lp (a) levels in people ≥70 years old show no correlation with aortic valve calcification or with the development of clinical AVS. Similarly, Capoulade et al. [19] found that metabolic syndrome, a disease that is closely related to the progression of AVS in younger populations, shows no apparent association with the occurrence of AVS in people ≥57 years old. Other studies have suggested that aging and the presence of bicuspid aortic valve are the two most prominent risk factors for AVS development, whereas other factors accelerate the progression of AVS, such as male sex, smoking, or having hypertension, obesity, metabolic syndrome, secondary hyperparathyroidism, renal failure, or elevated Lp (a) [20]. However, Ljungberg et al. [21] reported that although Lp (a) levels can predict AVS in patients with CAVD, there is no correlation between changes in Lp (a) levels and AVS in patients without calcified aortic valves.

MMPs are a family of zinc-dependent endopeptidases that break down the extracellular matrix and basement membrane under various physiological conditions. These zinc-dependent endopeptidases are usually produced by fibroblasts, neutrophils, macrophages, and tumor cells [22]. MMPs directly regulate the adhesion and migration of cells, while the degree of extracellular matrix degradation is strictly controlled by the equilibrium between the total amounts of activated MMPs and their inhibitors, tissue inhibitor of matrix metalloproteinases [23]. Furthermore, the overexpression and activation of MMPs have been linked to many diseases, such as cancer, rheumatoid arthritis, emphysema, atherosclerosis, corneal ulcer, and periodontitis [24–27]. MMP-28, also known as epilysin, is a newly identified member of the MMP family. MMP-28 was initially cloned from cDNA libraries of human keratinized epithelia and testicular tissues in 2000 by Lohi and Wilson [28]. Some researchers have found that the MMP-28 protein levels in some cancer tissues are higher than those in normal tissues [29]. Accordingly, MMP-28 is upregulated in malignant tumors and cancer cell lines [30]. However, not many studies have investigated the functional aspects of MMP-28 in cardiovascular health. Therefore, in this study, we focused on this aspect to provide some clinical evidence and data on the association of MMP-28 levels with the progression of CAVDs.

Using a mouse model, Ma et al. [31] found that the expression of MMP-28 in the left ventricle increased by 42% with age. However, in MMP-28 knockout mice (MMP-28$^{–/–}$), the levels of

![Figure 4](image-url)

**Figure 4.** (A–C) Correlation among peak transaortic valve flow velocity, mean transaortic pressure gradient, aortic valve area values, and MMP-28. MMP-28 level was positively correlated with peak transaortic valve flow velocity, mean transaortic pressure gradient, and aortic valve area values in patients with AVS; $P<0.01$.
many inflammatory factors, such as the macrophage inflammatory proteins MIP-1α and MIP-1β, and MMP-9 increase in the left ventricle. These results suggest that MMP-28 is involved in the regulation of myocardial inflammation and extracellular matrix responses in the heart tissue. Ma et al. [32] further showed that following induction of myocardial infarction, more noticeable ventricular remodeling and functional deterioration were observed in the hearts of MMP-28−/− mice compared to those in normal controls. In our study, we also noticed that in the patient group with severe AVS, MMP-28 levels were closely correlated with mean pressure gradient and peak blood flow velocity of the transaortic valve.

Liu et al. [33] found that plasma MMP-28 level also increases in patients with stable coronary heart diseases and is related to the severity of the lesions in the coronary artery, indicating that MMP-28 may play a role in atherosclerotic disease. After examining the role of MMP-28 in patients with atrial fibrillation, Zhan et al. [34] concluded that MMP-28 affected the inner diameter of the left atrium and the prognosis of heart failure. These studies have proven from multiple aspects that MMP-28 has value as a novel biomarker for cardiovascular diseases. In this study, the levels of MMP-28 were found to be significantly elevated as the severity of AVS increased, and the changes were also positively correlated with the mean pressure gradient and the peak blood flow velocity of the transaortic valve. Therefore, the results of this study confirmed that plasma MMP-28 level can be used as a clinical marker to assess the severity of AVS.

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Nevertheless, this study has some limitations. First, as a retrospective study, it is restricted by several limiting factors, including small sample size and selection bias. Second, given its retrospective nature, it was impossible to evaluate the association between MMP-28 gene expression and the onset of AVS. Lastly, the clinical manifestations of CAVD were assessed only with known clinical diagnostic criteria, and non-stenotic manifestations were not evaluated in the patients enrolled in this study.

**Conclusions**

The plasma MMP-28 level is markedly elevated in patients with severe CAVS-related aortic stenosis and has a positive correlation with the mean pressure gradient and peak blood flow velocity of the transaortic valve.

**Conflict of interest**

None.

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