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The Role of Plasma Calprotectin Levels in Patients with Severe Mitral Regurgitation

Şiddetli Mitral Yetersizliği Olan Hastalarda Plazma Kalprotektin Düzeylerinin Rolü

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ÖZET

Amaç: Kalprotektin, fagositlerin sitoplazmasında bulunan ve inflamatuar yanıtta ekstrasellüler matrikse salınan bir proteindir. Önceki çalışmalar, kalp yetersizliği ve akut koroner sendromlu hastalarda plazma kalprotektin düzeylerinin yüksek olduğunu göstermiştir. Bu çalışmada, plazma kalprotektin düzeylerinin fonksiyonel ve dejeneratif mitral yetersizliği etiyolojilerine göre farklılık gösterip göstermediği araştırıldı.
Yöntem: Çalışmaya şiddetli fonksiyonel mitral yetersizliği (FMY) tanısı alan 24 hasta, şiddetli dejeneratif mitral yetersizliği (DMY) tanısı alan 36 hasta ve 22 sağlıklı kontrol dahil edildi. Tüm katılımcılara ekokardiyografi uygulandı. Plazma kalprotektin düzeyleri enzyme-linked immunosorbent assay (ELISA) yöntemiyle ölçüldü.
Bulgular: Yaş, cinsiyet ve kardiyovasküler risk faktörleri açısından gruplar arasında anlamlı farklılık saptanmadı. Plazma kalprotektin düzeyleri FMY grubunda hem DMY grubuna hem de kontrol grubuna göre anlamlı derecede yüksek bulundu (sırasıyla p<0.001 ve p=0.002).
Sonuç: Bulgularımız, şiddetli FMY hastalarında plazma calprotectin düzeylerinin belirgin şekilde arttığını göstermektedir. Kalprotektin düzeyleri, mitral yetersizliğinden ziyade kalp yetersizliği ile daha fazla ilişkili görünmektedir.

Anahtar Kelimeler: Kalp yetersizliği, mitral yetersizliği, kalprotektin, akut koroner sendrom

ABSTRACT

Introduction: Calprotectin is an inflammatory protein complex which is stored in the cytosol of phagocytes and released into extracellular matrix during inflammatory response. Previous studies demonstrated that levels of plasma calprotectin were higher in patients with heart failure and acute coronary syndrome. We aimed to investigate whether levels of plasma calprotectin differed between two different etiologies of mitral regurgitation; functional and degenerative mitral regurgitation.
Methods: A total of 24 patients diagnosed with severe functional mitral regurgitation (FMR), 36 patients diagnosed with severe degenerative mitral regurgitation (DMR), and 22 control subjects were prospectively enrolled in this study. All participants underwent echocardiographic examinations. Plasma calprotectin levels were quantified using an enzyme-linked immunosorbent assay (ELISA) test kit.
Results: Age, gender, and cardiovascular risk factors did not exhibit significant differences between the FMR, DMR, and control groups. Plasma calprotectin levels were found to be higher in the FMR group compared to both the DMR group and the control group (p <0.001 and p= 0.002, respectively).
Conclusion: Our research revealed elevated plasma calprotectin levels among individuals diagnosed with severe FMR. It appears that calprotectin levels are influenced more by heart failure rather than specifically by mitral regurgitation.

Keywords: Heart failure, mitral regurgitation, calprotectin, acute coronary syndrome

INTRODUCTION

Primary mitral regurgitation constitutes the vast majority of mitral regurgitation (MR). Degenerative disease, rheumatic valve disease, senile degeneration and infective endocarditis are most common causes of primary MR (1). Degenerative disease is characterized as a spectrum that induces leaflet prolapse, whereby infiltrative or dysplastic alterations in tissue lead to elongation or disruption of the mitral valve chordae. Degenerative MR is a broad spectrum of diseases ranging from fibroelastic deficiency to Barlow's disease. Pressure and volume overload trigger cardiac remodeling which initially serves as a compensatory mechanism in primary MR. Left ventricular (LV) dysfunction and marked LV enlargement are associated with an unfavorable outcome in primary MR.

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Functional mitral regurgitation resulting from papillary muscle dysfunction associated with mitral annular dilation and/or LV dysfunction is a common condition in heart failure (HF) patients. In conjunction with elevated atrial pressure, there is a concurrent rise in left ventricular end-diastolic pressure, precipitating the progressive dilation of the left ventricle. Incidence of functional MR (FMR) increased due to increase in atherosclerotic coronary syndromes despite widespread availability of percutaneous coronary interventions. FMR has a poor prognosis since it is associated with HF. Chronic inflammation after acute coronary syndromes leads to cardiac remodeling which causes further progression of HF and FMR. Several inflammatory biomarkers were shown to be associated with cardiac remodeling and prognosis in HF patients (2). Calprotectin, alternatively recognized as S100A8/A9, myeloid-related protein 8/14 (MRP-8/14), calgranulin A/B, and leukocyte L1 antigen complex, denotes an inflammation-associated protein complex localized within the cytosol of neutrophils and monocytes. Calprotectin is released into extracellular matrix during inflammatory response (3).The extracellular calprotectin stimulates innate immune system via activating receptor of advanced glycation end products (RAGE) which consequently causes myocardial inflammation and HF (4). Previous studies demonstrated that calprotectin is associated with acute coronary syndromes (5-7). Elevated plasma calprotectin levels have been correlated with an unfavorable prognosis among individuals diagnosed with myocardial infarction (8). Several studies showed that level of plasma calprotectin was not only higher in patients with HF but also associated with severity of HF(9,10). Although association of calprotectin and HF is evident, association with different pathogenesis of mitral valve has not been studied yet. FMR is more related with inflammation, atherosclerosis and HF, whereas DMR seems to be less related. These substantial differences in pathogenesis of mitral valve disease raise suspicion about relationship between these two distinct etiologies and calprotectin. We aimed to investigate, for the first time, whether levels of plasma calprotectin differed between two different etiologies of mitral regurgitation: functional and degenerative MR (DMR).

MATERIALS AND METHODS

Compliance with Ethical Standards:

The study was reviewed and approved by the institutional research ethics board (Approval Number: 2024/4802), adhering to the principles of the Helsinki Declaration. Written informed consent was obtained from all participants. Artificial intelligence-supported technologies were not used in the study.

Study population

The study enrolled 60 patients diagnosed with severe MR who were referred for echocardiographic assessment. A control group consisting of 22 subjects without MR and possessing normal left ventricular ejection fraction (LVEF) was included for comparison. The patients were categorized into groups: DMR (n=36), FMR (n=24), and the control group (n=22)

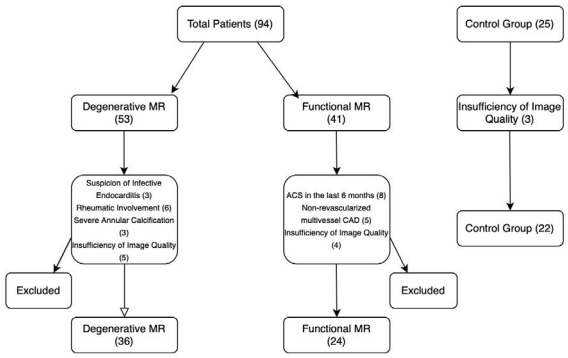


Figure 1. Flow diagram of the participants in the study

as depicted in Figure 1. Exclusion criteria involved patients with a history of acute coronary syndrome within the previous six months. Additionally, significant coronary artery disease (CAD) was ruled out either through coronary angiography or myocardial perfusion scintigraphy (MPS) among patients in the DMR group and the control group. Patients presenting with primary MR attributed to causes such as rheumatic etiology or mitral annular calcification, as well as those with infective endocarditis, were excluded from the study. Ethical approval was obtained from the local ethics committee.

Measurement of Calprotectin Levels

Blood samples were collected from the antecubital vein of patients 15 minutes prior to echocardiographic examination to determine plasma calprotectin levels and other hematological parameters. For calprotectin analysis, blood was drawn into pyrogen-free tubes containing EDTA and then centrifuged at 3000 revolutions per minute (rpm) for 10 minutes. The resultant plasma was stored at -70°C until further analysis. Plasma calprotectin levels were quantified using an enzyme-linked immunosorbent assay (ELISA) test kit (CALPROLAB Calprotectin ELISA (ALP); Calpro AS, Lysaker, Norway). Complete blood count (CBC) analysis was performed using a Beckman Coulter HMX-AL instrument (Brea, CA, USA).

Echocardiography

All patients underwent examination by the same experienced echocardiographer, who remained blinded to the study protocol. Standard echocardiographic assessments were conducted using a 1 to 5 MHz X5-1 transducer (iE33, Philips Healthcare, Inc., Andover, MA). Left ventricular end-diastolic (LVEDD) and end-systolic diameters (LVESD) were measured from the parasternal long-axis view utilizing M-mode imaging. Left ventricular ejection fraction (LVEF) was calculated using Simpson's Formula (11). Mitral inflow velocities were assessed using pulsed-wave Doppler, with recording of E and A wave velocities. The E/A ratio was subsequently calculated. Tricuspid annular plane systolic excursion (TAPSE) was measured using M-Mode, while the tricuspid annulus peak systolic velocity (Sm) was recorded using tissue Doppler imaging (TDI) in the apical four-chamber view to assess right ventricular function.

Left ventricular circumferential and longitudinal strain parameters (LV-GCS, LV-GLS) were evaluated utilizing 2D speckle-tracking imaging. The severity of mitral regurgitation (MR) was quantified by determining mitral regurgitant volume (RV) and effective regurgitant orifice area (EROA), following recommended guidelines (12). MR was classified as severe if RV was greater than 60 mL/beat or EROA exceeded 0.4 cm^2 (1). FMR were graded according to 2021 ESC/EACTS Guidelines for the management of valvular heart disease (1). However, in light of discrepancies in the determination of severe FMR between the 2020 AHA/ACC and ESC/EACTS guidelines, the severe FMR group was reclassified into high overload and low overload subgroups. The high overload group was defined as having an effective regurgitant orifice area (EROA) of ≥0.4 cm^2 or a regurgitant volume (RV) of ≥ 60 ml/beat, while the low overload group was characterized by an EROA of 0.2-0.4 cm^2 or an RV of 30-60 ml/beat (1,13). This arbitrary reclassification enabled us to comprehend similar RVs in both groups.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics 16.0 (SPSS, Chicago, IL) software. Sample size determination was based on previous studies with similar methodologies and patient populations. While no formal power analysis was conducted, the sample size was considered adequate to detect meaningful differences based on prior literature. Due to the rarity of the condition and the strict inclusion criteria, the final sample size was determined by the number of eligible patients within the study period. Continuous variables were expressed as mean and standard deviation, while categorical variables were presented as percentages. The conformity of the data to normal distribution was evaluated with the Shapiro-Wilk test. Categorical variables were compared using the Chi-Square or Fisher's Exact test as appropriate. The distribution of numerical data in 3 independent groups showing normal distribution was evaluated with ANOVA and Tukey's post hoc test, and if the variances were not homogeneous, with Welch and Tamhane post hoc test. The distribution of numerical data in 3 independent groups showing normal distribution was evaluated with Kruskal Wallis test. Dunn Bonferroni test was used in post hoc analysis of data with significant Kruskal Wallis test results. The relationship between numerical data was evaluated with the Pearson Correlation test. Receiver operating characteristic (ROC) curve analysis was employed to determine the optimal cut-off level for plasma calprotectin values in predicting severe FMR. Additionally, linear regression analysis was performed to identify predictors of plasma calprotectin levels. A p-value <0.05 was considered statistically significant for all results.

RESULTS

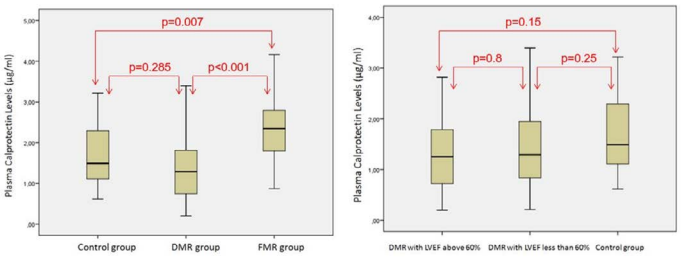
Twenty-four patients diagnosed with FMR and 36 patients diagnosed with DMR were prospectively enrolled in the study. Demographic, clinical, echocardiographic, and laboratory characteristics of the study population are presented in Table 1. There was no statistically significant difference observed between the control group and the study groups regarding

Table 1. Demographic, clinical, echocardiographic and laboratory characteristics of study population

	Control Group n:22	DMR n:36	FMR n:24	p value	Post hoc p1	p2	p3
Age, years	51.6±9.3	51.9±15.5	56.5±15.4	0.161			
Sex, Male (%)	14 (63.6)	27 (75.0)	19 (79.2)	0.468			
Hypertension (%)	4 (18.2)	11 (30.6)	8 (33.3)	0.471			
Diabetes Mellitus (%)	5 (22.7)	9 (25.0)	8 (33.3)	0.681			
Dyslipidemia (%)	4 (18.2)	8 (22.2)	7 (29.2)	0.667			
Urea (mg/dl)	31.4±5.8	34.3±11.3	67.8±51.2	0.018	0.674	0.022	0.045
Creatinine (mg/dl)	0.81±0.17	0.85±0.26	1.21±0.8	0.340			
Hemoglobin (mg/dl)	13.9±0.86	13.9±2.1	12.8±2.3	0.250			
Platelet(1000/mm^3)	264.4±52.3	214.4±38.5	199.6±95.5	0.026	0.059	0.007	0.271
Leukocyte(1000/mm^3)	8.1±1.6	7.5±2.3	9.6±3.7	0.073			
LV-ESD (cm)	2.9±0.43	3.51±0.66	5.16±0.75	<0.001	0.001	<0.001	<0.001
LV-EDD (cm)	4.73±0.45	5.76±0.75	6.53±0.83	<0.001	<0.001	<0.001	<0.001
LV-EF (%)	64.7±2.5	57.4±8.2	32.8±6.9	<0.001	0.016	<0.001	<0.001
LV-GCS (%)	-23.4±4.9	-19.4±5.8	-10.4±4.2	<0.001	0.030	<0.001	<0.001
LV-GLS (%)	-19.8±2.6	-16.9±5.6	-9.3±3.8	<0.001	0.036	<0.001	<0.001
LA diameter (cm)	3.29±0.38	4.17±0.75	4.66±0.75	<0.001	<0.001	<0.001	0.051
E/A ratio	0.9±0.3	1.75±0.55	2.2±0.96	<0.001	<0.001	<0.001	0.436
Tapse (mm)	25.9±4.8	25±5.3	17.7±4.5	<0.001	0.789	<0.001	<0.001
Sm (cm/s)	15±2.8	15.6±3.5	10.1±2.5	<0.001	0.790	<0.001	<0.001
ERO (mm^2)		68.5±27.6	32.2±9.5	<0.001			
RV (ml/beat)		94.2±30.8	49.4±13.5	<0.001			
Calprotectin (µg/ml)	1.70±0.79	1.36±0.78	2.45±0.85	<0.001	0.285	0.007	<0.001

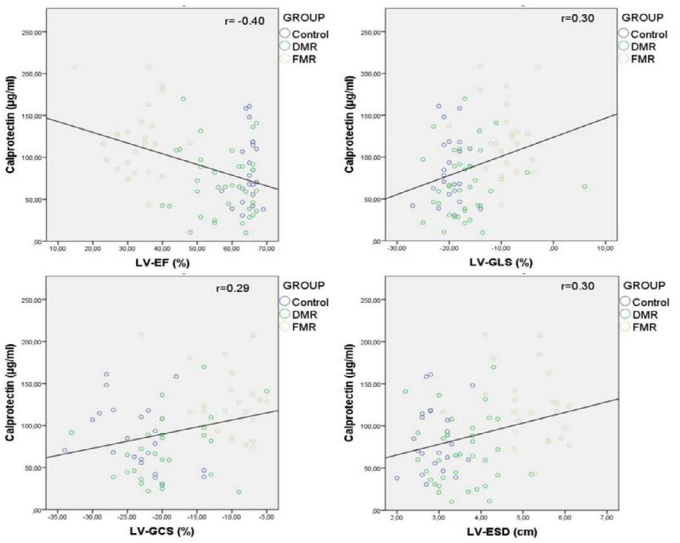
LV-EDD: left ventricle end-diastolic diameter; LV-ESD: left ventricle end-systolic diameter; LV-EF: left ventricle ejection fraction; LV-GCS: global circumferential left ventricular strain; LV-GLS: global longitudinal left ventricular strain; LA: left atrium; LAVI: left atrial volume index; Tapse: tricuspid annular plane systolic excursion; ERO: effective regurgitant orifice area; RV: regurgitant volume; p1: p value between controls and DMR; p2:p value between controls and FMR; p3: p value between DMR and FMR

age and gender distribution (p= 0.161, p= 0.468, respectively). Additionally, cardiovascular risk factors such as hypertension, diabetes mellitus, and dyslipidemia did not differ significantly between the groups (p= 0.471, p= 0.681, p= 0.667, respectively). Three patients in the DMR group and six patients in the FMR group exhibited a functional capacity of Class III according to the New York Heart Association (NYHA) Classification System, while the remaining MR patients were classified as NYHA Class II (p= 0.137). All patients with FMR had history of CAD and 10 (45%) had atrial fibrillation (AF). AF did not exist in DMR and control group. LVEDD and LVESD were largest in FMR group and smallest in control group (p<0.001 for all). LVEF, LV-GLS and LV-GCS were worst in FMR group and best in control group (p<0.001 for all). Left atrium (LA) diameter was largest in FMR group (p<0.001) and smallest in control group. E/A ratio was higher in FMR and DMR groups than control (p<0.001). FMR group had the worst right ventricle systolic function (TAPSE and Sm) (p<0.001 for all), although no difference existed between DMR group and controls (p>0.05). ERO and RV were larger in DMR group compared with FMR group (p<0.001). Plasma calprotectin levels were (1.70±0.79 µg/ml in control group; 1.36±0.78µg/ml in DMR group; 2.45±0.85 µg/ml in FMR group) higher in FMR group compared with DMR group and control (p<0.001, p=0.007; respectively), however no difference was present between DMR group and control (p=0.285) (Figure 2). Plasma calprotectin levels negatively correlated with LVEF (r=-0.40, p<0.001), TAPSE (r=-0.38, p=0.001) and Sm (r=-0.31, p=0.006), and positively correlated with LVESD (r=0.30, p=0.006), LV-GLS (r=0.30, p=0.007), LV-GCS (r=0.29, p=0.02) (Figure 3 and 4) in all study group. In FMR group, presence of AF did not have effect on plasma calprotectin levels (p=0.2 between FMR patients with and without AF). FMR group was dichotomized as high (EROA ≥0.4 cm^2, RV ≥ 60 ml/beat) and low (EROA: 0.2-0.4 cm^2, RV: 30-60 ml/beat) overload groups. Plasma calprotectin levels did not differ between high and low overload groups (2.48±1.04 µg/ml in high group (n: 10), 2.43±0.71 µg/ml in low group (n: 14), p=0.87). Plasma calprotectin levels were higher in high overload FMR group (n: 10) compared with DMR group and control (p<0.001, p=0.01; respectively). In ROC analysis, a cut-point of 1.85 µg/ml identified the patients with FMR in this study population (area under curve (AUC) =0.797, 95% CI 0.69- 0.89) (Figure 5). Plasma



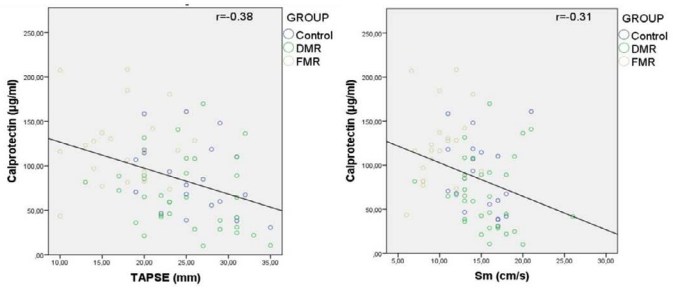
DMR: Degenerative Mitral Regurgitation FMR: Functional Mitral Regurgitation LVEF: Left Ventricular Ejection Fraction

Figure 2. Plasma calprotectin levels of control and MR groups.



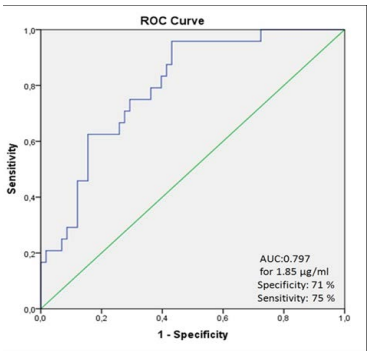
DMR: Degenerative Mitral Regurgitation FMR: Functional Mitral Regurgitation LVEF: Left Ventricular Ejection Fraction LV-GLS: Left Ventricular Global Longitudinal Strain LV-GCS: Left Ventricular Global Circumferential Strain LV-ESD: Left Ventricular End-Systolic Diameter

Figure 3. Correlation between plasma calprotectin level and left ventricle functions.



DMR: Degenerative Mitral Regurgitation FMR: Functional Mitral Regurgitation TAPSE: Tricuspid Annular Plane Systolic Excursion Sm: Systolic Myocardial Velocity

Figure 4. Correlation between plasma calprotectin level and right ventricle functions.



ROC: Receiver Operating Characteristic FMR: Functional Mitral Regurgitation

Figure 5. ROC curve of plasma calprotectin level for prediction of FMR.

Table 2. Linear regression analysis to identify independent predictors of calprotectin

	B	t	p
EF	-1.913	-4.543	<0.001
Severe MR (presence)	-15.912	-1.168	0.246
LA diameter	-11.977	-1.556	0.124
Age	0.131	0.374	0.709
Sex (male)	2.544	0.233	0.816

B: Unstandardized Coefficient EF: Ejection Fraction MR: Mitral Regurgitation LA: Left Atrium

calprotectin level of higher than 1.85 µg/ml demonstrated FMR with a sensitivity of 75%, a specificity of 71%. A linear regression model was constructed to estimate the calprotectin parameter from demographic and echocardiographic parameters. The patient group (combining DMR and FMR) was included versus the control group. According to the results of the linear regression analysis performed to determine the independent determinants of the calprotectin index, the LV EF parameter was determined to be an independent determinant of the calprotectin index (Table 2).

DISCUSSION

Calprotectin is a heterodimeric protein complex comprising two calcium-binding proteins. It is released from the cytosol of phagocytes into the extracellular matrix during inflammatory responses. Extracellular calprotectin plays a role in mediating inflammatory activity in endothelial cells, potentially through interaction with the RAGE. Experimental studies have demonstrated that activation of RAGE leads to the development of sustained myocardial inflammation and heart failure (4). Previous studies have indicated a positive correlation between calprotectin levels and high-sensitivity C-reactive protein (hsCRP), an established predictor of morbidity and mortality in heart failure (HF). These findings support the hypothesis of heightened inflammatory activity in HF (9). Previous studies have shown that calprotectin level was associated not only with the presence of HF and but also the severity (NHYA Classification) (9). Although calprotectin level was a predictor of one year mortality in elderly patients with HF, no correlation between calprotectin level and EF was demonstrated (10). BNP, a marker of cardiomyocyte stretch, was independent predictor of long-term mortality in patients with DMR (14). Previous studies demonstrated no association between NT-pro B-Type Natriuretic Peptide (NT-BNP) and calprotectin in patients with CHF (9). This finding concluded that inflammation is not related to stretching of cardiomyocytes. Additionally, sustained release of calprotectin contributes to development of post-ischemic HF through activation of RAGE (4). Studies have shown that calprotectin levels are elevated in patients with CAD. Calprotectin level was higher in acute coronary syndromes (ACS) compared with stable angina. Additional prognostic value of calprotectin was demonstrated in myocardial infarction(5-8,15). Present study found that plasma calprotectin level was higher in patients with severe FMR compared with patients with severe DMR and control group. High level of calprotectin in patients with FMR may be associated with presence of heart failure and coronary artery disease in this patient group. Additionally, the comparable plasma calprotectin levels in both high and low overload groups of FMR suggest that, in our study, MR-related volume overload does not affect the plasma calprotectin levels. Our findings indicate that volume overload, resulting in cardiomyocyte stretching, did not have an effect on calprotectin levels in patients with severe FMR. Atrial functional mitral regurgitation (AFMR) is a recognized subtype of secondary MR, often associated with atrial fibrillation (AF). In our study, 45% of the FMR group had AF, which may suggest a significant proportion of AFMR. Although we did not specifically classify AFMR, this condition might contribute to elevated plasma calprotectin levels due to chronic atrial inflammation and remodeling. Future studies should differentiate between AFMR and ventricular functional MR to assess their distinct impact on inflammatory biomarkers like calprotectin.

In contrast to the findings of other studies, our study demonstrated a correlation between EF and calprotectin levels in all study groups and in all MR patients. We also demonstrated that the right ventricular systolic function (TAPSE, Sm) was correlated with calprotectin levels in our study. Although previous study has shown that calprotectin level is higher in patients with AF, independent of heart failure, we did not demonstrate association between AF and calprotectin levels in patients with severe FMR (16). In patients with severe DMR without HF and CAD, we demonstrated that stretching of cardiomyocytes due to severe mitral regurgitation did not have an effect on calprotectin levels. Increased calprotectin levels in patients with severe FMR were related to heart failure. Further large-scale and comprehensive studies are needed to validate the reliability of calprotectin as an inflammatory biomarker in mitral regurgitation. Additionally, the underlying pathophysiological mechanisms involving calprotectin require further elucidation.

Limitations

The primary limitation of our study is the small sample size. Furthermore, since our study exclusively focused on patients with severe MR, there is a lack of sufficient comparable data between severe and mild or moderate MR cases. Additionally, the absence of BNP and an inflammatory marker such as C-reactive protein (CRP) in our study limits the comparison of these markers with calprotectin, which could further elucidate pathophysiological relationships. Moreover, the grading of MR using proximal isovelocity surface area (PISA) measurements may lead to overestimation of the severity of regurgitant

volume (RV) and effective regurgitant orifice area (EROA) in DMR patients.

Another limitation is the lack of differentiation between atrial functional MR (AFMR) and ventricular functional MR in the FMR group, particularly given that 45% of the patients had AF. Future studies should stratify FMR patients based on AFMR status to better understand the relationship between AF, MR subtype, and inflammatory markers such as calprotectin. This study acknowledges the potential confounding effects of CAD and AF on inflammation markers. Since CAD and AF were more prevalent in the FMR group, it is possible that observed differences in inflammation levels may not be solely attributable to mitral regurgitation itself. A multivariate regression analysis was not performed to adjust for these confounders, which represents a limitation of the study. Future studies with larger sample sizes and comprehensive statistical adjustments are needed to further clarify these associations.

CONCLUSION

Our study demonstrated elevated plasma calprotectin levels in patients diagnosed with severe FMR, whereas there was no significant increase observed in patients with severe DMR. Therefore, it appears that calprotectin levels are influenced more prominently by heart failure rather than by the presence of mitral regurgitation.

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