Correlation of Early and Late Ejection Fractions with CCL5 and CCL18 Levels in Acute Anterior Myocardial Infarction

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ABSTRACT

Background: Acute Myocardial Infarction (AMI) is the leading cause of disability and death in Iran and many other countries. **Objective:** To investigate the prognostic value of CCL5 and CCL18 in patients with acute myocardial ischemia. **Methods:** In this cohort study we recruited and followed 50 patients with acute anterior myocardial infarction (AAMI) for developing cardiovascular accidents in a 6-month period. CCL5 and CCL18 levels were measured on admission, at day 5 and at day 180 post-hospitalization. **Results:** CCL18 and CCL5 levels at day 180 were higher in patients with late (day 180) and early (day 5) LVEF less than 35% compared to those with higher LVEF (p=0.05 and p=0.042, respectively). There was a negative correlation between early and late LVEF and regional wall motion abnormalities (p=0.001 and p=0.002, respectively). There was also a trend of negative correlation between CCL18 levels at day 5 and LVEF levels at day 180 post-hospitalization (p=0.06). **Conclusion:** CCL18 has a correlation with cardiac function in patients with AAMI and it might be considered as an indicator of poor LVEF in patients with AAMI.

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Keywords: Acute Anterior Myocardial Infarction, CCL5, CCL18, Ejection Fraction

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INTRODUCTION

Biomarkers for the early detection, prognosis, and therapeutic follow-up of many diseases are still required. Cardiovascular diseases have remained the leading cause of disability and death during the past decade (1-3). Acute Myocardial Infarction (AMI) is still the leading cause of disability and death in Iran and many other countries. The primary cause of cardiovascular disease morbidity and mortality is atherosclerosis (4). Atherosclerosis, formerly considered a bland lipid storage disease, is increasingly recognized to be an inflammatory disease, in all stages from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis especially plaque rupture (4-9). Rupture of a plaque may lead to clinical consequences including acute myocardial infarction, unstable angina and stroke (4). During AMI, myocyte necrosis and the resultant increase in load trigger a cascade of biochemical intracellular signaling processes involving inflammatory cytokines (10). Inflammatory processes after myocardial infarction and reperfusion are key elements in determining the extension of myocardial damages, subsequent left ventricular remodeling and indicate worse left ventricular function and clinical outcomes (10-13). Insights gained from the link between inflammation and atherosclerosis would not only increase our understanding of this disease etiology but might also provide practical clinical applications in risk stratification of cardiovascular events and as guides to monitor therapy for this scourge of growing worldwide importance. Inflammatory biomarkers may help predict future cardiovascular risk and prognosis after ACS. Furthermore, they can lead to new therapeutic targets, possibly to neutralize specific inflammatory mediators and leukocyte recruitment, thus, interfere with the disease process and possibly improve cardiac function following an acute myocardial infarct (3,5,6,13-16).

Since the discovery of the super-family of chemokines and their receptors, there has been a considerable effort to define their particular role in the development of atherosclerosis and in ischemia-induced myocardial injury and left ventricular remodeling after acute myocardial infarction. Several studies suggested that baseline plasma RANTES levels increase in acute coronary syndromes and are independent predictors of cardiac mortality in patients with AMI (8,17). The critical role of inflammation and immune cells in the etiology of atherosclerosis makes it unsurprising that many chemokines and chemokine receptors have been linked to this disease (4,7). Chemokines are a family of low molecular weight heparin-binding proteins that cause selective chemoattraction and activation of circulating leukocytes at the site of inflammation. Chemokines induce chemotaxis through the activation of G-protein-coupled receptors. There are at least 50 human chemokines, which are divided into four major families (the CC, CXC, CX3C, and C chemokines) based on the configuration of the first two cysteines (2,3,7,8,17-20). The largest family of chemokines is known as the CC chemokines. CC chemokines tend to attract mononuclear cells and are found at sites of chronic inflammation (7).

CCL5 or RANTES (regulated on activation, normal T cell expressed and secreted) is a soluble CC chemokine of 7.8 KDa secreted by many different cell types, such as ECs, SMCs, activated T cells, macrophages, and the alpha granules of adhering platelets. After release from the activated platelets, RANTES is deposited onto endothelium via interactions with specific chemokine receptors (CCR1, CCR3, CCR4, and CCR5) and has been shown to mediate transmigration of monocytes and T-cells into the intima. In addition to a role in plaque development, chemokines such as CCL5 may be mediators

of plaque destabilization through activation of or release from platelets (4,8,9,18). Data regarding clinical significance of plasma RANTES levels in atherosclerosis and its role in plaque vulnerability remains controversial. On one hand, RANTES levels in patients with acute coronary syndrome have been demonstrated to be elevated, whereas levels in stable CAD have been shown to be downregulated. It is possible that high levels of RANTES would lead to a more cellular infiltrate in the plaques. This process may lead to initiation and progression of atherosclerosis. In addition, higher than normal levels of RANTES may lead to recruitment of more macrophages into the plaque, which could make these plaques unstable or vulnerable (6,8,9). Atherosclerotic vascular disease is also a significant clinical problem following coronary artery bypass grafting. Notably, CCL3, CCL4, CCL5 and their receptor CCR5 are expressed in the retrieved human saphenous vein graft tissue (4).

Chemokine Ligand-18 (CCL18)/pulmonary and activation-regulated chemokine (PARC) is a 7 KDa protein that plays a role in injury healing, physiological homing of mononuclear blood cells and inflammatory responses. CCL18 is expressed by monocytes/macrophages and dendritic cells and is secreted predominantly in the lungs. It is also expressed in atherosclerotic plaques, particularly at sites of reduced stability (2,21,22). Although the exact biological role of PARC/CCL-18 is not known, serum levels are elevated in acute coronary syndrome (2,21,22). CCL18 can activate fibroblasts, thereby contributing to myocardial fibrosis upon ischemia (16). The reliability of the plasma CCL18 levels to monitor the therapeutic efficiency in CAD patients deserve further validation with the aim of finding new biomarkers for specific pathological conditions (2,21,22).

However, despite all the previous attempts, the significance of chemokines in ischemic heart diseases is not fully understood. Thus, we decided to evaluate the prognostic value of CCL5 and CCL18 in patients with acute myocardial ischemia.

MATERIALS AND METHODS

Study population. In brief, 50 patients who were admitted with the diagnosis of acute anterior wall myocardial STEMI initially treated by streptokinase (no primary PCI) in Namazi and Shahid Faghihi hospitals in Shiraz between April 2012 and March 2013 were included in this prospective cohort and followed up for a period of 6 months for developing secondary cardiovascular events. All participants gave full informed written consent, which included consent for biomarker analysis prior to inclusion into the study. All patients with chest pain complaints, Increase in TnT levels and ST elevation in anterolateral and anteroseptal leads, if aged <75 years, were eligible for inclusion. A diagnosis of myocardial infarction was made by the treating physician based on the presenting electrocardiogram (ECG) in combination with serial TnT measurement. The diagnosis was later confirmed with selective coronary angiography in the hospital course. Patients with Chronic Renal Failure (CRF), autoimmune diseases, and cardiogenic shock were excluded from the study. All patients were monitored for 6 months. After 6 months echocardiography was done for all the patients for evaluation of LV systolic function. Although cardiac MRI is the better option for assessment of LV ejection fraction, due to its higher cost and problem in its access we chose echocardiography instead. All the echocardiographies were performed by a single blinded expert operator. Follow-up end points were defined as a new ACS (e.g. cardiac

ischemia and AMI) or a repeat coronary revascularization (PCI and CABG) after the initial event, which were combined as nonfatal events. The fatal events comprised all cases of all-cause mortality. Otherwise, follow-up ended at the date of withdrawal from the study or at 6 months after entry. For each patient, demographic and clinical information including: age, gender, and history of hypertension, hyperlypidemia, diabetes mellitus, obesity and BMI, and smoking were obtained and recorded. This datasheet as well as their laboratory data were used for statistical analysis.

Laboratory Methods. Five ml of venous blood was obtained at the time of admission (time [*t*]_0) and 5 (*t*_5) and 180 days (*t*_180) after admission using venipuncture method, then centrifuged, and serum aliquots were stored at -40°C until further analysis. Circulating levels of the chemokines were measured using a commercial RANTES ELISA assay (R&D Systems, USA) and a commercial PARC ELISA assay (Cell Sciences, USA), respectively, according to the manufacturers' instructions. ELISA kits contained samples with known concentrations which were used to generate the standard curve of optical density against concentration, to determine the concentration of circulating chemokines in sample sera. Besides determining the levels of the cytokines, all patients underwent echocardiography at the time of discharge and 180 days later. The final outcome was determined considering the mortality rate, re-hospitalization rate, left ventricular ejection fraction and the functional class based on NYHA classification.

Statistical Analysis. All statistical analyses were performed using SPSS 15 statistical software. Data are shown as mean ± standard deviation (SD) or number (%). For comparisons of the serum levels of CCL5 and CCL18 between two independent groups we applied the Student's *t*-test and used analysis of variance (ANOVA) for multiple comparisons. To assess the predictive value of CCL5 and CCL18 for the occurrence of refractory symptoms, independent of potentially confounding factors, a multivariate analysis was performed. The correlation between chemokine concentrations and cardiovascular risk factors were estimated using $\chi 2$ and ANOVA tests. In order to evaluate the added prognostic value of the chemokines for future cardiovascular events, receiver-operating characteristic (ROC) curves were constructed for each endpoint, using the predicted values from multivariable regression models with and without the studied chemokines. Two-sided p values less than 0.05 were considered to indicate statistical significance.

RESULTS

Subjects. The mean age of all patients was 56.98 ± 11.49 years (37 to 73 years) of which 35(70%) were male. Diabetes, arterial hypertension and hyperlipidemia were diagnosed in 12(24%), 27(54%) and 14(28%) patients, respectively. Positive family history of cardiovascular diseases was found in 3(6%) patients. A total of 27 (54%) patients were smokers, and 8(16%) had a diagnosis of previous coronary artery disease.

Clinical findings. Among patients, 19(38%) were on aspirin, 10(20%) were on beta blockers, 7(14%) were on statins and 14(28%) were on angiotensin converting enzyme inhibitors therapy before admission to hospital because of previous history of coronary artery disease, angina, hypercholesterolemia and hypertension, respectively. Division of the patient population based on the localization of myocardial ischemia showed that 27(54%) had anterolateral and anteroseptal involvement; 18(36%) had anterior and anteroseptal involvement; 2(4%) had anterolaterel involvement; 2(4%) had anteroseptal

and 1(2%) had anterior along with anterolateral involvement. ECG findings showed that 32(64%) of patients had normal axis and 18(36%) had left axis deviation. Five patients (10%) had evidence of left bundle branch block, 1(2%) had right bundle branch block and 5(10%) had intraventricular conduction delay. Thirty-six (72%) of patients showed no ECG evidence of 1st to 3rd degree of atrioventricular heart block based of PR segment study. Moreover, 11(22%) patients had evidence of left ventricular hypertrophy.

In total, 6 patients were re-hospitalized due to cardiac disease during the follow up of which 4(8%) unfortunately passed away. During the admission period (day 0 to day 5), 24(48%) of patients developed cardiac arrhythmia including: sinus arrhythmia in 17(34%), ventricular tachycardia in 5(10%) and ventricular fibrillation in 2(4%) patients. Evidence of AV block was observed in 7(14%) of patients. During the hospital course, fibrinolytic agents (streptokinase) were used for 45(90%) of patients, 2(4%) patients underwent rescue PCI, 29(58%) underwent facilitated PCI after initial management with antifibrinolytic agents (streptokinase), and 10(20%) patients underwent coronary artery bypass grafting. No other intervention besides antiplatelet therapy was used for 9(18%) patients. At coronary angiography, only 1(2%) patient showed left main-stem artery disease. LAD, LCX, RCA and PDA arteries were involved in 48(96%), 32(64%), 24(42%) and 11(22%), respectively.

Table 1. Plasma levels of CCL5 and CCL18 in diabetic and non-diabetic patients at the three time points of follow up.

CCL5	Patients Status	Mean ± SD (ng/ml)	P Value
Day 0	Diabetic (n=12) Non-diabetic (n=38)	73.67 ± 42.20 64.13 ± 35.37	0.440
Day 5	Diabetic (n=12) Non-diabetic (n=38)	57.23 ±22.82 54.63 ± 32.68	0.799
Day 180	Diabetic (n=9) Non-diabetic (n=37)	54.19 ±18.81 51.83 ± 19.62	0.746
CCL18	**Patients Status**	**Mean ± SD (ng/ml)**	**P Value**
Day 0	Diabetic (n=12) Non-diabetic (n=38)	189.49 ± 156.48 134.91 ± 97.04	0.273
Day 5	Diabetic (n=12) Non-diabetic (n=38)	236.69 ± 219.81 150.86 ± 141.92	0.224
Day 180	Diabetic (n=9) Non-diabetic (n=37)	239.94 ± 307.58 1.6.85 ± 47.70	0.231

On echocardiography, immediately before discharge (day 5), mean LVEF was found to be 41%. Seven patients (14%) had normal diastolic function. Grade 1, 2 and 3 diastolic dysfunction was found in 20(40%), 20(40%) and 3(6%) of patients, respectively.

All patients had normal right ventricular function and 11(22%) had left ventricular dysfunction as an increase in the left ventricular cavity size. Valvular function was normal in 21(42%) patients. Echocardiographic evidence of mitral regurgitation and tricuspid regurgitation was detected in 11(22%) and 8(16%) patients, respectively. Other patients had mixed valvular dysfunction. Cardiac aneurysm was detected in 3(6%) patients.

180 days later, mean LVEF was found to be 46%. Of 46 patients left, 4(8.7%) had normal diastolic function, 32(69.6%) and 10(21.7%) patients were noted to have Grade 1 and 2 diastolic dysfunction, respectively. At the end of the study, 38(82.6%), 4(8.7%) and 1(2.2%) of patients were classified as class 1, 2 and 3 based on the NYHA classification criteria.

Table 2. Plasma levels of CCL5 and CCL18 in patients with different revascularization statuses during follow up.

CCL5	Revascularization Status	Mean ± SD(ng/ml)	P Value
Day 0	PCI[#] (n=31)	72.51 ± 42.0	0.475
	CABG (n=10)	54.93 ± 27.27	
	None (n=9)	58.20 ± 22.46	
Day 5	PCI[#] (n=31)	62.74 ± 32.15	0.086
	CABG (n=10)	43.72 ± 24.60	
	None (n=9)	55.26 ± 30.41	
Day 180	PCI[#] (n=31)	52.63 ± 20.04	0.560
	CABG (n=10)	55.91 ± 21.15	
	None (n=9)	44.51 ± 10.65	
CCL18	**Revascularization Status**	**Mean ± SD(ng/ml)**	**P Value**
Day 0	PCI[#] (n=31)	143.33 ± 80.22	0.382
	CABG (n=10)	133.70 ± 157.76	
	None (n=9)	180.02 ± 164.30	
Day 5	PCI[#] (n=31)	151.52 ± 124.35	0.191
	CABG (n=10)	151.37 ± 171.37	
	None (n=9)	262.44 ± 256.13	
Day 180	PCI[#] (n=31)	147.38 ± 176.13	0.262
	CABG (n=10)	96.34 ± 62.24	
	None (n=9)	121.40 ± 49.17	

[#] Both rescue PCIs and Facilitate PCI are shown.

Experimental Data. We sought to assess whether CCL5 and CCL18 levels had predictive potential. Levels of CCL5 and CCL18 were analyzed for correlation with the occurrence of future refractory ischemic symptoms. Comparison of CCL5 and CCL18 levels at day 180 showed no statistically significant difference between patients who

were re-hospitalized (n=6, Mean = 55.81 ± 0.53 ng/ml and Mean = 142.72 ± 5.59 ng/ml, respectively) versus stabilized patients (n=40, Mean = 52.13 ± 19.7 ng/ml and Mean = 132.45 ± 149.94 ng/ml, respectively; CCL5 p=0.295, CCL18 p=0.840). No statistically significant correlations were found between CCL5 or CCL18 levels and diabetes (p>0.05, Table 1). No patients were undergone primary PCI, for 2(4%) patients rescue PCI and for 29(58%) facilitate PCI and for 10(20%) patients CABG had been done, while 9(18%) patients did not receive any revascularization. Although CCL5 level at day 5 was decreased in patients with a history of CABG (Figure 1), no statistically significant difference was observed in the CCL5 or CCL18 levels between patients with a different revascularization history (Table 2).

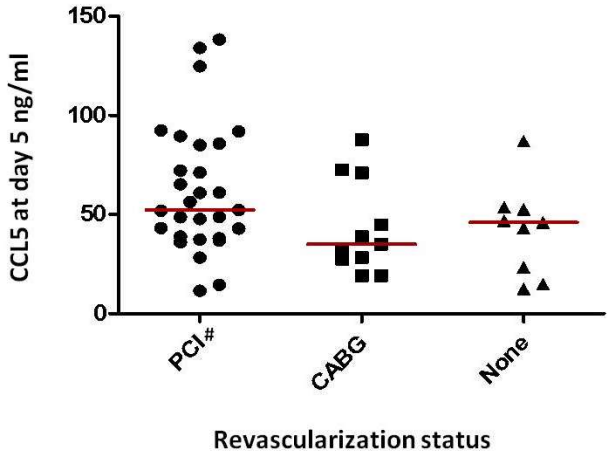

Figure 1. Comparison of CCL5 levels at day 5 between patients with a different history of revascularization.

Bivariate correlation analysis showed that there is a trend of negative correlation between CCL18 levels at day 5 (before discharge from hospital) and late LVEF at day 180 post-hospitalization (Pearson R=-0.27, p=0.06, Figure 2).

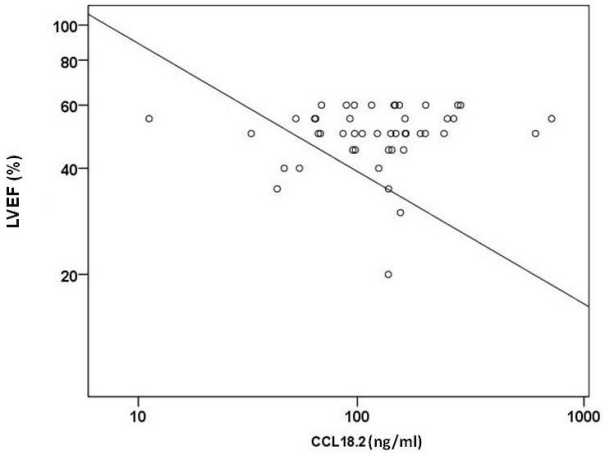

Figure 2. Correlation between CCL18 levels at day 5 post-hospitalization and late LVEF at day 180.

CCL18 levels (at the third measurement on day 180) were significantly higher in patients with late LVEF less than 35% compared to those with late LVEF greater than 35% (Mean = 162.04 ± 68.285 vs. 130.11 ± 152.16 ng/ml, p=0.056, Figure 3A). Similarly, CCL5 levels (at day 180) were significantly higher in patients with early LVEF less than 35% compared to those with higher late LVEF (Mean = 49.411 ± 19.954 vs. 51.765 ± 19.920 ng/ml, p=0.041, Figure 3B).

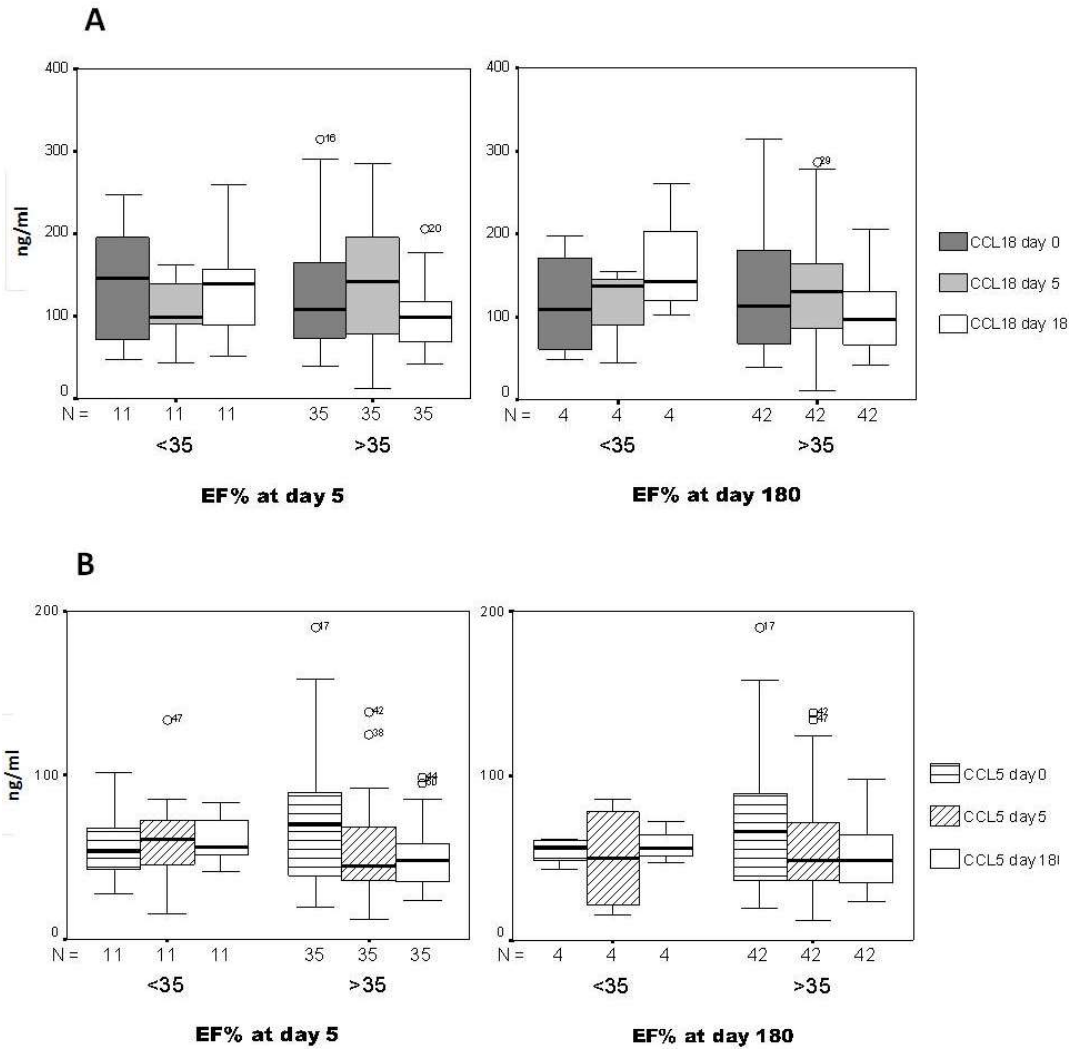

Figure 3. The differences in (A) CCL18 and (B) CCL5 levels between patients measured at days 0, 5 and 180 post-hospitalization based on early (day 5) and late (day 180) Ejection Fraction.

The prediction specificity and sensitivity of CCL5 and CCL18 levels for the death in recruited patients by ROC curve analysis showed a better potential for CCL18 levels at day 5 compared with day 0 (p=0.124, Figure 4).

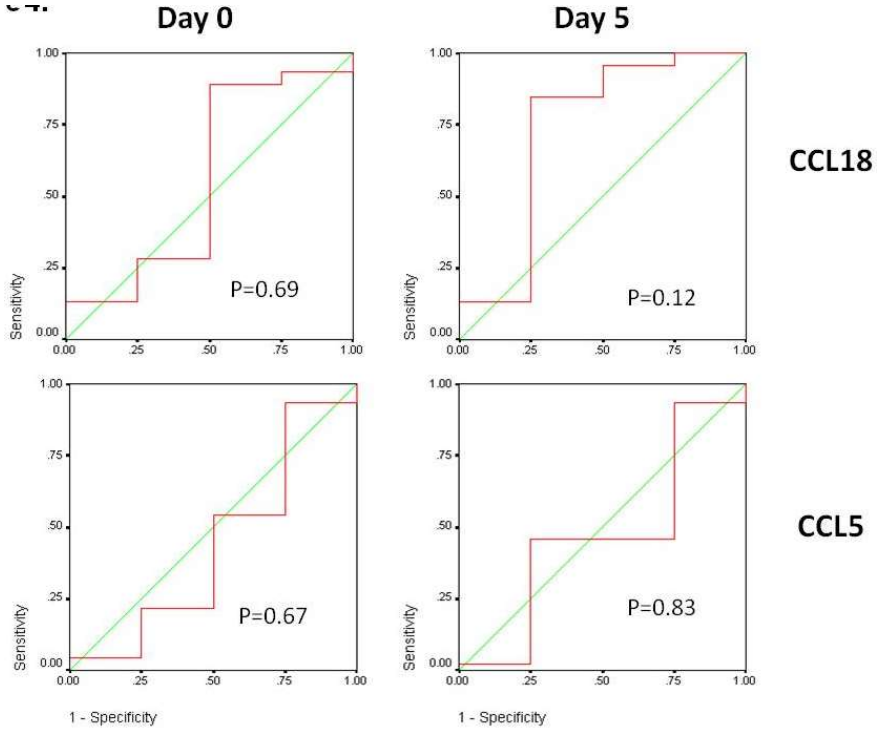

Figure 4. The receiver-operating characteristic (ROC) curves of CCL5 and CCL18 at days 0 and 5 post-hospitalization for prediction of death in patients.

CCL5 levels at day 5 were significantly higher among men (p=0.039, Figure 5A), but CCL18 levels at day 180 were significantly higher among women (p=0.036, Figure 5B).

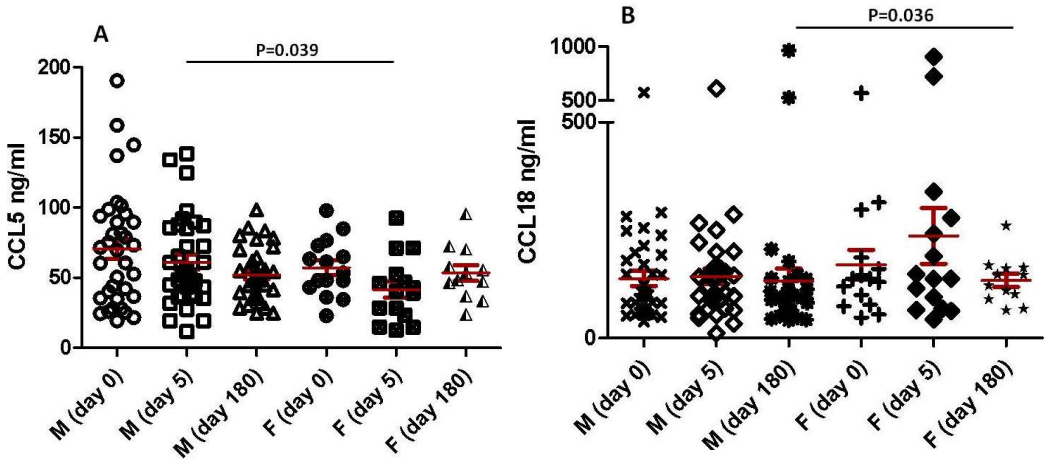

Figure 5. The differences in (A) CCL5 and (B) CCL18 levels between patients measured at days 0, 5 and 180 post hospitalization based on gender.

In addition, CCL18 levels were higher in smokers who had lower LVEF and also were higher in smoker men (157.56 ± 200.02 ng/ml) than non-smoker men (80.28 ± 32.44 ng/ml, p=0.01). However, its levels were non-significantly lower in smoker women (95.62 ± 38.00 ng/ml) than non-smoker women (152.94 ± 51.69 ng/ml). There was a borderline positive correlation between CCL5 levels and regional wall motion abnormalities (p=0.087). On the other hand, there was a negative correlation between early and late LVEF and regional wall motion abnormalities (EF_1: R=-0.477; p=0.001, EF_2: R=-0.448; p=0.002). CCL18 levels was much higher among expired patients (4 patients), although CCL5 levels among these patients did not differ significantly from other patients, the low number of expired patients hampered statistical analysis (Figure 6A and Figure 6B). Mean early LVEF was different between these subgroups, although small subgroups prohibited meaningful analyses (Figure 6C).

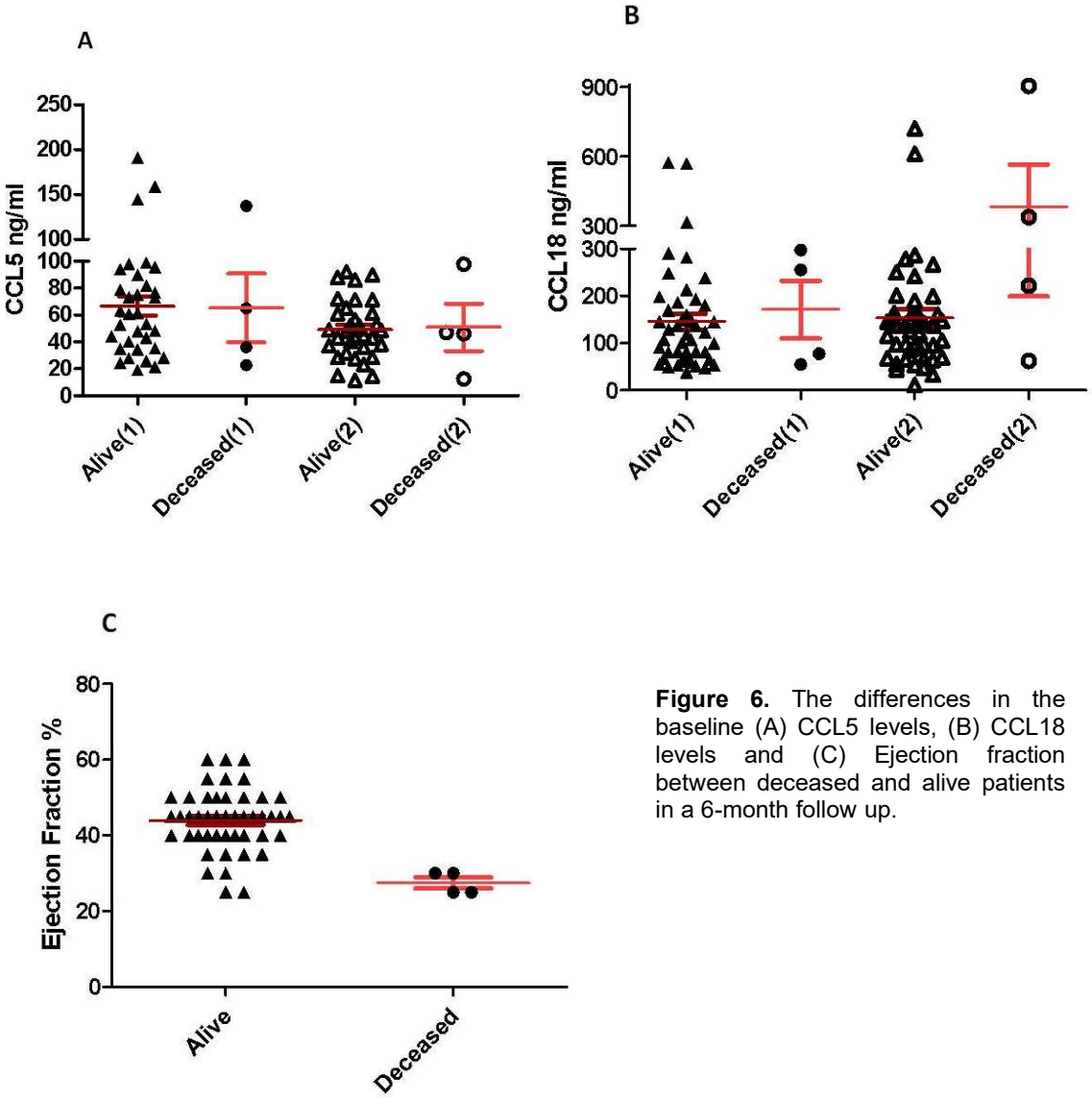

Figure 6. The differences in the baseline (A) CCL5 levels, (B) CCL18 levels and (C) Ejection fraction between deceased and alive patients in a 6-month follow up.

DISCUSSION

In our study, there was a negative correlation between CCL18 levels and cardiac output especially in long-term comparison. Patients with higher LVEF had lower CCL18 levels as compared to patients with lower LVEF. This was especially noticeable for CCL18 levels at day 5 after hospitalization which negatively correlated with late LVEF at day 180. There was also a correlation between CCL5 levels at day 180 and LVEF (both at day 5 and day 180). On the other hand there was a negative correlation between LVEF and regional wall motion abnormalities. There was also a borderline correlation between CCL5 levels (day 180) and regional wall motion abnormalities. Considering these findings, and considering the known importance of LVEF and regional wall motion abnormalities as predictive criteria for the extent of coronary artery disease and patient prognosis, there is a close and significant relationship between high CCL18 (especially in long term) and CCL5 levels and disease extent, complications and prognosis which is in concordance with the results by Versteylen *et al.* (23). CCL18 levels were seen to be transiently elevated at baseline in refractory versus stabilized patients in unstable angina. In these studies CCL18 also showed predictive features with regard to future cardiovascular events and clinical outcome (6,21). In our study Median serum concentrations of CCL18/PARC were significantly higher in patients with a cardiovascular event than in patients without an event ($p<0.01$), however, there was no significant relationship between CCL5 or CCL18 levels and re-hospitalization and developing refractory symptoms. Our findings are not in accord with the report from de Jager *et al.* who showed that patients with CCL5/RANTES and CCL18/PARC concentrations in the highest tertile had a 2 to 3.4-fold higher risk of mortality during follow up (16). Also De Sutter *et al.* suggested that high CCL18/PARC level was an independent predictor of future cardiovascular events in patients with stable coronary artery disease (21). Differences in study design, a larger population size in these studies (n=700 and n=250, respectively) as compared to our study (n=50), could explain this discrepancy. Having said so, there is a study with less number of cases which reported a positive correlation between early levels of MIP-1α and CCL5 with early LVEF in anterior and lateral myocardial infarction, respectively (24).

CCL18/PARC or Pulmonary and Activation-Regulated Chemokine, is expressed mainly in the lungs (20). Previous studies have highlighted its role in pulmonary disease. Accordingly, CCL18 is associated with the development of hypersensitivity pneumonia (25). Its correlation with progression of fibrosis and patient survival in idiopathic pulmonary fibrosis, and its increased concentrations in COPD also have been documented in previous studies (22). Therefore, we expect a correlation between CCL18 levels and smoking as a known and major risk factor of cardiovascular and pulmonary disease. This idea was supported by our findings showing that CCL18 levels were higher in smokers who had lower EF. Our results showed that CCL18 levels were slightly higher in smoker men than non-smoker men at day 180 ($p=0.01$). However, its levels were respectably lower in smoker women than non-smoker women and also lower than both smokers and non-smokers men, although small subgroups prohibited meaningful analyses. We could explain this in two ways: first, there is a higher possibility for smoker women to quit smoking after AMI as compared to smoker men; second, CCL18 level is influenced by demographic factors such as gender.

Table 3. Minimum and maximum levels of CCL5 and CCL18 in diabetic and non-diabetic patients.

	CCL5 (ng/ml) Day 0		CCL5 (ng/ml) Day 5		CCL5 (ng/ml) Day 180		CCL18 (ng/ml) Day 0		CCL18 (ng/ml) Day 5		CCL18 (ng/ml) Day 180	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Diabetic	19.22	158.74	36.02	97.66	35.21	85.33	47.55	47.55	43.83	720.90	42.30	961.82
Non-diabetic	21.56	190.62	11.60	138.35	23.59	98.33	38.70	38.70	11.26	904.41	41.61	260.30

No significant association between CCL5 and CCL18 levels and diabetes was shown in the present study, although, comparing minimum, maximum and mean plasma levels of these chemokines in diabetic and non-diabetic patients (Table 3) showed that CCL18 plasma levels in diabetics were higher than upper limits of normal subjects (72 ng/ml). These findings were not in complete agreement with the results of Boger *et al*. In their study, there was a relationship between RANTES level in ESRD diabetic patients and cardiovascular mortality (27). This discrepancy might be due to the fact that in our study CRF was an exclusion criterion and no diabetic participants had abnormal Creatinine levels.

In conclusion, CCL18 has a correlation with cardiac function in patients with AAMI and generally CCL5 and CCL18 can be considered as correlates of poor prognosis in patients with acute myocardial infarction. The finding that CCL18 levels at the time of discharge from hospital (day 5) negatively correlated with the late LVEF (day 180) in patients with AAMI may provide a tool for selection of patients with the higher risk of future cardiovascular events and a more intensive follow up. Moreover, these findings have important clinical implications in identifying innovative therapeutic strategies, to improve outcomes of individuals at risk for or affected by this scourge of growing worldwide importance.

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