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Non-coding RNA in the Diagnosis and Prognosis of Myocardial Infarction

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Abstract: This review primarily investigates the role of non-coding RNAs (ncRNAs) in the diagnosis and prognosis of myocardial infarction (MI). MI is a severe cardiovascular disease, largely dependent on traditional biomarkers and electrocardiograms. However, traditional biomarkers such as cardiac troponin (cTn) have limitations, including high false-positive rates, diagnostic complexity, and abnormal expression in multiple diseases. Thus, there is an urgent need for more sensitive and specific novel biomarkers. ncRNAs have been proven to play a crucial role in the pathogenesis of MI affecting the survival, apoptosis, proliferation, and fibrosis of cardiomyocytes. Compared to traditional MI biomarkers, ncRNAs exhibit better sensitivity and specificity, aiding in the rapid, accurate diagnosis and early treatment, thereby providing a better prognosis for patients. This review aims to summarize current research reports on ncRNAs in the diagnosis and prognosis of MI and discuss their limitations, with the hope of deepening the understanding of non-coding genes in MI.

Keywords: Myocardial Infarction (MI); Non-coding RNA (ncRNA); Diagnosis; Prognosis.

1. Introduction

Cardiovascular diseases (CVD) are the primary culprits behind the escalating global morbidity and mortality rates, posing a significant threat to human health and life. Myocardial infarction (MI), with its high mortality and disability rates, represents one of the most severe acute cardiovascular diseases (ACVD). MI, an acute myocardial necrosis, usually occurs on the backdrop of coronary atherosclerotic stenosis, induced by stimuli that cause plaque rupture, sudden coronary artery occlusion, leading to persistent severe hypoxia and ischemia in the myocardial tissue (neural innervation). According to data from the World Health Organization and the Global Burden of Disease study, cardiovascular diseases account for approximately 32% of all deaths globally, with predictions estimating that the number of deaths due to cardiovascular diseases will reach 23 million by 2030[1, 2]. The rapid onset and progression of MI can lead to serious complications such as acute and chronic heart failure, ventricular aneurysm, cardiac rupture, malignant arrhythmias, and even sudden death, resulting in high mortality and disability rates. Therefore, rapid and accurate diagnosis is key to successful treatment, protecting myocardial cells, improving heart function, and prognosis. At present, the diagnosis of MI in clinical practice relies not only on electrocardiograms (EKG), ultrasound imaging, and other diagnostic evaluations but also on laboratory tests, one of the most important examinations in the diagnosis of myocardial ischemia, coupled with plasma biomarker detection. Plasma biomarkers originating from damaged myocardial tissue, such as subtypes of cardiac troponin (cTnT and cTnI), creatine kinase (CK), and brain natriuretic peptide (BNP), among which troponin testing is the most common[3]. Owing to its exceptional specificity, cardiac troponin (cTn) has evolved into one of the most commonly used biomarkers for the diagnosis of MI[4-6]. However, traditional biomarkers like cTn have their limitations. Circulating levels of troponin rise approximately 3 hours after the onset of chest pain [7]and come with high false-positive rates that complicate the diagnosis[8]. It still abnormally expresses in patients with chronic kidney disease[9], myocarditis[10], and septicemia [11]. Measurements of circulating cTnI levels lack sensitivity and specificity, rendering it insufficient as a biochemical marker to distinguish between MI and other diseases, potentially failing to bring about better clinical outcomes. Therefore, there is still a need for more sensitive and specific novel biomarkers to detect early AMI. The development of new biomarkers with high sensitivity and specificity is urgent to realize early diagnosis of AMI, thereby improving clinical outcomes.

Non-coding RNAs (ncRNAs) are RNAs that do not encode proteins but participate in gene regulation[12] and play various roles in numerous cellular processes, such as DNA replication, transcriptional activity, and protein translocation. ncRNAs are mainly involved in processes requiring highly specific nucleic acid recognition, revealing hitherto hidden layers of internal signals that control gene expression at various levels during development and (patho)physiological processes. Therefore, ncRNAs are essential for maintaining the normal physiological state of the human body. In fact, ncRNAs dysregulation has been proven to be closely related to many diseases, including cardiovascular diseases[13, 14], and they have profound effects on heart development, vascular formation, myocardial fibrosis, atherosclerosis, etc[5, 12].In recent years, ncRNAs have played an important role in the pathogenesis of MI, affecting the survival, apoptosis, proliferation, and fibrosis of cardiomyocytes. They have also played a crucial role in diagnosing MI. Compared with standard MI biomarkers, such as cTn and CK, ncRNAs seem to provide better sensitivity and specificity, ensuring rapid and accurate diagnosis, early treatment, and thus providing a good prognosis for patients[15, 16]. Despite the fact that

ncRNAs cannot produce proteins, they still carry information and serve important functions .They play a key role in many physiological and pathological processes in organisms, including gene expression regulation, protein function influence, and signal pathway targeting. Specifically, in the cardiovascular field, ncRNAs have shown important roles, especially in the diagnosis and prognosis of MI, and are considered potential biomarkers and therapeutic targets. Some specific ncRNAs, such as miR-1[5, 18, 19], miR-133a[5, 18, 19], MALAT1, etc., have been studied as possible biomarkers for MI. In summary, ncRNAs provide new perspectives and possibilities for the diagnosis and treatment of cardiovascular diseases, although more research is needed to validate their clinical utility and understand their role in pathophysiological processes.

In this context, this field of study still poses challenges to the international scientific community. This review aims to summarize current research reports on the diagnosis and prognosis of MI by ncRNAs. With the most promising and latest data accumulation, we focus on microRNA(miRNA), long non-coding RNA (lncRNA), and circular RNA (cirRNA), emphasizing their important specificity and sensitivity, discussing their limitations, in the hope of achieving a deeper understanding of potential non-coding genes in MI.

2. miRNAs Associated with MI

With the rapid development of next-generation sequencing technology, miRNAs are considered potential diagnostic, prognostic, and therapeutic targets for various cardiovascular diseases. MiRNA is abundantly present in nearly all cells and exhibits remarkable conservation across different species. Many studies have shown that miRNAs can be a useful and reliable tool for diagnosing and predicting the prognosis of MI patients.

Early research found that the level of cTnI in the blood began to rise 4-8 hours after myocardial injury[20], while another study showed that a significant increase in miRNA could be observed within 1 hour after coronary artery ligation[21], providing the first clinical evidence of circulating miR-208a as a marker of cardiac injury. By detecting specifically expressed microRNA in human hearts, it was found that miR-208a was expressed in the heart[21]. As reported, miR-208a exhibits a sensitivity of 90.9% in the diagnosis of AMI, coupled with an exclusive cardiac specificity[18, 22]. This suggests that it might serve as a biomarker with greater potency than cTnI. The potential mechanism of miR-208's action is as follows: Following a myocardial infarction (MI), miR-208 is released from damaged myocardial cells into the peripheral circulating blood in the form of microvesicles. This released miR-208 then acts to suppress the expression of NLK, which serves as an effective target molecule associated with myocardial cell apoptosis, exhibiting conserved ERK-2/MAPK-like kinase activity. NLK not only promotes AngII-induced myocardial cell apoptosis but also enhances myocardial fibroblast proliferation and differentiation. Moreover, research indicates that reducing miR-208 levels may lead to an increase in myocardial cell apoptosis, primarily influencing the levels of reactive oxygen species (ROS) within myocardial cells. This effect is achieved primarily by inhibiting the protein expression of the p21 gene.[23] . In terms of prognosis, scholars like LIU[29] compared miR-208a in the blood of AMI patients with non-AMI patients and found that the former was significantly higher than the latter (AUC>0.7). This means that miR-208a functions as a predictor of adverse events in AMI patients.

miR-208b, a subtype of miR-208, has been shown in research to have a pooled sensitivity of 85% and a specificity of 95% [24] in the detection of MI. In their investigation, Lv and colleagues[25] have noted a significant correlation between the levels of miR-208b and the left ventricular end-diastolic volume (an indicator of cardiac function) in patients with AMI. Specifically, higher levels of miR-208b in the early stages of infarction correspond with a more pronounced increase in left ventricular end-diastolic volume. This suggests an increased risk of left ventricular remodeling (morphological and functional changes that may occur in the heart following MI as the concentration of miR-208b in patients with AMI rises. Furthermore, a study tracking patients six months post-Percutaneous Coronary Intervention (PCI) found that those who experienced Major Adverse Cardiac Events (MACE) had significantly higher expression levels of miR-208b compared to patients who did not experience MACE. This indicates that high levels of miR-208b could potentially increase the risk of MACE in patients with AMI.Therefore, miR-208b holds promise as a potential prognostic indicator for predicting the clinical outcomes of patients with AMI.

Another study has validated that miR-499 can also be detected within 1 hour after the onset of chest pain[18]. It is specifically expressed in the myocardium and skeletal muscle of mammals[26]. The estimated overall sensitivity and specificity of circulating miR-499 in distinguishing between AMI and non-AMI are 84% and 97% respectively[27]. Studies show that miRNA-499 negatively regulates the expression of b-catenin in the Wnt/b-catenin pathway, which plays a crucial role in cardiac development, tissue repair, and inflammation. Prognostic factors of left ventricular function and infarction area after MI are powerful predictors of prognosis after AMI. Devaux and associates [11] have identified that miR-499 only provides a moderate prognosis for left ventricular dysfunction (AUC <0.70), so more research is needed to support whether miR-499 can become a prognostic marker for MI.

miR-1 is a heart-rich miRNA, accounting for about 40% of heart miRNA [28]. It is expressed in both the heart and skeletal muscle. Some researchers have found that miR-1 is released from the heart into the bloodstream after ischemia or MI, indicating that an increase in circulating miR-1 can exacerbate ischemia-reperfusion injury in mouse models[29]. This is one of the heart's adaptive mechanisms to ischemia. The level of miR-1 in cardiac tissue decreases during ischemia-reperfusion (IR) injury, but the level of circulating miR-1 in patients with AMI who undergo PCI intervention significantly increases[22]. In summary, research indicates that miR-1 is a pathogenic miRNA in cardiac injury.

Research suggests that miR-133a has a pooled sensitivity of 81.1% and a specificity of 91.2%[30]. Additionally, it has been discovered that the expression of miR-133a significantly decreases after surgery. The reduction of this microRNA could possibly indicate signs of ischemic myocardial repair. The dynamic expression of these molecular biomarkers can serve as prognostic markers[30].

miR-21 is abundant in all major cardiovascular cell types, including vascular smooth muscle cells, endothelial cells (ECs), cardiomyocytes (CMs), and cardiac fibroblasts (CFs) [31]. It is a robust biomolecule for the discovery of selective cardioprotective agents and biomarkers[32]. Studies indicate

that miR-21 reduces infarct size through cardioprotective mechanisms such as improving angiogenesis, anti-apoptosis, and anti-inflammatory pathways. Consequently, it has been discovered that the cardioprotective effects of miR-21 may act synergistically to prevent the deterioration of cardiac function following ischemia[31]. Furthermore, treatment with miR-21 after MI can improve left ventricular ejection fraction (LVEF) scores, which is beneficial for cardiac protection. Moreover, as infarct size decreases with miR-21 treatment, an increasingly positive trend is seen in the protective effects on the myocardium[31] .

3. lncRNAs Associated with MI

With the global proliferation of miRNA research, the study of lncRNAs within ncRNA has also become a focal point for scholars. Compared to traditional protein biomarkers, lncRNA biomarkers are more stable at the circulating level.

The lncRNA Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1) shows a sensitivity of 55.5% and a specificity of 75% in AMI [33]. MALAT1, initially associated with tumor metastasis as reported in 2003[34], was discovered by Vausort et al. in 2014[35]to have elevated expression in the peripheral blood of MI patients. Research conducted by LI and their team[36] not only observed elevated levels of lnc-MALAT1 in AMI patients, but also found this elevation to be associated with an increased risk of AMI. The plausible rationale behind this could be that increased lnc-MALAT1 levels might accelerate the development of AMI through various mechanisms, such as enhancing atherosclerosis progression, exacerbating myocardial ischemia-reperfusion injury, and contributing to systemic inflammation[36]. Research has shown that among all the studied genes (MALAT1, miR-30e, miR-126, miR-155, CRP, HPSE, and EDN1), MALAT1 exhibited the highest AUC value, Hence, it serves as a biomarker, indicating the occurrence of the no-reflow phenomenon in patients with ST-segment elevation myocardial infarction (STEMI) undergoing PCI [37].

The expression of lncRNA H19 is significantly downregulated after AMI. Research indicates that H19 has a sensitivity of 60.9% and a specificity of 81.7% in AMI[33]. Studies suggest that H19 can inhibit the expression of CYP1B3 in a PBX1-dependent manner, thereby alleviating cardiomyocyte necrosis[38]. Another recent study found that H19 can reduce cardiomyocyte apoptosis, diminish inflammation, Consequently, this diminishes the dimensions of the infarction, augments the functional capacity of the heart, and hinders maladaptive alterations in myocardial structure. [39]. It was also demonstrated that H19 can regulate the expression of KDM3A by competitively binding to miR-22-3p, thereby improving AMI-induced myocardial injury and cardiac remodeling[39].

The lncRNA MI Associated Transcript (MIAT) is located on human chromosome 22, which is a sensitive region for AMI. The levels of MIAT show a positive correlation with AMI. In AMI, its sensitivity is 75.5% and specificity is 45.2%[33]. Initially identified as a susceptibility locus associated with MI in 2006[40], it has been shown to be the first pro-fibrotic lncRNA in the heart[41]. Research reveals the upregulation of MIAT in MI, and silencing it alleviates subsequent myocardial injury post-MI by miR-10a-5p-dependent repression of EGR2 [42]. Thus, inhibiting MIAT to alleviate MI resulting from myocardial injury represents a promising therapeutic strategy. In an animal study of MI, scholars found that MIAT levels significantly increased in the cardiac region, with further research indicating that high levels of MIAT were associated with poor prognosis[41]. This suggests that this lncRNA could serve as a potential diagnostic biomarker and therapeutic target.

lncRNA TUG1 is a prominent lncRNA in cancer biology. Recent studies have shown that lncRNA TUG1 mediates hypoxia-induced apoptosis of cardiomyocytes, suggesting its involvement in MI[43]. Research by Zhang et al. [44] indicates an influential role of TUG1 in cardiac fibrosis progression. Augmented TUG1 expression facilitates an increase in CTGF levels by acting as a molecular sponge for miR-133b, thereby promoting cardiac fibroblast activation and the resurgence of collagen synthesis. Another study's data suggests that high expression levels of lncRNA TUG1 have an AUC of 0.9038 in MI diagnosis, and are significantly associated with a lower survival period in MI patients. Therefore, this lncRNA may provide a new marker for the prognosis of MI[45].

4. circRNAs Associated with MI

circRNAs have a covalently closed-loop structure, making them resistant to ribonuclease[46]. They exhibit greater stability and longer duration of action. Thus, circRNAs have become a focus of research in recent years. Increasing evidence suggests that circRNAs play significant roles in cardiovascular diseases, especially in MI.

CircNfix is a cardiomyocyte-specific circRNA. Research shows that the super-enhancer-regulated heart-specific circRNA Nfix inhibits cardiomyocyte proliferation by promoting ubiquitin-dependent degradation of Ybx1 and suppressing the activity of miR-214[47]. It is suggested that the absence of circNfix may prevent the regeneration of heart and blood vessels after a MI and may promote cardiomyocyte apoptosis, thereby impacting cardiac function and prognosis[47]. Therefore, circNfix is considered a potential therapeutic target that could aid in restoring cardiac function after a MI and prevent heart failure.

CircRNA_104761 is a relatively new potential marker in MI. The work of Yang and colleagues [48] elucidates that circRNA_104761 can not only serve as an effective biomarker for the diagnosis of AMI but also differentiate between normal coronary arteries, mild coronary artery stenosis, and AMI. The same study found that knocking down circRNA_104761 with siRNA exacerbates hypoxia-induced AC16 cardiomyocyte damage, while overexpressing circRNA_104761 mitigates hypoxia-induced injury. Therefore, circRNA_104761 can be considered a potential therapeutic target.

CircRNA MICRA can enhance cell apoptosis and induce myocardial injury after MI[49]. Research shows that circRNA MICRA is associated with the degree of left ventricular dysfunction following a MI and suggests that this circRNA, aside from being able to predict whether a patient will develop left ventricular dysfunction, could also assist in fine-tuning risk stratification following a MI[49].

CircRNA CDYL is a novel regulator of cardiogenesis during myocardial regeneration and can improve cardiac function[50]. Prior research indicates that circCDYL operates via sponging associated miRNAs, suggesting this circRNA may be a valuable therapeutic target for inducing cardiac regeneration and improving prognosis after a MI.

5. piRNAs Associated with MI

Piwi-interacting RNAs (piRNAs) represent a novel and potent class of small ncRNAs in mammalian species. They exhibit an immense diversity and are arguably the least studied type of RNA. PiRNAs function in coordination with Piwi proteins to silence transposons through DNA methylation. Emerging research suggests that piRNAs also perform functional roles beyond the germline, including in somatic cells and various disease states, encompassing MI. Although the research on piRNAs in cardiac-related diseases is still in its infancy, it has already received substantial attention from researchers. Most of the current research on piRNAs is concentrated in the field of oncology, yet the potential for piRNA research in cardiac-related diseases is immense in the long run.

Researchers have validated the expression of piRNAs in cardiomyocyte hypertrophy models induced under in vivo and in vitro conditions through small RNA sequencing analysis. Using qPCR and RNA immunoprecipitation[51], they validated significantly differentially expressed piRNAs and predicted the retrotransposons and mRNAs potentially targeted by these piRNAs in the rat genome. They discovered that the expression levels of certain specific piRNAs in serum indicate potential diagnostic value in patients with MI. This study, for the first time, carried out a whole-genome analysis of a large number of piRNAs in the cardiac system, laying a new foundation for a deeper understanding of the role of piRNAs in the molecular etiology of cardiac-related diseases.

6. Conclusion and Future Perspectives

The potential benefits of ncRNAs in MI diagnosis principally encompass enhancing diagnostic precision, providing early detection, monitoring disease progression, and conducting risk evaluation and prognosis forecasting. These benefits pave the way for the possibility of an early diagnosis and bespoke treatment for MI. However, despite the prospective benefits of ncRNAs, their application as diagnostic or prognostic biomarkers for MI is not without its challenges.

Significant progress has been made in the use of ncRNAs as diagnostic and prognostic biomarkers, thus demonstrating potential for diagnosing various pathological conditions. Despite the prospective advantages of ncRNAs, employing them as diagnostic or prognostic biomarkers for MI still presents several challenges.

Primarily, the extensive application of ncRNAs in clinical MI settings remains a distant goal due to the limitations in detection methodologies. Presently, ncRNAs are primarily detected via laboratory methods such as PCR, RNA sequencing, which necessitate specialized equipment and personnel, along with complex operational steps. Consequently, these methods may not be suitable for large-scale and rapid testing in a clinical environment. Secondly, while certain ncRNAs have been discovered to play a role in MI, our understanding of their precise function and mechanisms within MI pathogenesis is incomplete. This might limit our capability to use ncRNAs for MI diagnosis and prognosis. Moreover, the ex vivo stability of ncRNAs is influenced by multiple factors, including sample handling and preservation conditions, activity of RNA degrading enzymes, among others. These factors could affect the detection results of ncRNAs, thereby impacting their accuracy and reliability as biomarkers. Non-coding RNA expression is also influenced by a myriad of factors like age, sex, genotype, environmental factors, other diseases, which could cause variations in ncRNA expression, thus affecting their specificity as MI biomarkers. Furthermore, contemporary ncRNA studies are primarily targeted towards scientific exploration, and it necessitates an extended timeframe to assimilate intricate ncRNA data into efficient networks for monitoring disease-related progression. Lastly, most of the research on ncRNAs is still in the laboratory stage, and more clinical trials are needed to validate their efficacy and value in clinical applications.

In summary, these are some of the limitations of nc RNAs in the diagnosis and prognosis of MI. Nevertheless, with the advancement of science and technology, we believe these issues will be addressed, and ncRNAs will play a more significant role in MI diagnosis and prognosis. This also highlights the need for substantial research and technological innovation in this field.

Future research should delve deeper into the specific role and mechanisms of ncRNAs in MI, including how they regulate myocardial cell survival, apoptosis, proliferation, and myocardial fibrosis. Simultaneously, to enhance the application potential of ncRNAs as biomarkers, we need to develop more sensitive and specific detection methods. These technologies should accurately detect trace amounts of ncRNAs and differentiate between different types and origins of ncRNAs. This will improve our ability to diagnose and prognosticate disease states, thereby increasing the application value of ncRNAs as biomarkers. Moreover, we need to address some challenges in the clinical application of ncRNAs, such as improving their stability in blood samples, and differentiating between MI and expression changes in ncRNAs caused by other diseases. In summary, the field of ncRNA is one full of unknowns and challenges, but also opportunities and hope. We look forward to revealing more secrets of ncRNAs through our efforts, providing new ideas and tools for the diagnosis and treatment of diseases.

Table 1. Abbreviation

Non-coding RNAs	ncRNAs
Myocardial infarction	MI
Cardiac troponin	cTn
Cardiovascular diseases	CVD
Acute Cardiovascular Diseases	ACVD
Electrocardiograms	EKG
Creatine Kinase	CK
MicroRNA	miRNA
Long non-coding RNA	lncRNA
Circular RNA	cirRNA
Reactive Oxygen Species	ROS
Percutaneous Coronary Intervention	PCI
Major Adverse Cardiac Events	MACE
Ischemia-Reperfusion	IR
Endothelial Cells	ECs
Cardiomyocytes	CMs
Cardiac Fibroblasts	CFs
Left Ventricular Ejection Fraction	LVEF
Metastasis Associated Lung Adenocarcinoma Transcript 1	MALAT1
ST-segment Elevation Myocardial Infarction	STEMI
MI Associated Transcript	MIAT
Piwi-interacting RNAs	piRNAs

Conflict of Interest

No potential conflict of interest was reported by the

author(s).

Author Contributions

TW and FL conceived the manuscript. FL, LD, CN and NG performed the relevant literature search. FL and DL drafted the manuscript. YT, WX and TW contributed to a critical revision of the manuscript. All authors have both read and approved the final version of the manuscript.

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