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Role of Monocyte Chemoattractant Protein-1 for Diagnosing Acute Myocardial Infarction

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ABSTRACT

Background: Acute myocardial infarction (AMI) controlled and promoted by inflammation within the coronary plaque. Monocyte chemoattractant protein-1 (MCP-1) is a pro-inflammatory mediator, that's playing a major role in plaque rupture. This study aimed to assess the diagnostic performance of MCP-1 for early diagnosis of AMI among chest pain (CP) patients. **Methods**: MCP-1 and cardiac Troponin I (cTnI) were performed for all studied patients. The receiver operating characteristic (ROC) curve was used to assess the diagnostic accuracy of biomarkers. **Results**: The baseline level of MCP-1 has a good capacity for discriminating patients with AMI from non-coronary chest pain (NCCP), stable angina (SA), and unstable angina (UA) patients with efficiency 91%, 91%, and 83%; respectively. Area under the curves (AUCs) of MCP-1 for diagnosis AMI patients at 0-6 hours and > 6-12 hours after onset time of CP were 0.69 ($P < 0.001$); and 0.71($P < 0.0001$); respectively, compared with cTnI were 0.58 ($P < 0.001$) and 0.67 ($P < 0.001$); respectively. However, at > 12-24 hours, cTnI has AUC 0.93 ($P < 0.0001$) compared with MCP-1 0.74 ($P < 0.0001$). **In conclusion**: Independent early baseline MCP-1 has given sufficient diagnostic information for patients with AMI.

KEY WORDS: Acute Myocardial Infarction, Biomarkers, Monocyte Chemoattractant Protein-1, Chest pain.

1. INTRODUCTION

Chest pain is caused by a broad band of causes, ranging from completely risk-free to instant life-threatening conditions. Acute coronary syndrome (ACS) is a complex clinical syndrome, represented about 45% of chest pain patients admitted to the emergency unit (Barstow et al., 2017). ACS signifies a degree of severity of coronary artery disease, ranging from UA through AMI, and occurs in response to inflammation (Kavsak et al., 2017). The early diagnosis of AMI among chest pain patients is required to restore blood flow to the heart quickly to reduce the degree of myocardial necrosis, which mostly impacts patient outcomes (Garg et al., 2017). The diagnosis of AMI is based on clinical symptoms (e.g. Characteristic chest pain), ischemic ECG changes, imaging, and elevated cardiac biomarkers, of which

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cardiac troponin as a gold standard biomarker (Dalal et al., 2016). Although that it is less than ideally suited for early diagnosis of AMI due to slow rise (4–10 h), late peak (at 12–48 h) after the onset time of symptoms of CP, and low specificity for coronary plaque rupture (Gardiner and Zhai, 2017). Inflammation is involved in every part of ACS and coronary atherosclerosis (Zakroysky et al. 2015). There is a lack of biomarkers to discriminate the AMI and UA. As well as, the present methods are insufficient for an ideal sensitive and specific diagnosis of AMI (Zhu et al., 2016). Clinical researches have provided new insight into the processes involved in the pathogenesis of ACS. As well as, it was observed that an excessive inflammatory reaction can suggest adverse remodeling and directly influence prognosis in AMI patients. It has been observed that elevated concentrations of circulating monocytes and neutrophils (Gruzdeva et al., 2017 & Gonzalez-Quesada and Frangogiannis, 2009). Monocyte chemoattractant protein-1 is one of the best members of the CC-chemokine family, which is expressed in astrocytes, neurons, and endothelial cells in response to oxygen lack (Strecker et al., 2013). MCP-1 is a potent chemoattractant for mononuclear cells that control and promote migration and infiltration of monocytes/ macrophages during inflammation into early atherosclerotic injury (Siddiqui and Partridge, 2017). The pro-inflammatory mediator MCP-1 plays a key role in plaque rupture and AMI (Wilbert-Lampen et al., 2010). Numerous studies have established that MCP-1 plays an important role in the pathogenesis of atherosclerosis and ACS and has been projected as a biomarker for patients with AMI (França et al., 2017). This study aimed to demonstrate the diagnostic performance of MCP-1 levels among chest pain groups and to compare the diagnostic values of MCP-1 and Troponin I in early diagnosis of AMI.

2. MATERIALS AND METHODS

Patients

A total of 120 patients suffering from typical chest pain aged 35-72 years admitted to the emergency department at Damietta Al- Azhar University Hospital. The main exclusion criteria were patients with cardiomyopathy, patients with cardiogenic shock, patients with liver cell failure, patients with chronic renal failure, and patients haven't 3 times samples after onset time of CP (0-6 hours as baseline time, > 6-12 hours s and > 12-24 hours s). The final diagnosis of all patients was assessed by the same cardiologist based on common criteria depend on the patient's history, clinical examination including ECG and laboratory investigations. Informed consent from each patient was provided and this study protocols followed the world ethical guidelines.

Blood samples and laboratory tests

Blood samples were taken from all patients by vein-puncture after admission to the emergency department. Repeated blood samples were drawn at > 6-12 hours s and >12-24 hours after onset time of CP for the determination of cTnI and MCP-1 levels. Sera were separated from blood samples and tested fresh for routine investigation; liver enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], kidney functions [urea and creatinine], lipid profiles [cholesterol, triglycerides high-density lipoprotein (HDL) and low-density lipoprotein (LDL)], random blood sugar (RBS) and cardiac enzyme CK-MB were detected on an automated biochemistry analyzer (BT1500; Biotecnica instruments S.P.A, Italy). Troponin I was determined by one-step, sandwich enzyme-linked fluorescent immunoassay using an automated VIDAS instrument for Troponin I Ultra technique (bioMérieux, Marcy L'Etoile, France).

The Measurement of serum MCP-1 level

MCP-1 level was determined using the Human MCP-1 quantitative sandwich enzyme immunoassay technique (Elabscience Biotechnology Co, Ltd, USA). 100 µl diluted serum samples and standard (1:100) were pipetted into the wells and then incubated for 90 minutes at 37℃ with gentle shaking. The liquid of each well

was removed, without washing. Immediately 100 µl of biotinylated detection Ab was added and incubated for 60 minutes at room temperature with shaking. After three washes, 100 µl of Avidin-Horseradish Peroxidase Conjugate was added and incubated for 30 minutes at 37°C with shaking. After three washes, 90 µl of the substrate was added and incubated for 15 minutes at 37°C in dark with shaking. The reaction was stopped by added 50 µl of stop solution before measuring the optical density of each well at once, at 450 nm with a microtiter plate reader (Tecan Austria GmbH, Sunrise – Basic TECAN). The concentration of MCP-1 was determined by interpolation from the standard curve.

Statistical analysis

All patients' data were analyzed with descriptive statistical analysis using the Statistical Package for the Social Sciences (SPSS) (SPSS Inc., Chicago, IL, USA) software, version 15.0, all study variables were expressed as mean ± standard deviation (SD) or percentage. Box plot test was performed and the overall significance of differences among the groups was determined by the ANOVA test. Mann–Whitney U test was used to compare between levels of biomarkers in studied chest pain patients groups. AUCs were calculated for biomarkers to find the best biomarkers cutoff for differentiating between groups of chest pain patients. Moreover, the diagnostic sensitivity, specificity, efficiency, positive predictive (PPV), and negative predictive (NPV) values were calculated for biomarkers using a 2 × 2 possibility table.

3. RESULTS

The baseline characteristics of studied chest pain patients were summarized in **Table 1**. 62% were male, with a mean age of 58.7 years. As expected, we found a high prevalence of cardiovascular risk factors. 55 (45.8%) of the selective studied chest pain patients were diagnosed as patients with AMI [25 (20.8%) were admitted for non-ST segment elevation myocardial infarction (NSTEMI) and 30 (25%) were admitted for ST-segment elevation myocardial infarction (STEMI)], 25 (20.8%) as patients with UA, 20 (17.7%) as patients with SA and 20 (17.7%) as NCCP patients. Baseline levels of MCP-1 and other laboratory parameters are summarized in **Table 2**.

Table 1: Studied chest pain patients' baseline parameters

Variables	N (%)
Male gender	**74 (62%)**
Female gender	**46 (38%)**
Mean±SD age (years)	**58.7±12.4**
Hypertension	**91 (76%)**
Diabetes Mellitus	**72 (60%)**
Smoking	**62 (52%)**
Obesity	**97 (81%)**
Dyslipidemia	**110 (92%)**

Variables were expressed as number (%) and age was expressed as Mean ± Stander deviation (SD)

Table 2: Baseline levels of laboratory tests in studied chest pain patients

Variables	Mean ± SD
ALT	38.2±15.4
AST	36.8±11.6
Urea	32.8±9.0
Creatinine	1.1±0.29
RBS	130.3±40
Cholesterol	204.2±44.5
Triglycerides	142.8±50.7
HDL	32.0±7.0
LDL	143.7±44
CK-MB	21.9±14.9
Troponin I	0.038±0.03
MCP-1	197.2±106.6

Variables were expressed as mean ± Stander deviation (SD).

*References values: ALT, alanine aminotransferase up to 42 IU/L; AST, aspartate aminotransferase up to 40 IU/L; Urea up to 50 mg/dl; Creatine up to 1.2 mg/dl ; RBS, random blood sugar up to 150 mg/dl ; Cholesterol up to 200 mg/dl; Triglycerides up to 150 mg/dl; HDL, high-density lipoprotein 35 – 55 mg/dl; LDL, low-density lipoprotein 60- 175 mg/dl; CK-MB, Creatine kinase- MB up to 25 IU/L; Troponin I up to 0.01 ng/ml and MCP-1, monocyte chemoattractant protein-1 up to 100 ng/ml.

Baseline levels of MCP-1 within groups of studied chest pain patients

The (median, mean ± SD) of baseline MCP-1 levels (ng/ml) within groups of studied chest pain patients; NCCP, SA, UA, and AMI were (103,124 ± 69), (104,138 ± 77), (209,186±112) and (220,250±97); respectively. The overall significance of differences among the groups was determined by ANOVA for MCP-1. So there was an extremely significant difference ($P < 0.0001$) between MCP-1 levels within groups of studied chest pain patients; **Fig. 1**.

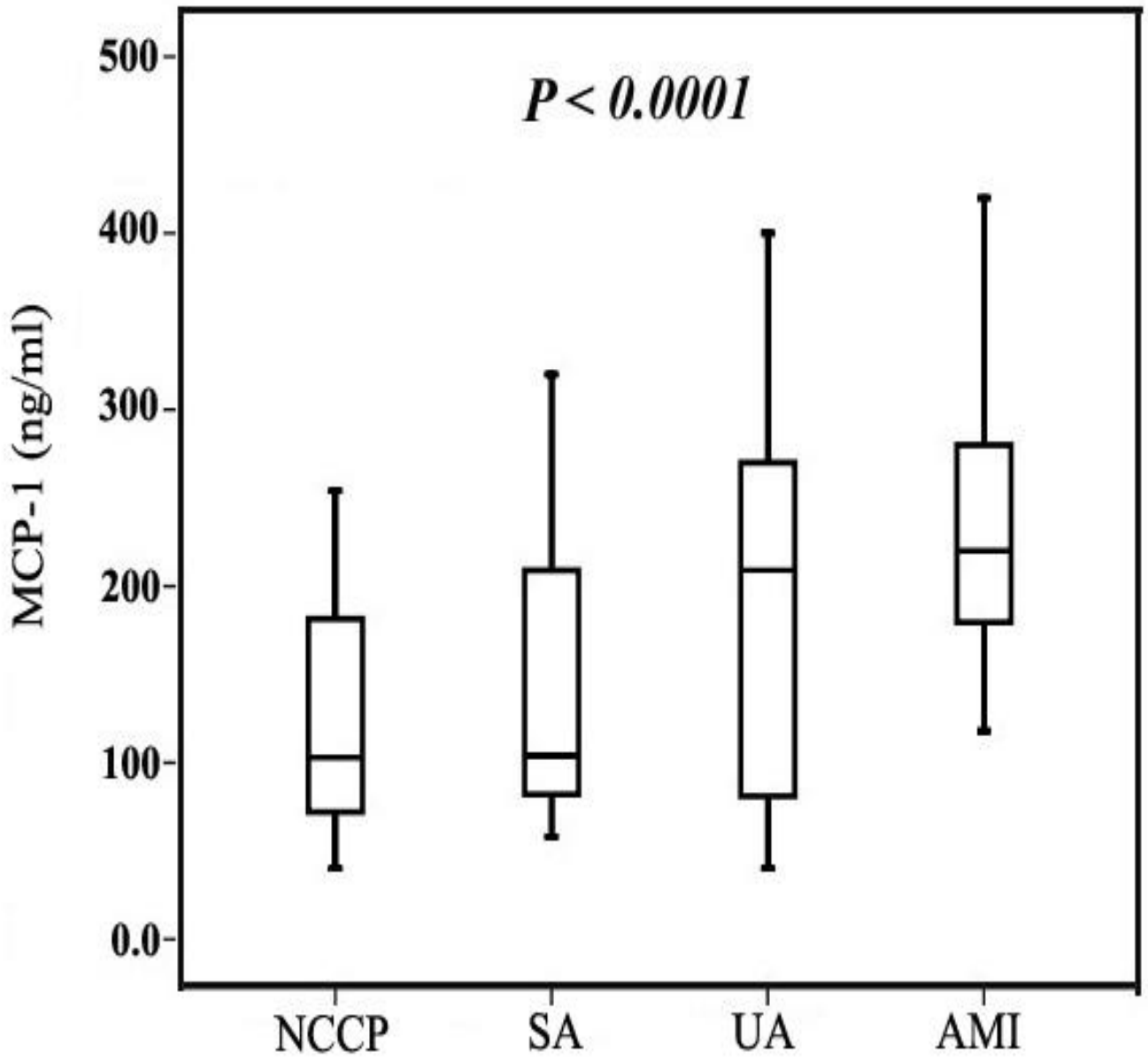

Figure 1: Box plots for baseline MCP-1 levels within groups of studied chest pain patients**.** A statistically extremely significance differences (P < 0.0001) for baseline MCP-1 levels were shown within groups of studied chest pain patients.

The diagnostic value of baseline level of MCP-1 for discriminating between chest pain patients groups

Diagnostic value of the baseline MCP-1 levels for discriminating between chest pain patients groups were presented in **Table 3**. **SA vs NCCP:** AUC of MCP-1 level for differentiating SA patients from NCCP patients was 0.56 (P > 0.05)**. UA vs NCCP:** AUC of MCP-1 level for characterizing UA patients from NCCP patients was 0.64 (P > 0.05). **MI vs NCCP:** AUC of MCP-1 level for discriminating AMI patients from NCCP patients was 0.87 (P < 0.0001). **UA vs SA:** AUC of MCP-1level for distinguishing UA patients from SA patients was 0.61 (P < 0.001). **AMI vs SA:** AUC of MCP-1 level for differentiating AMI patients from SA patients was 0.83 (P < 0.0001). **AMI vs UA:** AUC of MCP-1 level for discriminating AMI patients from UA patients was 0.69 (P < 0.001).

Table 3: Diagnostics value of baseline MCP-1 levels for discriminating between chest pain patients groups and for diagnosing of AMI among ACS patients at different times after onset time of CP

		Cut-off level (ng/ml)	Sens%	Spec%	PPV%	NPV%	Effi%
SA vs NCCP		97	55%	50%	53%	53%	53%
UA vs NCCP		123	60%	70%	72%	59%	65%
AMI vs NCCP		125	98%	70%	90%	94%	91%
UA vs SA		122.5	48%	70%	67%	52%	58%
AMI vs SA		124.5	98%	70%	90%	94%	91%
AMI vs UA	0-6hrs	131	97%	52%	82%	87%	83%
	> 6-12hrs	176	93%	56%	83%	78%	82%
	>12-24hrs	219	82%	60%	82%	60%	75%

Abbreviations: NCCP = non coronary chest pain; SA = stable angina; UA = unstable angina; AMI = acute myocardial infarction; Sen = sensitivity; Spec = specificity; PPV = Positive predictive value; NPV = Negative predictive value and Effi = efficiency and hrs = hours.

Diagnostic estimates of MCP-1 for diagnosing AMI from ACS patients at different times

The cutoff points and diagnostic accuracy of MCP-1 for diagnosing AMI from ACS patients at different times were presented in **Table 3**. ROC curves for MCP-1 in comparison to troponin I for diagnosing AMI from ACS patients at different times: are presented in **Fig. 2**, AUCs for all time points, 0-6 hours, > 6-12 hours and > 12-24 hours after onset time of CP were 0.69 ($P < 0.001$), 0.71 ($P < 0.0001$) and 0.74 ($P < 0.0001$); respectively for MCP-1, however were 0.58 ($P < 0.001$), 0.67 ($P < 0.001$) and 0.93 ($P < 0.0001$); respectively for cTnI.

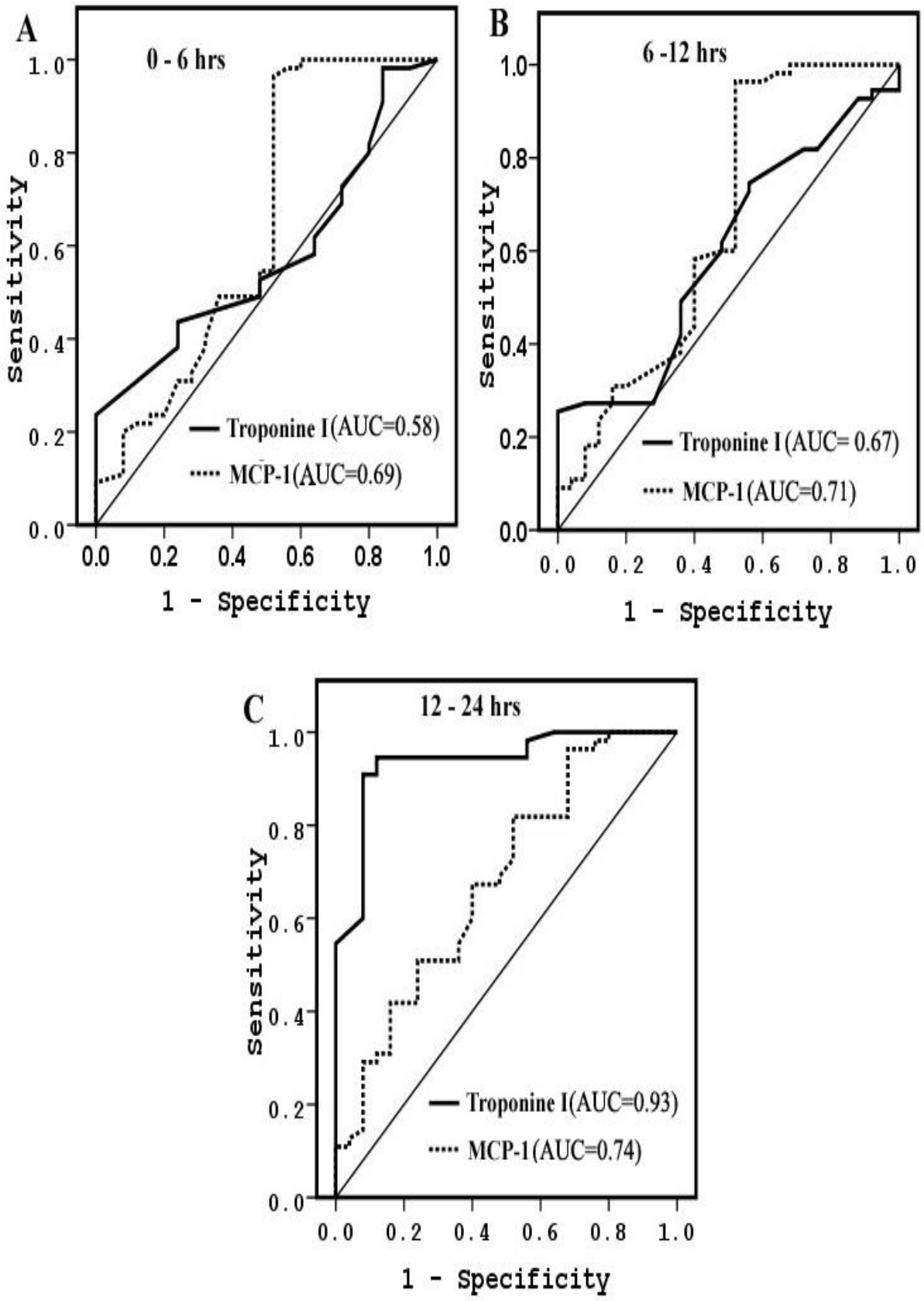

Figure 2: ROC curves of MCP-1 levels in comparison to cTnI at three times, **A-** 0-6 hours s, **B-** > 6-12 hours and **C**-> 12-24 hours after onset time of CP for diagnosing AMI from ACS patients in the study.

DISCUSSION

Myocardial infarction triggers local inflammatory responses which produce the recruitment of leukocytes and subsequent myocardial injury and healing. MCP-1, plays a vital role in the inflammatory response and myocardial damage after ischemia/reperfusion (Al-Amran et al., 2014). MCP-1 is critically involved in the pathogenesis of atherosclerosis and in the pathological consequences of atherosclerosis, may contribute to plaque destabilization, and considers a necessary mediator in adverse remodeling after a myocardial infarction (Chen et al., 2016). In the present study, we have evaluated the diagnostic importance of inflammatory mediator MCP-1 in chest pain patients. The value of the baseline level of MCP-1 increased in accordance with the grouping of studied chest pain patients from the NCCP group to the AMI group with a statistically extremely significant difference ($P < 0.0001$). In addition, we assessed the power of the baseline level of MCP-1 for discriminating between studied chest pain patients groups. Finally, our results show that MCP-1 have a high good capacity for discriminating patients with AMI from NCCP, SA, and UA patients with efficiency 91%, 91%, and 83%; respectively. Our results agree with earlier researches; As well as, several authors reported that in the coronary heart disease patients, the plasma MCP-1 level was significantly higher than that in the normal control group ($P<0.001$) (Tuñón et al., 2014). Furthermore MCP-1 is an independent diagnostic biomarker of the risk of acute incidents and chronic phase after acute coronary incidents (Tuñón et al., 2017). **Provatoriv et al., (2006)** reported that UA patients had a significantly higher plasma level of MCP-1 than those with SA (Provatoriv et al., 2006). Also, several authors found that the MCP-1 level was significantly higher in patients with AMI and UA than in patients with SA and NCCP (Zhong et al., 2015). Previous studies reported that MCP-1 release from the human heart is suppressed following AMI (Sun et al., 2012). On the other hand, **Li et al., (2015)** found that the expression of mRNAs related to MCP-1 was significantly up-regulated ($P< 0.01$) in the AMI group compared with SA and control groups (Li et al., 2015). In the present study, the diagnostic accuracy of MCP-1 and cTnI were assessed for diagnosis of AMI patients. AUCs in our study demonstrated that, MCP-1 has a better diagnostic accuracy within 12 hours after the onset time of CP compared with cTnI. However, cTnI has better diagnostic accuracy after 12 hours after onset time of CP. Our results agree with several studies that established that the level of cTnI was elevated to its peak at> 12-24 hours s after AMI onset time of CP, therefore it considers as a late ideal biomarker for diagnosing AMI (Ali et al., 2016). Also, there is a recommendation from The European Society of Cardiology 2015 guidelines, for the second sample of cTnI after 3hours of presentation to improve its sensitivity for diagnosis AMI patients (Park et al., 2017). Many authors observed that AUCs of baseline levels of cTnI for early diagnosis of AMI ranged from 0.51 to 0.76 (Boeddinghaus et al., 2017 & Hamza et al., 2016). In agreement with our results; MCP-1 was a suitable marker of myocardial response to ischemic injury containing a very early phase reaction. Meanwhile, MCP-1 value was strongly elevated in the very early phase (0-4 hours s), to reduce in the early period (after 6-8 hours s) (Turillazzi et al., 2014). Furthermore, previous authors have compared several markers with cTnI for early AMI diagnosis (Yao et al., 2015 & Gerede et al., 2015). To conclude, our study observed that MCP-1 has a good efficiency for discriminating AMI patients from NCCP, SA, and UA patients. MCP-1 has better AUCs than Troponin I for diagnosis AMI patients from ACS patients within 0-12 hours after onset time of CP. Meanwhile, Troponin I have a better AUC than MCP-1within > 12-24 hours after onset time of CP.

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