The soluble major histocompatibility complex class I chain-related gene A (sMICA) as an early biomarker for diagnosing acute myocardial infarction

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Abstract

Introduction: It is necessary to identify tests that have high diagnostic power in the early hours of acute myocardial infarction.
Objectives: In this study, we investigated the major histocompatibility complex class I chain-related molecule A (MICA) in the serum of patients with myocardial infarction (MI).
Patients and Methods: In this study, 65 patients with MI were studied. Creatine phosphokinase-MB (CPK-MB), troponin I, and MICA biomarkers were measured at different times after hospitalization (0, 3, 6, 9, 12 and, 24 hours). These biomarkers were evaluated at different times after chest pain (0 to 3, 3 to 6, and more than 6 hours).
Results: Serum MICA biomarker increased significantly from admission to the hospital until 3 hours. Later on, it decreased until 24 hours. However, CPK-MB biomarkers as well as troponin I, change from admission up to 24 hours. Regarding diagnostic power, it was found that the diagnostic power of MICA is high in the early hours which indicates the high diagnostic power of the test.
Conclusion: The diagnostic value of MICA is significant in the early hours after MI. Therefore, due to the high accuracy of MICA in diagnosing MI, it should be used as a diagnostic test along with other tests to confirm MI in the early hours.

Introduction

Ischemic heart disease (IHD) refers to the lack of oxygen due to insufficient blood supply which, in turn, results from an imbalance of myocardial oxygen supply. The most common cause of myocardial ischemia is atherosclerotic coronary artery disease (1-3). Patients with IHD are classified into two major groups; patients with persistent angina secondary to chronic coronary artery disease and patients with acute coronary syndromes. The second group includes patients with acute myocardial infarction (AMI) with ST-segment elevation, unstable angina, and AMI without ST-segment elevation (4).

AMI is one of the most common diagnoses in patients admitted to industrialized countries. In the United States, approximately 650 000 people experience new myocardial infarction (MI) and 450 000 have recurrent MI each year. The early mortality rate of MI is about 30% with more than half of all deaths occurring at home. Although the death rate from hospital admissions has decreased by about 30% in

Key point

The soluble major histocompatibility complex class I chain-related gene A (sMICA) could be employed as a diagnostic test along with other tests to confirm MI in the early hours. However, it is crucial to measure MICA in the early hours.

the last two decades, one in 25 patients who discharged from hospital dies within the first year after a heart attack. The survival rates are significantly reduced in elderly patients (over 75 years of age) (5).

The cardiac biomarkers that are used to diagnose AMI include cardiac myoglobin and creatine phosphokinase-MB (CPK-MB). Measurement of troponin I is the gold standard test in diagnosing AMI (6). An increase in troponin is seen in patients with IHDs and some other diseases such as severe heart failure, chronic kidney disease, atrial fibrillation, sepsis, shock, and damage to the myocardium (7). Troponin also facilitates the early detection of AMI. In AMI, troponin increases within six hours after chest pain.

Therefore, due to the delay in troponin release, it is necessary to introduce a new and effective biomarker for the early diagnosis of AMI (8,9). The adaptive complex is part of a gene map on the small arm of chromosome 6, most of which encodes polypeptides in lymphocyte surface antigens. In 1994, a new group of polymorphic genes of tissue-compatible complex type 1 of the family of class A compatible complex polypeptide of chain A or MHC class I chain-related was introduced. This has two subsets; major histocompatibility complex class I chain-related molecule A (MICA) and major histocompatibility complex class I chain-related molecule B (MICB) (10). The MICA gene encodes a polypeptide that contains 383 amino acids and is present on the surface of several cells. MICA has a molecular structure similar to the classical type 1 chain-linked complex family complex. MICA is a natural ligand that activates natural killer (NK) cells and membrane receptors of membrane D that appear on the surface of NK cells. The binding of MICA to membrane D receptors causes a signal that stimulates NK cells and releases cytotoxic molecules which, in turn, identify and lyse the target cell with NK cells. MICA can be activated in several normal tissues through a variety of stimuli including the endoplasmic reticulum stress (ERS), radiotherapy, some drugs and ischemic tissue damage. However, its exact function in stressed tissues is not known (6). In addition to the occurrence of MICA on the cell membrane surface, stressful conditions in tissues with MICA increase the amount of MICA from the membrane surface to the outside of the cells appearing as a soluble form. A recent study showed that the serum level of MICA is higher in patients with AMI and is more sensitive than troponin in diagnosing ischemia (6).

Objectives
This study aimed to assess MICA as an early biomarker for diagnosing MI in patients with AMI in Ahvaz, Iran. The results of this study can help emergency medicine specialists or cardiologists to early diagnose AMI.

Patients and Methods
Study patients
This study was a cross-sectional study and 65 patients with AMI were enrolled. These patients were referred to the emergency departments of Imam and Golestan hospitals, Ahvaz, Iran. Informed consent was obtained from the studied samples. The inclusion criteria included age over 18 years that had chest pain without a history of any other heart diseases. The study excluded patients with recent MI, recent percutaneous coronary intervention, peritoneal dialysis, hemolysis, acute and chronic infections, renal impairment, renal failure (GFR<15 mL/min/1.73 m² or dialysis), and cancer.

To detect AMI with the international criteria (11), 2 mL of blood was taken from the participants at 0, 3, 6, 9, 12, and 24 hours. To separate the serum, the samples were placed in a centrifuge at 3000 rpm for 5 minutes and the serum of these patients was isolated. The serum was then used to measure the levels of CK-MB, troponin, and sMICA biomarkers.

Patients with MI were divided into three subgroups based on their chest pain as the following; chest pain between 0 and 3 hours, chest pain lasting 3 to 6 hours, and chest pain lasting more than 6 hours. Human sMICA was measured by ELISA(enzyme-linked immunosorbent assay) kits. The ELISA method was also used to measure troponin concentration and CK-MB activity.

Data analysis
The mean and standard deviation were calculated for descriptive statistics, quantitative variables, central indices and dispersion. Frequency and percentage were calculated for qualitative variables. One-way ANOVA and Pearson's correlation were applied to analyze the hypothesis. All statistical analysis were conducted using SPSS 21.

Results
In this study, 65 patients with AMI were included. The mean age of the patients was 57.03 ± 12.25 years (age range of 30-59 years) since 61.5% of the patients were male. Around 87.7% of the patients reported a set of cardiovascular risk factors including diabetes, hyperlipidemia, family history of cardiac disease, smoking, and hypertension. Regarding the type of MI, 64.6% had STEMI (ST-segment elevation myocardial infarction) and the rest of the patients had non-STEMI. The patient characteristics are shown in Table 1.

Table 1. The frequency of demographic and clinical variables of the studied participants

	Variable	Frequency	Percent
Gender	Male	40	61.5
	Female	25	38.5
Age group (y)	18-29	1	1.5
	30-59	38	58.5
	≥60	26	40
Risk factors	Diabetes	1	1.5
	Hyperlipidemia	1	1.5
	Family history	2	3.2
	Smoking	3	4.6
	High blood pressure	1	1.5
	A collection of the above	57	87.7
MI	STEMI	42	64.6
	Non-STEMI	23	35.4
Electrocardiogram changes	Lower leads	17	26.2
	Side leads	8	12.3
	Right anterior leads	2	3.1
	Wide anterior leads	16	24.6
	New LBBB	4	6.2
	A set of items listed	18	27.8
Time to start pain (h)	<3	26	40
	3-6	34	52.3
	>6	5	7.7

MI, Myocardial infarction; STEMI, ST-segment elevation myocardial infarction; LBBB, Left bundle branch block.

Troponin I, sMICA, and CPK-MB levels at different time-intervals after hospitalization

Tables 2 and 3 show the trend of changes for troponin I, CPK-MB, and MICA based on the time of patient referral (0, 3, and 6 hours). The trend of changes in MICA biomarkers at 0, 3, 6, 12, and 24 hours after the referral of patients with pain onset times of "0–3 hours" and "3–6 hours" shows the mean score of this biomarker over time. The fluctuations have been relatively increasing and decreasing. The MICA rate at 3 hours of referral had an increasing trend compared to the time of referral and then again, had a decreasing trend until 24 hours of referral. However, patients with pain onset time over 6 hours had a relatively decreasing trend during the zero to 24 hours after referral. We found a statistically significant relationship between serum MICA and chest pain at 0 to 3, 3 to 6, and more than 6 hours ($P<0.001$). The trend of changes in the CPK-MB biomarker in patients with pain onset times of "0–3 hours" and "3–6 hours" during the zero to 24 hours after referral had a completely increasing trend. This increasing trend was statistically significant ($P<0.001$). However, in the group of patients with pain onset time over 6 hours, there were relative increasing and decreasing fluctuations. The trend of troponin I biomarkers during the zero to 24 hours after the referral was different based on the pain onset group. The level of troponin I in the group of patients with the onsets of pain "0–3 h" and "3–6 h" during zero to 24 hours after referral showed an entirely increasing trend which was statistically significant ($P<0.001$). However, the group of patients with the time of pain onset over 6 h had a decreasing trend (Tables 2 and 3).

MICA biomarker changes according to patient referral time

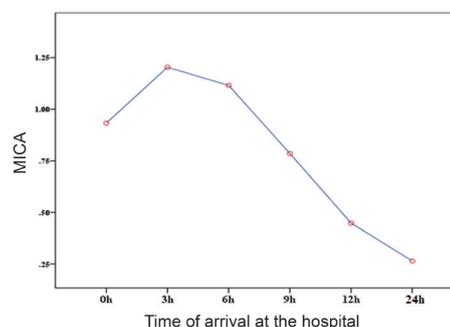As shown in Figure 1, the MICA biomarker reaches its

Figure 1. The trend of changes in the MICA biomarker according to the time of patient admission to the hospital.

maximum concentration within three hours of admission. It then begins to decrease and this decreasing trend continues until 24 hours. Among the biomarkers we measured in this study, the MICA biomarker reaches its peak concentration sooner than CPK-MB and troponin I. After reaching the causal peak, this biomarker gradually began to decrease and nine hours later it decreased to zero time. This decreasing trend continued for up to 24 hours.

Changes in CPK-MB biomarkers according to patient referral time

As shown in Figure 2, the rate of CPK-MB cardiac biomarkers increased over time. The amount of increase in this biomarker increased regularly after the patient was admitted to the hospital. The increasing trend continued for 24 hours. However, the amount of this biomarker, unlike MICA, does not decrease within 24 hours.

Troponin I biomarker changes according to the patient referral time

As shown in Figure 3, the level of troponin I increase from hospital admission to 24 hours after admission.

Table 2. Trends in serum levels of biomarkers (MICA, CPK-MB and troponin I) by patient referral time and time of chest pain onset

Chest pain time		Referral time								
		Zero hours			3 hours			6 hours		
		MICA	CPK-MB	Troponin I	MICA	CPK-MB	Troponin I	MICA	CPK-MB	Troponin I
0-3 hours	26	0.93±0.3	20.35±4.53	0.34±0.2	1.53±0.31	26.88±3.15	0.8±0.25	1.48±0.25	32.15±3.3	1.24±0.32
3-6 hours	34	1.73±0.64	31.97±2.75	0.78±0.29	1.29±0.48	34.47±2.39	1.22±0.21	0.97±0.35	37.24±2.03	1.69±0.19
>6 hours	5	0.17±0.03	39.20±3.03	1.86±0.22	0.16±0.02	40 ±1.87	1.64±0.22	0.16±0.03	40 ±2.83	1.59±0.14
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

MICA (%): Major histocompatibility complex class I chain-related molecule A, CPK-MB (IU/L): Creatine phosphokinase-myocardia band, troponin I (ng/mL).
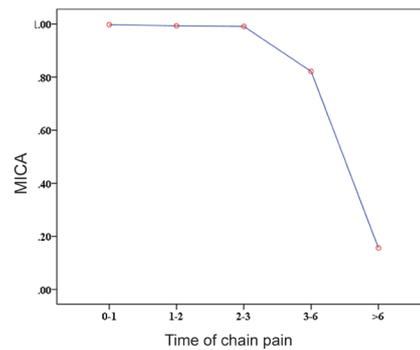
Table 3. Trends in serum levels of biomarkers (MICA, CPK-MB and troponin I) by patient referral time and time of chest pain onset

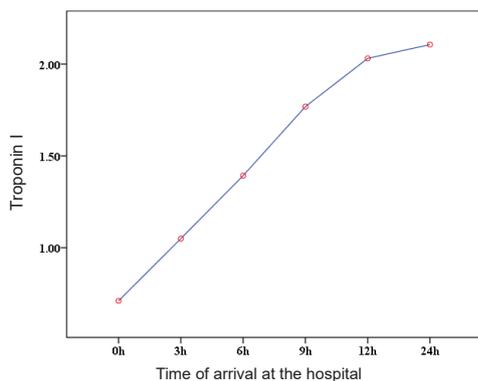| Chest pain time		Referral time								
		9 hours			12 hours			24 hours		
		MICA	CPK-MB	Troponin I	MICA	CPK-MB	Troponin I	MICA	CPK-MB	Troponin I
0-3 hours	26	1.12±0.2	37.42±2.74	1.78±0.29	0.58±0.33	41.35±2	2.18±0.18	0.31±0.27	43.12±1.84	2.27±0.16
3-6 hours	34	0.40±0.25	39.44±2.81	2.03±0.17	0.31±0.18	41.59±2.64	2.18±0.17	0.23±0.13	44.09±3.78	2.28±0.2
>6 hours	5	0.15±0.10	39.4±4.1	1.48±0.15	0.15±0.02	38.2±4.6	1.44±0.13	0.15±0.02	37.80±4.91	1.43±0.15
P value		<0.001	0.013	<0.001	<0.001	0.229	0.001	<0.001	0.002	0.001

MICA (%): Major histocompatibility complex class I chain-related molecule A, CPK-MB (IU/L): Creatine phosphokinase-myocardia band, troponin I (ng/mL).
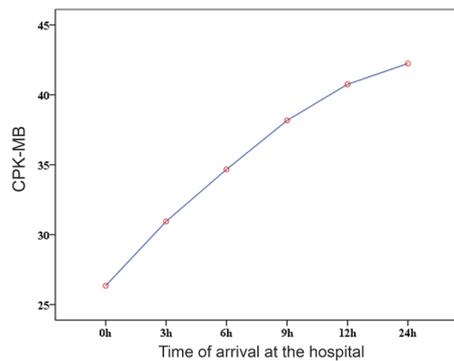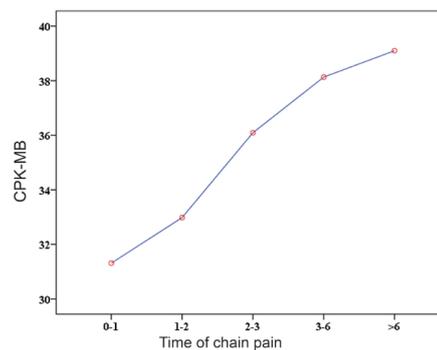
Figure 2. The trend of changes in the CPK-MB biomarker according to the time of patient admission to the hospital.

Figure 3. The trend of changes in the troponin I biomarker according to the time of patient admission to the hospital.

Figure 4. The trend of changes in the MICA biomarker according to the time of chest pain onset.

Figure 5. The trend of changes in the CPK-MB biomarker according to the time of chest pain onset.

Figure 6. The trend of changes in the troponin I biomarker according to the time of chest pain onset.

This upward trend is similar to the rise in the CPK-MB biomarker. Unlike MICA, troponin I levels do not decrease after 24 hours of hospitalization.
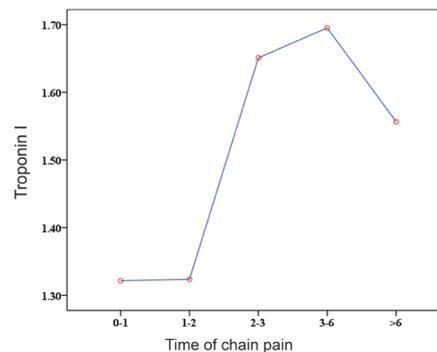
MICA biomarker changes by time of onset of chest pain
As shown in Figure 4, the level of MICA in the patient serum reaches its maximum at zero to one hour after chest pain, and this maximum level remains until 2 to 3 hours after chest pain. From this time onwards, the serum MICA level begins to decrease. Therefore, at 6 hours onwards, this concentration decreased significantly.

CPK-MB biomarker changes by time of onset of chest pain
As shown in Figure 5, the level of CPK-MB biomarker in the serum of patients with zero to more than 6 hours after chest pain continued to increase. No decrease in the level of this biomarker was observed in the serum of patients with myocardial infarction after 6 hours.

Troponin I biomarker changes by time of onset of chest pain
As shown in Figure 6, after 1 to 2 hours of chest pain, the level of troponin I in the patient serum does not change, and then, the level of troponin increases. After 3 to 6 hours of chest pain, the level of troponin reached its maximum concentration. Furthermore, after 3 to 6 hours, the level of

this biomarker in the serum of patients with MI decreased.

Correlation between MICA, troponin I, and CPK-MB biomarkers in patients with myocardial infarction
The evaluation of the correlation between different biomarkers of the study and the results of Spearman's correlation coefficient test showed a significant inverse relationship between the level of troponin I and the level of MICA at an alpha level less than 0.01. As the amount of troponin I increase, the amount of the MICA biomarker decreases and vice versa. In addition, a direct and significant relationship between troponin I and CPK-

MB was detected. As the amount of troponin I increase, the amount of the CPK-MB biomarker increases and vice versa (Table 4).

Table 4. The correlation coefficient between different biomarkers

Correlation	MICA	CPK-MB	Troponin I
MICA	1	-	-
CPKMB	-0.65	1	-
Troponin 1	-0.59	0.88	1

MICA, Major histocompatibility complex class I chain-related molecule A; CPK-MB, Creatine phosphokinase-myocardia band, troponin I.

Discussion

Coronary artery disease is one of the most common causes of hospitalization and an important cause of death in Western countries. To identify cardiovascular disease, in addition to measuring the lipid profile, the measurement of serum cardiac markers is a good indicator for diagnosing MI. MI causes death in myocardial tissue, releases intracellular components such as the cardiac enzyme CPK and its MB isoenzyme (CPK-MB), cTnT, and cTnI into the bloodstream. For years, CPK-MB has been considered the gold standard in the diagnosis of AMI. Troponin I, which is not synthesized in tissues other than heart tissue, has recently been considered as a valuable indicator for diagnosing MI. Therefore, an increase in the amount of troponin I in the blood indicates a heart attack. These two biomarkers have been used as the gold standard for diagnosing MI for many years (12). In recent years, researchers have tried to identify a biomarker that rises rapidly in the bloodstream after MI to detect the disease earlier. One of the biomarkers that we measured in this study is the serum MICA biomarker.

This study was conducted on 65 patients with AMI who had been referred to the hospitals between October 2016 and March 2016. Of these patients, 40 (61.5%) were male and 25 38% were female. The serum levels of troponin I, CK-MB, and MICA were measured in these patients at 0, 3, 6, 9, 12, and 24 hours after hospitalization. The results of our study showed that, patients' troponin level increased up to 24 hours from the time of hospitalization. This indicates that cardiac troponin I was elevated in patients with MI. We concluded in our study that after 1 to 2 hours of chest pain, the level of troponin I in the patients' serum does not change however then, the level of troponin begins to increase. This increase reaches its maximum level after 3 to 6 hours of chest pain. Nonetheless, six hours after the chest pain, the troponin biomarker begins to decrease. Chest pain is one of the symptoms of MI that may help to diagnose this disease. In addition, our study showed that troponin and CPK-MB were significantly increased in all of the studied times since, only MICA was decreased over time. The results of our study showed the diagnostic power of MICA in the early hours of MI and had a level below the curve of 0.98, which indicates the high diagnostic power of the test. In general, to choose a highly sensitive biomarker, the tissue distribution of that biomarker should be considered in both physiological and pathological conditions. The rate at which the biomarker is released from damaged tissue is also important. Therefore, the presence of a biomarker in the bloodstream immediately after injury may facilitate early diagnosis (12).

Serum troponin I is one of the biomarkers that has been employed for several years for the early detection of MI. This release of this biomarker shows an initial peak concentration at 12-24 hours after injury and a second peak at 2-4 days after injury. Continuous release of troponin leads to its long-term while its sustained increasing helps in diagnosis. These properties of troponin have made this biomarker as a golden choice in the diagnosis of MI (13,14). The unique amino acid sequence of cardiac troponin I makes it an ideal biomarker for laboratory diagnosis of MI (15). Another study that evaluated the use of the sensitive method of measuring troponin I for early detection of MI is in accordance with the results of our study. They showed that employing sensitive methods for measuring troponin I can be used in the early diagnosis of MI (16).

The present study also showed that the association between CPK-MB serum concentration and duration of patient admission has an increasing trend. In addition, a direct relationship between CPK-MB and chest pain duration was detected. After more than six hours of chest pain, CPK-MB was still increasing and unlike troponin, later decreased. The serum concentration of this biomarker was absent after more than six hours of chest pain. These results indicate that the CPK-MB biomarker is an important biomarker in the diagnosis of MI. Currently, the CPK-MB isoenzyme in combination with troponin I is the gold standard for diagnosing AMI. Studies show that CPK-MB in the myocardium makes up 10-30% of total creatinine kinase. Therefore, damage to the heart causes this biomarker to increase in the blood. While this isoenzyme is not significantly concentrated in external cardiac tissues, it is a relatively specific cardiac marker for the diagnosis of infarction (17).

In accordance with the results of our study, a recent investgtion showed a significant difference between troponin I and CPK-MB levels in individuals who had MI versus those patients who had cardiac diseases but not MI. Therefore, the use of troponin I and CK-MB is essential in the timely diagnosis and treatment of MI. In this study, the sensitivity and specificity of troponin I and CPK-MB were evaluated. Recent studies showed that the sensitivity and specificity of troponin I were 100% and 97.5%, respectively, and is higher than the sensitivity (91%) and specificity (75%) of CK-MB (18). Harris et al compared cardiac troponins I, T, and CPK-MB for mild myocardial injury. They showed that troponin I was more sensitive and specific than the other two biomarkers. Therefore, they concluded that troponin I is more specific for early detection of myocardial injury (19).

The CPK-MB biomarker is not specific to the heart muscle and is found in skeletal muscle and the gastrointestinal tract and also the uterus of pregnant women. In addition, in patients with some forms of myopathy, skeletal CPK-MB is significantly increased. Since CPK-MB can become complex with immunoglobulins, elevated CPK-MB levels may occur due to other causes such as measurement errors, trauma, rapid muscle destruction, myopathies, renal failure due to myopathies, or before and a few weeks after delivery. Calculating the CPK-MB to CPK ratio increases the specific performance of the CPK-MB measurement. However, the simultaneity of skeletal muscle and heart damage significantly reduces the calculation sensitivity. In other studies, troponin I and T was shown to provide sufficient information, except for in patients that have renal insufficiency (20).

Although both troponin and CPK-MB are employed to diagnose MI and various studies have confirmed their effectiveness, researchers seek to identify biomarkers to diagnose MI earlier. One of these markers is the plasma MICA level. The results of our study showed that MICA biomarker reached its maximum concentration only within three hours after the admission of patients to the hospital, while serum MICA concentration began to decrease after that time. Moreover, the level of MICA in the patients' serum is at its maximum value at zero to one hour after chest pain, and this maximum level remains until 2 to 3h after chest pain. Over time, serum MICA levels begin to decline. A highly sensitive and specific biomarker for disease is its release and appearance in the blood immediately after the injury. This facilitates early diagnosis of the disease (12). As shown in our study, serum MICA levels peaked faster than troponin and CPK-MB and could, therefore, help to diagnose MI more rapidly.

Under physiological conditions, MICA is expressed only in gastrointestinal epithelial cells and its concentration are very low in most normal cells and tissues. However, through various stimuli, such as ERS, ischemia, and/or reperfusion, the expression of MICA increases, and in turn, the level of this biomarker increases in the blood (6). Hence, one of the reasons for the increase of plasma MICA in our patients could be the effect of inflammation and stress. Although MICA is elevated in MI, few studies have been investigated the mechanism and function of this biomarker. The study by FU et al, showed that MICA is more sensitive than troponin in the early diagnosis of MI (6). We concluded that the level of sMICA increases in patients with MI. The increase in sMICA can be a new biomarker for diagnosing myocardial damage in patients. Although in our study the sensitivity of MICA was not compared with troponin, MICA was found to have high diagnostic power in the diagnosis of AMI in the early hours. It can be evaluated as a suitable factor in the early hours and diagnose AMI with high accuracy.

The mechanisms of serum production of MICA and the mechanism of action of these compounds are not yet well understood. The rate of this marker increases in MI and other heart diseases. Therefore, understanding the signaling mechanisms responsible for the effects of sMICA is important to design new treatment strategies and target the cascading pathway of SMIC signaling in patients with MI as well as to target cardiac regeneration.

Conclusion

According to the results of our study, the serum level of MICA reaches its maximum concentration much earlier after MI compared to troponin I and CPK-MB. Therefore, it can be used as a very sensitive biomarker for diagnosing MI. In the study of diagnostic power, it was found that the diagnostic power of MICA is high in the early hours and has a level below the curve of 0.98, which indicates the high diagnostic power of the test. Nevertheless, large-scale prospective cohort studies are necessary to determine the potential relationship between sMICA and AMI.

Study limitations

The low sample size is a limitation of the current study. In addition, the patients of this study were only followed up for 24 hours. We recommend future studies follow up larger samples for a longer time.

Conflicts of interest
There are no any conflicts of interest.

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