REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

MicroRNA-499-5p and chemokine (C-C motif) ligand18 as new diagnostic markers of Acute Myocardial Infarction

Elen N. Halem[a]*, Dina M. Abo-Elmatty[a], Gamela M. Nasr[b], Noha M. Mesbah[a], Ahmed S. Salem[b], Asmaa R. Abdel-Hamed[a]

[a]Department of Biochemistry, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt; [b]Department of Cardiology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.

Received: 23. 06. 2023

Revised: 30. 06. 2023

Accepted: 01. 07. 2023

*Correspondence Author:

Tel: +201220761763

E-mail address:

Elengoreg361@gmail.com

Abstract

Acute myocardial infarction (AMI) is the acute necrosis of myocardial tissue due to chronic and severe ischemia. AMI stays a main cause of morbidity and mortality worldwide. Accurate and rapid diagnosis is useful for the clinical management and prognosis of AMI early. Thus, exploration of new potential biomarkers that will contribute to this direction is particularly important. CCL18 Chemokines is a class of chemotactic cytokines, come into play in response to acute cardiovascular events, coordinating inflammation, necrosis, neovascularization, and leukocyte recruitment. MicroRNAs (miRNAs) are small non-coding RNAs that mediate the expression of target genes. Recently, a few numbers of miRNAs are emerging as potential biomarkers of AMI. MiRNA-499-5p is a newly discovered member of miRNAs and is essentially expressed in myocardium.

Keywords: CCL18, miRNA-499-5p, acute myocardial infarction.

1. Introduction

Acute myocardial infarction (AMI) is a form of severe heart attack that damages the heart muscle due to a lack of oxygen result from blockage of blood flow to the heart **(Li et al., 2020)**. Acute myocardial infarction can be divided into two categories, non-ST-segment elevation MI (NSTEMI) and ST-segment elevation MI (STEMI). Unstable angina is like NSTEMI. However, cardiac markers are not elevated **(Nascimento et al., 2019)**.

An AMI results in irreversible damage to the heart muscle due to a lack of oxygen., which lead to impairment in diastolic and systolic function and make the patient prone to arrhythmias. In addition, an AMI can lead to several serious complications.

The key is to repercuss the coronary heart and restore blood flow. The earlier the treatment (less than 6 hours from symptom onset), the better the prognosis **(Mechanic et al., 2022)**.

2. Pathophysiology of Acute Myocardial Infarction

Arteriosclerosis is the thickening, hardening, and loss of elasticity of the walls of arteries. This process gradually restricts the blood flow to one's organs and tissues and can lead to severe health risks brought on by atherosclerosis, which is a specific form of arteriosclerosis caused by the buildup of fatty plaques, cholesterol, and some other substances in and on the artery walls. It can be brought on by smoking, a bad diet, or many

genetic factors **(Dos Santos et al., 2021)**.

Atherosclerosis (fatty buildups) is a pattern of the disease arteriosclerosis. in which the wall of the artery develops abnormalities, called lesions. These lesions may lead to narrowing due to the buildup of atheromatous plaque **(Figure 1)**. At onset there are usually no symptoms, but if they develop, symptoms generally begin around middle age. When severe, it can result in coronary artery diseases such as AMI, stroke, peripheral artery disease, or kidney problems, depending on which arteries are affected **(Gibbons et al., 2022)**.

3. Risk Factors of Acute Myocardial Infarction

The most common cause of a myocardial infarction is the rupture of an atherosclerotic plaque on an artery supplying heart muscle **(reed et al., 2017)**. Plaques can become unstable, rupture, and additionally promote the formation of a blood clot that blocks the artery, this can occur in minutes. Blockage of an artery can lead to tissue death in tissue being supplied by that artery. Atherosclerotic plaques are often present for decades before they result in symptoms **(Thygesen et al., 2018)**. As atherosclerosis is the predominant cause of acute myocardial infarction, there are other modifiable risk factors that include cigarette smoking, exercise, hypertension, diabetes, obesity, cholesterol, LDL, triglyceride levels, and Cocaine abuse can also lead to vasospasm **(Bracey and Meyers, 2021)**. In contrast, non-modifiable risk factors include age, sex, and a family history of early myocardial infarction (55 years of age) is also a high-risk factor of AMI **(Pop et al., 2019)**.

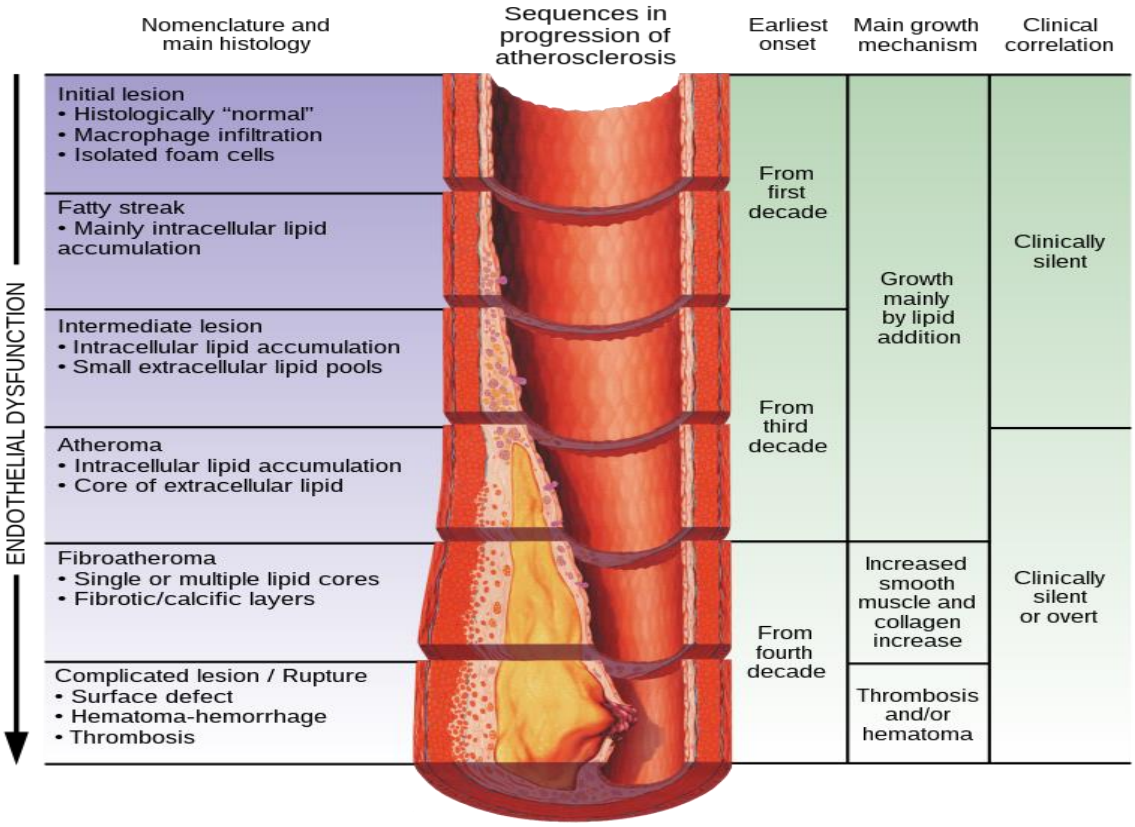

Figure 1: Stages of endothelial dysfunction in atherosclerosis of arteries. *By Yitzhak Nat - Own work and based on. Made with MS Visio., CC BY-SA 4.0* **(Gibbons et al., 2022)**.

4. Clinical Presentations of Acute Myocardial Infarction

Onset of myocardial ischemia is the initial step in the development of AMI which result from an imbalance between oxygen supply and demand **(Padro et al., 2020)**.

Myocardial ischemia is a clinical setting can most often be identified from the patient's history and from the ECG, which helps differentiate between STEMI and NSTEMI unstable angina. Possible

ischemic symptoms include various combinations of chest, upper extremity, mandibular, or epigastric discomfort during exertion or rest. Often, the discomfort is diffuse; not localized, nor positional, nor affected by movement of the region **(Luciano et al., 2019)**.

However, these symptoms are not specific for myocardial ischemia and can be observed in other conditions such as gastrointestinal, neurological, pulmonary, or musculoskeletal complaints. AMI may occur with atypical symptoms such as palpitations or cardiac arrest, or even without symptoms **(Thygesen et al., 2019)**. Though a small percentage of patients have no symptoms or changes in their ECG **(Wang et al., 2020)**. As ECG has limited sensitivity and specificity for the diagnosis of AMI, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) established AMI criteria. To be diagnosed with AMI, a patient must exhibit at least two of the following traits. The first is characteristic elevation in cardiac markers (such as creatinine kinase-MB (CK-MB) isoenzymes), particularly serum cardiac troponins I or T (cTnI or cTnT), and the second is ECG changes with ST elevations and abnormal Q waves **(Aydin et al., 2019)**. Though AMI causes significant morbidity and mortality, measuring a variety of cardiac biomarkers is very useful for early diagnosis, risk classification, and tailoring appropriate treatment in the management of these high-risk patients. The optimal biomarkers for identifying myocardial injury are exhibited at significantly higher levels inside cardiac tissue, have good clinical sensitivity and specificity, and can be detected in the bloodstream early following the commencement of clinical manifestations such as chest pain **(Niccoli et al., 2019)**.

5. Cardiac Biomarkers

New understanding in pathophysiology of atherosclerosis has implicated inflammation as a central contributor to initiation and progression of the disease. Chemo attractant cytokines, such as monocyte chemo attractant protein-1 (MCP-1), mediate transmigration of inflammatory cells into the sub endothelial space and macrophage colony-stimulating factor (M-CSF) contributes to differentiation of monocytes into macrophages were transformed into foam cells, key element of the fatty streak. Mononuclear cells release cytokines, which recruits further inflammatory cells, resulting in further uptake and oxidation of low-density lipoproteins (LDLs) **(Gimbrone and García-Cardeña, 2016)**.

Therefore, inflammation and biochemical modifications, causing endothelial and smooth muscle cells to proliferate, produce extracellular matrix molecules, and form a fibrous cap over the developing atheromatous plaque. Plaques lead to clinical symptoms by producing flow-limiting stenosis (causing stable angina) or by provoking thrombi that interrupt blood flow on either a temporary basis (causing unstable angina) or a permanent one (causing myocardial infarction) **(Figure 2) (Luciano et al., 2019)**.

Several risk factors were known to promote atherosclerosis, and various biomarkers were shown to identify patients at risk for CAD. Some studies found an association among inflammatory biomarkers and cardiovascular diseases suggesting their utility to identify the risk of an acute ischemic event and the detection of vulnerable plaques **(Gimbrone and García-Cardeña, 2016)**.

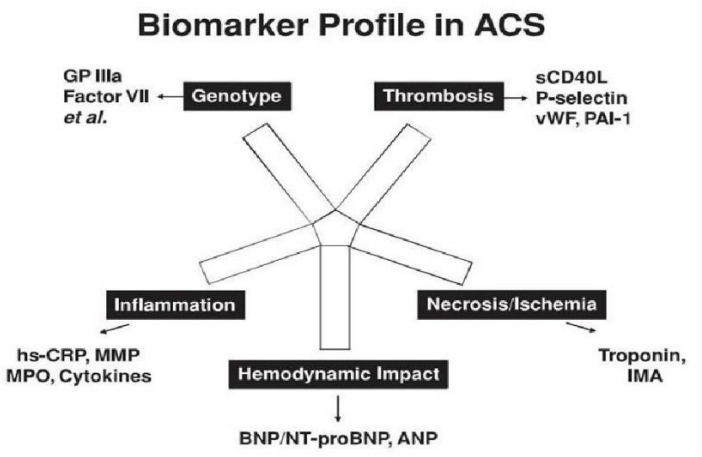

Figure 2: Conceptual application of a multimarket approach to characterization of the patient with ACS **(Morrow and Braunwald, 2002).**

Table 1. Various cardiac markers used for early diagnosis of acute myocardial infarction (Muhammad et al., 2022)

Biomarker	Molecular Weight (D)	Initial Elevation (hr.)	Peak Elevations	Time to Return to Normal Range
MB-CK	86,000	3-12	24 hr.	48-72 hr.
cTnI	23,500	3–12	24 hr.	5-10 d
cTnT	33,000	3-12	12 hr-2 d	5-14 d
Infrequently Used in Clinical Practice				
Myoglobin	17,800	1–4	6-7 hr.	24 hr.
MB-CK tissue isoform	86,000	2–6	18 hr.	Unknown
MM-CK tissue isoform	86,000	1–6	12hr.	38hr.

Inflammatory processes after myocardial infarction and endothelial dysfunction are key elements in determining the extension of myocardial damages **(Gimbrone and García-Cardeña, 2016)**.

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 **(Gimbrone and García-Cardeña, 2016)**. 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. Since the discovery of the super-family of chemokines and their receptors, there has been a considerable effort to define their role in the development of atherosclerosis and in ischemia-induced myocardial injury and left ventricular remodeling after acute myocardial infarction **(Braunersreuther et al., 2010).**

5.1. Chemokines

Chemokines a family of low molecular weight heparin-binding proteins that cause selective chemo-attraction 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., The largest family of chemokines is known as the CC chemokines **(Jones et al., 2011)**.

Chemokine (C–C motif) Ligand-18 (CCL 18) pulmonary and activation -regulated chemokine (PARC) is a polypeptide composed of 69 amino acids with a molecular weight of 7.85 KDa protein that plays a role in injury healing, it. CCL18/ PARC has specific chemotactic activity on T cells and this chemokine can activate fibroblasts, thereby directly contributing to lung fibrosis and possibly

myocardial fibrosis upon ischemia **(Duffy and Criner, 2019)**.

Physiological homing of mononuclear blood cells and inflammatory responses. CCL 18 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. Although the exact biological role of (CCL 18) is not known, serum levels are elevated in acute coronary syndrome **(De Jager et al., 2012)**.

5.2. Micro RNAs

Nowadays, microRNAs (miRNAs) are receiving growing attention because they are frequently dysregulated in a variety of pathological conditions, microRNAs (miRs), non-coding single-stranded small RNA consisting of 21-23 nucleotides, are negative regulators of gene expression by binding to the 3′ untranslated regions (3’ UTR) of mRNA **(Saliminejad et al., 2019)**.

MiRNAs have been shown to have a role in apoptosis, proliferation, differentiation, migration, and cell conversion, which are all critical in regulating cellular activities. According to previous reports, several miRNAs, including miR-34a, miR-126, miR-132, and miR-495, are involved in angiogenesis in AMI response. This beneficial effect may make miRNAs a useful tool for preventing severe heart failure following MI (**Chen et al., 2019; Fu et al., 2019; Huang et al., 2020; Ma et al., 2021)**. MiRNA-499-5p is a crucial regulator in different human infections, including congenital heart disease, pulmonary fibroblasts, autoimmune diseases, and hepatocellular carcinoma **(Wang et al., 2020)**.

MiRNA-499-5p are elevated in AMI patients, suggesting that they could be used as biomarkers for heart injury. miRNA-499-5p is a newly identified member of the myosin gene family's miRNAs, located in an intron of the Myh7b gene. It is highly conserved across species, inhibits cardiomyocyte progenitor cells proliferation and promotes cell differentiation and its expression in plasma was shown to be higher in patients with AMI **(Xin et al., 2016)**.

miRNAs used to be considered existing in cells only for some time. However, recent studies discovered that miRNAs are stably present in human serum/plasma **(Chen et al., 2019)**.

7. Conclusion

Acute myocardial infarction (AMI) basically is one of the main causes of morbidity and mortality in the worldwide, for that reason an effective and accurate diagnostic biomarker would be mostly needed to help decrease the mortality of AMI patients. AMI patients had significantly higher serum expression of miRNA-499-5p and plasma levels of CCL18, which were positively linked with serum cTnI and CK-MB. Expression of miRNA-499-5p was positively correlated with plasma CCL18 level in AMI patients.

8. Conflict of Interest

The authors declare that there is no conflict of interest.

References

Aydin S, Ugur K, Sahin I, Yardim M. Biomarkers in acute myocardial infarction current perspectives. Vasc Health Risk Manag. 2019; 15: 1–10.

Bracey A, Meyers H P. Posterior Myocardial Ischemia. StatPearls [Internet]; Treasure Island (FL). 2021.

Braunersreuther V, Pellieux C, Pelli G, Burger F, Steffens S, Montessuit C. Chemokine CCL5/RANTES inhibition reduces myocardial reperfusion injury in atherosclerotic mice. J Mol Cell Cardiol. 2010; 48: 789-98.

Chen A, Fang Z, Chen X, Yang S, Zhou Y, Mao L, Xia Y, Jin H, Li Y, You M, Wang X, Lei H, He Q, Hu B. Microglia-derived TNF-alpha mediates endothelial necroptosis aggravating blood brain-barrier disruption after ischemic stroke. Cell Death Dis. 2019; 10: 487.

De Jager S, Bongaerts B, Weber M, Kraaijeveld A, Rousch M, Dimmeler S, Khabbazi S, Jacques R, Moyano C, Mueller A. Chemokines CCL3/MIP1α, CCL5/RANTES and CCL18/PARC are independent risk predictors of short-term mortality in patients with acute coronary syndromes. PloS one. 2012; 7: e45804.

Dos Santos V P, Pozzan G, Castelli V, Caffaro R. Arteriosclerosis and monckeberg medial calcific sclerosis: what is the difference. J Vasc Brasileiro. 2021; 20: e20200211.

Duffy S, Criner G. Chronic obstructive pulmonary

disease evaluation and management. Med Clin N Am. 2019; 103: 453–461

Fu J, Bai P, Chen Y, Yu T, Li F. Inhibition of miR-495 improves both vascular remodeling and angiogenesis in pulmonary hypertension. J Vasc Res. 2019; 56: 97–106.

Gibbons G, Seidman C, Topol E. Conquering atherosclerotic cardiovascular disease -50 years of progress. N Eng J Med. 2022; 384(9): 785-788.

Gimbrone M, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res. 2016; 118(4): 620-636.

Huang J, Xu Y, Yin X, Lin F. Exosomes derived from miR-126-modifiedMSCs promote angiogenesis and neurogenesis and attenuate apoptosis after spinal cord injury in rats. Neuroscience. 2020; 424: 133–145.

Jones K, Maguire J, Davenport A. Chemokine receptor CCR5 from AIDS to atherosclerosis. Br J Pharmacol. 2011; 162: 1453-1469.

Li M, Chen F, Zhang Y, Xiong Y, Li Q, Huang H. Identification of post-myocardial infarction blood expression signatures using multiple feature selection strategies. Front Physiol. 2020; 11: 483.

Luciano L, Silva R, Londero Filho O, Waldrich L, Panata L, Trombetta A, Preve J, Fattah T, Giuliano L, Thiago L. Analysis of the appropriate use criteria for coronary angiography in two cardiology services of southern brazil. Arq Bras Cardiol. 2019; 112(5): 526-531.

Ma Y, Chen Y, Meng Q, Shao L. Role of neutrophils in cardiac injury and repair following myocardial infarction. Cells. 2021; 10: 1676.

Mechanic O, Gavin M, Grossman S. Acute Myocardial Infarction. StatPearls [Internet]; Treasure Island (FL). 2022.

Morrow DA, Braunwald E. Future of biomarkers in acute coronary syndromes: moving toward a multimarker strategy. Circulation. 2003; 108(3): 250-252.

Muhammad S, Hannana M, Abid A, Mahnoor F, Waqar A. A comparative study of biochemical markers in the early diagnosis of acute myocardial infarction (AMI). Saudi J Pathol Microbiol. 2022; 7(8): 345-357.

Nascimento B, Brant L, Marino B, Passaglia L, Ribeiro A. Implementing myocardial infarction systems of care in low/middle-income countries. Heart. 2019; 105(1): 20-26.

Niccoli G, Rocco A, Borja I, Holger T, Filippo C, Gerd H, Heerajnarain B, Derek J, Hausenloy C, Thomas S, Paolo G, Camici, Ingo E. Optimized treatment of ST-elevation myocardial infarction. Circ Res. 2019; 125: 245–258.

Padro T, Manfrini O, Bugiardini R, Canty J, Cenko E, De Luca G, Duncker D, Eringa E, Koller A, Tousoulis D. ESC Working Group on Coronary Pathophysiology and Microcirculation position paper on coronary microvascular dysfunction in cardiovascular disease. Cardiovasc Res. 2020; 116: 741–755.

Pop C, Matei C, Petris A. Anticoagulation in acute coronary syndrome: review of major therapeutic advances. Am J Ther. 2019; 26(2): e184-e197.

Reed G, Rossi E, Cannon C. Acute myocardial infarction. Lancet. 2017; 389 (10065): 197–210.

Saliminejad K, Khorram Khorshid H, Soleymani Fard S, Ghaffari SH. An overview of microRNAs: biology, functions, therapeutics, and analysis methods. J. Cell Physiol. 2019; 234: 5451–5465.

Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction. J Am Coll Cardiol. 2018; 72(18): 2231-2264.

Wang X, Zhang F, Zhang C, Zheng L, Yang J. The biomarkers for acute myocardial infarction and heart failure. Biomed Res. 2020; 2018035.

Xin Y, Yang C, Han Z. Circulating miR-499 as a potential biomarker for acute myocardial infarction. Ann Transl Med. 2016; 4(7): 135.