Relation of plasma matrix metalloproteinase-8 levels late after myocardial infarction with left ventricular volumes and ejection fraction

Miyokart enfarktüsü sonrası geç dönemde plazma matriks metalloproteinaz-8 seviyelerinin sol ventrikül hacimleri ve ejeksiyon fraksiyonu ile ilişkisi

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ABSTRACT

Objectives: Enhanced matrix metalloproteinase-8 (MMP-8) activity in the early post-myocardial infarction (MI) period has been related to early remodeling. However, it has been demonstrated that plasma MMP-8 level has a biphasic profile, and the relation between the late plasma levels and remodeling is unclear. We evaluated the plasma MMP-8 levels and its correlates 20 ± 3 months after acute MI.

Study design: 58 post-MI patients and 26 control subjects underwent quantitative single-photon emission computed tomography (SPECT) and echocardiography. The plasma MMP-8 levels were measured and its correlates were investigated.

Results: The MMP-8 levels were significantly higher in post-MI patients [median 3.88 ng/ml, interquartile range (1.88-6.43) *vs.* 0.67 ng/ml (0.34-2.47); p<0.001]. Plasma MMP-8 levels were significantly correlated with left ventricular ejection fraction (LVEF) (ρ=0.34, p=0.009), end diastolic volume index (EDVi) (ρ=-0.39, p=0.002) and end systolic volume index (ESVi) (ρ=-0.40, p=0.002).

Conclusion: Plasma MMP-8 levels were found to still be high in post-MI patients 20 ± 3 months after the index event. The levels were significantly correlated with left ventricular volume indices and LVEF. We speculate that, in contrast to the relation between the higher early MMP-8 activity and the extent of cardiac remodeling, higher late levels may be associated with relative preservation of left ventricular systolic function.

ÖZET

Amaç: Miyokart enfarktüsü (ME) sonrası erken dönemde artmış matriks metalloproteinaz-8 (MMP-8) aktivitesinin erken yeniden şekillenme ile ilişkisi olduğu bilinmektedir. Ancak MMP-8'in bifazik bir profile sahip olduğu gösterilmiştir ve geç dönem plazma seviyeleri ile yeniden şekillenme arasındaki ilişki net değildir. Çalışmamızda ME'nin 20 ± 3 ay sonrasında plazma MMP-8 seviyelerini ve klinik parametrelerle olan ilişkisini inceledik.

Çalışma planı: Miyokart enfarktüsü geçirmiş 58 hasta ve 26 bireylik kontrol grubuna kantitatif tek-foton emisyon bilgisayarlı tomografi (SPECT) ve ekokardiyografi yapıldı. Plazma MMP-8 seviyeleri ölçüldü ve korelasyonları incelendi.

Bulgular: Plazma MMP-8 seviyeleri ME geçirmişlerde anlamlı olarak daha yüksek idi [medyan 3.88 ng/ml, çeyreklerrarası aralık (1.88-6.43) ve 0.67 ng/ml (0.34-2.47); p<0.001]. Plazma MMP-8 seviyeleri sol ventrikül ejeksiyon fraksiyonu (ρ=0.34, p=0.009), diyastol sonu hacim endeksi (ρ=-0.39, p=0.002) ve sistol sonu hacim endeksi (ρ=-0.40, p=0.002) ile anlamlı olarak korelasyon göstermekte idi.

Sonuç: Plazma MMP-8 seviyeleri ME'den sonra 20 ± 3 ay geçmiş olsa bile hala yüksek bulunmuştur. MMP-8 plazma düzeyleri, sol ventrikül hacim endeksleri ve ejeksiyon fraksiyonu arasında anlamlı korelasyon bulunmuştur. Erken dönemdeki yüksek MMP-8 seviyeleri ve yeniden şekillenmenin boyutu arasındaki pozitif ilişkinin aksine, geç dönemdeki yüksek MMP-8 seviyelerinin sol ventrikül sistolik fonksiyonunun göreceli olarak korunması ile ilişkili olabileceğini düşünüyoruz.

Left ventricular (LV) myocardial remodeling is an important process in the development of heart failure in post-myocardial infarction (MI) patients. The rate and extent of cardiac remodeling have been proven to be independent predictors of morbidity and mortality. This process encompasses a complex and dynamic interaction of extracellular matrix (ECM) components, neurohormonal factors and myocytes.[1] Alterations within the ECM network cause loss of structural support exposing the cardiomyocytes to abnormal stress patterns, resulting in changes in LV geometry and myocardial dysfunction.[2] The matrix metalloproteinases (MMPs) are zinc-dependent proteolytic enzymes that have an important role in the modulation of the ECM and in the progression of LV remodeling both in the early and late post-MI period.[3,4]

Among MMP types, MMP-8 and MMP-9 exhibit significantly higher levels in the early post-MI period. Increased early levels of these two MMPs have been associated with early remodeling and even infarct rupture.[5,6] However, these MMPs may have a biphasic plasma profile.[5] This biphasic profile, rather than the absolute level of MMP activity, may be important for LV remodeling. It was previously demonstrated that despite the relation between the early high levels and the extent of remodeling, higher plateau plasma MMP-9 levels were associated with relative preservation of LV systolic function.[5] We hypothesized that there may be a similar relationship between the late plasma MMP-8 levels and relative preservation of left ventricular ejection fraction (LVEF). Thus, we evaluated the plasma MMP-8 levels and its correlates at 20±3 months' post-MI.

PATIENTS AND METHODS

Study population

Seventy-nine patients with a history of a prior MI and revascularization (range: 390-810 days) were included in the study. Thirty-eight patients (65.5%) had undergone primary percutaneous coronary intervention and 20 patients (34.5%) had undergone coronary artery bypass graft (CABG) surgery. The presence of an infarct area was confirmed in all patients by single-photon emission computed tomography (SPECT). Thirty-two age-matched controls had normal scintigraphic findings, except for intermediate lesions in their coronary angiograms. The exclusion criteria were a history of recurrent MI, presence of an active infection, peripheral arterial disease, aortic aneurysm, malignancy, chronic inflammatory disease, uncontrolled hypertension (>140/90 mmHg), LV hypertrophy (>1.2 cm) on echocardiogram, and renal and hepatic failure. Thus, six patients with uncontrolled hypertension, four with LV hypertrophy, one with reduced glomerular filtration rate, and two with an active infection were initially excluded from the study. Afterwards, an additional eight patients were excluded from the study due to the conditions that were neither diagnosed nor declared (2 with Behçet's disease, 1 with familial Mediterranean fever, 2 with peripheral arterial disease, and 3 with urinary tract infection). Of the control group, four with active infections and two with newly diagnosed uncontrolled hypertension were also excluded.

The investigation complies with the principles outlined in the Declaration of Helsinki. The study protocol was reviewed and approved by the local ethics committee. All subjects gave written informed consent that their blood samples could be used for scientific purposes.

Echocardiography

All echocardiograms were performed by two experienced sonographers using a Vivid 3 with a 2.5-3.5 MHz transducer (GE, Vingmed Ultrasound, Horten, Norway). Measurements were made according to the criteria defined by the American Society of Echocardiography.[8] Two-dimensional echocardiographic studies of the left ventricle included parasternal long- and short-axis, apical four- and two-chamber views, and two-dimensionally derived M-mode images from the parasternal long axis. Doppler echocardiographic mitral valve inflow velocities were recorded from the apical four-chamber view with a cursor at the tips of the mitral valve leaflets with measurements of E wave velocity, A wave velocity and E wave deceleration time. Tissue Doppler velocities were recorded from both the septal and the lateral mitral annulus. End-diastolic volume (EDV), end-systolic volume (ESV) and LVEF were estimated using the bi-planar modified Simpson's method from apical two- and four-

Abbreviations:	
ACE	*Angiotensin converting enzyme*
ECM	*Extracellular matrix*
EDV	*End-diastolic volume*
ESV	*End-systolic volume*
IQR	*Interquartile range*
LV	*Left ventricular*
LVEF	*Left ventricular ejection fraction*
MI	*Myocardial infarction*
MMPs	*Matrix metalloproteinases*
SPECT	*Single-photon emission computed tomography*

chamber views. Isovolumetric relaxation time (IVRT) was measured from a modified apical view.

Quantitative SPECT analysis

Treadmill exercise was the first-choice test modality. Patients unable to exercise adequately and those with left bundle branch block underwent pharmacologic stress. Exercise test was performed according to the Bruce protocol. Beta blockers, calcium antagonists and nitrates were discontinued at least 48 hours before testing. The pharmacological test was performed with intravenous dipyridamole infusion at 0.56 mg/kg dose over four minutes. Patients underwent rest and stress Tc-99m-sestamibi gated SPECT studies, 45-

60 minutes after injection of 10 mCi and 25-30 mCi of Tc-99m-sestamibi, respectively. Images were obtained in the supine position with a rotating γ camera equipped with low-energy, high-resolution collimators. Myocardial perfusion quantitative analysis was performed using a commercially available software. The activity of each of the 17 sectors was expressed as the mean activity of all pixels belonging to this sector divided by the highest value of pixel activity in the myocardium. Infarct size was defined as the percentage of the left ventricle with pixel activities <60%. The EDV and ESV of the left ventricle and LVEF were also calculated. The images were rated by an experienced blinded nuclear medicine physician.

Table 1. The main clinical, laboratory and scintigraphic data

	Post-MI group (n=58)			Control (n=26)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Baseline characteristics							
Age (years)			58.5±11			57±8	0.64
Male	51	87.9		19	73.1		0.12
Body mass index (kg/m^2)			28±5			27±4	0.93
NYHA 3-4	7	12.1		0	0		0.10
Prior CABG	20	34.5		0	0		**<0.001**
Age of infarct (mo)	–	–	20±3	–	–	–	–
Diabetes Mellitus	14	24.1		2	7.7		0.13
Hypertension	23	39.7		8	30.8		0.47
Hyperlipidemia	32	55.2		3	11.5		**<0.001**
Ex-smoker	26	44.8		10	38.5		0.64
Stable angina	15	25.9		0	0		**0.004**
Unstable angina	4	6.9		0	0		0.3
Medication							
Aspirin	44	75.9		11	42.3		**0.006**
Clopidogrel	15	25.9		0	0		**0.004**
Beta blocker	49	84.5		0	0		**<0.001**
ACE inhibitor	27	46.6		0	0		**<0.001**
ARB	14	24.1		7	26.9		0.79
Statin	34	58.36		3	11.5		**<0.001**
SPECT parameters							
Infarct size		28.5 (15.75-41)		0	0		**<0.001**
LVEF		40 (31.75-48.25)			65.5 (63.2-71.5)		**<0.001**
Ischemia	18	31		0	0		**<0.001**

MI: Myocardial infarction; NYHA: New York Heart Association; CABG: Coronary artery bypass graft; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; SPECT: Single-photon emission computed tomography; LVEF: Left ventricular ejection fraction.

Plasma MMP-8 measurements

After an overnight fasting, blood samples were collected into heparinized tubes and were centrifuged. Plasma was separated, aliquotted, and frozen at -80 °C until analysis. Total MMP-8 concentrations were measured using enzyme-linked immunosorbent assay (R&D Systems Inc, Minneapolis, MN) according to the manufacturer's instructions with 1:20 dilutions of the plasma. These are high sensitivity assay systems with a detection range of 0.01-0.06 ng/ml. All samples were analyzed in duplicate and averaged. The intra-assay coefficient of variation was 5.2%.

Statistical analysis

Continuous variables were tested for normality on the basis of tests of skewness and kurtosis. Depending on the distribution, continuous variables were presented as either mean±standard deviation or median with the corresponding interquartile range (IQR). Comparisons were made using either Student t-test or Mann-Whitney U-test. Categorical variables were presented as number and corresponding percentage. Differences between groups were assessed using the chi-square test. As the levels were not normally distributed, Spearman's rank correlation coefficients were calculated, as a nonparametric test, for the relationships between plasma MMP-8 levels and echocardiographic and scintigraphic parameters. Two-sided tests were used throughout, and values of $p<0.05$ were considered statistically significant. The Statistical Package for the Social Sciences (SPSS) software package version 14.0 (SPSS, Chicago, IL, USA) was used for data analysis.

RESULTS

Baseline characteristics and plasma MMP-8 levels

The study consisted of 84 subjects (58 post-MI patients and 26 age-matched control subjects). The mean age was 58±10 years (range: 32-79 years). The mean time after acute MI was 598.5±91.9 days (range: 390-810 days). Among post-MI patients, 15 had stable angina and four had unstable angina. In 18 of these patients with angina, ischemia was detected by SPECT analysis. The main clinical, laboratory, scintigraphic, and echocardiographic data are presented in Table 1. Comparison of plasma MMP-8 levels according to the main clinical characteristics revealed that the only parameter that significantly alters the plasma MMP-8

levels is the presence of infarct. The correlation between the plasma MMP-8 levels and the days after MI was weak (rho: 0.13, p=0.33). The median and IQR of plasma MMP-8 levels in the post-MI patients and control group were 3.88 ng/ml (1.88-6.43) and 0.67 ng/ml (0.34-2.47), respectively (p<0.001) (Table 2, Fig. 1a).

Relationship between left ventricular volumes, infarct size and plasma MMP-8 levels in post-MI patients

Interobserver variation, assessed in a subset of the cohort (N=30; mean±SD) was 6.1±2.8% for EDV, 6.5+7.1% for ESV, and 5.8+4.9% for LVEF. There was a positive correlation between plasma MMP-8 level and LVEF ($\rho=0.34$, p=0.009) calculated by biplanar modified Simpson's method (Fig. 1b). There were significant negative correlations between the plasma MMP-8 levels and end-diastolic volume index (EDVi) ($\rho= -0.39$, p=0.002) and end-systolic volume index (ESVi) ($\rho= -0.40$, p=0.002) measured by echocardiography. Furthermore, there was a weak correlation between plasma MMP-8 levels and wall motion score index (WMSI) ($\rho= -0.22$, p=0.05) and infarct size ($\rho= -0.26$, p=0.05) (Table 3). There were no other factors significantly correlated with the LV volume indices or ejection fraction.

Quantitative SPECT analysis, left ventricular function and plasma MMP-8 levels

The LV volumes, LVEF and infarct size measured by SPECT significantly correlated with the volumes and LVEF measured by echocardiography (p<0.001). The median (IQR) of percentage of infarct size was 28.5 (15.75-41) in the post-MI patients. Ischemia was detected in 18 of the post-MI patients. The medians (IQRs) of plasma MMP-8 level in ischemia-present and -absent post-MI patients were 5.57 ng/ml (2.44-7.77) and 3.59 ng/ml (1.74-6.24), respectively (p=0.12).

DISCUSSION

This study demonstrated that the plasma level of MMP-8 was significantly higher in post-MI patients even months after the index event compared to those without a history of MI, with patients having coronary artery lesions of intermediate severity without any infarct. Moreover, plasma MMP-8 level of the post-MI patients was positively correlated with LVEF. It has been demonstrated that metalloproteinases may have

Table 2. Plasma MMP-8 levels (ng/ml) according to the main clinical and scintigraphic data

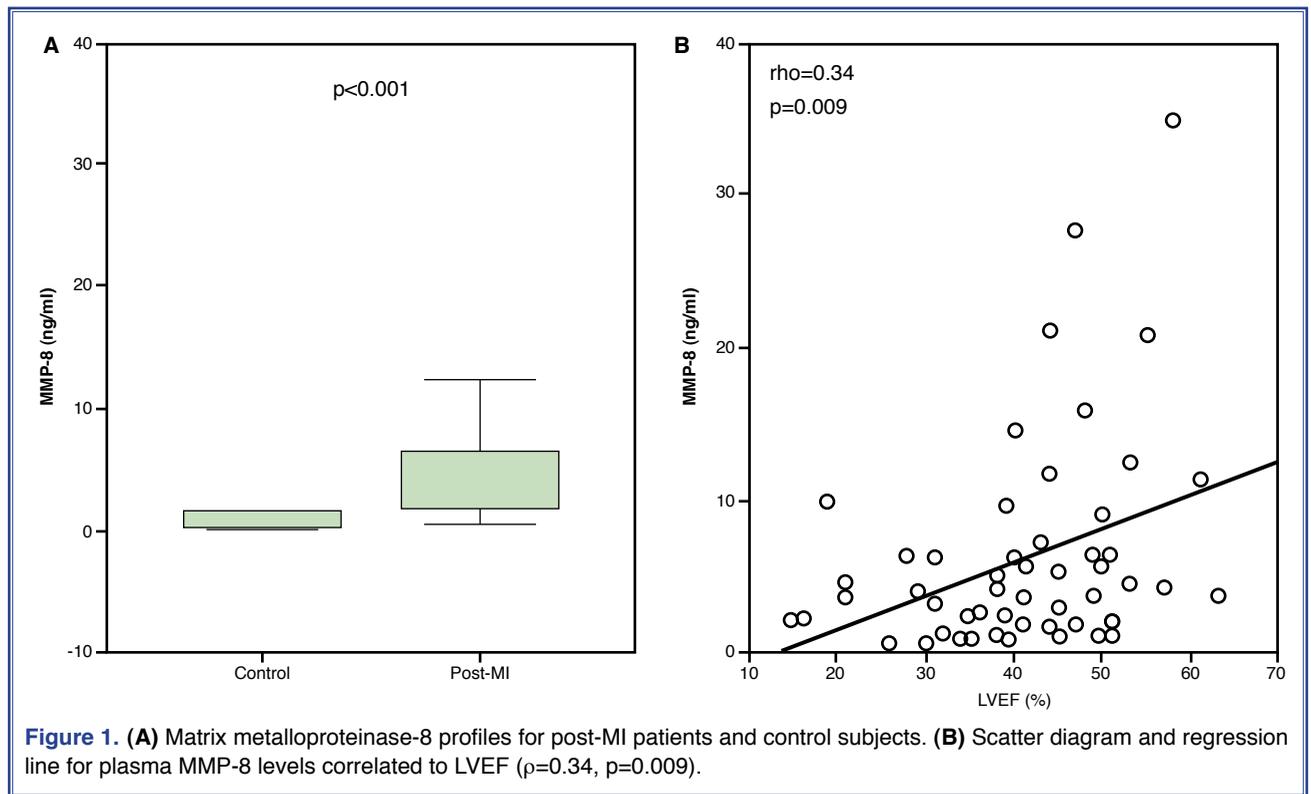| Variables	Median (IQR)	*p*
Gender		
Female	2.37 (0.95-5.6)	0.71
Male	3.37 (0.97-6.41)	
Prior CABG		
Yes	3.66 (1.38-5.97)	0.36
No	2.4 (0.72-6.52)	
Diabetes Mellitus		
Yes	4.13 (1.98-9.82)	0.06
No	2.3 (0.85-5.97)	
Hypertension		
Yes	2.62 (1.05-5.44)	0.68
No	2.81 (0.79-6.32)	
Hyperlipidemia		
Yes	3.61(1.3-5.75)	0.19
No	1.81 (0.68-6.45)	
Ex-smoker		
Yes	3.55 (0.69-5.66)	0.43
No	2.59 (1.02-7.78)	
Stable angina		
Yes	2.62 (1.81-6.5)	0.23
No	2.81 (0.79-5.93)	
Unstable angina		
Yes	3.54 (2.35-5.81)	0.57
No	2.71 (0.97-6.33)	
Aspirin		
Yes	3.61 (1.05-6.41)	0.056
No	1.44 (0.59-4.93)	
Clopidogrel		
Yes	4.21 (1.72-6.24)	0.23
No	2.5 (0.79-6.26)	
Beta blocker		
Yes	3.49 (1.68-5.51)	0.22
No	1.12 (0.52-8.47)	
ACE inhibitor		
Yes	4.21 (1.81-7.16)	0.052
No	2.28 (0.73-6.17)	
Statin		
Yes	4.05 (1.22-6.78)	0.07
No	2.28 (0.71-6.11)	
Infarct in SPECT		
Yes	3.88 (1.88-6.43)	**<0.001**
No	0.67 (0.34-2.47)	

IQR: Interquartile range; CABG: Coronary artery bypass graft; ACE: Angiotensin converting enzyme; SPECT: Single photon emission computed tomography.

a biphasic profile during MI. Although higher early MMP-8 activity leads to early and extensive LV remodeling, higher late levels may be associated with relative preservation of LVEF.

The MMPs are the proteolytic enzymes responsible for ECM degradation.[4] These enzymes have a pivotal role in both early and late ventricular remodeling.[7,9,10] Previous studies have suggested that the monitoring of plasma MMP levels after MI may provide important diagnostic and prognostic information with respect to LV remodeling.[2,7,11] Although plasma levels of MMPs are indirect measures of the local myocardial levels, it has been demonstrated that they reflect the relative protein abundance in the myocardium.[2,12]

The plasma levels of MMP-8 and MMP-9 are significantly high in the early post-MI period.[7] Increased early levels of MMP-8 and MMP-9 have been associated with early remodeling and infarct rupture.[5,6] However, there is a specific temporal biphasic profile of MMP release after MI. This biphasic profile, rather than the absolute level of MMP activity, may be important for LV remodeling. Kelly et al.[5] demonstrated that despite the relation between the early high levels and the extent of remodeling, the higher plateau plasma MMP-9 level was associated with relative preservation of LV systolic function. This finding may also be valid for plasma MMP-8 levels. We found that plasma MMP-8 level was still higher in post-MI patients even 20 months after MI. This may indicate that cardiac remodeling is active even years after MI, and MMP-8 has an active role in this process. When we analyzed the post-MI patients in order to determine the correlates of MMP-8 levels, we found a positive correlation between late plasma MMP-8 levels and LVEF. Enhanced MMP activity soon after MI results in proteolysis, which in the early post-MI period, leads to matrix degradation, early remodeling and even myocardial rupture.[6,13] However, later in the process, this same proteolytic activity allows infiltration of other cell types, which mediate wound healing.[14] Thus, the high levels in the late post-MI period may be related to a successful repair process and relative preservation of LVEF.

Selective MMP inhibition has been shown to reduce LV remodeling after MI in experimental models.[15] However, Spinale et al.[16] demonstrated that

Figure 1. (A) Matrix metalloproteinase-8 profiles for post-MI patients and control subjects. **(B)** Scatter diagram and regression line for plasma MMP-8 levels correlated to LVEF (ρ=0.34, p=0.009).

MMP inhibition conferred a beneficial effect on survival early post-MI, but that prolonged MMP inhibition was associated with higher mortality rates and adverse LV remodeling. Thus, there may be an optimal time window with respect to pharmacological interruption of MMP activity in the post-MI period, and increased MMP activity later in the process may be a requirement for healing. We found that the plasma MMP-8 levels tended to be higher in patients using aspirin, angiotensin converting enzyme (ACE) inhibitors and statin. Drug therapies including ACE inhibitors,[17,18] statins,[19,20] angiotensin II receptor antagonists,[21] and acetylsalicylic acid[22] have been suggested to regulate gelatinase activity. However,

Table 3. Spearman's correlation of plasma MMP-8 concentrations		
Variable	Correlation coefficient (ρ)	*p*
Age	-0.15	0.27
Body mass index	-0.17	0.20
Infarct size (%)	-0.26	0.05
Leukocyte count	0.15	0.24
Left ventricular ejection fraction (%)	0.34	0.009
End-diastolic volume index (ml/m^2)	-0.39	0.002
End-systolic volume index (ml/m^2)	-0.40	0.002
Wall motion score index	-0.22	0.05
Left atrial volume index (ml/m^2)	-0.20	0.13
E/E' septal	-0.06	0.66
E/E' lateral	-0.08	0.53
MMP: Matrix metalloproteinases.		

there are no data about the relationship between drug therapy and plasma MMP-8 levels. The response to these drugs may change over time in parallel to the changes in the remodeling process. Thus, some of the benefits from antiischemic medications appear to be caused by the improved healing process associated with the increased levels of MMPs in the later phases of remodeling. Further trials are warranted to clearly explain this issue.

There are several limitations to our study. First, the number of subjects was small. Second, the plasma MMP-8 levels may represent total levels released from both cardiac and noncardiac sources. Despite the exclusion criteria, some potential noncardiac sources such as inflammatory periodontal diseases could not be excluded.[23] Furthermore, the plasma levels of MMPs cannot provide information on proteolytic activity within the myocardium. However, the previous studies have suggested that the plasma levels are likely to reflect the local myocardial levels.[2,12] We cannot comment regarding plasma levels of other MMP entities. Moreover, there is an interaction between MMPs and the tissue inhibitors of matrix metalloproteinases (TIMPs) and other mediators of inflammation such as C-reactive protein, cytokines, chemokines, and angiogenic factors.[24,25] The interaction between plasma MMP-8 levels and these factors was beyond the scope of the present analysis; yet, it should be investigated further. The absence of brain natriuretic peptide (BNP) data for the cohort is another limitation. Furthermore, we obtained plasma samples at only one post-MI time point. Therefore, further studies with serial plasma measurements in the early and late post-MI period may be warranted.

In conclusion, plasma MMP-8 levels remain high for a long period in post-MI patients. Moreover, plasma MMP-8 levels late after MI correlated positively with LVEF. This study does not establish causality. However, it supports the notion that MMP-8 continues to play a pivotal role in LV remodeling late after MI. In contrast to the relation between higher early MMP-8 activity and the extent of cardiac remodeling, higher late levels may be associated with relative preservation of LVEF.

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