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Investigation of the relationship between comprehensive echocardiograhic findings and CRP/prealbumin ratio in patients with metabolic syndrome

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Abstract

The predictive value of the C-reactive protein / Prealbumin (CRP/PAB) ratio for the assessment of left atrial (LA) functions in metabolic syndrome (Met-S) remains unclear. We enrolled 100 patients with newly diagnosed Met-S and 53 individuals as a control group. Detailed conventional and tissue Doppler echocardiographic examinations were performed, including measurements of volumes and functional indexes of LA. Mean CRP/PAB ratio values were not found to be different between groups (p=0,107). Mean mitral-A, tricuspid-A, and mitral-a' velocities were found to be significantly different between groups (p-value for all<0.05). None of the volumetric and functional indexes of LA were found to be different between groups (p-value for all >0.05). After dividing the patients into groups as presenting wleft-right/left ventricular diastolic dysfunction (RVDD- LVDD) or not, again, none of the volumetric and functional indexes of LA were found to be different between groups (p-value for all >0.05). Finally, the CRP/PAB ratio was not found to be correlated with any of the indices of LA in patients with Met-S, while only active emptying volüme of LA was found to be correlated with the CRP/PAB ratio in the control group. We did not find any association between the CRP/PAB ratio and LA functions. To evaluate the predictive value of the CRP/PAB ratio for the assessment of LA functions in Met-S needs further studies with a large cohort population.

Keywords: C-reactive protein-to-prealbumin ratio; metabolic syndrome, left atrium function, left atrium volume

1. Introduction

Metabolic syndrome (Met-S) is defined as a sum of metabolic risk factors, including hypertension (HT), obesity, hyperglycemia, and hyperlipidemia, and it has been shown that Met-S has a strong association with an increased risk of cardiovascular disease (CVD), stroke, and all-cause mortality (1). Inflammatory pathways contribute a major role in the pathogenesis of the development of this disease (2). CRP has been shown to be a sensitive and systemic biomarker for both Met-S (3). Prealbumin (PAB) is known as a negative acute-phase reactant protein, and it has been found to be associated with a higher mortality rate in patients with heart failure (HF) (4). Recently, as a novel inflammatory marker, CRP/PAB ratio has been reported to be a better predictive value for recurrence of gastric cancer, the severity of organ dysfunction in critically ill patients, and higher mortality in patient HF patients (5-7). Structural and functional changes of the left atrium (LA) are related to various CVDs, including ischemic stroke and atrial fibrillation (AF), and have been proposed as very important risk factors for cardiovascular mortality (8). It has been shown that Met-S is associated with electrical and structural remodeling of the LA (9). During the cardiac cycle, LA functions have three components a reservoir during systole, a conduit during early diastole, and an active contractile function in late diastole. LA volumes measured by echocardiographically have been described as 1: maximal volume (Vmax, 2: preatrial contraction volume (VpreA), and 3: minimal volume (Vmin) (10). Recently, shown that Met-S had a greater Vmax (p = 0.03), VpreA (p = 0.001) than the control group. In that study, LA mechanical function was found to be impaired in patients with Met-S (10). So functional and morphological changes of LA in patients with Met-S have been evaluated many times before however, to the extent of our knowledge, the importance or predictive value of CRP/PAB ratio for early detection of any sign of functional and morphological changes of LA in patients population have not been examined before so we aimed to evaluate this relationship.

2. Materials and Methods

2.1. Subjects

This study was carried out as a cross-sectional study. Patients newly diagnosed with Met-S were admitted to this study. One hundred fifty-three consecutive patients (73 female patients, 80 male patients, mean age:57,3 ± 8,5) were enrolled for assessment in the clinic of Cardiology in Kirsehir Ahi Evran University Medical Faculty Education and Research Hospital between April and May 2023. Patients were divided into three

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groups: group-1, which included the patients diagnosed as Met-S but without diabetes mellitus (DM) (Non-DM group, n= 49, mean age: 58 ± 8,7); group-2, which included the patients diagnosed Met-S with DM (DM group, n=51, mean age: 60 ± 8,5): and group-3 which included healthy individuals (control group, n= 53, mean age: 59 ± 7,2). Met-S was defined by the criteria proposed by NCEP-ATP III (1). At least 3 or more of the following components were needed to meet the metabolic syndrome criteria: a) fasting blood glucose ≥ 100 mg/dl or the patient's self-reported history of DM or use of DM medications; b) blood pressure ≥ 130/85 mmHg or the patient's self-reported history of HT or use of antihypertensive medications; c) triglycerides (TG)≥ 150 mg/dl; d) high-density lipoprotein (HDL-C) <40 mg/dl and e) BMI >30 kg/m2. Participants were aged 20 years and above and had no history of DM, cancer, neurovascular, cardiovascular, and/ or renal diseases. They also did not have any history of taking medication for HT hyperglycemia, and hyperlipidemia. The protocol of study has been approved by the ethics committee of Kirsehir Ahi Evran University of Medical Faculty (04.04.2023 date and registration number 2023-07/43), and written informed consent was obtained from all of the study participants before their participation in this study.

2.2. Clinical and laboratory assessments

After detailed medical history, anthropometric assessments, including body-mass index (BMI), body surface area (BSA), waist circumference, and blood pressure measurements, were measured by trained medical doctors who were blind to the study protocol. Following at least 12 hours of fasting, venous blood samples were collected from the patients. All samples were centrifuged for 10 minutes. Then, all serums were kept at – 80'C deep and frozen until they were studied. On the obtained serum, routine biochemical parameters including TG, total cholesterol (T-Chol), HDL-C, low-density lipoprotein cholesterol (LDL-C), plasma glucose (Glu), uric acid (Ua), creatinine (Cre), vitamin D (Vit-D), hemogram well as CRP and PAB were studied with routine methods. All parameters, including prealbumin and CRP, were studied using a Cobas 501 (Roche Diagnostics, Germany) autoanalyzer.

2.3. Echocardiographic examination

We used a Vivid 5 pro echocardiographic unit (GE Healthcare, GE, USA), including a 3,5 MHz probe for echocardiographic assessment. All test subjects were evaluated by a standard two-dimensional and Doppler evaluation according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging by a single experienced cardiologist who was blinded to the test subjects and all clinical findings (11). The following parameters were obtained by conventional echocardiographic imaging (CEI): Left ventricular (LV) end-diastolic dimension (LV-Dd), LV systolic dimension (LV-Sd), LV ejection fraction (LVEF, %) according to the method of Simpson's method; mitral annular plane systolic excursion (MAPSE) and tricuspid annular plane systolic excursion (TAPSE) by the M mode at the mitral lateral and tricuspid lateral annulus, LV and right ventricular (RV) diastolic functions (LVDF; RVDF) from the filling velocities (early peak (E) and late diastolic (A) wave velocities, E/A ratios with deceleration times (DT) using pulsed wave doppler with the sample volume positioned at the tips of the mitral and tricuspid valve leaflets. Epicardial fat thickness (EFT) was considered as the echo-free distance between the outer surface of the myocardium and the vis¬ceral stratum of the pericardium. We measured EFT values from the parasternal long-axis imaging at vertical to the right ventricular free wall at the end of the diastole. The tissue Doppler imaging echocardiography (TDIE) study was performed in the lateral mitral annulus, interatrial septum, and lateral tricuspid annulus. The recordings of all diastolic functions of LV were obtained by evaluation of early peak (e') and late (a') diastolic wave velocities. In addition, the e'/a' ratio, DT of e' wave from mitral lateral annulus, and systolic velocity of tricuspid lateral annulus (t-S') were also obtained at the lateral tricuspid annulus by the TDIE. Diastolic dysfunction was accepted as E/A <1,0 (11).

2.4. Left atrial mechanical functions

LA volume measurements were performed with the disk method from the apical four-chamber window. Maximum left atrial volume (Vmax) was recorded just at the time of mitral valve opening; minimum left atrial volume (Vmin) was recorded just at the time of mitral valve closure; presystolic or preatrial contraction left atrial volume (VpreA) was recorded at the onset of atrial systole (P wave on ECG). All LA volumes were corrected/indexed by body surface area (BSA = mm^3 /m^2). End diastolic and end systolic left ventricular volumes and BSA ratios were recorded. LA emptying functions were calculated with the following formula:

Left atrial passive emptying volume (LA-PEV) = Vmax – VpreA;

Left atrial passive emptying fraction (LA-PEF) = LA-PEV / Vmax;

Left atrial active emptying volume (LA-AEV) = VpreA – Vmin;

Left atrial active emptying fraction (LA-AEF) = LA-AEV / VpreA;

Left atrial total emptying volume (LA-TEV) = Vmax – Vmin;

Left atrial total emptying fraction (LA-TEF) = LA-TEV – Vmax.

All measurements were done by one operator who was blinded to subjects at twice during different times, and the average of the measurements was obtained (12).

2.5. Reproducibility

To calculate the intra-observer and inter-observer coefficients of variation for measurements of echocardiographic recordings and CRP/PAB ratio results, 20 randomly selected patients in the severe group were assessed by repeating the measurements under the same baseline conditions. To test the interobserver variability, we performed the measurements offline from video recordings by a second observer. The intra-observer and inter-observer coefficients of variation for the echocardiographic and CRP/PAB ratio measurements were found to be <5% and insignificant.

2.6. Statistical analysis

The continuous variables are presented as mean ± standard deviation (SD) or median (inter-quartile range). The categorical variables are presented as frequency (percentage). The data were checked for normality using Kolmogorov-Smirnov and Shapiro–Wilk tests. ANOVA and Kruskal-Wallis tests were used to examine the differences between the continuous variables when appropriate. Bonferroni test was used as the Post-Hoc analysis then the Mann-Whitney -U test was used to examine the differences between variables. Pearson chi-squared test or Spearman's test was used to determine the potential correlation between the CRP/PAB ratio and other variables. The statistical analyses were performed using SPSS for Windows (version 21.0, SPSS Inc., Chicago, IL, USA). All analyses were two-tailed, and a p-value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline demographics and laboratory findings

The demographic characteristics and echocardiographic parameters of all participants are presented in Table 1. A total of 100 patients with Met-S (49 patients non-DM or group-1 and 53 patients DM or group-2) and 53 normal healthy people (control or group-3) were included in our study. Mean age was found to be significantly different between groups (group-1:58 ± 8,7, group-2: 60 ± 8,5 and group-3: 59 ± 7,2; p=0,372). Comparisons of other variables of laboratory parameters revealed that BMI, waist-circumference, PAB, Glu, TG, white blood cell (WBC), and neutrophil (Neu) were significantly found to be different between groups (p<0.05 for all). However, the CRP/PAB ratio was not found to be different between groups (group-1:0.014 (0.007 - 0.027) vs group-2:0.009 (0.005 - 0.024) vs group-3:0.006 (0.003 - 0.015), p=0,107). Other variables included CRP, Ua, Vit-D, T-Chol, LDL-C, HDL-C, Cre, hemoglobin (Hb), and platelets (Plt) levels were found to be indifferent between groups (all for p>0.05).

Table 1. Baseline demographics and laboratory results

Variables	Non-DM group Female (n = 22,) Male (n = 27) n = 49 (32%) Group-1	DM group Female (n = 26) Male (n = 25) n = 51 (33,3%) Group-2	Control group Female (n = 25) Male (n = 28) n = 53 (34,6%) Group-3	p μ, Ω	Variables (to continued)	Non-DM group n = 49 Group-1	DM group n = 51 Group-2	Control group n = 53 Group-3	p μ, Ω
Age (years)	58 ± 8.7	60 ± 8.5	59 ± 7.2	0.372 μ	**Mitral- E velocity (cm/s)**	81.2±18.9	78.7 ± 19.4	84.7 ± 17.1	0.503 μ
BMI (kg/m²)	28 ± 3.8	33 ± 5	34 ± 4.9	**<0.0001** μ	**Mitral- A velocity (cm/s)**	91 ± 18.4	92.6 ± 17.8	81 ± 17.1	**0.041** μ
BSA (m²)	1.9 ± 0.2	2 ± 0.2	2 ± 0.2	0.184 μ	**Tricuspid-E velocity (cm/s)**	65.2±12.7	62.8 ± 15.6	68.5 ± 14.6	0.349 μ
Waist - Circ (cm)	98 ± 9.8	109 ± 8.8	111 ±10.6	**<0.0001** μ	**Tricuspid-A velocity (cm/s)**	55.9 ± 9.1	68 ± 12.7	55.9 ± 9.1	**0.002** μ
CRP/PAB ratio	0.014 (0.007 - 0.027)	0.009 (0.005 - 0.024)	0.006 (0.003 - 0.015)	0.107 Ω	**Mitral-e'- velocity (cm/s)**	65.2 ± 12.7	62.8 ± 15.6	69.5 ± 13.9	0.225 μ
PAB (mg/dL)	24 ± 4.8	26 ± 5	23 ± 3.7	**0.029** μ	**Mitral-a'- velocity (cm/s)**	63.6±16.4	68 ± 12.7	55.8 ± 9.5	**0.006** μ
CRP (mg/dL)	0.27 (0.2 -0.5)	0.23 (0.1 -0.5)	0.14 (0.08-0.3)	0.078 Ω	**t-S'- velocity (cm/s)**	18.8 (16.5-23.1)	18.9 (17.0-23.5)	17.8 (15.4 -23.4)	0.447 Ω
Ua (mg/dL)	5 ± 1.3	5 ± 1.1	4.9 ± 1.3	0.511 μ	**Vmax / Indexed (mm³/m²)**	12.1 ± 4	14.7 ± 6.5	12.3 ± 3.5	0.089 μ
Vit-D (nmol/L)	18 ± 5.4	21 ± 10.5	17 ± 8.1	0.324 μ	**VpreA / Indexed (mm³/m²)**	9.1 (7.6~11.8)	10.2 (6.2~12.3)	10.8 (8~14)	0.372 Ω
Glu (mg/dL)	97 (91-102)	134 (104-178)	93 (85-101)	**<0.0001** Ω	**Vmin / Indexed (mm³/m²)**	7.4 ± 3.1	9.4 ± 6.2	7.3 ± 2.7	0.157 μ
T-Chol (mg/dL)	198.5 (177-220)	201 (187-232)	204 (169-225)	0.604 Ω	**LA passive emptying**	2.4 ± 2	2.6 ± 1.5	2.4 ± 1.7	0.920 μ

					volume (LA-PEV) = Vmax–VpreA				
LDL-C (mg/dL)	122 ± 8.6	122 ± 6.6	120 ± 7.5	0.983 μ	**LA passive emptying fraction (LA-PEF) = LA-PEV/Vmax**	18.3±12.9	18.6 ± 12.1	19.5±11.6	0.932 μ
HDL-C (mg/dL)	50 ± 12.7	48 ± 11.5	54 ± 13.2	0.198 μ	**LA active emptying volume (LA-AEV) = VpreA –Vmin**	2.3 (0.7~3.5)	2.5 (1.3~3.9)	2.2 (1.4~3)	0.768 Ω
TG (mg/dL)	167 (130-238)	181 (145-233)	115 (83-168)	**0.002** Ω	**LA active emptying fraction (LA-AEF) = LA-AE/VpreA**	24.5±15.8	25.3 ± 15.6	25.5 ± 12	0.963 μ
Cre (mg/dL)	0.89 ± 0.25	0.85±0.26	0.77±0.13	0.131 μ	**LA total emptying volume (LA-TEV) =Vmax – Vmin**	4.7 ± 2.5	5.4 ± 2.1	4.9 ± 2.3	0.547 μ
Wbc (10^3/mm^3)	8.28 ± 2.05	8.34±1.59	7.13 ± 2	**0.045** μ	**LA total emptying fraction (LA-TEF) = LA-TEV /Vmax**	38.7±15.2	39.3 ± 15.9	40.1 ± 13	0.936 μ
Hgb (g/dL)	14.7 ± 1.7	13.8 ± 1.7	14.2±1.6	0.193 μ	**EFT (mm)**	5.7 ± 1.8	10.3 ± 19	6.7 ± 2.5	0.285 μ
Neu (%)	4.76 ± 1.83	5.09±1.32	3.96±1.45	**0.036** μ	**MAPSE (mm)**	141 ± 20	13.6 ± 2.6	16 ± 3.2	**0.020** μ
Plt (10^3/mm^3)	270 ± 46	284 ± 59	255 ± 53	0.167 μ	**TAPSE (mm)**	21.5 ± 4.3	20.6 ± 4.6	22 ± 3.7	0.458 μ

Baseline and demographic features: BMI: Body-mass-index, BSA : Body- surface-area, Waist – Circ: Waist- circumference, CRP/PAB: CRP/Prealbumin, Ua: Uric acid, Vit-D: Vitamin-D, Glu: Glucose, Chol: Cholesterol, LDL-C: LDL- Cholesterol, HDL-C: HDL-Cholesterol, TG:Triglycerides, Cre: Creatinin, Wbc: White Blood Cell, Hgb:Hemoglobin, Neu: Neutrophil, Plt: Platelet, t-S´- velocity: Systolic velocity of tricuspid lateral annulus on tissue doppler imaging echocardiography (TDIE), LA Vmax / Indexed: the maximal left atrial volume indexed by BSA, LA-VpreA: the pre-atrial contraction left atrial volume indexed by BSA, LA-Vmin : the minimal LA volume indexed by BSA, EFT: Epicardial fat thickness, MAPSE: Mitral annular plane systolic excursion, TAPSE: Tricuspid annular plane systolic excursion, μ: ANOVA, Ω: Kruskal-Wallis test

3.2. Echocardiographic findings

Among conventional echocardiographic parameters, mean mitral and tricuspid-E velocities were not found to be different between groups (p-value for all >0.05), however, mean mitral-A and tricuspid-A velocities were found to be significantly different between groups (p-value for all<0.05). During TDIE, mean mitral-a' velocity was found to be different between groups (p=0.006); however, mean mitral-e' and tricuspid-S' velocities were not by TDIE (p for all >0.05). Also, mean EFT and TAPSE were not found to be different (p for all >0.05), while mean MAPSE was found to be significantly different between groups (p=0.020, Table 1).

3.3. LA functions

As for the parameters indicating LA volumes and mechanical functions, all groups were similar with respect to mean Vmax (indexed to BSA), mean Vpre-A (indexed), and mean Vmin (p-value for all>0.05, Table 1). Also, all kinds of measurements of mechanical functions of LA (LA-PEV, LA-PEF, LA-AEV, LA-AEF, LA-TEV, LA-TEF) were found to be indifferent among groups (p value for all >0.05, Table 1).

3.4. Post-hoc analysis

Post-hoc analysis was depicted in Table 2. Mean age was found to be significantly different only between groups 2 and 3 (p=0.013, Table 2). BMI and waist-circumference were found to be significant different between control and Met-S groups (group 1 vs. 2 and 2 vs. 3; p<0.0001 for all). PAB and Neu counts were found to be significantly different only between groups 2 and 3 (p<0.05 for all). Mean Glu level was found to be different between group 1 vs. 2 with group 2 vs. 3 (p<0.001 for all), while mean TG was found to be different between group 1 vs. 3 and 2 vs. 3 (p<0.05 for all). Mean MAPSE was found to be different between group 2 vs. 3; however, mean mitral-a' velocity was found to be significantly different between group 1 vs. 3 (p=0.004). Tricuspid- A velocity was found to be significantly different between group 1 and 3 and group 2 and 3 (p<0.05 for all, Table 2).

Table 2. Post-hoc analysis

Variables	Non - DM vs. DM (group 1 vs. 2)	Non – DM vs. Control (group 1 vs. 3)	DM vs. Control (group 2 vs. 3)
Age	Ns. β	Ns. β	**0.013** β
BMI	Ns. β	**<0.0001** β	**<0.0001** β
Waist – Circ (cm)	Ns. β	**<0.0001** β	**<0.0001** β
PAB	Ns. β	Ns. β	**0.024** β
Glu	**<0.0001** ¥	Ns. ¥	**<0.0001** ¥
TG	Ns. ¥	**0.006** ¥	**0.002** ¥
Neu	Ns. β	Ns. β	**0.038** β
Mitral-a'- velocity	Ns. β	**0.004** β	Ns. β
MAPSE	Ns. β	Ns. β	**0.016** β
Tricuspid-A velocity	Ns. β	**0.020** β	**0.003** β

Post-hoc analysis of groups. β: Bonferroni Test, ¥: Mann-Whitney U test. PAB: Prealbumin

3.5. Comparisons and correlations

A separate comparison of the groups is depicted in Table 3, 4. We rearranged the groups as having RV diastolic dysfunction (RVDD) or not and LV diastolic dysfunction (LVDD) or not: *1*: Comparison of the patients with and without RVDD (with-RVDD n=32, without-RVDD n=48) revealed that mean age, mean Plt volume (MPV), e-GFR, TAPSE, Mitral-E, A; Tricuspid- E, A; Mitral-e', a' and t-S' velocity parameters were found to be significantly different between groups (p<0.05 for all, Table 3). CRP/PAB ratio was not different between groups (p>0.05). However, none of the volumetric and functional indices of LA were found to be significantly different between with-RVDD and without-RVDD groups (p>0.05 for all in Table 3). *2:* Comparison of the patients with and without LVDD (with-LVDD n=42, without-LVDD n=38) revealed that mean age, PAB, e-GFR, TAPSE, Mitral-A, Tricuspid- E, Mitral-e' and t-S' velocity parameters were found to be significantly different between groups (p<0.05 for all in Table 3). CRP/PAB ratio was not different between groups (p>0.05). Again, among these groups none of the, none of the volumetric and functional indices of LA were found to be significantly different (p>0.05 for all in Table 3). We later examined the patients only who had RVDD and LVDD, and again, they were divided into 3 groups as Non-DM, DM and control groups. These sub-group comparisons, which were restricted to include the patients only with RVDD and LVDD presented in Table 4: *3-A*: Sub-groups analysis in the RVDD group revealed that only mean Glu level was found to be significantly different between DM, Non-DM, and control groups (p=0.001). CRP/PAB ratio and none of the volumetric and functional indices of LA were found to be different between groups (p>0.05 for all in Table 4). *3-B:* Sub-groups analysis in the LVDD group revealed that Tricuspid-A velocity, waist-circum. and BMI parameters were found to be significantly different between DM, Non-DM and control groups (p<0.05 for all). Again, the CRP/PAB ratio and none of the volumetric and functional indices of LA were found to be different between groups (p>0.05 for all in Table 4). Finally, the correlation chart of the CRP/ PAB ratio with variables in three main separate groups was presented in Table 5. CRP/PAB ratio was found to be significantly negatively correlated with EFT and LA active emptying volume (indexed) in the control group (r: - 0,386; p=0.047 and r: – 0,383; p=0.049 respectively, in Table 5) and positively correlated with mean monocyte count and red cell distribution (RDW) in DM group (r: 0,440; p=0.032 and r: 0,452; p=0.026 respectively) and also positively correlated with BMI, waist-circumference and mean platelet volume (MPW) in Non-DM group (r: 0,51; p=0.005, r: 0,417; p=0.027 and r: 0,413; p=0.036 respectively in Table 5).

Table 3. Comparison of groups as right ventricular diastolic dysfunction (RVDD) is present or not are depicted as main group and left ventricular diastolic dysfunction (LVDD) is present or not are depicted as main group

Variables	RVDD is present (n = 32)	RVDD is not present (n = 48)	p μ, Ω	Variables	LVDD is present (n = 42)	LVDD is not present (n = 38)	p μ, Ω
Age (years)	61 ± 6.8	55 ± 8.7	**0.001** μ	**Age (years)**	61 ± 7.5	53 ± 7.8	**<0.0001** μ
MPV	9.98 ± 0.9	10.5 ± 0.8	**0.017** μ	**PAB**	25.4 ± 4.8	22.8 ± 4.1	**0.012** μ
e-GFR	81 ± 19	93 ± 13	**0.001** μ	**e-GFR**	83 ± 18	94 ± 13	**0.04** μ
CRP/PAB ratio	0.009 (0.005 - 0.024)	0.009 (0.004 -0.020)	Ns. Ω	**CRP/PAB ratio**	0.007 (0.004 - 0.022)	0.014 (0.006-0.022)	Ns. Ω
MAPSE (mm)	14.93 ± 2.7	14.98 ± 3.4	Ns. μ	**MAPSE (mm)**	15 ± 3	15 ± 4	Ns. μ
TAPSE (mm)	19.71 ± 4.3	22.47 ± 3.8	**0.004** μ	**TAPSE (mm)**	**20 ± 4**	23 ± 4	**0.001** μ
Mitral- E velocity (cm/s)	73 ± 17	87 ± 17	**<0.0001** μ	**Mitral- E velocity (cm/s)**	66 ± 13	60 ± 13	Ns. μ
Mitral- A velocity (cm/s)	94 ± 18	84 ± 18	**0.025** μ	**Mitral- A velocity (cm/s)**	61 ± 13	71 ± 13	**0.001** μ

Tricuspid-E velocity (cm/s)	56 ± 9	72 ± 14	**<0.0001** μ	**Tricuspid-E velocity (cm/s)**	60.33 ± 13.2	71.32 ± 13.4	**<0.0001** μ
Tricuspid-A velocity (cm/s)	69 ± 13	59 ± 13	**0.001** μ	**Tricuspid-A velocity (cm/s)**	66 ± 13	60 ± 13	Ns. μ
Mitral-e'- velocity (cm/s)	56 ± 9	72 ± 14	**<0.001** μ	**Mitral-e'-velocity (cm/s)**	61 ± 13	71 ± 13	**<0.0001** μ
Mitral-a'- velocity (cm/s)	68 ± 14	59 ± 13	**0.004** μ	**Mitral-a'-velocity (cm/s)**	65 ± 14	60 ± 13	Ns. μ
t-S'- velocity (cm/s)	19 ± 4	21 ± 6	**0.044** μ	**t-S'-velocity (cm/s)**	21 ± 5	18 ± 4	**0.010** μ
LA Vmax / Indexed (mm^3/m^2)	13 ± 4	13 ± 5	Ns. μ	**LA Vmax / Indexed (mm^3/m^2)**	13 ± 5	13 ± 5	Ns. μ
LA VpreA / Indexed (mm^3/m^2)	10 ± 4	11 ± 5	Ns. μ	**LA VpreA / Indexed (mm^3/m^2)**	10.5 (6.9 - 12.4)	9.95 (7.7 - 12.1)	Ns. Ω
LA Vmin / Indexed (mm^3/m^2)	6.7 (4.8-9.4)	7.7 (5.7-9.3)	Ns. Ω	**LA Vmin / Indexed (mm^3/m^2)**	6.95 (4.8 - 10.3)	7.3 (5.6 - 9.11)	Ns. Ω
LA passive emptying volume / Indexed (PEV) (mm^3/m^2)	1.9 (0.9-3.05)	2.25 (1.3-3.6)	Ns. Ω	**LA passive emptying volume / Indexed (PEV) (mm^3/m^2)**	1.9 (0.6 - 3.1)	2.25 (1.4 - 3.6)	Ns. Ω
LA passive emptying fraction (PEF)	17 ± 11	20 ± 13	Ns. μ	**LA passive emptying fraction (PEF)**	17 ± 12	21 ± 11	Ns. μ
LA active emptying volume (AEV) / Indexed (mm^3/m^2)	2.6 ± 1.4	2.5 ± 1.97	Ns. μ	**LA active emptying volume (AEV) / Indexed (mm^3/m^2)**	2.35 (1.3 - 3.9)	2.25 (1.3 - 3.2)	Ns. Ω
LA active emptying fraction (AEF)	28 ± 16	23 ± 13	Ns. μ	**LA active emptying fraction (AEF)**	26 ± 16	24 ± 13	Ns. μ
LA total emptying volume (TEV) / Indexed (mm^3/m^2)	4.86 ± 2.14	5.02 ± 2.46	Ns. μ	**LA total emptying volume (TEV) / Indexed (mm^3/m^2)**	5 ± 2	5 ± 3	Ns. μ
LA total emptying fraction (TEF)	40 ± 16	39 ± 14	Ns. μ	**LA total emptying fraction (TEF)**	39 ± 15	40 ± 14	Ns. μ

Comparison of variables between groups of RVDD is present and not as well as LVDD is present group and not. μ: ANOVA, Ω: Kruskal-Wallis test, e-GFR: estimated glomerular filtration rate.

Table 4. Comparison of groups only when right ventricular diastolic dysfunction (RVDD) is present and left ventricular diastolic dysfunction (LVDD) is present and they were separately as control, Non-DM and DM groups

Variables in RVDD is present (n = 32)	**Control group (n = 3)**	**Non-DM group (n = 13)**	**DM group (n = 16)**	**$p^{\mu,\Omega}$**	**Variables in LVDD is present (n =42)**	**Control group (n = 9)**	**Non-DM group (n = 14)**	**DM group (n = 19)**	**$p^{\mu,\Omega}$**
CRP/PAB ratio	0.004 (0.002-0.006)	0.011 (0.008-0.03)	0.009 (0.005-0.024)	Ns. Ω	**CRP/PAB ratio**	0.004 (0.003 - 0.006)	0.010 (0.005 - 0.026)	0.007 (0.004 - 0.024)	Ns. Ω
Glu (mg/dL)	101	95	136.5	**0.001** Ω	**Tricuspid-A velocity**	57 ± 8.2	72 ± 15.4	65 ± 11.6	**0.028** μ

	(89-111)	(92 – 99)	(106-175)		**(cm/s)**				
LA Vmax / Indexed (mm3/m2)	13.8 ± 6.4	11.4±3.7	13.4 ±4.6	Ns. μ	**Waist-Circ(cm)**	97 ± 9.7	108±9.4	110±10.4	**0.009** μ
LA VpreA / Indexed (mm3/m2)	10.4 ± 6.1	9.6 ± 3.1	11±3.9	Ns. μ	**BMI (kg/m^2)**	27 ± 3.9	32 ± 5.5	33 ± 4.5	**0.009** μ
LA Vmin / Indexed (mm3/m2)	5.4 (3.6 - 16.1)	5.9 (4.7- 9)	7 (4.8- 9.8)	Ns. Ω	**LA Vmax / Indexed (mm3/m2)**	12 ± 3.8	11.2 ± 3.6	14.3± 5.2	Ns. μ
LA passive emptying volume / Indexed (PEV) (mm3/m2)	3.4 ± 2.7	1.8 ± 1.8	2.4 ± 1.6	Ns. μ	**LA VpreA / Indexed (mm3/m2)**	11 (8.5 - 11.8)	10.15 (6.1- 10.8)	11.1 (7.5- 15.2)	Ns. Ω
LA passive emptying fraction (PEF)	24.6 ± 18.8	14.6±11.1	17.3±102	Ns. μ	**LA Vmin / Indexed (mm3/m2)**	7.1 (6.3 – 8.1)	5.8 (4.6- 9.4)	8.3 (4.8- 12.1)	Ns. Ω
LA active emptying volume (AEV) / Indexed (mm3/m2)	2 ± 0.8	2.7 ± 1.3	2.7 ± 1.3	Ns. μ	**LA passive emptying volume / Indexed (PEV) (mm3/m2)**	1 (0.4 - 2.9)	1.5 (0.5-2.2)	2.6 (1 - 3.9)	Ns. Ω
LA active emptying fraction (AEF)	26 ± 18.6	29.3 ± 14.9	27.2±16.9	Ns. μ	**LA passive emptying fraction (PEF)**	10 (3.2-14.2)	14.7 (4.8- 21.9)	20.7 (10 -25.5)	Ns. Ω
LA total emptying volume (TEV) / Indexed (mm3/m2)	5.4 ± 2.4	4.4 ± 2.2	4.4 ± 2.2	Ns. μ	**LA active emptying volume (AEV) / Indexed (mm3/m2)**	2.8 (1.4 - 3.7)	2.35 (0.5- 3.3)	2.2 (1.2 - 4.1)	Ns. Ω
LA total emptying fraction (TEF)	52 (20.6- 60.2)	41 (25 -50.5)	44.3 (25 -51.8)	Ns. Ω	**LA active emptying fraction (AEF)**	27 ± 12.9	27 ±16.4	26 ± 16.7	Ns. μ
					LA total emptying volume (TEV) / Indexed (mm3/m)	4.1 ± 1.5	4.4 ± 2.1	5.5 ± 2.2	Ns. μ
					LA total emptying fraction (TEF)	36 ± 14	40 ± 15.6	40 ± 15.7	Ns. μ

Comparison of variables between groups of RVDD is present and not as well as LVDD is present group and not. μ: ANOVA, Ω: Kruskal-Wallis test

Table 5. Correlations of CRP/PAB ratio with variables in three separate groups

Variables	Control group		Variables	DM group		Variables	Non-DM group	
	Sperman's r:	p		Sperman's r:	p		Sperman's r:	p
EFT (mm)	- 0.386	**0.047**	**Monocyte**	0.440	**0.032**	**BMI**	0.519	**0.005**
LA active emptying volume (AEV) / Indexed (mm^3/m^2)	- 0.383	**0.049**	**RDW**	0.452	**0.026**	**Waist-Circum**	0.417	**0.027**
						MPV	0.413	**0.036**

Correlations of CRP/PAB ratio with variables in three separate groups. MPV: mean platelet volume, RDW: Red cell distribution width.

4. Discussion

Circulating levels of inflammatory markers have been shown to be involved with different features of Met-S. CRP has been recognized as a marker of systemic inflammation and is reported to be related to several features of CVD and Met-S (13). Serum albumin and PAB are among the widely used nutritional biomarkers. It has been shown that PAB could predict mortality in patients with HF [14]. CRP/PAB ratio was reported to be superior to either hs-CRP or PAB alone in assessing not only the severity but the prognosis of patients with acute kidney injury, fistula closure, and other critically ill patients. In a prospective study including 682 patients with ST-elevation myocardial infarction (STEMI). The median CRP/PAB ratio (0.02) was set as the cutoff value, and patients were divided into 2 groups according to this cut-off value as high- CRP/PAB ratio (CRP/PAB ratio ≥0.02) and a low-CRP/PAB ratio group (CRP/PAB ratio <0.02). The accumulated incidence rate of major adverse cardiovascular events (MACE) was found to be significantly higher in the high CRP/PAB ratio group (38,7% vs. 12,0%, p<0.01) during a median follow-up of 18 months (15). In another trial, an investigation of the possibility of using the hs-CRP/PAB ratio to predict in-hospital MACE in a total of 659 patients with acute coronary syndrome (ACS) showed that the occurrence rate of in-hospital MACE and acute HF was found to be higher in the high hs-CRP/PAB ratio groups (p<0.001) (16).

Atrial enlargement has been known to be associated with increased mortality in the general population, and atrial remodeling, which is frequently accompanied by increased interstitial fibrosis, is a hallmark of pathological changes in atrial dilatation. These changes have a strong association with many diseases like HF, HT, obesity and Met-S (17). One of the possible mechanisms of the predisposing of atrial remodeling is inflammation and oxidative stress, and the CRP and oxidants have been reported to be elevated in patients with AF. Functional changes of LA could occur earlier than morphological changes of LA, and functional impairment may occur with or without alteration in LA size. In a previous study, LA size was found to be influenced by insulin resistance and obesity independently of the LV hypertrophy and LV geometry in non-diabetic hypertensive patients. So, LA size has been known to be influenced by systemic chronic inflammatory situations in non-diabetic patients (18-19). Atrial dilatation has been found to be accompanied by atrial mechanical dysfunction, and it has been shown before that the reservoir and conduit functions of LA were found to be significantly lower in patients with Met-S than in controls (p<0.001); however, LA booster function was found to be not different between groups (20). Along with these results, Yilmaz et al. found that the Met-S group had a greater LA Vmax (p=0.03), VpreA (p=0.001), and LA-AEV active emptying volume (p=0.001). However, LA-PEF was lower in the Met-S group (p=0.001) (10). Along with the importance of these chronic systemic inflammations in the pathogenesis of dilatation and mechanical dysfunction of LA in Met-S, we tried to find any possible relationship between LA functions and a CRP/PAB ratio among patients with/without DM. Unfortunately, the CRP/PAB ratio and other volumetric and functional indexes of LA were not found to be different between groups (p>0.05 for all, Table 1). Only mitral and tricuspid A velocity and mitral-a' velocity were found to be different between groups (p<0.05 for all, Table 1). In posthoc analysis, only mitral-a' velocity and tricuspid-A velocity was found to be different between groups (Table 2). As a summary, the functional index of LA, the mitral -a' velocity, and a right atrial functional index, tricuspid-A velocity, late kicking, or booster function were found to be different between Met-S and control groups (Table 2). In contrast to our results, in a previous study, it has been demonstrated that passive LA emptying volume was found to be decreased in diabetic patients and it was found to be associated with higher end-diastolic LV pressures. In addition, active LA emptying volume, which was found to be associated with greater LA contraction compensatory mechanisms, was found to be increased in patients with DM (21). In another study, LA reservoir function as an index of LA compliance was found to be significantly lower in patients with Met-S. After 5-year follow-up, compared to surviving subjects, LA reservoir function was decreased in both all-cause and CVD mortality groups, of note markedly impaired in those who died from CVD (22). In the other part of our examination, when we divided the patients as having LVDD or RVDD, again, functional and volumetric parameters of LA were not found to be different between diabetic or non-diabetic groups (Table 3-4). LA and right atrial (RA) booster functional indexes were again found to be different between groups (Table 3 4). These results are different from previous studies, which can be explained by including lower patients. In the last part of our analysis, the CRP/PAB ratio was found to be positively correlated with monocyte count in the DM group and waist-circumference, BMI, and MPV in the Non-DM group. None of the volumes and functional indexes were found to be correlated with the CRP/PAB ratio in DM or Non-DM groups (Table 5). These results were inconsistent with the previous studies, which indicated that diabetic patients have several alterations in their LV and LA functions. In a previous trial, total and passive LA emptying fractions (EF), demonstrating LA reservoir and conduit function, were significantly lower in DM patients than in controls. Active LA EF, the parameter of LA booster pump function, was found to be similar between DM and controls (23). Along with these results, we found that the mitral and tricuspid late diastolic (A) wave velocities (mitral and tricuspid-A-velocities) and mitral tissue doppler late (a') diastolic wave velocity (mitral-a'-velocity) were significantly higher in DM group than non-DM and control groups. It represents that parameters of late active contractile functions of LA and RA were higher in patients with DM. LA-AEF contributes to 15%–30% of the LV stroke volume by its contraction during the final phase of diastole, and in line with

present results, a study by Gulmez et al. compared the 56 diabetic patients with 56 controls. Their results showed higher LA-AEV in the diabetic patients, while in contrast to us, the A and E waves and their ratios were not different between the groups (24). Although the CRP/PAB ratio has been knowing to reflect a more sensitive inflammatory state than either CRP or PAB, its value in the assessment of LA functions and metabolic syndrome is still ambiguous. In our study, this predictive value has been aimed to be determined, but it has not been determined fully, so in the near future, more studies are needed to reveal this value.

One of the limitations of our study is nonrandomized patient selection and grouping, which could have affected the results. The relatively small number of patients in the 3 subgroups is another important limitation of this study. Also, information on the duration of Met-S individual risk factors was not available; this would have likely added to a precise determination of the effect of systemic inflammation on the LA remodeling. Phasic LA function analysis could have been informative to further evaluate the mechanism of atrial dysfunction and remodeling. Finally, due to cross-sectional study design, causal inferences are limited.

The CRP/PAB ratio was known to be a novel marker for evaluating the systemic inflammatory state, and it has been reported to have predictive value in assessing the severity and prognosis of various diseases. Chronic systemic inflammation, which is accompanied by increased interstitial fibrosis in atrial tissue, is frequently associated with Met-S. This study aimed to assess the predictive value of CRP/PAB ratio in LA functions in patients with Met-S, which showed a lack of any association between the CRP/PAB ratio and LA functions. However, late atrial active kicking function has been found to be associated with DM. To assess the predictive value of the CRP/PAB ratio in Met-S further studies with a large cohort population.

Conflict of interest

The authors have no conflicts of interest to declare.

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Authors' contributions

Concept: Y.B., B.İ., Design: Y.B., B.İ., Data Collection or Processing: Y.B., B.İ., Analysis or Interpretation: Y.B., B.İ., Literature Search: Y.B., B.İ., Writing: Y.B., B.İ.

Ethical Statement

The protocol of study has been approved by the ethics committee of Kirsehir Ahi Evran University of Medical Faculty (04.04.2023 date and registration number 2023-07/43), and written informed consent was obtained from all of the study participants before their participation in this study.

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