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Research Article

Role of microRNA-499-5p in Early Diagnosis of Acute Coronary Syndrome and its Subtypes Compared with Highly Sensitive Cardiac Troponin –I

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ABSTRACT

Background: Acute coronary syndrome (ACS) is still one of the main causes of morbidity and mortality worldwide, to decrease mortality rates if diagnosed early. The ACS classification into three subtypes depends on electrocardiogram. miRNA-499-5p was found to be substantially elevated in AMI patients as compared with the non-AMI group and healthy control and it was already detectable in the plasma 1h after the onset of chest pain in AMI patients
Objectives: To evaluate the role of measuring serum miRNA-499-5p value in early diagnosis of ACS and compare with hscT-I
Subjects and Methods: A total of 120 patients (72 males and 48 females) aged≥30 years were consecutively selected from those who were admitted and diagnosed with ACS. The healthy subjects as controls for this study were recruited from those who had no current illness. The serum miRNA-499-5P and hscT-I were measured.
Results: It was shown that miRNA-499-5p levels had an overall significant difference among study groups ($p<0.001$), also the miRNA-499-5p mean level was significantly different between each ACS subgroup and controls ($P<0.001$)
miRNA-499-5p showed a significant positive correlation with hscT-I 0hrs in STEMI and NSTEMI but UA showed a non-significant correlation. miRNA-499-5p level had perfect AUC and high sensitivity and specificity for discrimination between subgroups of ACS patients.
Conclusions: The present study found the values of serum miRNA-499-5p expression in patients with ACS patients are significantly higher compared with controls after 1h of onset of chest pain**,** additionally, miRNA-499-5p expression have high sensitivity and specificity for differentiation between subgroups of ACS and from controls.

Introduction

An inadequate supply of blood to the myocardium was the result of coronary heart disease (CHD). It was primarily caused by the formation of atherosclerotic plaques within the intima of coronary arteries. (1) The plaque may erode or rupture, initially resulting in thrombosis and then a closure of the vessel that impedes blood flow and leads to ischemia or myocardial infarction (MI) (2).
Myocardium doesn't receive adequate blood supply in CHD, either acutely as it does in MI or chronically as it does in unstable angina pectoris. Angina at rest can only be caused by stenosed lesions at least 90%. Thrombosis is caused by tissue factor being exposed during a plaque rupture. (3) three subtypes of ACS may result from this type of thrombosis, which could result in subtotal or total lumen occlusion (4).4 The three types of ACS include MI with the electrocardiogram (ECG) showing ST-segment elevation (STEMI), the other MI with the ECG showing no ST-segment elevation (NSTEMI) and the third type is unstable angina (UA) (5).

Early diagnosis of MI can decrease the mortality rate for MI patients, as ACS is still one of the most prevalent causalities of morbidity and mortality around the world. Measurement of the blood level of cardiac-specific troponins (cTn-I and cTn-T) has been regarded as the preferred or the standard biomarker for diagnosis of myocardial infarction. An acute myocardial infarction begins with an elevation of serum troponin level that peaks four to ten days after onset and stays heightened for four to ten days afterward (6). Since high-sensitivity cardiac troponins detect very low levels of serum troponin, the newer generation of these cardiac troponins can detect cardiac injury more instantly than conventional cardiac troponins (7).

The management of the three ACS subtypes was not fixed so obtaining unexplored cardiac biomarkers for early diagnosis and differentiation of its subtypes would be of great importance. Recently, MI patients have been reported to have a significantly higher serum expression of a micro RNA (miRNA) of the type miRNA-499-5p which was positively correlated with serum levels of cTn-I and creatine kinase isoenzymes – MB (CK-MB) (8). The miRNA-499-5p was detectable in the plasma 1 h after onset of chest pain in MI patients while not in chest pain patients with no MI or a healthy control group (9). As miRNAs may be a promising method of diagnosing cardiovascular disease, particularly when there is diagnostic uncertainty, their integration with or without currently available biomarkers is a promising tool (10). miRNA-499-5p was highly expressed in the heart and was produced almost exclusively in the heart. Also, it was that found miRNA-499-5p may be involved in myocardial injury and remodeling and miRNA-499-5p was shown to be involved in cardiomyocyte differentiation(11). This study aimed to explore the role of miRNA-499-5p in the common clinical environment for early diagnosis and differentiation of subtypes of ACS compared with cTn-I.

Subjects and Methods

Study patients were recruited from the coronary care unit at Al-Yarmouk Teaching Hospital during the period between the 1st of November 2022 to the 1st of September 2023. One hundred twenty patients (72 males and 48 females), aged ≥ 30 years were consecutively selected from those who were admitted and diagnosed as ACS by specialist cardiologists. The diagnosis of ACS was based on the presence of two out of three criteria:

- Clinical presentation of the patient
- ECG changes
- A positive troponin test

Based on the same adopted criteria, ACS patients comprised three subgroups; namely, STEMI, NSTEMI, and UA. The healthy subjects as a control group were recruited from those who had no current illness with consideration of age and sex matching with the ACS patients. They had no history of CHD or other systemic diseases and have had normal ECG recordings.

Blood samples were collected from patients and controls. The serum was separated, divided into aliquots, and used for measurement of the level of hscT-I and the value of miRNA-499-5p ¯3 UUUGUAGUGACGUUCAGAAUU ¯5). The assay of hscT-I was done by using enzyme-linked immunosorbent assay (ELISA) kits that were supplied by MyBioSource Company, USA, and followed the manufacturer's instructions. The miRNA-499-5P value was estimated by SaCycler-96 Real-Time PCR system

Total RNA was extracted from serum samples of all patients and healthy controls(. All samples of RNA were converted to cDNA (EasyScript *First-Strand cDNA Synthesis SuperMix AE301-02)* by Reverse transcription PCR (Italy). Which was then submitted to qRT-PCR for micro-RNA-499-5P *level* expression and was normalized to the reference gene (GAPDH) by Amplification Kit Use Sybr. Fold change data was calculated using the relative comparative method 2-(ΔΔCt) (called the Livak method calculator) (12).

Table 1: Cycles And Thermal Profile Of qPCR

qPCR Steps	Temp.	Time	Cycle(s)
Initial activation	94°C	30sec	1
Denaturation	94°C	5 sec	45
Annealing	60°C	35 sec	
Melt curve	60-90°C	15 sec	1

The study was conducted after obtaining approval from the scientific committees in the Karkh Health Department in Baghdad. The objectives of the study were explained to the patients and their consent was obtained before starting the blood draw procedure and completing the study.

Data were analyzed using the statistical package of SPSS-24. After assuring that the data was normally distributed, data presentation was done by simple measures like mean, standard error or standard deviation of the mean, and percentage. ANOVA test was used to detect the presence of difference in means among more than two groups while the LSD test was used for the difference between two means. Pearson's correlation analysis was performed to determine the correlation between micRNA-499-5p and the other parameters. It was considered statistically consequential if the P value<0.05. In all study groups, Hanley and McNeil's method was used to analyze the ROC curve and measure the area under the curve (AUC). (13)

Results

The clinical characteristics of the study subjects, which the patients were 64.1% males and 35.8% females, and the control subjects had a similar sex distribution (64 % males, 35.1% females). The age range of study patients who were ≤ 50 years in age constituted 33.3% and those who were > 50 years old constituted 66.66%. Regarding BMI, 20% of patients were normal weight, 32.5% were obese, and 47.5% were overweight. Patients with ACS included those with STEMI (40 patients), NSTEMI (40 patients), and UA (40 patients).

Micro-RNA-499-5P gene expression fold change

Gene expression of micro-RNA-499-5P was detected in samples of all ACS and healthy controls. The expression of micro-RNA-499-5P in different patient subgroups is shown in Figure 1**.** The mean relative value of micro-RNA-499-5P *expression* was 39.98 ±11.23 in the STEMI group, 33.01 ±7.88 in NSTEMI, and 17.98 ±2.37 in UA group while in the control group, it was 1.00 ±0.00 and the difference among subgroups of ACS patients and healthy controls was statistically significant (P ≤ 0.01).

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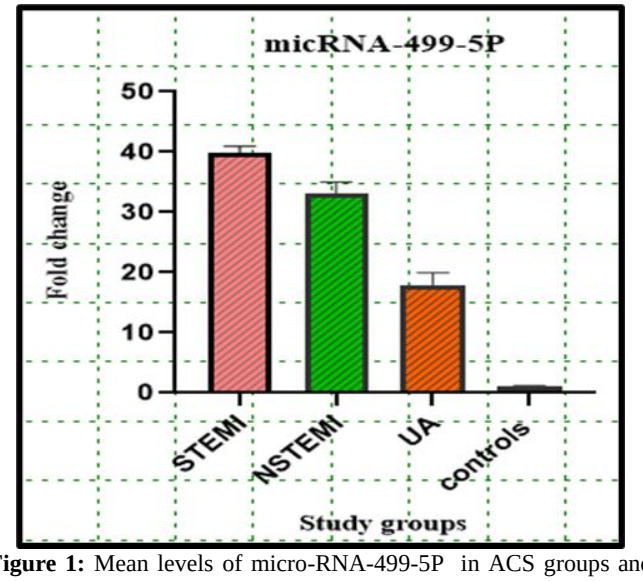

Figure 1: Mean levels of micro-RNA-499-5P in ACS groups and controls

Comparison of micRNA-499-5p among subtypes of acute coronary Syndrome

A comparison was made about the levels of micRNA-499-5p by using ANOVA analysis. It was revealed that study groups had extremely different levels of micRNA-499-5p ($P < 0.001$).

Further analysis by LSD test revealed that the micRNA-499-5p mean level was significantly different between each ACS subgroup and control group ($P < 0.001$). Additionally, STEMI levels were higher than NSTEMI ($P<0.01$) and UA ($P < 0.001$) levels. Also, a significant difference in micRNA-499-5p level was detected between NSTEMI and UA subgroups ($P = 0.028$).

Comparison of hscT-I levels among subgroups of acute coronary syndrome on admission and controls

A comparison was made in regard to the levels of hscT-I on admission among groups of study using the ANOVA test Figure 2. The ANOVA test revealed a significant difference in hscT-I levels among groups of study ($P< 0.05$).

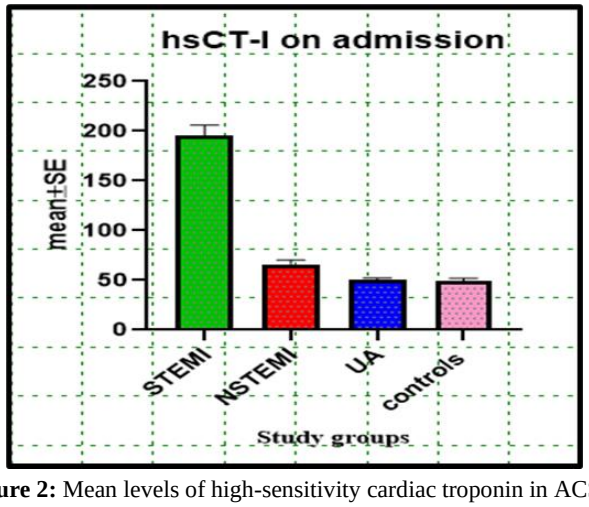

Figure 2: Mean levels of high-sensitivity cardiac troponin in ACS groups on admission and controls

Further analysis by LSD test revealed that hscT-I mean level on admission was significantly higher in STEMI and in NSTEMI subgroups compared with controls ($P = 0.033$ and $P = 0.047$, respectively) while no significant difference was detected among controls and UA. STEMI had an increased mean level of hscT-I than NSTEMI and UA ($P = 0.032$ and $P = 0.041$, respectively), while the NSTEMI and UA subgroups did not show any significant difference in hscT-I levels.

Comparison of hscT-I level three hours after admission among subgroups of acute coronary syndrome and controls

The hscT-I levels were compared in Figure 3. Among study group (ACS) and control groups exhibited overall significant differences in levels of hscT-I by an ANOVA test ($P< 0.001$)

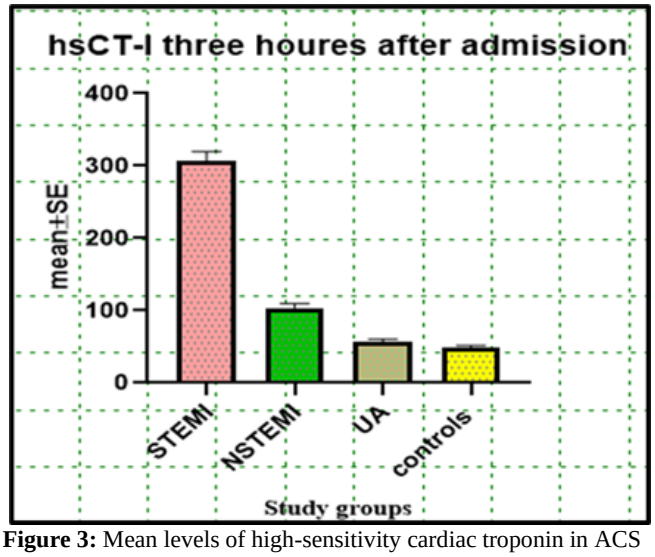

Figure 3: Mean levels of high-sensitivity cardiac troponin in ACS groups three hours after admission and controls

Further analysis by LSD test revealed that hscT-I mean levels were notably greater in both NSTEMI and STEMI subgroups than in the control group ($P = 0.000$) with no significant difference among controls and UA subgroups. The mean level of hscT-I was also significantly higher in STEMI than in both NSTEMI and UA ($P = 0.001$) but at this time a significantly higher mean level of hscT-I was detected between NSTEMI and UA subgroups ($P = 0.001$).

The correlation analysis of research biomarkers in patients with ACS. The micRNA-499-5p levels in the STEMI group showed a significant positive correlation with hscTn-I at admission ($r = 0.382$, $p = 0.041$) and also at three hours after admission ($r = 0.582$, $p = 0.021$). In NSTEMI subgroup, the micRNA-499-5p levels showed also significant positive correlation with hscTn-I levels at admission ($r = 0.127$, $p = 0.035$) and three hours after admission ($r = 0.323$, $p = 0.039$) while in UA subgroup, the micRNA-499-5p levels showed no significant correlation with hscTn-I levels whether at admission ($r = 0.223$, $p = 0.061$) or three hours after admission ($r = 0.324$, $p = 0.053$).

To test the diagnostic and differential discrimination power of study biomarkers among study groups, then ROC analysis was conducted. The ROC analysis between STEMI versus NSTEMI subgroups of ACS patients is presented in Table 2 and figure 4. For micRNA-499-

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5p levels, the results showed that the AUC was 1.00 and at a cut-off value of 38.65, the sensitivity was 97.1 % and the specificity was 100 % with a diagnostic accuracy of 99.5 %. For hscT-I levels at admission, the AUC was 0.791, and at 76.8 ng/ml cut-off value, 75.8 % was test sensitivity while 78.9 % was specificity with a diagnostic accuracy of 78.3 %. For hscT-I levels three hours after admission, the AUC was 0.971 and at 132.58 ng/ml cut-off value, 97.5 % test sensitivity, and 83 % specificity with a diagnostic accuracy of 89.2 %.

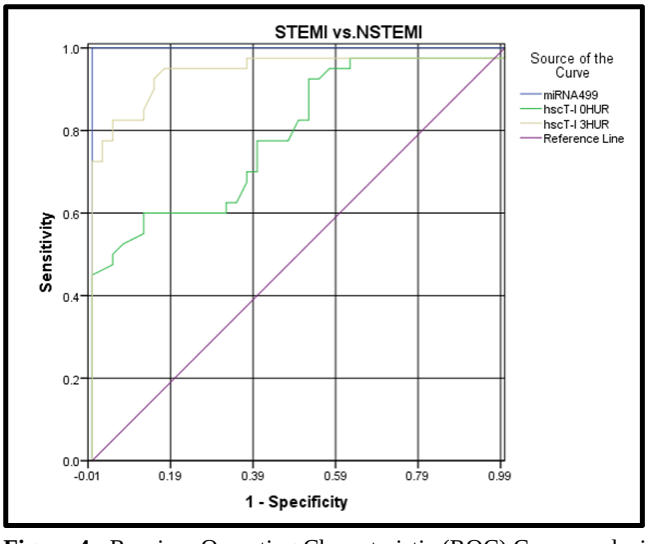

Figure 4: Receiver Operating Characteristic (ROC) Curve analysis of core study biomarkers in the STEMI subgroup of acute coronary syndrome patients versus NSTEMI

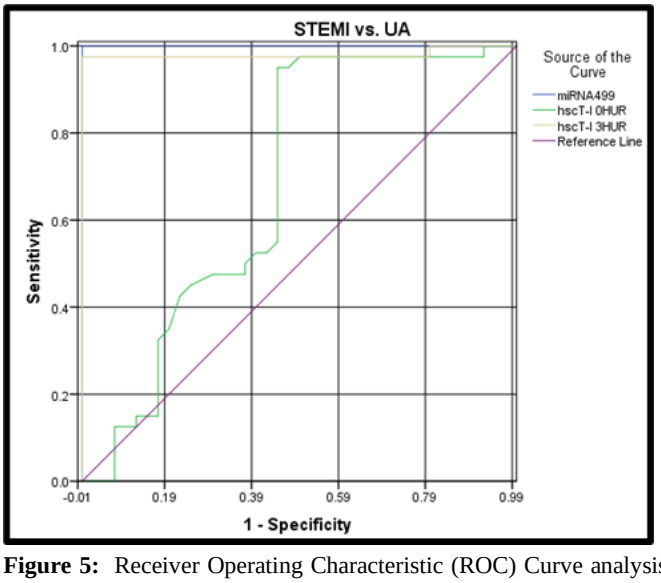

Figure 5: Receiver Operating Characteristic (ROC) Curve analysis of core study biomarkers in STEMI subgroup of acute coronary syndrome patients versus UA

The ROC analysis between STEMI versus UA subgroups of ACS patients was presented in Table 3 and figure 5. For micRNA-499-5p levels, the results showed that the AUC was 1.00 and at a cut-off value of 38.65, the sensitivity of the test was 97.5 % and the specificity was 100 % with a diagnostic accuracy of 99.5 %. For hscT-I levels at admission, the AUC was 0.678 and with an 87.7 ng/ml cut-off value, the test was 76.5% sensitive, 70.8% specific, with 78.3% diagnostic accuracy. For hscT-I levels at three hours after admission, the AUC was 0.981 and with a cut-off value of 123.44 ng/ml, the sensitivity of the test was 97.5% and the specificity was 74.2% with a diagnostic accuracy of 82.6%.

The ROC analysis between NSTEMI versus UA subgroups of ACS patients was presented in Table 4 and figure 6. For micRNA-499-5p levels, the results showed that the AUC was 0.977, and at a 30.10 ng/ml cut-off value, the test was 90% sensitive, 96 % specific with 92.5 % diagnostic accuracy. For hscT-I levels at admission, the AUC was 0.760 and had 43.1 ng/ml as a cut-off value, and the test was 71.5% sensitive, 68.7% specific, and 77.1% diagnostic accuracy. For hscT-I levels at three hours after admission, the AUC was 0.885 with 56.25 ng/ml cut-off value, 85 % test sensitivity, and 81% specificity with a diagnostic accuracy of 86.2%.

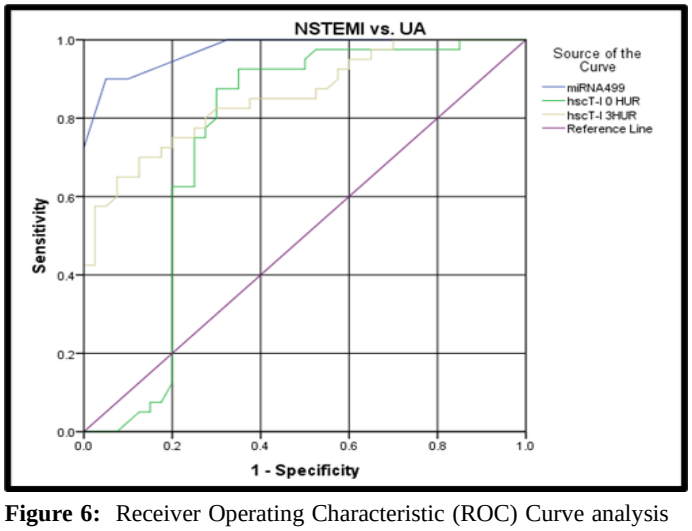

Figure 6: Receiver Operating Characteristic (ROC) Curve analysis of core study biomarkers in the NSTEMI subgroup of acute coronary syndrome patients versus UA

Discussion

Laboratory investigation of certain biomarkers, principally the cardiac troponins, was complementary to the clinical evaluation and ECG recording during the steps of diagnosis, triage, and management of patients with suspected ACS. The interval of 1–2 hours that allows early diagnosis or ruling out of acute MI is currently the most significant clinical hurdle to overcome. The release of cardiac troponin I (cTn-I) is relatively delayed after the onset of MI. The ruling out of acute MI by using ECG and troponins was time-consuming owing to the need for serial blood sampling to determine changes in troponin concentrations, especially in patients with non-ST elevation ACS. It was crucial to conduct successive assessments during the downtime for acute MI diagnosis and such extended monitoring of patients in emergency medical and/or cardiology centers drives a need for the development of fresh rule-in and rule-out tactics for the timely identification of acute MI

(11). Accordingly, an early diagnosis and clinical subtyping of the heterogeneous patients who present with suspected ACS may be improved by the finding of other biomarkers that their levels may change faster and so could be used for earlier diagnosis of patients with chest pain.

In a search for newer biomarkers that may aid in the early diagnosis of ACS and may have importance in the understanding of its progression, this study has evaluated a certain novel biomarker, which is micRNA 499-5P, whose levels are changed in the first few hours after onset of chest pain (often after 1 hour of chest pain) this agrees with (9).

Table 2: Discriminative ability of micRNA-499-5P and hscTn-I between STEMI vs. NSTEMI subgroups of ACS patients

Parameter	AUC	Cut-off value	P-value	Sensitivity	Specificity	Diagnostic accuracy %	discrimination	95 CI	
								Lower	Upper
micRNA-499-5p	1.000	38.65	0.001	97.1	100	99.5	perfect	1.00	1.00
hscT-I (pg/ml)/ 0hr.	0.791	76.8	0.001	75.8	78.9	78.3	fair	0.693	0.889
hscT-I (pg/ml)/ 3hr.	0.971	132.58	0.001	97.5	83.0	89.2	perfect	0.992	1.00

Table 3: Discriminative ability of micRNA-499-5P and hscTn-I between STEMI vs. UA subgroups of ACS patients

Parameter	AUC	Cut-off value	P-value	Sensitivity	Specificity	Diagnostic accuracy %	discrimination	95% CI	
								Lower	upper
micRNA-499-5p	1.000	38.65	0.001	97.5	100	99.5	Perfect	1.00	1.00
hscT-I (pg/ml) /0hr.	0.678	87.7	0.006	76.5	70.8	78.9	Poor	0.554	0.809
hscT-I (pg/ml) /3hr.	0.981	123.445	0.001	97.5	74.2	82.6	Perfect	0.943	1.00

Table 4: Discriminative ability of micRNA-499-5P and hscTn-I between NSTEMI versus UA subgroups of ACS patients

Parameter	AUC	Cut-off value	P-value	Sensitivity	Specificity	Diagnostic accuracy %	discrimination	95 CI	
								Lower	Upper
micRNA-499-5p	0.977	30.10	0.001	90.0	96.0	92.5	Perfect	0.977	1.00
hscT-I (pg/ml) / 0hr.	0.760	43.1	0.038	71.5	68.7	77.1	Fair	0.505	0.973
hscT-I (pg/ml) / 3hr.	0.885	56.25	0.001	85.0	81.0	86.2	Good	0.766	0.930

Discussion

This study revealed that the miRNA-499-5p expression mean level was significantly higher in ACS patients than in apparently healthy subjects. This finding is consistent with previous studies that reported an elevated miRNA-499-5p expression level in patients with acute myocardial infarction and in symptomatic patients referred for coronary angiography or in symptomatic patients referred for echocardiographic characteristics of atherosclerosis that agree with (8) due to 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 was highly conserved across species, inhibits cardiomyocyte progenitor cell proliferation, and promotes cell differentiation and its expression in plasma was shown to be higher in patients with AMI

This study showed a highly significant positive correlation between miRNA-499-5p expression and the levels of the established

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biomarker of MI which is the high sensitivity troponin-I in all three subgroups of ACS patients, this agrees with (14) due to suggest miRNA-499-5p was expressed at higher levels in myocardial infarction patients compared to those with other traditional AMI biomarkers, and that these levels were related positively with circulating CKMB and cTnI. As a result, miRNA-499-5p can be considered an early and specific biomarker that is nearly recognized in the blood 1 hour after heart muscle damage.

The mean levels of serum miRNA-499-5p expression in all subgroups of ACS patients were found to be significantly higher in ACS subgroups than in the control group. Such finding is consistent with many previous studies. The miRNA-499-5p level was reported to be significantly and positively correlated with serum cTn-I as well as creatine kinase (CK-MB) levels in acute MI patients (8). In one recent study, the miRNA-499-5p was found substantially elevated in acute MI patients as compared with no acute MI subgroup of ACS or with a healthy controls group (15). In another study, the miRNA-499-5p was detectable in the plasma one hour after the onset of chest pain in acute MI patients (9).

All these findings are consistent with the previous reports that showed that miRNA-499-5p was highly expressed in the heart and is produced almost exclusively in the heart due to this miRNAs are important for the development and proper functioning of the myocardium, and therefore their dysregulation was associated with the occurrence and progression of heart disease. Specifically, miRNA-499-5p was released into the bloodstream in patients with AMI due to cardiomyocyte damage, among other factors, and therefore up-regulation of their plasma levels can be observed. (16)

Also was consistent with the idea that miRNA-499-5p may be involved in myocardial injury and remodeling and that miRNA-499-5p was involved in cardiomyocyte differentiation (11).

The enhanced diagnostic capability of miRNAs can be attributed to their short, noncoding nature that regulates gene expression post-transcriptionally and to their remarkable stability in circulation. A lot of research has been conducted on the diagnostic efficiency of these molecules, and they have been suggested as biomarkers for diagnosing various diseases such as aortic dissection where the plasma of these patients has exhibited human cytomegalovirus-encoded miRNA expression profile (11).

ROC analysis revealed that the highest AUC value for the level of miRNA-499-5p expression was in discrimination between subgroups of ACS (STEMI, NSTEMI, and UA) and in differentiation of ACS subgroups from controls with a high sensitivity and specificity for differentiation between members of ACS. These findings suggest that miRNA-499-5p expression may be useful in undiagnosed acute chest pain with non-diagnostic ECG and normal troponin level and so may support an earlier diagnosis and management of ACS.(17)

ROC analysis revealed the fair to poor AUC for high sensitivity cardiac troponin level on admission and low sensitivity and specificity for differentiation between all subgroups of ACS (STEMI, NSTEMI, and UA) and in the differentiation of ACS from controls. On the other hand, the level of hscT-I, three hours after admission had a good AUC and a high sensitivity and specificity for differentiation between all subgroups of ACS (STEMI, NSTEMI, and UA) and in differentiation of ACS from controls in patients with acute coronary syndrome compared with the healthy control subjects. (18) Besides, ECG, cardiac biomarkers, and in particular troponins were used to diagnose acute MI. However, ruling out AMI with ECG and troponins is time-consuming owing to the need for serial blood sampling to determine the changes in troponin concentrations, especially in patients with non-ST-elevation ACS. The release of high-sensitivity cardiac troponin I (hscTn-I) was relatively delayed in comparison with myocardial infarction onset. However, the HSCT I was very sensitive which to a high number of false-positive results (19).

Circulating miRNA-499-5p a family member of miRNA-499 was shown to have the highest increase in NSTEMI patients by ~80-fold, the diagnostic accuracy of miRNA-499-5p was evaluated with ROC analysis and was comparable to that of cTn-T. In elderly patients with acute NSTEMI, a study showed that circulating miRNA-499-5p had better accuracy in the diagnosis compared with cTn-T. (20)

Conclusion

In the present study, the values of serum miRNA-499-5p expression are significantly higher in patients with ACS patients when compared with controls in early diagnosis ACS patients after 1 h of onset of chest pain that means diagnose the small amount of miRNA-499-5P, also showed a complete miRNA-499-5p expression AUC and a high sensitivity and specificity for differentiation between members of subgroups of ACS

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Conflict of Interest

Authors declare no conflict of interest.

Data availability

Data are available upon reasonable request

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