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Diagnostic Utility of Circulating MicroRNA-21 in Acute Myocardial Infarction

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KEYWORDS

Acute myocardial infarction, micro-RNA-21, Troponin I, biomarker, qRT-PCR, diagnosis

ABSTRACT:

Introduction: Acute myocardial infarction (AMI) is a leading cause of morbidity and mortality worldwide. Early and accurate diagnosis is crucial for improving outcomes. Circulating microRNAs, particularly microRNA-21 (miR-21), have emerged as promising non-invasive biomarkers due to their stability in the bloodstream and involvement in myocardial injury and remodelling. This study aimed to evaluate the diagnostic utility of circulating miR-21 in AMI patients. This study aimed to evaluate the diagnostic utility of circulating miR-21 in AMI patients.

Methods: An observational study was conducted at Mahatma Gandhi Medical College and Research Institute, India, enrolling 83 AMI patients and 30 healthy controls. Serum cardiac Troponin I (cTnI) was measured using enzyme-linked fluorescence assay, and miR-21 expression was quantified by qRT-PCR using the 2^-ΔΔCt method with U6 as an internal control. Statistical analysis included Student's t-test, Mann–Whitney test, χ^2 test, Spearman correlation, and receiver operating characteristic (ROC) curve analysis to assess diagnostic performance.

Results: Circulating miR-21 levels were significantly elevated in AMI patients compared to controls ($p < 0.001$). ROC curve analysis showed that miR-21 discriminated AMI patients with an area under the curve (AUC) of 0.886, sensitivity of 87%, and specificity of 83% at a cut-off value of 6.5. Cardiac Troponin I demonstrated superior diagnostic accuracy (AUC = 0.990, sensitivity = 90%, specificity = 100%). A significant positive correlation was observed between miR-21 expression and Troponin I levels ($r = 0.576$, $p < 0.001$), indicating that higher miR-21 levels are associated with greater myocardial injury.

Conclusions: Circulating miR-21 is significantly upregulated in AMI patients and shows good diagnostic performance, correlating with established markers of myocardial injury. MiRNA-21 may serve as a complementary biomarker to Troponin I, enhancing early detection and risk assessment in AMI.

1. Introduction

Acute myocardial infarction (AMI) contributes for almost one-third of the 17.9 million deaths annually that are linked to cardiovascular diseases (CVDs), which continue to be the leading cause of death worldwide [(1).] AMI, sometimes known as a "heart attack," is brought on by a sudden obstruction of coronary blood flow, usually as a result of an

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atherosclerotic plaque rupture followed by thrombus development [2]. If left untreated, the resulting myocardial necrosis and ischaemia set off a series of cellular and molecular processes that decrease heart function and raise the risk of death [3]. Reducing the size of the infarct, initiating reperfusion therapy, and enhancing long-term results all depend on an early and precise diagnosis. AMI is often diagnosed by combining electrocardiographic (ECG) findings, elevated serum indicators of myocardial damage, and clinical presentation [4].

Cardiac troponins (cTnI, cTnT) are the gold standard among the biomarkers that are now accessible because of their great specificity for myocardial damage [5]. Due to their higher diagnostic accuracy, troponins have mainly replaced the commonly used creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH) [6]. Even troponins have limitations, too. They may not enter the bloodstream until 3–6 hours after the onset of symptoms, which lowers sensitivity in the early stages of AMI [7]. Furthermore, in some clinical settings, reduced specificity might result from high troponin levels seen in various pathological states, including sepsis, pulmonary embolism, myocarditis, and renal failure [8]. In order to increase early detection, specificity, and overall diagnostic accuracy in AMI, new biomarkers are desperately needed.

Finding novel circulating biomarkers that are more sensitive and specific for AMI has been the reason for an abundance of study in recent years. Non-coding RNAs have drawn interest as prospective possibilities among them, especially microRNAs (miRNAs) (9,10). Because of their stability in the bloodstream and capacity to reflect pathological alterations at the molecular level, they have emerged as promising instruments for the precise and early diagnosis of cardiovascular disorders.

MicroRNAs are non-coding RNA molecules with a small size (18–24 nucleotides) that regulate the expression of genes after transcription by attaching to complementary sequences on target messenger RNAs (mRNAs) and causing translational repression or destruction [11]. They play a crucial role in controlling a variety of biological processes, including as stress reactions, differentiation, apoptosis, and cell proliferation [12]. The stability of miRNAs in circulation is one of their exceptional qualities. Since miRNAs are contained in exosomes, micro vesicles, apoptotic bodies, or linked to proteins like Argonaute-2 (Ago2), they are immune to RNase degradation, in contrast to mRNAs, which are extremely labile [13]. They are appealing as non-invasive biomarkers for illness diagnosis because of their stability and detectability utilising sensitive methods such quantitative real-time polymerase chain reaction (qRT-PCR) [14]. Research has demonstrated that distinct miRNA signatures are changed in a number of clinical conditions, such as cardiovascular diseases, neurological conditions, and malignancies [15]. Several miRNAs, including miR-1, miR-133, miR-208, and miR-21, have been suggested as potential prognostic and diagnostic markers in AMI [16]. One of the most frequently reported microRNAs to be dysregulated during myocardial damage among the many microRNAs examined in cardiovascular disease is microRNA-21 (miR-21). It is abundantly expressed in endothelial cells, fibroblasts, and cardiomyocytes and is encoded on chromosome 17q23.2 [17]. In terms of function, miR-21 has been demonstrated to control several cellular pathways:

Apoptosis: miR-21 activates the PI3K/AKT pathway to prevent apoptosis by targeting phosphatase and tensin homolog (PTEN) and programmed cell death protein 4 (PDCD4) [18]. During ischaemic stress, this protective action might lessen the mortality of cardiomyocytes.

Fibrosis and remodelling: By activating MAPK signalling pathways, miR-21 stimulates extracellular matrix deposition and fibrosis in cardiac fibroblasts [19]. Excessive exercise leads to negative ventricular remodelling, even if it may initially help wound healing.

Inflammation: miR-21 alters the balance of pro- and anti-inflammatory cytokines via modulating inflammatory signalling, which may have an effect on infarct healing [20]. These diverse functions imply that increased levels of miR-21 in the bloodstream after AMI may represent important pathogenic mechanisms engaged in myocardial remodelling and

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healing in addition to being a result of cell damage.

According to these findings, circulating miR-21 is a promising non-invasive biomarker that might be used in conjunction with current diagnostic techniques, particularly in the early hours after the onset of symptoms when conventional indicators might not yet be high. By evaluating its sensitivity, specificity, and overall diagnostic performance in relation to traditional cardiac biomarkers, the current study aims to determine the diagnostic relevance of circulating miR-21 in patients who have experienced an acute myocardial infarction.

2. Materials and Methods:

2.1 Blood Samples:

An observational study was conducted in Mahatma Gandhi Medical College and Research Institute in Pondicherry, with a time period of twelve months. The research study, MGMCRI/RAC/2021/02/IHEC/27, has been approved by the Institutional Human Ethics Committee (IHEC) at MGMCRI, SBV. The study included subjects who were newly diagnosed with AMI within the age group of 35 to 65 years who were admitted to the emergency unit as cases. Healthy individuals from the master health check-up were included as a control group. Patients with lung and CKD, those who had undergone any surgery, and those with anaemia or cancer were excluded. The study includes 83 AMI study subjects with 30 controls groups, totally which had 113 participants. A consent form was got signed from all patient attendants. 5 ml of venous blood was collected in a red stopper tube. After collecting the blood, it was sent to the Central Clinical Laboratory, MGMCRI. Centrifugation process was used to separate the serum for 10 minutes at 3000 rpm.

2.2 Biochemical Parameters:

Routine biochemical parameters were analysed. Serum cardiac Troponin I (cTnI) was estimated using the miniVIDAS system (Biomerieux) and the enzyme-linked fluorescence assay (ELFA) method. A 1.5 ml Eppendorf tube containing the leftover serum sample was aliquoted and kept at 20 °C until the time of analysis of microRNA.

2.3 miRNA21 Quantification:

Isolation of RNA by Pure Link™ RNA Mini Kit (Invitrogen - Cat.No:12183018A), followed by TaqMan advanced miRNA cDNA synthesis kit (Cat. No: A28007) Subsequently, the miRNA qPCR Detection kit (SYBR Green) was used in real-time PCR for relative quantification of miRNAs with U6 as an internal control. The PCR primers were synthesized by Bio serve Biotechnology (Hyderabad, India). The amplification reactions were performed using the 7500 FAST Real-Time PCR System (Applied Biosystems). Relative miRNA expression level was calculated by 2-ΔΔCt method

Table 1:
Primer sequence

Primers	Sequence
miR-21 forward	5'-CGGGATCCTGGGGTTCGATCTTAACAGGC- 3'
miR-21 reverse	5'-CGGAATTCCCACAATGCAGCTTAGTTTTCC- 3'
U6 forward	CTCGCTTCGGCAGCACA
U6 reverse	AACGCTTCACGAATTTGCGT

2.4 Statistical Analysis:

The means were presented as means ± SD, and the Student's T-test was used to compare regularly distributed continuous data, whereas the Mann-Whitney test was used for continuous data that was not normally distributed. To compare the categorical variables, the $\chi 2$ test was used. In patients with AMI, the relationship between Troponin I and MiRNA 21 was determined using Spearman's correlation. An AMI patient's cut-off MiRNA 21 level was established using a receiver operating characteristic (ROC) curve. The p-value was regarded as highly significant if it was less than 0.001 and statistically significant if it was equal to or less than 0.05. SPSS software, version 23, was used to analyse the data.

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2. Results

A total of 83 patients with AMI and 30 controls were enrolled in this study. The baseline clinical and biochemical characteristics of the study groups are summarized in Table 2. Patients with AMI were older and had significantly higher systolic blood pressure compared to controls ($p < 0.001$), while diastolic blood pressure showed no difference. The prevalence of hypertension, diabetes mellitus, and dyslipidemia was markedly higher among cases than controls (all $p < 0.001$). Although smoking was more frequent in cases (44.6% vs. 16.7%), the difference was not statistically significant. Cardiac assessment revealed that two-thirds of patients had reduced LVEF (<40%), and 39.8% belonged to Killip's class II. Biochemical analysis showed significantly higher random blood glucose, triglycerides, VLDL, and troponin I, along with lower HDL cholesterol in cases compared to controls (all $p < 0.05$). No significant differences were observed in total cholesterol or LDL levels between the groups

Table: 2 Mean and SD of biochemical parameters in Control and Case

Parameter	Control (N =30)	Case (N=83)	'P' Value
Age	52.1 ±4.5	55 ±11.7	<0.001*
Gender(M/F)	10/20	46/37	-
SBP (mm/Hg)	120.9±1.9	144.2±2.6	< 0.001*
DBP (mm/Hg)	80.4 ± 1.3	82.3±11.3	0.955
Smoking (%)	5(16.7%)	37 (44.6%)	0.18
Hypertension (%)	2(5%)	56(67.5%)	< 0.001*
Diabetes Mellitus (%)	3(10%)	53(63.9%)	< 0.001*
Dyslipidimia (%)	4(13.3%)	47(56.6%)	< 0.001*
Echo LVEF < 40	-	42	-
LVEF > 40	-	21	
Killip's Score (I)	-	50	-
(II)		33	-
Random Blood Glucose (mg/ml)	101.9±29.7	196.5±80	<0.001*
T. Chol (mg/ml)	197.3±34.3	203±38.3	0.411
TAG (mg/ml)	127.4±53	190±81.3	<0.001*
HDL (mg/ml)	45.1±8.9	39.4±10.7	0.002*
LDL (mg/ml)	126.7±27.5	123.4±34.6	0.812
VLDL (mg/ml)	25.5±10.6	38±16.4	<0.001*
Cardiac Troponin I(ng/ml)	0.40±0.80	13.6±8.5	<0.001*

***P' Value < 0.001 is Highly significant. Mann–Whitney U for continuous variables, Chi-square test for categorical variables.**

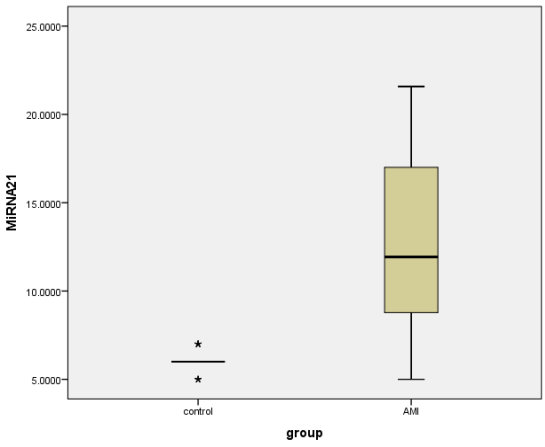

Fig: 1 Relative expression of MiRNA 21 in Control and AMI

In **Fig:1** The relative expression levels of circulating miRNA-21 were significantly elevated in AMI patients compared to controls (Figure X). In the control group, miRNA-21 expression values were tightly clustered around lower levels, with only

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minimal variability. In contrast, AMI patients demonstrated markedly higher expression with a wider distribution, as reflected by the higher median and interquartile range. The difference between groups was statistically significant ($p < 0.001$), indicating that circulating miRNA-21 is upregulated in AMI

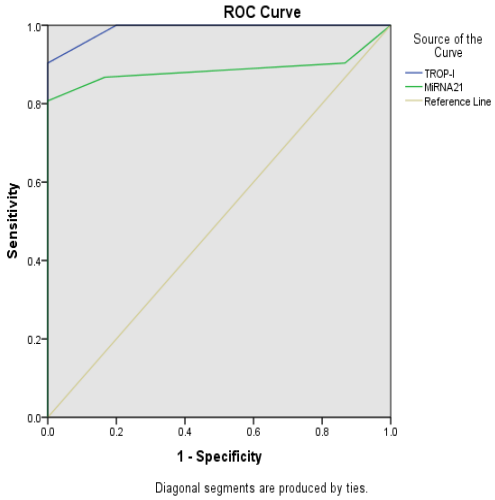

Fig: 2 ROC of serum MiRNA 21 and troponin I in diagnosis of AMI

In Fig: 2, The diagnostic performance of cardiac Troponin I and circulating miRNA-21 was assessed using ROC curve analysis. Troponin I demonstrated an excellent diagnostic accuracy with an AUC of 0.99 (95% CI: 0.979–1.000, $p < 0.001$). At an optimal cut-off between 4–7 ng/ml, Troponin I yielded a sensitivity of approximately 90% and a specificity of 100%. Circulating miRNA-21 also showed good discriminative ability with an AUC of 0.886 (95% CI: 0.823–0.950, $p < 0.001$). At a cut-off value of 6.5, miRNA-21 achieved 87% sensitivity and 83% specificity, while higher cut-offs (≥7.5) improved specificity to 100% but with a reduction in sensitivity. These findings indicate that although Troponin I remain the superior biomarker for AMI diagnosis, miRNA-21 also exhibits strong diagnostic potential and may serve as a complementary biomarker

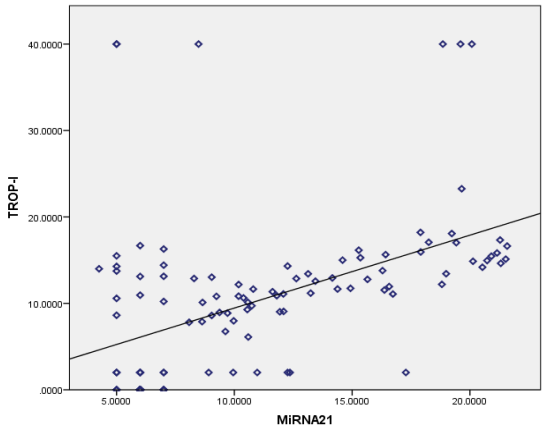

Fig: 3 Correlation of MiRNA 21 expression with Troponin I

In **Fig 3** Circulating miRNA-21 expression showed a significant positive correlation with cardiac Troponin I levels in AMI patients ($r = 0.576$, $p < 0.001$) (Figure 3). This indicates that higher miRNA-21 expression is associated with elevated Troponin I concentrations, reflecting greater myocardial injury. The moderate strength of correlation suggests that while Troponin I remain the gold-standard biomarker, miRNA-21 may serve as a useful complementary indicator of myocardial damage

Discussion:

In the present study, we evaluated the diagnostic and prognostic utility of circulating miRNA-21 in patients with acute myocardial infarction (AMI) and compared its performance with the conventional cardiac biomarker Troponin I. Our findings demonstrate that miRNA-21 expression was significantly upregulated in AMI patients compared to controls, with good diagnostic accuracy as indicated by ROC curve analysis. Furthermore, miRNA-21 levels showed a moderate but significant positive correlation with Troponin I, suggesting that it may serve as a complementary biomarker reflecting myocardial injury. Consistent with previous studies in Thygesen et al., Troponin I emerged as the most sensitive and specific marker for AMI, with an AUC of 0.990 and nearly perfect diagnostic accuracy. These results reaffirm its established role as the gold standard biomarker for myocardial necrosis [(4).] However, Troponin

elevation typically occurs only after myocardial damage has begun, which limits its role in very early detection. Importantly, our study found that circulating miRNA-21 also exhibited strong diagnostic potential, with an AUC of 0.886, sensitivity of 87%, and specificity of 83% at an optimal cut-off. Similar findings were reported by Cheng et al. and Devaux et al., who demonstrated elevated miRNA-21 expression in AMI patients and its potential to discriminate them from non-AMI individuals [21,22]. Supporting evidence has accumulated from recent clinical and meta-analytic data. Zhang et al. (2016) observed that the diagnostic accuracy of plasma miRNA-21 was comparable to that of CK-MB and Troponin I, with significantly higher levels in AMI patients than in angina or healthy controls [25]. Furthermore, in Zhou et al., a pooled analysis of 14 clinical trials demonstrated that miRNA-21 had a sensitivity of 83% and specificity of 81% for AMI diagnosis [27]. Similarly, in Li et al., another systematic review and meta-analysis including 2,413 participants reported a pooled AUC of 0.77, indicating a robust discriminatory capacity of miRNA-21 in distinguishing AMI from non-AMI cases [28]. These findings align closely with the diagnostic accuracy observed in our study.

The biological plausibility of miRNA-21 as a biomarker is well supported. miRNA-21 is known to regulate multiple pathways involved in cardiomyocyte survival, apoptosis, and fibrosis. It exerts anti-apoptotic effects through the PTEN/Akt pathway and has been implicated in post-MI remodelling and adverse outcomes [23, 24]. In our study, the significant positive correlation between miRNA-21 and Troponin I ($r = 0.576$, $p < 0.001$) indicates that increased miRNA-21 expression parallels the degree of myocardial injury, further supporting its clinical relevance. Several studies have also linked higher baseline levels of circulating miRNA-21 with adverse cardiovascular events and mortality after AMI, highlighting its potential role beyond diagnosis, in risk stratification and prognosis [25, 26]. Although Troponin I remain the most reliable biomarker for AMI, our findings—together with emerging meta-analytic evidence suggest that circulating miRNA-21 may provide additional diagnostic and prognostic information, particularly in early or atypical presentations.

Limitations

The number of controls in our study was smaller than the number of AMI cases, which may have introduced selection bias. Although miRNA-21 shows promise, it is not yet widely established as a routine biomarker in clinical examination, and further large-scale validation across diverse patient populations is required. In addition, subgroup analysis dividing patients into STEMI and NSTEMI was not performed, which could have provided additional diagnostic insights.

Conclusion:

In conclusion, circulating miRNA-21 is significantly elevated in AMI patients and demonstrates good diagnostic performance, with good correlation to Troponin I. MiRNA-21 may serve as a promising complementary biomarker for diagnosis and risk assessment in acute myocardial infarction.

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Informed Consent Statement: The Consent was obtained from all patient's attenders involved in the research.

Conflicts of Interest: The authors have declared that there are no conflicts of interest related to this research.

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