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# Non-coding RNAs as biomarkers of myocardial infarction

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ABSTRACT

Non-coding RNAs (ncRNAs) encompass a family of ubiquitous RNA molecules that lack protein-coding potential and have tissue-specific expression. A significant body of evidence indicates that ncRNA's aberrant expression plays a critical role in disease onset and development. NcRNAs' biochemical characteristics such as disease-associated concentration changes, structural stability, and high abundance in body fluids make them promising prognostic and diagnostic biomarkers. Myocardial infarction (MI) is a leading cause of mortality worldwide. Acute myocardial infarction (AMI), the term in use to describe MI's early phase, is generally diagnosed by physical examination, electrocardiogram (ECG), and the presence of specific biomarkers. In this regard, compared to standard MI biomarkers, such as the cardiac troponin isoforms (cTnT & cTnI) and the Creatinine Kinase (CK), ncRNAs appears to provide better sensitivity and specificity, ensuring a rapid and correct diagnosis, an earlier treatment, and consequently a good prognosis for the patients. This review aims to summarize and discuss the most promising and recent data on the potential clinical use of circulating ncRNAs as MI biomarkers. Specifically, we focused primarily on miRNAs and lncRNAs, highlighting their significant specificity and sensitivity, discussing their limitations, and suggesting possible overcoming approaches.

## 1. Introduction

Myocardial infarction (MI) is a cardiovascular disease (CVD) that is expected to become the main leading cause of mortality worldwide [1]. MI is a result of a sudden and extended lack of oxygen and nutrient supply (ischemia) to the heart muscle (myocardium), which ultimately causes myocardial damage and cardiac tissue death induced by a series of abnormal metabolic and biochemical events [2]. MI, often triggered by spasms or coronary atherosclerosis [3], is associated with a sedentary lifestyle, smoking, high alcohol consumption, and high blood cholesterol [4]. Acute myocardial infarction (AMI) is the term used to describe MI's early phase, which includes many pathological alterations like ischemia, hypoxia, edema, and necrosis. AMI diagnosis is generally based on physical examination and electrocardiogram (ECG) [5], as well as the presence or absence of specific biomarkers [6,7].

By definition, biomarkers are biological molecules that mark a biological event or process [8]. They are mainly used to improve the diagnosis and monitor diseases as they can be quantified and are associated with normal and pathological processes or pharmacological therapy responses [9]. Several types of cardiac biomarkers have been developed for MI diagnosis. These include (i) biomarkers originating from damaged myocardial tissues, e.g., cardiac troponin isoforms (cTnT & cTnI), creatinine kinase (CK), brain natriuretic peptide (BNP), or (ii) biomarkers released from non-myocardial tissues as a result of MI-induced systems reactions, e.g., Vascular Endothelial Growth Factor (VEGF), Interleukins (ILs), Matrix Metalloproteinases (MMPs), or (iii) biomarkers present (or absent) in blood circulation before MI occurrence, e.,g. circulating non-coding RNAs (ncRNAs) such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) [6,7]. In the last decade, ncRNAs have emerged as promising prognostic and diagnostic biomarkers [4,10,11]. Indeed, they possess good biomarkers characteristics, including high abundance and stability in body fluids and the capability to change their concentration following physio-pathological conditions and pharmacological treatments [12]. In addition, compared to standard MI biomarkers, such as cTnT and CK, whose effectiveness decrease after 0–3 h of AMI diagnosis [13], ncRNAs

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appear to provide better sensitivity and specificity, ensuring a rapid and correct diagnosis, an earlier treatment, and consequently a good prognosis [12]. Although neglected for several years because of their lack of protein-coding potential, recent evidence demonstrated that ncRNAs are functionally active molecules that regulate gene expression at both epigenetic, transcriptional, and post-transcriptional levels [14–20].

Based on the nucleotides (nt) number, ncRNAs are classified into (i) small ncRNAs (less than 200 nt) such as microRNA (miRNA), small interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), and (ii) long ncRNAs (more than 200 nt) [21]. MiRNAs are the most abundant class of small ncRNAs and generally act at the RNA level by binding the 3′UTR of target mRNAs to destabilize and inhibit their translation [22,23]. In contrast, long non-coding RNAs (lncRNAs) are similar to messenger RNAs; indeed, they are transcripted by the RNA polymerase II, capped, spliced, and polyadenylated, but they are without apparent protein-coding potential. In recent years, lncRNAs have been recognized as critical players in a wide range of biological and physiological processes as they regulate gene expression (at both transcriptional and post-transcriptional levels), protein translation, and stability [24–26].

NcRNAs circulate in body fluids and extracellular space, where they work as messengers in a hormone-like manner regulating autocrine, paracrine, and endocrine communications. Circulating ncRNAs are easily detected in plasma, serum, urine, and seminal and cerebrospinal fluid, which makes them particularly suitable as pathophysiological markers [27,28]. They are stored and transported either encapsulated into membranous vesicles like apoptotic bodies, microvesicles, and exosomes or interconnected with RNA binding proteins such as lipoprotein complexes, nucleophosmin, and Argonaute protein 2 (Ago2) [28,29]. Eventully, when necessary, they are selectively released from these carriers at specific body sites to promote their functions. Typically, ncRNAs are stable and easily measured in various body fluids; however, their potential as biomarkers has been better characterized for miRNAs than other ncRNAs species, such as lncRNAs or circRNAs [29].

In the context of CVDs, ncRNAs have to overcome several challenges to be considered promising cardiac biomarkers. Firstly, they must be quantitatively altered in AMI and exhibit a myocardiocyte-specific expression pattern [30]. More importantly, they should be immediately released into circulation upon heart damage and show significantly different detectable levels than normal conditions [31]. In this regard, because of their peculiar characteristics, several ncRNAs have been reported as promising cardiac biomarkers, including (i) ncRNAs that are down- or up-regulated in AMI, (ii) ncRNAs showing a significant increase during the first 4 h of MI [32], (iii) miRNAs with a very high level of specificity for AMI [11], and (iv) some lncRNAs that are decreased in AMI patient's blood as a result of hypoxic conditions [32], or those that are up-regulated in AMI patients compared to healthy controls [2].

This review will gather and discuss some of the most promising and recent data on the potential clinical use of circulating ncRNAs as MI biomarkers focusing on miRNAs and lncRNAs and highlighting their significant specificity and sensitivity.

## 2. Circulating miRNAs as potential biomarkers of myocardial infarction

MiRNAs ability as AMI diagnostic biomarkers is generally assessed by experimental (e.g., quantitative PCR, microarray, high-throughput small RNA-sequencing) and computational methods (e.g., miRBase database, miR2Disease) [33,34] or a combination of both. MiRNAs sensitivity and specificity, namely the ability to accurately detect AMI patients and the capability to correctly reject healthy individuals, are also important parameters for evaluating biomarkers' reliability [35]. Therefore, a good sensitivity means that a specific miRNA is closely associated with the AMI diagnosis, whereas, a good specificity demonstrates the probability of having non-AMI patients when that miRNA is detected. Furthermore, statistical analyses like the receiver operating characteristic (ROC) curve and the area under the curve (AUC) are generally used to evaluate each miRNA's diagnostic capability. Precisely, sensitivity is plotted against specificity in a ROC curve, and each point on the curve represents a sensitivity/specificity pair. The area under the curve (AUC) measures how well a parameter can distinguish between two diagnostic groups, the diseased and the normal.

Circulating miRNAs as potential MI biomarkers are here described by distinguishing them in miRNAs upregulated and downregulated in AMI patients including also cardiac-specific miRNAs and non-cardiac-specific miRNAs, where the latter refers to miRNAs playing a crucial role in AMI-associated pathophysiological events (e.g. plaque rupture, endothelial dysfunction, platelet aggregation, myocardial ischemia, coronary thrombosis, inflammation, and reperfusion injury). Then up-/down-regulated miRNAs as biomarkers in STEMI, NSTEMI, and other cardiac-related pathological conditions are also described.

### 2.1. Promising upregulated miRNAs in AMI patients

MiR-1, miR-208a/b, and miR-499 are well-known cardiac-specific miRNAs highly expressed in the myocardium with a critical role in cardiogenesis and the heart's functionality [36]. MiR-1 for instance, regulates cardiac development and both differentiation and reprogramming of other cell types to cardiomyocytes [36,37]. According to several autors [38–40], circulating miR-1 levels are increased in AMI patients compared to healthy individuals. In this regard, Ai et al. [38] showed that this elevation was accompanied by a wider QRS complex (the combination of three of the graphical deflections seen on a typical ECG, indicating the abnormal ventricular depolarization that happens when electrical activity takes a long time to travel throughout the ventricular myocardium) implying a relationship between cardiac functional impairment and high circulating miR-1 in AMI patients. However, despite miR-1 showed (i) excellent time correlation with cTnT in patients with AMI, (ii) a high specificity value (0.82), and (iii) a relatively high predictive value (AUC, 0.84), in these particular works [40,41]. it also showed a relatively lower pooled sensitivity compared to cTnT suggesting that its diagnostic value was not superior to cTnT in these studies.

Furthermore, a *meta*-analysis by Liu et al. [40] analyzed the predictive biomarker potential for AMI of two other cardiac miRNAs, miR-208 and miR-499, which play a central role in cardiogenesis, cardiac physiopathology. MiR-208 affects cardiomyocyte proliferation and is associated with cardiac disease prognosis [13]. In comparison, miR-499 plays a role in cardiac cell recovery and stem cell functional and structural differentiation [42]. Moreover, miR-208 and miR-499 are released into the circulation during AMI early stages and are upregulated in AMI patients. [13,31,38]. Liu's *meta*-analysis included eight publications concerning miR-208, with a total number of 2941 participants (1362 AMI and 1379 controls), whereas, regarding miR-499, eight publications with a total number of 2741 participants (1362 AMI and 1379 controls) were analyzed. Although both miR-208 and miR499 displayed high predictive values, the ROC analysis results revealed that miR-499 had the most accurate predictive value (AUC of 0.91, sensitivity of 0.83, and specificity of 0.90) not only compared to miR-208 (AUC 0.89, sensitivity 0.80, and specificity 0.95) and miR-1 but also compared to the most reliable biomarkers cTnT and creatine kinase- muscle brain isoform (CK-MB) [40]. MiR-499 reliability as a diagnostic biomarker in AMI patients has been recently confirmed by a *meta*-analysis combining fourteen studies and a total of 3816 participants [43]. MiR-499 sensitivity and specificity were 84 % and 97 %, respectively and miR-499 diagnostic accuracy in distinguishing AMI from non-AMI individuals exceeded CK-MB and equaled cTnI [43]. More importantly, miR-499 is detectable in

the plasma as early as 1 h after chest pain onset and gradually increases (within 9 h) in AMI patients [44]. Moreover, miR-499 showed a high positive correlation with CK-MB and cTnI, confirming its great potential as a marker for early AMI diagnosis [44]. Going back to miR-208, a recent *meta*-analysis analyzing 13 publications, 1703 AMI patients, and 1589 controls reassessed its AMI diagnostic capabilities, showing that miR-208 is able to distinguish AMI patients with chest pain from healthy controls with a sensitivity, specificity, and AUC of 83 %, 97 %, and 93 % respectively [45].

According to Xue et al. [46], expression levels of circulating miR-17-5p, miR-126-5p, and miR-145-5p are increased in AMI early phase (4 h of symptoms onset). MiR-17 and miR-126 are enriched in endothelial cells [47], where the former is beneficial for ischemic tissue recovery and the latter for stabilizing the atherosclerotic lesion's size [48,49]. MiR-145 is instead enriched in smooth muscle cells and has a role in reducing plaque size in aortic sinuses, decreasing the necrotic area, and increasing the plaque collagen content [50]. Statistical analysis done by Xue et al. [46] before and after percutaneous coronary intervention (PCI) declared their validity as single markers and emphasized the improved diagnostic accuracy of the three if used in combination. MiR-17-5p exhibited the best diagnostic accuracy showing the highest AUC and a positive correlation with the highly sensitive troponin T (hsTnT) [46].

The other miRNAs up-regulated in AMI patients are miR-21 and miR-19a [51,52]. Zhang et al. [51] studied miR-21 plasma levels in a cohort of patients with AMI and angina pectoris (AP), reporting a significant elevation of circulating miR-21 in AP and AMI patients compared to the control group. However,the observed increase was more significant in AMI than in AP patients. The conventional biomarkers CK, CKMB, and cTnI were also correlated with miR-21 plasma levels, and they were all significantly higher in the AMI group compared with the AP or control group, as well as their AUC values which were similar to miR-21 (0.892). These results suggest that miR-21 might be a AMI complementary biomarker rather than an independent one. Indeed, miR-21 is not a cardiac-specific marker but it as also a good diagnostic marker even for cancer and other diseases [53,54]. The inflammation-related miR-19a, known for having a prominent role in vascular homeostasis and inflammatory responses [55,56], exhibited a 122-fold increase in AMI patients and a significant diagnostic accuracy with an AUC value of 0.997 [52]. Moreover, biochemical assays revealed the absence of a positive correlation between miR-19a and classic biochemical markers such as CK, CK-MB, hs-TnI, and BNP, except for ApoA1, a component of high-density lipoprotein (HDL) which transports good cholesterol to arteries [52]. Such findings prove that miR-19a is closely related to AMI occurrence and diagnosis and highlight its great accuracy as an independent AMI biomarker [52].

Because AMI is a complex pathophysiological process involving several cell types, Wang et al. [57] investigated the expression of the non-cardiac-enriched miRNAs, miR-19b-5p, miR-134-5p, and miR-186–5, which, as per a previous microarray analysis were found upregulated in AMI patients [58]. MiR-19b is involved in aging-associated heart failure and positively regulates cardiomyocyte hypertrophy by targeting atrogin-1 and MuRF-1 [59]. MiR-134-5p is a brain-specific miRNA regulating the neuronal cell death caused by ischemia [58]; miR-186-5p is involved in smooth muscle cells' contractility and differentiation and is considered an atherosclerosis biomarker [60]. In their paper, Wang et al. [57] showed that the expression levels of all three selected miRNAs were significantly up-regulated in AMI early phase [57]. In particular, miR-19b-3p and miR-134-5p reached their peak expression at T0 (collection time within the first 4 h after the onset of chest pain symptoms), while miR-186-5p achieved its peak expression 4 h after T0 [57]. All three miRNAs were detected earlier than the standard AMI biomarker cTnI, which reached its peak expression 8 h after T0. Although each miRNA displayed a moderate ability to discriminate between AMI and non-AMI groups, their discriminatory power and diagnostic accuracy resulted significantly improved when the three miRNAs were combined [57]. However, these results were not confirmed in the recent study by Wang et al, which showed unsatisfactory results concerning miR-19b, miR-134, and miR-186 reliability as AMI biomarkers [61]. In this study, the plasma levels of miR-22-5p and miR-122-5p resulted significantly decreased and increased, respectively [61]. miR-122-5p upregulation confirmed previous findings by Cortez-Dias et, which reported miR-122-5p increased in patients who died of AMI [62]. Moreover, no significant difference in miR-122-5p expression after PCI was observed compared to the control group. This finding indicates that the expression level of miR-122-5p returned to normal levels after PCI and suggests the high sensitivity of the studied miRNA as AMI diagnostic biomarkers. [61].

According to Zhu et al. [63], circulating miR-181 is a valuable biomarker for the diagnosis of AMI [63]. This miRNA is involved in the cardiovascular system inflammatory response and is activated via stress, ischemia, and hypoxia, reflecting the severity of vessel lesions in CVDs [63]. The authors of this paper reported that miR-181a plasma levels were highest in the AMI patients' group in comparison with healthy and unstable angina (UA) groups [63]. MiR-181 levels increased promptly at 6 h, 12, and 24 h, then decreased between 3 and 7 days after symptoms' onset. Moreover, miR-181 showed an AUC of 0.834 as well as a positive correlation with CK-MB and cTnI, although the AUC value of cTnI (0.873) was higher. Therefore, the authors recommended the combination of both miR-181 and cTnI to enhance the sensitivity and discrimination ability of the proposed method [63]. Interestingly, miR-181a plasma levels were also analyzed before and after PCI, resulting significantly lower after PCI than before it. Therefore, miR-181a appears to be a valuable biomarker for predicting myocardial ischemia\reperfusion injury in AMI patients [63]. Indeed, AMI is closely associated with endothelial dysfunction and damage as well as with the parallel releasing of endothelial injury-related biomarkers such as heart-type fatty acid-binding protein (H-FABP), von Willebrand factor (vWF), and cTnI [64–67].

Two recent studies [66,67] highlighted the correlation between, Kruppel-like factor 2 (KLF2), a regulator of AMI-associated endothelial proliferation, and miR-32-5p [66] and miR-363-3p respectively [67], suggesting a relationship between the two miRNAs and AMI-related endothelial injury. By combining the target prediction tool, miRanda, with a luciferase activity assay, Dai et al [66] showed that miR-32-5p modulates KLF2 activity by binding its 3′UTR. Authors also suggested a negative correlation between miR-32-5p and KLF2; indeed, the increased expression of miR-32-5p corresponded with the KLF2 expression decreasing. In addition, miR-32-5p overexpression suppressed endothelial cell proliferation, which was instead enhanced by miR-32-5p knockdown. Furthermore, elevated serum levels of miR-32-5p, besides having a relatively high diagnostic accuracy in distinguishing AMI patients from healthy controls (ROC value of 0.949), were also positively correlated with the release of endothelial injury and myocardial damage markers, such as cTnI, H-FABP and vWF [66]. Similar results were reported in the study by Gao et al [67]. In this work theauthors showed that miR-363-3p is a promising diagnostic biomarker (ROC value of 0.896) since its expression level in AMI patients serum was higher than healthy control. Serum levels of miR-363-3p were also positively correlated with those of endothelial injury biomarkers. Interestingly, miR-363-3p knockdown improved the AMI-associated endothelial damage by targeting KLF2 (Table 1) [67].

**Table 1**
Summary of promising upregulated miRNAs in AMI patients.

| | miRNA | Main Function | AUC | Sensitivity | Specificity | Relationship to traditional biomarkers | Detection time after symptom onset |
|---|---|---|---|---|---|---|---|
| Cardiac- specific | miR-1 | Regulates cardiac development and differentiation and reprogramming of other cell types to cardiomyocytes | 0.84 | 73 % | 82 % | Not superior to cTnT | |
| Cardiac- specific | miR-208a \b | Affects myocardiocyte proliferation and is associated with cardiac disease prognosis | 0.89 | 80 % | 95 % | | |
| Cardiac- specific | miR-499 | Plays a role in cardiac cell recovery as well as stem cell functional and structural differentiation | 0.91 | 83 % | 90 % | Superior to CK-MB and equal to cTnT. positively correlated with both CK-MB and cTnT | 1 h |
| Non-cardiac specific (endothelial cells enriched) | miR-17-5p | Beneficial for ischemic tissue recovery | Pre PCI-0.857 - post PCI 0.913 | Pre PCI-85.2 % - post PCI 87.0 % | Pre PCI-85.7 % - post PCI 85.7 % | Positively correlated with hsTnT | 4 h |
| Non-cardiac specific (endothelial cells enriched) | miR-126-5p | Beneficial for stabilizing the atherosclerotic lesion's size | Pre PCI-0.802 - after PCI 0.847 | Pre PCI-100 % - post PCI 95.8 % | Pre PCI-61.9 % - post PCI 66.7 % | | 4 h |
| Non-cardiac specific (smooth muscle cells enriched) | miR-145-5p | Has a role in reducing plaque size in aortic sinuses, decreasing the necrotic area, and increasing the plaque collagen content | Pre PCI-0.720 - after PCI 0.727 | Pre PCI-81.8 % - post PCI 82.6 % | Pre PCI-61.9 % - post PCI 61.9 % | | 4 h |
| | miR-17-5p, miR-126-5p, miR-145-5p panel | | Pre PCI-0.857 - after PCI 0.921 | Pre PCI-84.0 % - post PCI 95.7 % | Pre PCI-85.7 % - post PCI 81.0 % | | |
| Non-cardiac specific | miR-21 | | 0.892 | | | Positively correlated with CK, CK-MB, and cTnT | |
| Non-cardiac specific (inflammation related) | miR-19a | Main role in vascular homeostasis and inflammatory responses | 0.997 | | | No positive correlation with CK, CK-MB, hs-TnI, and BNP, except for ApoA1 | |
| Non-cardiac specific | miR-19b-5p | Involved in aging-associated heart failure and it is a positive regulator of cardiomyocyte hypertrophy by targeting atrogin-1 and MuRF-1 | Higher AUC when combined with miR-134-5p and miR-186–5 | | | Earlier than cTnT in terms of detection time | 4 h |
| Non-cardiac specific (brain specific) | miR-134-5p | Regulating the neuronal cell death caused by ischemia | Higher AUC when combined with miR-19b-5p and miR-186–5 | | | Earlier than cTnT in terms of detection time | 4 h |
| Non-cardiac specific | miR-186–5 | Involved in smooth muscle cells' contractility and differentiation and is considered an atherosclerosis biomarker | Higher AUC when combined with miR-134-5p and miR-19b-5p | | | Earlier than cTnT in terms of detection time | 8 h |
| | miR-181 | Involved in the inflammatory response in the cardiovascular system and is activated via stress, ischemia, and hypoxia, reflecting the severity of vessel lesions in CVDs. Valuable biomarker to predict myocardial ischemia\reperfusion in AMI patients | 0.834 | | | For better sensitivity and diagnostic power, combination between miR-181 and cTnT is recommended | 6 h |
| | miR-32-5p | Modulates KLF2 activity by binding its 3′UTR | 0.949 | | | | |
| | miR-363-3p | miR-363-3p knockdown improved the AMI-associated endothelial damage by targeting KLF2 | 0.896 | | | | |

### 2.2. Promising downregulated miRNA as AMI biomarkers

Along with the up-regulated miRNAs mentioned so far, some other miRNAs have been reported down-regulated during AMI. Chen et al. [68] studied four dysregulated miRNA panels for early AMI diagnosis in 80 AMI patients and 80 controls (patients with coronary angiographic stenosis less than 50 %). MiR-1291, miR-217, miR-455-3p, and miR-566 were found significantly decreased in AMI patients compared to controls with AUC values of 0.84, 0.825, 0.86, and 0.84, respectively. Interestingly, the combination of the four miRNAs showed more significant diagnostic biomarker potential, giving an AUC value of 0.90, with 85 % sensitivity and 82.86 % specificity [68]. The association between the four miRNAs and AMI was also confirmed by the KEGG pathway bioinformatic analysis, which showed that all four miRNAs were significantly enriched in AMI progression-associated signaling pathways (e.g., NF-kappa B, PI3K-Akt, AMPK, et.c) [68]. Furthermore, measurements of miR-1291, miR-217, miR-455-3p, miR-566, CK-MB, and cTnI peripheral blood concentrations at different time points following the chest pain onset revealed that all miRNAs reached their highest peak at 6 h while CK-MB and cTnI at 12 h, suggesting a greater ability of the miRNA panel

as early diagnostic indicator/discriminator of AMI from other chest pain-associated diseases. Finally, considering the results, the authors suggest all four miRNAs might be associated with plaque rupture and platelet activation and thus be abundant in plaques and platelets [68].

MiRNAs can be carried within exosomes, vesicles responsible for cell-to-cell communication, which, in addition to miRNAs, also contain proteins, lipids, and other bioactive substances [69]. Exosomes have been reported to play a crucial role in repairing myocardial injury by transferring myocardial protective miRNAs into damaged cardiomyocytes [70,71]. Chen et al. [72] combined next-generation sequencing technology with bioinformatics analysis to compare the differential miRNA expression profile of serum exosomes from AMI and healthy patients [72]. Among 544 upregulated and 518 downregulated miRNAs found in AMI patients, miR-6718 and miR-4329 stood out for a significantly lower expression in patients with AMI compared to normal controls [72]. However, as the authors highlighted, further studies are required to better understand whether miR-6718 and miR-4329 are superior to cTnT and CK-MB in AMI diagnosis. Moreover, identifying the source of exosomal miR-6718 and miR-4329 in plasma need furtert investigation [72].

miR-379 also displayed good AMI biomarker potential; indeed, plasma miR-379 levels were found significantly decreased in AMI patients compared with controls. ROC analysis revealed an AUC value of 0.751, and miR-379 negatively correlated with CK-MB and cTns [73]. In addition, since miR-379 upregulation affects smooth muscle cells (VSMCs) functions, which play a crucial role in CVDs pathogenesis [74], it might have a critical role in AMI progression (Table 2) [73].

### 2.3. Upregulated and downregulated miRNAs as biomarkers of STEMI and NSTEMI

MI is classified into ST elevation MI (STEMI) and ST non-elevation MI (NSTEMI), where the pattern of the ECG's ST segment is increased in the former but normal in the latter [75]. STEMI is a condition of complete occlusion of one or more infarcted coronary arteries, while NSTEMI is referred to as partial occlusion. Both conditions need rapid diagnosis and treatment in order to decrease the incidence of MI mortality [76]. For instance, STEMI is a serious condition that, in most cases, leads to sudden heart failure and cardiac death due to irreversible ventricle remodeling [77]. Thus, a great effort to discover novel biomarkers for STEMI has been made, including the discovery of either STEMI- or NSTEMI-related miRNAs.

In this regard, miR-203 is emerging as a promising biomarker. Primarily known as a cancer biomarker since it plays a crucial role in different cancers (e.g., esophageal, liver, colon cancer), including being an early-phase cervical cancer biomarker [78–81], miR-203 also has a protective effect on heart function, and its overexpression inhibits myocardial apoptosis and fibrosis [13,82]. According to a study by Li et al. [83], miR-203 expression is higher in the STEMI patients than in healthy individuals. Interestingly, miR-203 ROC analysis revealed a significant diagnostic accuracy with an AUC area of 0.912 that exceeded conventional biomarkers such as CK-MB (AUC = 0.818), cTnI (AUC = 0.645), and myoglobin [83].

Interestingly, a study by Maciejak et al. [84] revealed for the first time a crucial association between STEMI and miR-22-5p. Indeed, although mainly known as a tumor suppressor [85], miR-22-5p also plays a critical role in oxidative stress, cardiac autophagy, and fibrosis [86,87]. Employing a miRNA expression profile analysis, the authors compared plasma samples of AMI patients at admission with samples from the same patients in the stable stage (collected six months following AMI). Selected miRNAs were validated by RT-qPCR analysis, confirming that, among 32 dysregulated miRNAs, miR-22-5p was the most significantly upregulated in AMI patients' serum. Besides, ROC curve analysis revealed an AUC of 0.847, indicating a great discrimination ability for miR-22-5p [84]. On the contrary, Wang et al. [61] reported plasma levels of miR-22-5pa significantly decreased in AMI patients compared to non-AMI. The study ROC analysis (AUC value of 0.975) also indicated a remarkable diagnostic efficiency of this miRNA [61]. In addition, the absence of significant change between spinal cord injury patients and healthy volunteers suggested miR-22-5p cardiac specificity, supporting thus its potential AMI biomarker role [61]. Therefore, despite its heterogeneous expression, both studies agreed about miR-22-5p promising AMI biomarker ability.

Another up-regulated miRNA in STEMI is miR-23b, a regulator of cancer and autoimmune diseases progression [88]. This miRNA is also highly expressed in the heart, where it can negatively affect hypoxic cardiomyocytes by promoting cell death and inhibiting cell growth [89]. Zhang et al. [90] investigated miR-23b expression in 80 STEMI patients and 60 healthy subjects. Blood samples were collected for 7 days after the onset of symptoms. A significantly elevated expression (with a peak at 48 h) of miR-23b was found in STEMI patients compared to controls. At the same time, the ROC analysis disclosed a separation compared to CK-MB and cTns, suggesting that miR-23b might be another diagnostic biomarker with a temporally or spatially restricted expression pattern [90].

In a study by Horváth et al. [91], three different groups of patients (20 STEMI, 20 with no coronary atherosclerosis, and 20 with stable artery disease) were enrolled for identifying miRNA associated with the vulnerable plaque (VP) rupture to be employed as biomarkers of this condition. Based on an extensive scale screening, 12 miRNAs were selected for further analysis, and two of them, miR-331 and miR-151-5p, significantly distinguished STEMI patients from the two other groups. Moreover, ROC analysis showed that both miR-331 and miR-151-5p had effective diagnostic accuracy and STEMI discrimination ability.

**Table 2**
Summary of promising downregulated miRNAs in AMI patients.

| | miRNA | Main Function | AUC | Sensitivity | Specificity | Relationship to traditional biomarkers | Detection time after symptom onset |
|---|---|---|---|---|---|---|---|
| Non-cardiac specific (plaques and platelets enriched) | miR-1291 | Enriched in AMI progression-associated signaling pathways (association confirmed by the bioinformatic analysis) | 0.84 | 85 % as a panel | 82.86 % as a panel | Greater ability of miRNA panel as an early diagnostic indicator for distinguishing AMI from other diseases involving chest pain | 6 h |
| | miR-217 | | 0.825 | | | | |
| | miR-455-3p | | 0.86 | | | | |
| | miR-566 | | 0.84 | | | | |
| | | | 0.90 (panel of the four) | | | | |
| | miR-6718 | | | | | Further studies are required to better investigate their superiority to cTnT and CK-MB in the diagnosis of AMI. | |
| | miR-4329 | | | | | | |
| | miR-379 | Have a critical role in AMI progression | 0.751 | | | Negatively correlated with CK-MB and cTns | |

However, the combination of both miRNAs panels did not improve the accuracy, sensitivity, or specificity [91]. Interestingly, miR-331 and miR-151-5p were detected significantly elevated in patients with early STEMI, whereas markers of myocardial necrosis (cardiac troponin I, miR-208 and miR-499) tested negative, suggesting that miR-331 and miR-151-3p source might be outside the myocardium, making such biomarkers non-cardiac specific. On the other hand, platelet-derived miRNAs, miR-223 and miR191, resulted increased in the STEMI group, suggesting that the miR-331 and miR-151-5p might be platelet-derived but also that STEMI patients suffered from Type 1 MI due to the VP rupture [91].

In terms of AMI severity prediction, Xiao et al. [92] showed that miR-146a can serve as a predictor of major adverse cardiovascular events (MACE) development in AMI patients. By analyzing microarray-based gene expression profiles data (data obtained from blood samples of STEMI patients collected within 4 h after onset of chest pain and healthy controls), and combining these data with the bioinformatic tool, miR-tarbase(a tool that explores the interactions between miRNAs and genes), Xiao et al. [92] found that miR-146a and the S100 calcium-binding protein A12 (S100A12) were significantly elevated in STEMI patients compared to healthy controls [92].

MiR-146a is known for being highly expressed in endothelial cells, smooth muscle cells, cardiomyocytes, and atherosclerotic arteries [93,94], while the S100A12 protein for playing a role in proinflammatory cytokines production, smooth muscle cells migration, and vascular endothelial cell adhesion expression [95]. STEMI patients-associated miR-146a elevation was validated by qRT-PCR, and further data revealed that miR-146a increase indicated a significant incidence of MACE in STEMI patients compared with those with low miR-146a levels during the 3-year follow-up period [92]. Furthermore, since miR-146a is also associated with inflammation progression, it might function in the STEMI pathogenesis by targeting S100A12, which in turn may induce an inflammatory response [92].

Healthy subjects and STEMI patients were enrolled by Bukauskas et al. [95] to analyze the expression levels of miR-30d-5p, miR-23a-3p, and miR-146a-5p and assess their diagnostic value as predictive biomarkers [96]. All the investigated miRNAs were found downregulated in STEMI patients compared to the control group, with miR-23a-3p recording the lowest expression level (4.857-fold) compared to miR-30d-5p (1.581-fold) and miR-146a (4.048-fold). Moreover, miR-23a-3p revealed a fair diagnostic accuracy (AUC = 0.806) with an impressive correlation with the disease severity. On the contrary, miR-30d-5p had no diagnostic accuracy, and miR-146a was not correlated with the disease's severity. Interestingly, severe STEMI patients had significantly lower expression of miR-23a-3p than non-severe STEMI patients, suggesting that miR-23a-3p downregulation may be correlated with increased STEMI severity and elevated risk of mortality [96]. Therefore, miR-23a-3p is not only a STEMI biomarker but also a predictor of disease severity.

Finally, compared to control subjects, miR-4478 downregulation and increased soluble leptin receptor (sLEPR) levels were found in NSTEMI patients [97]. Since high blood levels of sLEPR were reported in heart failure conditions [98], while miR-4478 had the highest target score (=90) for LEPR, the authors speculated that miR-4478 levels might affect LEPR serum levels. Indeed, a statistically significant negative correlation between miR-4478 expression and serum sLEPR concentrations was reported in the work. Moreover, miR-4478 and sLEPR levels correlated with the variations of the cardiac biomarkers CKMB, cTnI, and cholesterol. Finally, miR-4478 and sLEPR ROC analysis indicated high diagnostic accuracy (AUC of 0.936 and 0.862, respectively), providing evidence that both molecules might have the ability to discriminate between NSTEMI and healthy individuals, a hypothesis further supported by their high sensitivity and specificity (87.5 % sensitivity and 98.8 % specificity for miR-4478) (Table 3) [97].

**Table 3**
Summary of upregulated and downregulated miRNAs biomarkers in STEMI and NSTEMI.

| | miRNA | Main Function | Blood levels | AUC | Sensitivity | Specificity | Relationship to traditional biomarkers | Detection time after symptom onset |
|---|---|---|---|---|---|---|---|---|
| Cancer biomarker | miR-203 | Protective effect on heart function and its overexpression inhibits myocardial apoptosis and fibrosis | Higher in STEMI group than in control. | 0.912 | | | Diagnostic accuracy exceeded CK-MB (0.818), cTnI (0.645), and myoglobin | |
| Tumor suppressor | miR-22-5p | Playing a role in oxidative stress, cardiac autophagy, and fibrosis | Significant elevation in STEMI patients | 0.847 | | | | |
| Cancer regulator | miR-23b | Regulator of cancer and autoimmune diseases progression | Elevated in STEMI | | | | | 48 h |
| Non-cardiac specific (platelet-derived) | miR-331 miR-151-5p | | Significantly elevated in STEMI | | | | Cardiac troponin I, miR-208 and miR-499 tested negative when miR-331 and miR-151-5p were detected | Early |
| Non-cardiac specific (platelet derived) | miR-146a | May serve for estimating whether AMI patients have a risk for developing major adverse cardiovascular events (MACEs) | Markedly elevated in STEMI | | | | | |
| | miR-30d-5p | | Downregulated in patients with STEMI | No diagnostic accuracy | | | | |
| | miR-23a-3p | | | 0.806 | | | Correlated with increased STEMI severity and elevated risk of mortality was not correlated with disease's severity | |
| | miR-146a-5p | | | 0.997 | | | | |
| Non-cardiac specific | miR-4478 | | Downregulated in patients with NSTEMI | 0.936 | 87.5 % | 98.8 % | | |

## 3. Other cardiac-related pathological conditions

Fulminant myocarditis (FM) is defined as a condition of myocardial inflammation that leads to hemodynamic abnormality and HF [99]. Its mortality rate reaches 50 %-70 % and can even lead to sudden death [99]. FM traditional diagnosis parameters are similar to those used in AMI, including BNP, cTnI, and CK. However, their specificity for FM is poor as they can undergo changes during either heart malfunction or myocadiac injury [99,100]. Using microarray analysis and qRT-PCR validation, Nie et al. [101] investigated the expression profiles of different miRNAs for the FM diagnosis. Three upregulated miRNAs, miR-4763-3p, miR-4281, and miR-3960, and one downregulated, miR-151a-3p, were detected in the court of the enrolled individuals. While miR-4281 expression resulted elevated in MI patients compared to controls, indicating a cardiac injury-derived elevation, miR-4763-3p, miR-3960, and miR-151a-3p expression levels were not changed in MI patients, suggesting their association with FM inflammatory processes or other pathological conditions other than heart injury [101]. Besides, miR-4763-3p and miR-151a-3p demonstrated the most significant specific dysregulation in FM patients. Follow-up expression analysis during treatment showed that miR-151a-3p was still downregulated after treatment, while miR-4763-3p and miR-4281 returned to normal. ROC analysis suggested that miR-4763-3p and miR-4281 had a considerable potential in terms of diagnostic accuracy, but miR-4763-3p (AUC of 0.850) resulted more sensitive and specific as a biomarker for FM diagnosis than miR-4281 (AUC of 0.78) [101]. Finally, correlation studies between the levels of both miRNAs and the endemic myocardial area in FM patients suggested that miR-4763-3p expression level had a strong positive correlation with FM severity, while miR-4281 was moderately positively correlated. In view of these data, Nie et al. suggested that miR-4763-3p is a novel promising biomarker for FM [101].

Another non-AMI disease requiring a quick diagnosis biomarker is Unstable Angina (UA), a type of angina pectoris caused by insufficient blood supply to the heart muscle, which ultimately leads to a severe ischemic cardiac condition [102,103]. Elgebaly et al. [103] investigated Nourin-associated miRNAs in UA and acute STEMI. Nourin is an early inflammatory mediator released within five minutes after initial ischemic injury of the heart. It is reported for being specifically related to cardiac disease conditions; hence it might be used to distinguish and rule out non-cardiac patients with myocardial ischemia [103]. Using bioinformatic analysis, the authors retrieved two different networks based on their relationship with the Nourin protein and the ischemic myocardium, CTB89H12.4/miR-137/FTHL-17 and CTB89H12.4/miR-106b-5p/ANAPC11. FTHL-17 and ANAPC11 are target genes for miR-137 and miR-106b-5p, respectively, whereas the lncRNA CTB89H12.4 is common to both networks, showing a high tendency to interact with each other through lncRNA sharing [103]. Gene expression profiling and qRT-PCR indicated that miR-137 (cell necrosis marker) and miR-106b-5p (inflammatory marker) were elevated by 1382-fold and 192-fold, respectively, in UA and acute STEMI patients when compared to healthy volunteers. Also, ROC analysis revealed that both miRNAs have critical specificity, sensitivity, and predictive value. For instance, 97 % sensitivity, 94 % specificity, and 0.99 AUC were reported for miR-137 in distinguishing UA patients from controls, whereas 87 % sensitivity, 88 % specificity, and 0.90 AUC were detected for miR-106b-5p [103]. In addition, in support of the bioinformatics data, a significant association of miR-137 and miR-106b-5p with their regulatory target genes FTHL-17, ANAPC11, and CTB89H12.4 was found, highlighting a novel myocardial ischemic injury-associated signaling (Table 4) [103].

## 4. Circulating long non-coding RNAs as potential biomarkers of myocardial infarction

Similarly to miRNAs, investigating lncRNAs as biomarkers for several diseases has recently become an increasing area of interest. Indeed, transcriptome-wide studies revealed the significant tissue- and cell-specificity of some lncRNAs, indicating that investigating their expression profiles might be helpful in predicting disease prognosis [104]. For a better understanding of lncRNAs functions and their potential use as AMI biomarkers, recent studies focused on lncRNA-miRNA-mRNA networks, where lncRNAs are the key modulators [105,106]. Most of the studies used bioinformatic tools and\or profile-based analysis to identify dysregulated lncRNAs and then investigate the selected lncRNAs' functions, pathways, and their association with relative miRNA and mRNA. QRT-PCR is the most used method for validating results, and ROC analysis is employed to determine diagnostic accuracy. Besides, Pearson's correlation analysis is utilized to assess any profound correlation between network members.

Among 27 studied genes, based on their expression level in AMI patients al., Zheng et al. [107] selected three genes, namely Cell Division Cycle 42 (CDC42), Jansus kinase 2 (JAK2), and CHUK,. All three genes have a role in CVDs. For instance, JAK2 can reduce atherosclerotic plaque size by inhibiting specific pathways [108], and a mutation of this gene is observed in patients with thrombosis, ischemia and other cardiovascular complications [109]. CDC42 instead contributes to exacerbate vascular endothelial cells senescence, leading to atherosclerosis and vascular inflammation in response to pathogens [110]. Zheng et al. [107] found that both JAK2 and CDC42 are associated with the lncRNA-miRNA-mRNA network containing the lncRNA XIST.

[107]. Indeed, all three network's components were found up-regulated in AMI patients compared to healthy volunteers, and the Pearson's analysis confirmed a positive correlation between JAK2 and CDC42 expression levels and those of XIST. Moreover, ROC analysis revealed that XIST has a higher diagnostic accuracy value (AUC of 0.886) than JAK2 (AUC = 0.706) and CDC42 (AUC = 0.692), indicating that this lncRNA, in addition to playing a significant role in AMI

**Table 4**
Summary of significant miRNAs biomarkers in cardiac-related pathological conditions.

| Cardiac-related pathological conditions | miRNA | Main Function | Blood levels | AUC | Notes |
|---|---|---|---|---|---|
| Fulminant myocarditis (FM) | miR-4281 | Elevated in MI patients compared to controls, indicating a cardiac injury-derived elevation | Up-regulated | 0.78 | Restored to normal after treatment. Both correlated positively with FM severity (strongest with miR-4281 and moderate miR-4763-3p |
| | miR-4763-3p | Expression levels were not changed in MI patients, suggesting an association with FM inflammatory processes or other pathological conditions other than heart injury | Significant Up-regulated | 0.850 | |
| | miR-3960 | | Up-regulated | | |
| | miR-151a-3p | | Significant down-regulated | | Still downregulated after treatment |
| Unstable Angina (UA) | miR-137 | Cell necrosis marker | Markedly elevated in UA and STEMI | 0.99 | |
| | miR-106b-5p | Inflammatory marker | | 0.90 | |

development by targeting JAK2 and CDC42, may be a novel AMI diagnostic biomarker[107].

The NRF (necrosis-related factor) lncRNA is increased in myocardial injury and is strongly associated with cardiomyocyte necrosis. Specifically, when NRF is silenced, the miR-873 expression increases and myocardial necrosis decreases [111]. Yan et al. [112] investigated NRF expression and its role in heart failure (HF) diagnosis after AMI intending to find a biomarker for HF early detection. Their study showed a sharp elevation of NRF in AMI patients with HF post-PCI compared to AMI patients without HF. Moreover, NRF levels were positively correlated with the levels of cardiac biomarkers TnI and NT-proBNP (*N*-terminal pro-brain natriuretic peptide), and correlation analysis revealed a positive association of NRF with HF severity. Concerning the NRF clinical significance, ROC analysis indicated an AUC value of 0.975, suggesting this lncRNA may represent a risk marker of post-AMI HF development [112].

Employing two AMI and healthy samples microarray datasets, Li et al. [113] tried to identify and investigate the predictive role of AMI-related lncRNAs [113]. Eleven lncRNAs were differentially expressed in AMI samples compared with healthy ones; eight were upregulated (LOC145474, LOC100129518, BRE-AS1, MIR22HG, MIR3945HG, ATP2B1-AS1, CATIP-AS1, and LINC00528), and three were downregulated (WDR66-AS1, A2M-AS1, and LINC00612). Moreover, statistical enrichment analysis revealed their association with AMI pathogenesis or AMI-related processes, such as inflammation and immune response. The diagnostic value was determined by the cross-validation approach LOOCV (Leave One Out Cross-Validation), which suggested that the lncRNA risk classifier has good discrimination between AMI patients and healthy subjects with an AUC value of 0.955 [113].

According to Xie et al. [114], the two lncRNAs, TTTY15 (testis-specific transcript Y-linked 15) and HULC (highly up-regulated in liver cancer) are promising AMI biomarkers able to compete with the traditional ones [114]. QRT-PCR assay was used to assess the lncRNAs levels in 80 AMI patients and 36 healthy controls. TTTY15 and HULC were found to be, respectively, up-regulated and downregulated in AMI patients compared to healthy individuals. ROC analysis revealed a higher diagnostic power for both lncRNAs compared to conventional markers such as CKMB and TnT; indeed, the reported AUC values were 0.915 for TTTY15 and 0.905 for HULC versus 0.768 for CKMB and 0.869 for TnT [114]. Moreover, authors reported that TTTY15 and HULC could also be used as novel therapeutic targets in AMI treatment; indeed, TTTY15 suppression improved cell viability, reduced apoptosis, alleviated oxidative stress, and diminished the infraction size, while HULC overexpression relieved cell injury [114].

lncRNAs diagnostic potential has also been studied in STEMI patients. In a study by Li et al. [115], nine MI-associated lncRNAs were selected from LncRNADiseaese and PubMed databases and their plasma expression levels were checked by qRT-PCR. The mitochondrial long non-coding RNA uc022bqs.1 (LIPCAR) showed great potential as AMI-STEMI biomarker and an excellent ability to predict coronary heart disease (CHD) severity and progression of [115]. Indeed, LIPCAR expression levels were significantly increased in patients with STEMI during the first 4 h of symptom onset (peaked at 12–24 h) compared to control patients. Besides, LIPCAR showed the highest predictive value (AUC of 0.782, sensitivity of 82 % and specificity of 75 %) along with a positive correlation with CK-MB and cTnI. Further analysis demonstrated that LIPCAR plasma levels were higher in STEMI patients with 2 or 3 branch lesions than in patients with 1 branch lesions. Also, levels decreased after PCI, reflecting myocardium condition. Hence, LIPCAR positively correlated with the STEMI severity score, reflecting patients' higher risk of MACE development [115].

LncRNAs as biomarkers for predicting the PCI-associated no-reflow phenomenon have also been studied. In this regard, Yang et al. [116], stated that the lncRNA MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) may function as an effective biomarker for predicting the risk of no-reflow in STEMI patients [116]. This lncRNA has been reported to contribute to several diseases pathogenesis by sponging miR-30e, miR-126 and miR-155 [117,118]. For instance, by sponging miR-155, MALAT1 can enhance cardiac stem cell proliferation under ischemic conditions [119]. Based on a study by Yang et al [116], MALAT1 is noticeably up-regulated in STEMI patients diagnosed with no-reflow phenomenon receiving PCI compared to patients who had normal flow; while miR-30e, miR-126, and miR-155 are instead down-regulated, reflecting the sponge effect of MALAT1. Besides, MALAT1 AUC was 0.95 as per ROC analysis, indicating its ability to distinguish normal reflow from no-reflow in STEMI patients [116].

Inflammation and lipid metabolism are strongly correlated with AMI [120]. In this context, Wang et al., studied peripheral blood mononuclear cells (PBMC) derived lncRNAs as AMI biomarkers [121]. The study involved 132 AMI patients and 103 healthy individuals. Ten lncRNAs were selected for their reported association with CVDs and then verified by RT-PCR. The plasma levels of three lncRNAs, H19, MIAT, and MALAT1, resulted significantly elevated in AMI patients compared to healthy participants [121]. All three lncRNAs are known for having crucial roles in CVDs development and progression; indeed, H19 promotes lipid accumulation in atherosclerosis [122], whereas MIAT (myocardial infarction-associated transcript) and MALAT1 are positively correlated with AMI [123] and cardiac remodeling in mice [124], respectively. The highest AUC value among the tested lncRNAs, was recorded for lncRNA H19 (0.753), while the AUC values for MIAT and MALAT were 0.609 and 0.636, respectively; however, the combination of the three gave an AUC of 0.75, indicating a moderate diagnostic power [121]. Overall the results suggested that H19, MIAT, and MALAT1 might play a crucial role as AMI predictive biomarkers.

PBMC-enriched lncRNAs were also reported by Li et al. [125]. Using profiling studies and transcriptome-wide analysis acquired from 93 coronary artery disease (CAD) patients and 48 healthy volunteers, 1210 lncRNAs and 890 mRNAs were found to be differentially expressed between CAD and healthy subjects [125]. Among all the lncRNAs, seven were selected and further validated by qRT-PCR [125]. Two novel lncRNAs, ENST00000444488.1 and uc010yfd.1, resulted significantly decreased in CAD patients and, in combination with CVD risk factors, had the better performance for discriminating CAD patients from healthy controls (AUC of 0.902 as combination against 0.851 AUC of the two lncRNAs alone) (Table 5) [125].

## 5. Conclusions and future directions

The finding that circulating ncRNAs are present in body fluids, along with their high stability, easy detection, and disease-associate changes in such fluids, has paved the way to consider them promising, non-invasive diagnostic biomarkers for several pathological conditions, including cancer, diabetes, neurodegenerative and cardiovascular diseases [14–18]. Several differentially expressed ncRNAs with a high level of specificity for AMI have been reported as promising cardiac biomarkers. Many of them show greater diagnostic accuracy, especially for AMI early diagnosis. Indeed, they are detectable in circulation earlier than conventional cardiac biomarkers and exhibiting a greater specificity in identifying AMI from other non-AMI diseases. However, many studies point out that the combination of ncRNAs with traditional biomarkers could be a better way of employment to compensate for the lack of sensitivity or specificity of both and provide a better result in terms of diagnostic accuracy. Therefore, despite several promising results, validated ncRNAs biomarkers for AMI diagnosis are still missing. Future work should be directed at improving and refining standard pre-analytical (e.g. sample collection, processing, and quality control) and post-analytical (data normalization) methods as well as the approaches to be used in discriminating among AMI closely related ncRNAs. As a matter of fact, those above could be some of the ascribable reasons for the failed success of ncRNAs as diseases biomarkers. Indeed, results can significantly differ depending on whether plasma or serum is used, some

**Table 5**
Summary of circulating long non-coding RNAs as potential biomarkers in myocardial infarction.

| lncRNA | Genes\ miRNAs targeted \| lncRNA function | Regulation in patients' blood levels | AUC |
|---|---|---|---|
| lncRNA XIST | JAK2 (reduce the size of atherosclerotic plaque) and CDC42 (exacerbate vascular endothelial cells senescence) | Up-regulated in AMI patients | 0.886 |
| lncRNA-NRF | miR-873 (expresses increased expression upon NRF silencing, hence myocardial necrosis decreases) | Sharply elevated in AMI patients with Heart Failure (HF) post-PCI compared to AMI patients without HF | 0.975 |
| lncRNA-TTTY15 | TTTY15 suppression improved cell viability, reduced apoptosis, alleviated oxidative stress, and diminished the infraction size | Upregulated in AMI patients | 0.915 |
| lncRNA-HULC | HULC overexpression relieved cell injury | Downregulated in AMI patients | 0.905 |
| LncRNA- LIPCAR | LIPCAR was positively correlated with STEMI severity score which reflects the higher risk of developing MACE | Significantly increased in patients with STEMI during the first 4 h of symptoms onset | 0.782 |
| lncRNA MALAT1 | MALAT1 effective biomarker for predicting the risk of no-reflow in STEMI patients | Up-regulated in STEMI patients diagnosed with no-reflow phenomenon receiving PCI compared to patients who had normal flow | 0.95 |
| lncRNA H19 | H19 promotes lipid accumulation in atherosclerosis | Significantly elevated in AMI patients compared to healthy participants | 0.753 |
| ENST00000444488.1 and uc010yfd.1 | PBMC-enriched | Significantly decreased in CAD patients | 0.902 and 0.851 |

anticoagulants used for plasma collection may interfere with reverse transcriptase and DNA polymerase enzyme activity, and factors such as age, gender and lifestyle may affect the level of circulating ncRNAs independently from the disease. Therefore, considering all the above-mentioned factors and effectively working on their improvement may enhance miRNAs' diagnostic value in a given context. In conclusion, circulating ncRNAs own the potential to become routine clinical biomarkers for AMI detection, but their translation from bench to clinical applications is still far from being achieved.

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Data Availability Statement

All the data presented in this study are available in this article.

## CRediT authorship contribution statement

**Heba Almaghrbi:** Writing – original draft. **Roberta Giordo:** Writing – review & editing, Writing – original draft, Conceptualization. **Gianfranco Pintus:** Funding acquisition, Supervision, Writing – review & editing, Conceptualization. **Hatem Zayed:** Supervision, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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