The Role of Lymphocyte-To-Monocyte Ratio In Predicting The Severe Post-Calcific Stenotic Aortic Dilatation In A Chinese Case-Control Study

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Abstract

Background: Calcific aortic valve stenosis (CAVS) represents a serious public health threat to elderly patients. Post-calcific stenotic aortic dilatation, a common feature in CAVS patients, might progress into aneurysm and even dissection, potentially lethal consequences of CAVS, and predicts a dismal prognosis. This study sought to testify the role of lymphocyte-to-monocyte ratio (LMR), an inflammatory biomarker, in predicting the severe post-calcific stenotic aortic dilatation in a Chinese case-control study.

Materials and Methods: 208 consecutive patients with CAVS were recruited retrospectively in a Chinese case- control study, from July 1, 2015 to June 31, 2018. The LMR was statistically analyzed for its prognostic value in the severe post-calcific stenotic aortic dilatation.

Results: The LMR was significantly reduced in patients with severe post-calcific stenotic aortic dilatation (2.72 vs. 3.53, $p=0.002<0.05$) compared to patients without severe post- calcific stenotic aortic dilatation. There was an inverse correlation observed between the maximal diameter of ascending aorta and the LMR in the overall patients ($r=-0.217$, $p=0.002<0.05$). For severe post-calcific stenotic aortic dilatation, the incidence of high- LMR group was statistically lower than that of low-LMR group (19.7% vs. 43.9%, $p<0.001$). And maximal diameter of ascending aorta was significantly reduced in the high-LMR group (4.35vs. 4.76, $p=0.003<0.05$) compared to low-LMR group. Additionally, the LMR was identified in the multivariate analysis as an independent predictor of severe post-calcific stenotic aortic dilatation (OR 0.743, 95% CI: [0.573- 0.964], $p=0.025$).

Conclusions: This study provided the evidence of an inverse correlation between the severe post- calcific stenotic aortic dilatation and LMR. And the LMR is potentially applied as an independent predictor of severe post-calcific stenotic aortic dilatation.

1. Introduction

Calcific aortic valve stenosis (CAVS) is the most prevailing heart valve disorder and affects nearly 1.7% in the population >65 years old in developed countries (1). The prevalence has also rapidly elevated in developing countries with the ageing of the population(2). Post-calcific stenotic aortic dilatation, is a common feature in CAVS patients, especially in those with bicuspid aortic valve (BAV) (3). It might progress into aneurysm and even dissection, potentially lethal consequences of CAVS, and predicts a dismal prognosis (4). Thus, post-calcific stenotic aortic dilatation warrants regular medical monitoring and possible early radical surgical intervention (including surgical aortic valve, root and ascending aorta replacement) to prevent catastrophic dissection or rupture. In the management of patients with CAVS, it is necessary to decipher additional risk for post-calcific stenotic aortic dilatation, in an attempt to optimize the assessment of dilatation progression, and clinical decision-making of a combined aorta replacement surgery. However, current data are scarce regarding the determinants and predictors of post-calcific stenotic aortic dilatation.

The pathophysiology of post-calcific stenotic aortic dilatation remains largely undetermined. Current evidence supported that this entity of aortic dilatation might be due to the unfavorable haemodynamic conditions downstream of stenotic valves, or due to the valve anatomy (BAV and tricuspid aortic valve [TAV]) as well as the intrinsic pathology of aorta (5). Given a pivotal role of inflammation widely recognized in the pathogenesis of CAVS, inflammation might also be linked with the development of post-calcific stenotic aortic dilatation. Of note, several inflammatory diseases as well as inflammatory biomarkers have been correlated with the occurrence of aortic dilatation, suggesting the effects of systemic and localized inflammation on the pathophysiology (6–9).

Lymphocyte-to-monocyte ratio (LMR) is an inflammatory biomarker calculated from peripheral blood count of lymphocytes and monocyte/macrophages. It has recently been emphasized as associated with systemic inflammation and prognosis in various malignancies (10–14). A lower LMR has been demonstrated linked with an increased level of systemic inflammation (15). Here the LMR is hypothesized to function as a practical predictive indicator of severe post-calcific stenotic aortic dilatation. To our best knowledge, such investigation is still missing, focused on the potential relationship of LMR and severe post-calcific stenotic aortic dilatation in a Chinese case-control study.

2. Material And Methods

2.1. Participants and study design

This study was a single-center retrospective case-control study. It was approved by the Ethics Committee of Shandong Provincial Hospital affiliated to Shandong First Medical University and Shandong University and the approval code for this study is NSFC2019-021. Due to its retrospective design, the written informed consents had to be waived. The study was performed in accordance with the Good Clinical Practice (GCP) and principles of the Declaration of Helsinki (16). 208 patients were consecutively included in the study from the hospital above-mentioned, from July 1, 2015 to June 31, 2018. The time interval of this study was based on its funding which spanned roughly a similar period. All the included patients met the following criteria: (i) older than 18 years; (ii) having a clear diagnosis of CAVS based on the criteria by the American College of Cardiology (ACC) and the American Heart Association (AHA). The subjects were excluded due to the following exclusion criteria: (i) the presence of rheumatic aortic valve stenosis or insufficiency, severe stenosis or insufficiency of mitral or tricuspid valves, endocarditis, coronary artery disease, atrial fibrillation, autoimmune diseases, malignancies and renal, hepatic or hematologic disorders; (ii) whose related data were not sufficient. The recruited patients underwent a comprehensive preoperative evaluation of transthoracic echocardiography (TTE) and aortic CT angiography (CTA). Full blood counts were routinely collected for calculating the LMR by dividing the number of lymphocytes by the number of monocytes.

2.2. The definition of severe post-calcific stenotic aortic dilatation

The maximal diameter of ascending aorta was measured by aortic CTA and the severe post-calcific stenotic aortic dilatation was defined as the maximal diameter equal to or greater than 50 mm.

2.3. The calculation of LMR and grouping by LMR

The LMR was measured according to the lymphocyte and monocyte counts in the blood routine test. The cut-off LMR was decided by the diagnostic test as described below. The included patients were accordingly grouped as the low-LMR group (with their LMR values less than the cut-off values) and high-LMR group (with their LMR values greater than the cut-off values).

2.4. Statistical analysis

All statistical analysis was performed using the software SPSS Statistics 25.0. The continuous variables were present in the form of mean ± standard deviation (SD) if the data conforms to normal distribution, or expressed as median (quartile deviation) if the data inconsistent with the normal distribution. The categorical variables were shown as frequencies (n) with percentages (%). For analyzing the continuous variables, the Student t-test was used when the normal distribution was conformed. Otherwise, the non-parametric Mann-Whitney U test was applied if a skewed distribution was met. The Chi-square or Fisher's exact test was carried out for analyzing the categorical variables. The cut-off LMR was determined by the diagnostic tests using the receiver operating curve (ROC). The binary logistic regression analysis was employed for the univariable and multivariable analyses. When the efforts were made to construct a multivariable predictive model, all candidate variables derived from the univariable analysis (with a p value less than 0.1) as well as those possible predictive variables were selected. A two-sided p value less than 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of patients

3.1.1. Inclusion of patients

From July 1, 2015 to June 31, 2018, 243 patients were recruited in sequence. 23 subjects were excluded because of the presence of rheumatic aortic valve stenosis (11 cases), severe stenosis or insufficiency of other valves (15 cases), endocarditis (2 cases), coronary artery disease (8 cases), atrial fibrillation (12 cases), autoimmune disease (2 cases), malignancies and renal, hepatic or hematologic disorders (3 cases); 12 patients excluded whose preoperative and intraoperative data were insufficient (Figure 1).

3.1.2. Detailed information of patients

For the patients with severe post-calcific stenotic aortic dilatation, 71.9% were male patients with a median age of 60.0 (11.0) years. 54.4% of patients were cigarette smokers, 33.3% had hypertension and 5.3% were with type 2 diabetes. 59.6% of patients had tricuspid aortic valve. The median LVEF was 57.0 (7.5). For the patients without severe post-calcific stenotic aortic dilatation, 62.3% were male patients with

a median age of 60.0 (12.0) years. 41.7% of patients were cigarette smokers, 37.1% had hypertension and 9.9% were with type 2 diabetes. 52.3% of patients had tricuspid aortic valve. The median LVEF was 60.0 (7.0). The detailed information of patients with and without post-calcific stenotic aortic dilatation were summarized in the Table 1.

Table 1
Clinical Characteristics of Patients with post-calcific stenotic aortic dilatation or not

	Post-calcific stenotic aortic dilatation	Not	P Value
Patient population (n)	57	151	
Demographic data			
Age (y)	60.0(11.0)	60.0(12.0)	0.909
Sex, male (n)	41(71.9%)	94(62.3%)	0.174
Medical history			
Hypertension (n)	19(33.3%)	56(37.1%)	0.638
Smoking (n)	31(54.4%)	63(41.7%)	0.094
Diabetes (n)	3(5.3%)	15(9.9%)	0.435
LV (cm)	6.02(1.74)	5.45(1.49)	0.011
LVEF (%)	57(7.5)	60(7)	0.006
Tricuspid aortic valve (n)	34(59.6%)	79(52.3%)	0.321
Preoperative laboratory tests			
Leukocyte (10^9/L)	6.11(2.06)	5.89(1.96)	0.405
Neutrophil (10^9/L)	3.48(1.54)	3.49(1.51)	0.896
Platelet (10^9/L)	178(75.5)	195.5 (71.5)	0.183
Monocyte (10^9/L)	0.59(0.37)	0.50(0.24)	0.006
Lymphocyte (10^9/L)	1.74(0.68)	1.84(0.68)	0.675
LMR	2.72(1.62)	3.53(1.75)	0.002
LDL-C (mmol/L)	2.78(1.15)	2.80(1.19)	0.843
CRP (mg/L)	0.93(0.91)	0.91(1.62)	0.388
MPV (fl)	10.60(1.15)	10.90(1.25)	0.329

	Post-calcific stenotic aortic dilatation	Not	P Value

Abbreviations: LV: left ventricle; LVEF: left ventricular ejection fraction; LMR: Lymphocyte-to-monocyte ratio; LDL-C: Low density lipoprotein cholesterol; CRP: C-reaction protein; MPV: mean platelet volume

NOTE. The categorical variables in the table are presented by the number of cases (with percentage) and the continuous variables are expressed by the median (with interquartile range) or mean (with standard deviation).

P values were the results of unpaired t-test or Mann-Whitney U test for continuous variables, and $\chi 2$ test or Fisher's exact test for categorical variables.

P Value: Compare the patients with and without ascending aorta dilatation.

3.2. LMR and severe post-calcific stenotic aortic dilatation

3.2.1. LMR in patients with severe post-calcific stenotic aortic dilatation or not

The LMR was significantly reduced in patients with severe post-calcific stenotic aortic dilatation (2.72 vs. 3.53, p=0.002<0.05) compared to patients without severe post- calcific stenotic aortic dilatation.

3.2.2. The correlation of LMR and maximal diameter of ascending aorta

There was an inverse correlation observed between the maximal diameter of ascending aorta and the LMR in the overall patients (r=-0.217, p=0.002<0.05) (Figure 2).

3.2.3. Severe post-calcific stenotic aortic dilatation in the high-LMR and low-LMR groups

The cut-off level of LMR was calculated from a diagnostic test with a ROC curve on the occurrence of severe post-calcific stenotic aortic dilatation, which was 2.72. Accordingly, the subjects were assigned into the high-LMR (n=142) and low-LMR group (n=66). The detailed information of two groups was summarized in Table 2. For severe post-calcific stenotic aortic dilatation, the incidence of high-LMR group was statistically lower than that of low-LMR group (19.7% vs. 43.9%, p<0.001). And maximal diameter of ascending aorta was significantly reduced in the high-LMR group (4.35vs. 4.76, p=0.003<0.05) compared to low-LMR group (Figure 3).

Table 2
Clinical Characteristics of Patients with High-LMR or Low-LMR

	High-LMR	Low-LMR	P Value
Patient population (n)	142	66	
Demographic data			
Age (y)	59 (13)	63(8.25)	0.005
Sex, male (n)	86(60.6%)	49(74.2%)	0.048
Medical history			
Hypertension (n)	42(29.6%)	33(50.0%)	0.004
Smoking (n)	62(43.7%)	32(48.5%)	0.488
Diabetes (n)	14(9.9%)	4(6.1%)	0.372
LV (cm)	5.41(1.43)	6.29(1.41)	<0.001
Post-calcific stenotic aortic dilatation (n)	28(19.7%)	29(43.9%)	<0.001
Maximal diameter of the ascending aorta (cm)	4.35(1.03)	4.76(1.60)	0.003
LVEF (%)	60(7)	58(7.5)	0.031
Tricuspid aortic valve(n)	61(43.0%)	52(78.8%)	<0.001
Preoperative laboratory tests			
Leukocyte (10^9/L)	5.74(1.93)	6.16(1.90)	0.020
Neutrophil (10^9/L)	3.33(1.48)	3.73(1.26)	0.004
Platelet (10^9/L)	193(69)	187(85.25)	0.818
Monocyte (10^9/L)	0.47(0.20)	0.79(0.43)	<0.001
Lymphocyte (10^9/L)	1.88(0.51)	1.54(0.67)	<0.001
LDL-C (mmol/L)	2.87(1.18)	2.68(1.12)	0.101
CRP (mg/L)	0.77(1.43)	1.18(2.07)	0.134
MPV (fl)	10.90(1.30)	10.60(1.15)	0.287

	High-LMR	Low-LMR	P Value

Abbreviations: LV: left ventricle; LVEF: left ventricular ejection fraction; LMR: Lymphocyte-to-monocyte ratio; LDL-C: Low density lipoprotein cholesterol; CRP: C-reaction protein; MPV: mean platelet volume

NOTE. The categorical variables in the table are presented by the number of cases (with percentage) and the continuous variables are expressed by the median (with interquartile range) or mean (with standard deviation).

P values were the results of unpaired t-test or Mann-Whitney U test for continuous variables, and $\chi 2$ test or Fisher's exact test for categorical variables.

P value: Compare the overall patients with Low-LMR or High-LMR.

3.3 The LMR predicting the severe post-calcific stenotic aortic dilatation Multivariable analysis of risk factors for severe post-calcific stenotic aortic dilatation was carried out by including all possible predictive variables (including age, sex, hypertension, diabetes, smoking, LMR, neutrophil, platelet, C-reaction protein, low- density lipoprotein cholesterol and tricuspid aortic valve). The results showed that the LMR independently predicted the occurrence of severe post-calcific stenotic aortic dilatation (OR 0.743, 95% CI: [0.573-0.964], p=0.025).

4. Discussion

In this case-control study, 208 patients were enrolled and the correlation between the LMR and the occurrence of severe post-calcific stenotic aortic dilatation was analyzed. The results presented the evidence of a lower LMR in the patients with severe post- calcific stenotic aortic dilatation compared to the patients without post-calcific stenotic aortic dilatation. And the incidence of severe post-calcific stenotic aortic dilatation in the high-LMR group was statistically lower than that in the low-LMR group. Finally, the LMR was considered as a novel predictor for severe post-calcific stenotic aortic dilatation after adjusting other possible variables.

The severe post-calcific stenotic aortic dilatation is often clinically silent until its catastrophic complication, acute aortic dissection or rupture, occurs(17). Although Davies and colleagues demonstrated that the ascending aorta with a diameter within 35–39 mm is not associated with aortic rupture or dissection, the risk of rupture or dissection increased dramatically by 27-fold if the diameter of ascending aorta reaches 60 mm or more (18). Thus, it is a clinical priority to identify the predictive biomarkers or modifiable risk factors in the prevention and treatment of severe post-calcific stenotic aortic dilatation.

The associated risk factors for post-calcific stenotic aortic dilatation in the previous reports were mainly male gender, bicuspid aortic valve, hypertension and smoking (19- 21). Aortic dilatation has been recently reported caused by inflammatory diseases such as infectious aortitis, Takayasu arteritis, and giant cell arteritis (7, 8, 22). And levels of several inflammatory biomarkers such as C-reactive protein (CRP) and interleukin (IL)- 6 are elevated in patients with thoracic aortic aneurysms, suggesting the effects of systemic inflammation on the pathophysiology (6). Of note, an increased activity of matrix

metalloproteinases (MMPs) has been described in the media of thoracic aortic aneurysm, a characteristic of localized inflammation (9, 23). Recent evidence from basic research has also suggested the role of several canonical inflammatory signaling pathways, AP-1 and the ERK1/2 signaling pathway, in contributing to the inflammation in post-calcific stenotic aortic dilatation (24). However, the detailed mechanisms underlying the inflammatory reaction in post-calcific stenotic aortic dilatation is to still a large extent undetermined. And identifying feasible inflammatory biomarkers will be constructive in predicting the high-risk patients and supportive in early diagnosis and intervention.

LMR is calculated from the exact amounts of lymphocyte and monocyte of peripheral blood and has been uncovered as an independent predictive indicator of clinical outcomes in various cancers(10–14). As an inflammation-related indicator, a lower LMR appears to be associated with decreased survival and increased recurrence in malignancies(15). Our findings demonstrated that the LMR is significantly lower in the patients with severe post-calcific stenotic aortic dilatation compared to the patients without post-calcific stenotic aortic dilatation. And an inverse correlation was observed between the maximal diameter of ascending aorta and the LMR. It indicated that as the maximal diameter of ascending aorta develops from the normal status to dilatation, the LMR might reduce proportionally. Thus, the patients with CAVS having a lower LMR could be potentially categorized into the high-risk population of post-calcific stenotic aortic dilatation. With the aid of risk stratification of post-calcific stenotic aortic dilatation by LMR, early identification of patients at high risk might be realized, which would lead to the close monitoring and early initiation of efficient preventive and therapeutic strategies. And a more accurate cut-off LMR might also be used in early diagnosis of post-calcific stenotic aortic dilatation if more prospective studies with larger sample sizes in multiple ethnicities are available to confirm it.

5. Limitations

Several limitations were present and special attention should be paid to interpret the results in this study. First of all, the study design, a single-center retrospective observational study, inevitably introduced a source of potential bias. The second limitation lies in a small simple size. Third, some confounding variables, such as other inflammatory markers, might influence the role of LMR in post-calcific stenotic aortic dilatation. Fourth, the association of LMR and mid- and long-term endpoints was not investigated. Fifth, the case-control design of this study did not evaluate the causal relationships between LMR and post-calcific stenotic aortic dilatation.

6. Conclusions

The LMR is inversely correlated with the incidence and severity of post-calcific stenotic aortic dilatation and might independently predict the occurrence of post- calcific stenotic aortic dilatation. Further large-scale case-control studies are needed to confirm these results in the future.

List Of Abbreviations

Term	Abbreviations
Calcific Aortic Valve Stenosis	CAVS
Bicuspid Aortic Valve	BAV
Tricuspid Aortic Valve	TAV
Lymphocyte-to-monocyte ratio	LMR
Good Clinical Practice	GCP
American College of Cardiology	ACC
American Heart Association	AHA
Transthoracic Echocardiography	TTE
CT Angiography	CTA
Standard Deviation	SD
Receiver Operating Curve	ROC
C-reactive Protein	CRP
Matrix Metalloproteinases	MMPs

Declarations

Ethics approval and consent to participate:

This study was approved by the Ethics Committee of Shandong Provincial Hospital affiliated to Shandong First Medical University and Shandong University and the approval code for this study is NSFC2019-021.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

SC and ZW analyzed and interpreted the patient data regarding the severe post-calcific stenotic aortic dilatation. XM and YY were major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Disclosure Statement: we have no conflict of interest to declare in the manuscript.

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Figures

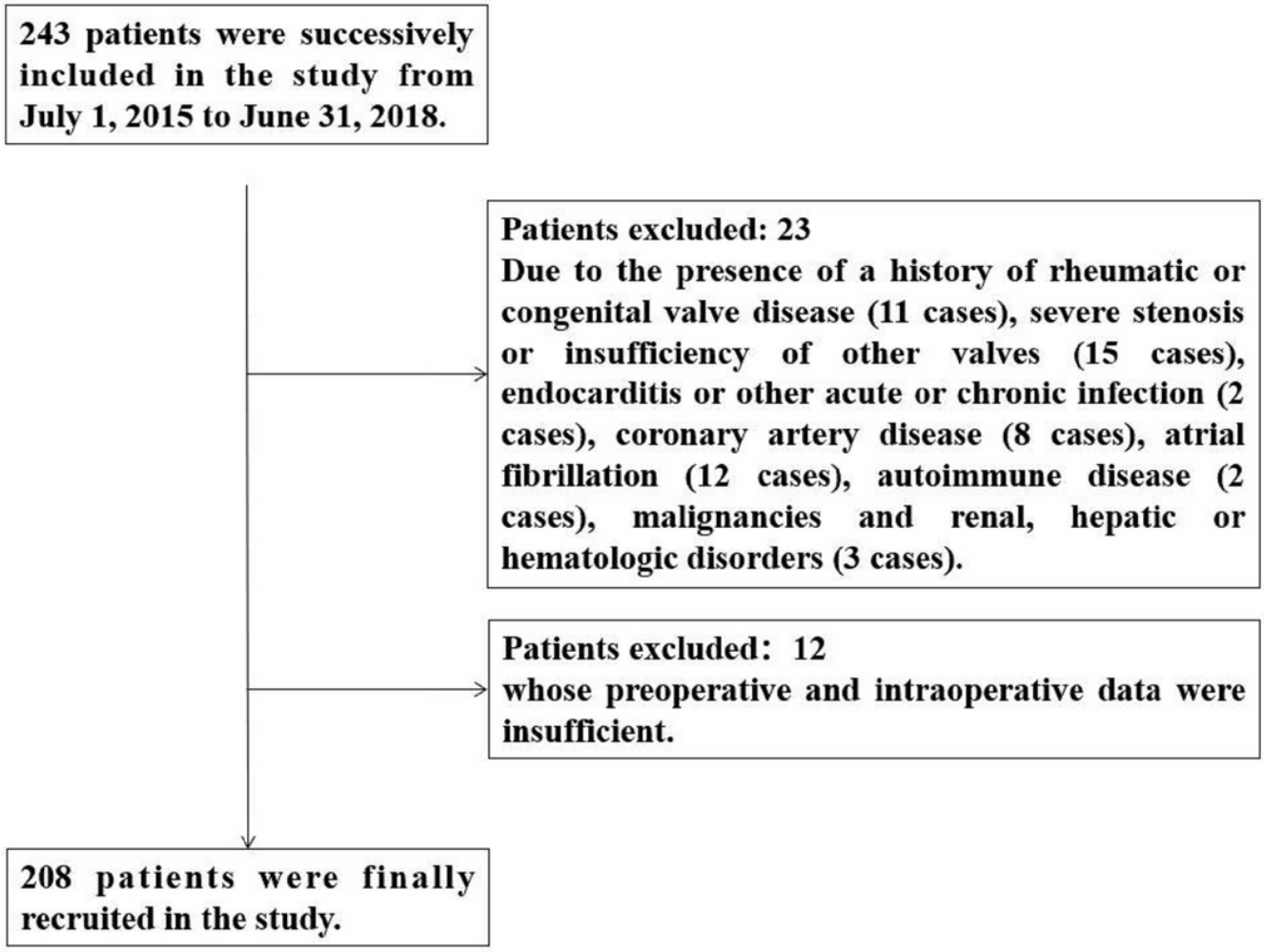

Figure 1

Flow diagram of exclusion and enrollment of study patients describes the exclusion and enrollment of study patients.

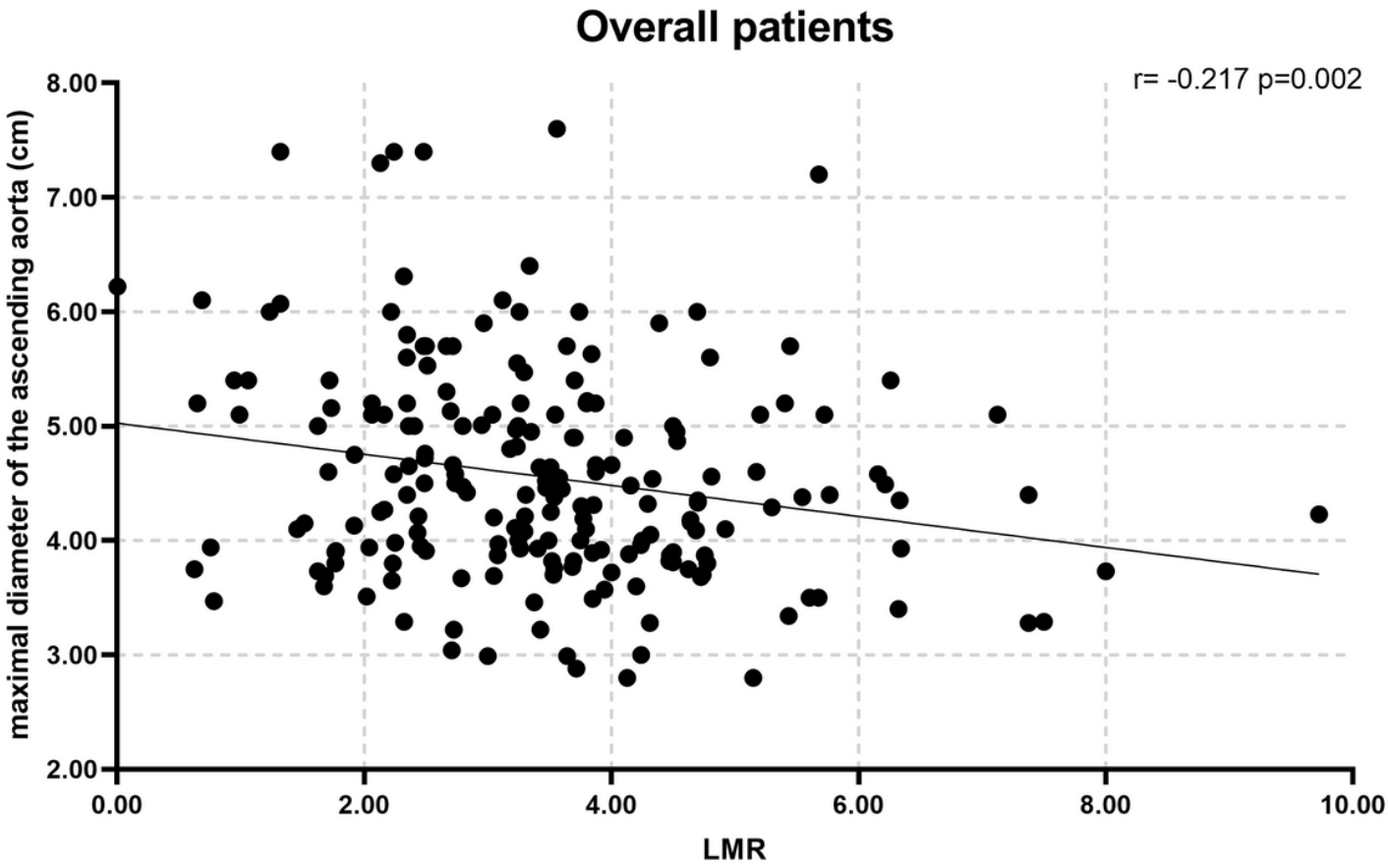

Figure 2

The correlation of LMR and maximal diameter of ascending aorta shows the inverse correlation between the maximal diameter of ascending aorta and the LMR in the overall patients (r=-0.217, p=0.002<0.05). LMR, Lymphocyte-to-Monocyte Ratio.

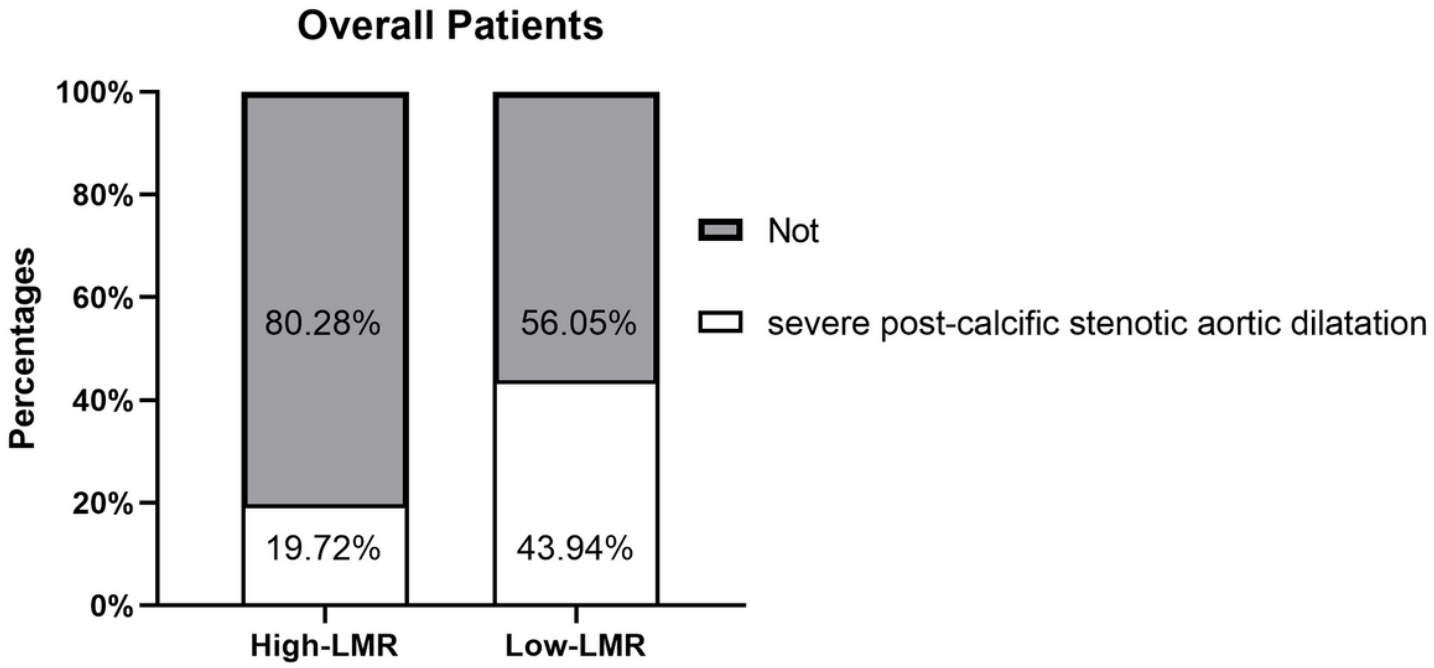

Figure 3

The incidence of Severe post-calcific stenotic aortic dilatation in the high- LMR and low-LMR groups depicts the incidence of Severe post-calcific stenotic aortic dilatation in the high-LMR and low-LMR groups. LMR, Lymphocyte-to-Monocyte Ratio.