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Impact of microRNAs on cardiovascular diseases and aging

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Abstract

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality for both men and women among all ethnicities worldwide. Although significant improvements in the management of CVD occurred in the 20th century, non-invasive, universal, early diagnostic biomarkers and newer therapeutic drugs are needed for clinical treatment by physicians. MicroRNAs (miRNAs) are a class of endogenous, non-coding, single-stranded, small RNA molecules that are critically controlled by all human biological processes. Moreover, dysregulated miRNA expression is directly involved in various CVDs, including stable coronary artery disease and acute coronary syndrome. Several miRNAs that are enriched in the plasma of CVD patients have potential as clinical biomarkers, and overexpression or inhibition of specific miRNAs has novel therapeutic significance in the management of CVD. Aging is a multifactorial physiological process that gradually deteriorates tissue and organ function and is considered a non-modifiable major risk factor for CVDs. Recently, several studies established that various miRNAs essentially regulate aging and aging-related disease processes. This narrative review briefly discusses the recently updated molecular involvement of miRNAs in CVDs, their possible diagnostic, prognostic, and therapeutic value, and their relationship to the aging process.

Keywords

Cardiovascular disease, microRNA, diagnosis, prognosis, therapeutic, aging

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Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in both developing and developed countries, among all races and in both sexes, and causes a huge societal economic burden.[1] Although significant improvements have

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occurred in the primary prevention, diagnosis, prognosis, and treatment of CVD, its prevalence has substantially increased in recent years because of unhealthy lifestyles, lack of physical exercise, an increased proportion of overweight individuals, low vitamin D levels, increased consumption of saturated fatty foods, stressful job environments, air pollution, often poorly treated major atherosclerotic events such as dyslipidemia, uncontrolled hypertension, type-2 diabetes mellitus, the aging population, and the substantial influence of genes. Hence, it is essential to explore the molecular pathological process of CVD in-depth and discover novel, effective clinical biomarkers and safer, more advanced drugs for CVD management that will reduce its future incidence.[2,3]

Accumulating basic and clinical research studies using next-generation sequencing have revealed that microRNAs (miRNAs, miRs) are predictive biomarkers and therapeutic targets for CVD. These miRNAs are small, noncoding, endogenous, highly specific, single-stranded, functional RNA molecules with a length of 21 to 25 nucleotides that regulate nearly half of all protein-coding gene expression, usually by binding with the 3′-untranslated region of target messenger RNAs (mRNAs).[3]

Mature miRNAs play a key role in multiple human biological processes such as cell cycling, cell proliferation, cellular aging, cellular apoptosis, angiogenesis, autophagy, mitochondrial metabolism, hematopoiesis, and cardiovascular development. Additionally, dysregulated miRNA expression is directly involved in various CVDs including stable and unstable atherosclerotic coronary artery disease (CAD), acute myocardial infarction (AMI), cardiomyopathy, heart failure, atrial fibrillation, hypertension, metabolic syndrome, and stroke.[3,4] Several miRNAs, including miR-15a-5p, miR-199a-3p, miR-34a, miR-146a, and miR-217, are involved in cellular senescence, endothelial dysfunction, inflammation, and progression of atherosclerosis, whereas miR-342-5p protects against endothelial cellular injury during atherosclerosis.[5] Interestingly, expression levels of circulating plasma miR-423, miR-320, miR-765, miR-149, miR-21, miR-126, and miR-1 are altered in stable CAD and AMI patients, which suggests that these miRNAs could be used as diagnostic or prognostic biomarkers and may have a therapeutic impact for ischemic heart disease patients.[6–7]

MiR-221/222, miR-125b, miR-30d-5p, and miR-126a-5p were shown to be directly regulated by various pathological processes of heart failure, suggesting that these miRNAs might be potential targets for the diagnosis and treatment of heart failure.[8] Hypertension is a global burden among CVDs. Recently, several researchers found that dysregulation of circulating miR-122, miR-199, miR-223, miR-29, miR-182, miR-30, and miR-510 expression was a major risk factor for essential hypertension, and these miRNAs may represent advanced biomarkers and new molecular targets for hypertension management.[9–10]

Aging is a non-modifiable major risk factor for CVDs, and its underlying molecular mechanisms are complex. Recently, several studies identified a set of dysregulated miRNAs including miR-101, miR-142, and miR-146 that critically regulate the aging process.[11–12] Alzheimer's disease (AD) is a multifactorial, age-related, progressive, neurodegenerative disorder characterized by a gradual deterioration of numerous cognitive functions in the aged population. Several miRNAs (miR-132, miR-539, miR-26, miR-143, miR-195, miR-20, and miR-17) play crucial roles in the initiation and progression of AD through regulation of tau phosphorylation, amyloid β peptide metabolism, synaptic function, and neuroinflammation.[13] Li et al. found that miR-219 remarkably reduced AD progression in mice by

inhibiting tau phosphorylation through regulation of tau tubulin kinase 1 and glycogen synthase kinase 3β expression.[14] Microglia that were regulated by miR-155 were shown to acquire the neurodegenerative phenotype (MGnD) and the interferon-γ-responsive pre-MGnD mechanism to prevent neurodegenerative molecular pathological progression and preserve cognitive function in a mouse AD model. Thus, miR-155 is a potential molecular target for the management of AD.[15] The main aim of this narrative review is to broadly discuss the impact of miRNAs as clinical biomarkers, their therapeutic applications, their associated molecular insights into CVDs, and their correlation with aging.

Literature search strategy

This review followed the Scale for the Assessment of Narrative Review Articles methods.[16] We used several combinations of keywords including CVD and miRNAs, CAD and miRNAs, stable angina and miRNAs, unstable angina and miRNAs, ACS and miRNAs, the severity of CAD and miRNAs, atherosclerotic heart disease and miRNAs, biomarker's role of miRNAs in CAD and AMI, the therapeutic significance of miRNAs in CAD and AMI, and aging and miRNAs when searching various scientific databases including PubMed Central, MEDLINE, Scopus, Embase, Web of Science, Google Scholar, and miRNA target databases (TargetScan, miRbase, miRDB, PicTar) to obtain articles published up to July 2024.

Role of miRNAs in CAD

Dyslipidemia plays a vital role in the development of atherosclerotic coronary heart disease (CHD). Recently, Vancheri et al. demonstrated that hsa-miR-200c-3p expression was distinctly downregulated in CAD patients, allowing significant discrimination between CAD patients and healthy individuals. Additionally, this miRNA had a strong positive relationship with lipid disorders and creatinine clearance, indicating it as a clinical biomarker.[17] Mishra et al. noticed that the endothelium-enriched circulating miRNA miR-122 was decreased in CAD patients and plays key roles in small dense low-density lipoprotein (LDL) metabolism, apoptosis, oxidative stress, and the endothelial inflammation process.[18]

Abdallah et al. showed that circulating miR-133a was downregulated and miR-182, miR-205, and miR-145 were upregulated in CAD patients, exhibiting the highest areas under the receiver operating characteristic (ROC) curve (AUCs), suggesting these miRNAs as non-invasive biomarkers for CAD. Furthermore, miR-133a showed a significant correlation with obesity and family history of CAD. The authors also reported that miR-135b and 140b exhibited positive correlations with the wall motion severity index, fatty acid biosynthesis, and endothelial cellular interaction during the inflammatory process, providing new insights into CAD pathogenesis.[19]

Recently, Coban et al. showed circulating miR-26a-5p was highly elevated in CAD patients compared with that in non-CAD patients and that it had a high sensitivity rate; therefore, it is considered to have diagnostic importance in CAD patients. They also found strong correlations of this miRNA with diabetic risk factors including HbA1c, blood glucose, and body mass index; therefore, it could be a major risk factor and new molecular therapeutic target for CAD patients.[20]

Circulating exosomal miR-122-5p was significantly increased while miR-378 expression was prominently reduced in patients with coronary stenosis and was correlated with the Gensini score. Furthermore, the LDL level had a significant inverse relationship with miR-378 expression. Therefore, these miRNAs may serve as important risk

factors and promising non-invasive biomarkers for coronary atherosclerosis staging.[21–22] In patients with CHD, the expression levels of peripheral blood miR-26a and miR-195 were decreased compared with those of control subjects. These miRNAs showed high AUC values and were able to distinguish CHD patients from healthy individuals. Moreover, miR-26a was inversely associated with triglycerides (TGs), total cholesterol, C-reactive protein, and interleukin (IL)-1β, and miR-195 was negatively linked with total cholesterol, LDL cholesterol, tumor necrosis factor (TNF)-α, and IL-6. Reduced circulating miR-26a and miR-195 levels comprised a significant risk factor for the development of CHD and may also serve as clinical biomarkers for CHD patients.[23]

In CHD patients, circulating miR-128 was apparently downregulated and displayed a significant AUC value that could potentially distinguish CHD patients from controls. It was also negatively correlated with LDL cholesterol, inflammatory cytokines (IL-1β, IL-6, TNF-α), and cellular adhesion molecules (ICAM-1, VCAM-1), which critically regulate the pathogenesis of CHD. Therefore, a reduced miR-128-3p level and an elevated level of its target long noncoding RNA HULC have strong clinical value for determining the severity of coronary stenosis and for treatment of CHD patients.[24] Individuals with severe coronary artery stenosis (≥90%) showed remarkably lower has-miR-130b-5p and miR-18a-3p levels than individuals with less stenosis or non-CAD participants (≤20% stenosis), and these miRNAs were revealed to be positively associated with high-density lipoprotein and negatively correlated with fasting TG levels. Furthermore, the level of peripheral blood miR-130b-5p showed a negative link to CAD in female patients. Both miRNAs might be considered diagnostic markers for the development and progression of CAD.[25]

Vascular endothelial growth factor (VEGF) is directly correlated with the development of atherosclerotic CHD. Low expression levels of serum miR-296 and high levels of VEGF were detected in patients with severe coronary artery stenosis compared with those of controls, and these miRNAs were inversely related to cardiac troponin-I (cTnI), brain natriuretic peptide, and high-sensitivity C-reactive protein. Low levels of peripheral miR-296 have a strong clinical diagnostic value for the degree of severity of coronary artery stenosis.[26] MiR-27a and miR-23a were highly upregulated and Sirtuin 1 (SIRT1) expression was downregulated in peripheral blood mononuclear cells of patients with atherosclerotic CAD; thus, they are potentially correlated with the grading of coronary artery stenosis. Furthermore, miR-27a exhibited a high AUC value, suggesting it has a potential role in the progression of coronary atherosclerosis and may be a new diagnostic biomarker for CAD.[27]

The relative expression levels of plasma miR-125b and miR-423-5p were decreased in stable CAD patients and could accurately distinguish these individuals from controls and unstable CAD patients. This finding suggests their possible clinical application as biomarkers to determine severity in CAD patients.[3,28]

Our prior research exhibited that CAD patients with blockage of one, two, or three or more vessels had increased plasma miR-21 concentrations resulting in significant AUC values that could accurately differentiate them from healthy individuals. Moreover, miR-21 was highly upregulated, and its target, PDCD4, was greatly downregulated in hypoxia-reoxygenation-induced human umbilical vein endothelial cells (HUVECs) compared with that in controls. Furthermore, inhibition of miR-21 evidently reduced caspase-3 activity and reactive oxygen species (ROS) generation and greatly improved cellular viability. Therefore,

miR-21 may be a biochemical marker as well as a new therapeutic target for ischemic heart disease patients (Table 1).[29]

Biomarkers and therapeutic role of miRNAs in acute coronary syndrome

Acute coronary syndrome (ACS) usually develops because a vulnerable coronary atherosclerotic plaque ruptures and subsequently forms a thrombus, which leads to a critical blockage of coronary artery blood flow to the myocardium. This results in the development of myocardial ischemia and later produces myocardial injury followed by cell death, which is called a heart attack or AMI. Globally, this process causes premature death in both men and women.[1]

Early and accurate diagnosis and immediate appropriate management may remarkably decrease the cardiac mortality rate. AMI is usually diagnosed based on ischemic chest pain, electrocardiogram changes, and elevation of cardiac enzymes.

Table 1. Role of circulating (plasma/serum) miRNAs in CAD.

miRNAs	Expression	Role	Associated with	Important target genes	References
miR-200c-3p	Downregulated	Diagnostic, prognostic	Lipid disorders	9p21, SLC30A7	17
miR-122	Downregulated	Diagnostic	Endothelium inflammation		18
miR-133a	Downregulated	Diagnostic	Obesity and CAD pathogenesis		19
miR-135b, miR-145	Upregulated	Diagnostic	Age and dyslipidemia	MEF2C gene, TGFBR2, TGF-β1	19
miR-26a-5p	Upregulated	Diagnostic, therapeutic	Blood glucose, HbA1c, and BMI	TRPC3, Cox5a	20
miR-378	Downregulated	Diagnostic	LDL	BMP4	21
miR-122-5p	Upregulated	Diagnostic	Gensini score		22
miR-26a, miR-195	Downregulated	Diagnostic	Dyslipidemia, TNF-α, IL-1β, and IL-6	Lnc-UCA1	23
miR-128	Downregulated	Diagnostic, therapeutic	Inflammatory cytokines (IL-1β, IL-6, TNF-α), adhesion molecules (ICAM-1, VCAM-1), and pathogenesis of CAD	Lnc-HULC	24
miR-130b-5p, miR-18a-3p	Downregulated	Diagnostic	HDL, TG, and progression of CAD		25
miR-296	Downregulated	Diagnostic	Grading of CAD stenosis	VEGF-B	26
miR-27a	Upregulated	Diagnostic	Progression of coronary atherosclerotic lesions	FOXO1, SIRT1	27
miR-125b	Downregulated	Diagnostic	Severity of CAD lesions	lncRNA MALAT1	28
miR-21	Upregulated	Diagnostic, therapeutic	ROS and Caspase-3	PDCD4	29

CAD, coronary artery disease; BMI, body mass index; LDL, low-density lipoprotein; TNF, tumor necrosis factor; IL, interleukin; ROS, reactive oxygen species; miRNA, microRNA; HDL, high-density lipoprotein; TG, triglyceride.

However, older adults and patients with diabetes generally present atypical chest pain, and although electrocardiogram monitoring is helpful for the diagnosis of ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) patients, it only has 50% to 60% sensitivity. The cardiac markers cTnI and troponin T (cTnT) are currently used internationally and are the most useful clinical biomarkers for the diagnosis of AMI. However, they are usually released into the bloodstream within 4 to 6 hours of cardiomyocyte injury, and the peak concentration is observed approximately 12 to 24 hours after AMI. Therefore, repeated measurements are needed to make clinical decisions. Additionally, troponin levels in NSTEMI patients are generally increased in later stages. Furthermore, troponin levels are evidently increased in patients with chronic stable angina, end-stage renal failure, and severe heart failure. Although thermolytic drugs and primary percutaneous intervention (PCI) are currently used for management of AMI patients, these are not suitable for all patients, and PCI is not available in all hospitals, especially in developing countries and those with low socioeconomic levels. Therefore, universal, novel, biochemical markers for the early evaluation of AMI and new molecular drugs are essential for cardiac clinicians to manage AMI patients.[3,30,31]

Recently, several excellent basic and clinical research studies demonstrated that various cardiac-specific miRNAs are released into the peripheral circulation during AMI, which may be used as novel diagnostic biomarkers for the early detection of AMI.[3,4,30] Moreover, inhibition or mimicking of cardiomyocyte-enriched miRNAs could prevent ischemia and cardiac cell death by regulating various target proteins, which may have potential therapeutic value for the treatment of AMI patients.

Serum miR-497 levels were significantly upregulated in ACS patients and were positively linked with Gensini scores, vascular endothelial injury, and adhesion factors. Furthermore, an elevated miR-497 level was strongly associated with development of major adverse cardiovascular events (MACEs) during a 6-month follow-up after PCI, suggesting serum miR-497 as a possible clinical biomarker for the diagnosis of ACS.[31] Meng et al. reported that plasma miR-143 and miR-145 expression was markedly decreased in patients with ACS compared with that in controls. These two miRNAs were inversely related to the Gensini score, revealing their high diagnostic value for ACS onset.[32]

Zhang et al. demonstrated that the expression of serum miR-361-5p in patients with ACS was markedly increased and positively interrelated with the Gensini score and the expression of endothelial dysfunction markers including VCAM-1, ICAM-1, and E-selectin. Additionally, serum miR-361-5p expression patterns clearly distinguished ACS patients from healthy individuals and stable CHD patients. Moreover, a high level of circulatory miR-361-5p was an individual risk factor for the development of MACEs following a 30-day hospitalization period. The results indicated that upregulated serum miR-361-5p might be a useful diagnostic and prognostic biomarker for the evaluation of ACS patients, and it has a significant impact on the prediction of MACE onset.[33]

Elgebaly et al. found that the expression levels of serum miR-137 and miR-106b-5p were distinctly elevated by 1382-fold and 192-fold in patients with unstable angina (UA) compared with those in healthy individuals and were increased by 2.5-fold and 4.6-fold in STEMI patients compared with those in individuals with UA. Furthermore, an early inflammatory mediator, Nourin, was significantly increased in ACS patients but not in healthy participants, and Nourin

is a direct target of miR-137 and miR-106b. The results suggested that Nourin is dependent on these two miRNAs and might be a novel blood-based biomarker for the diagnosis of UA and STEMI.[34]

Plasma miR-183-5p expression was increased by 8-fold in ACS patients with NSTEMI, and miR-15a-5p and miR-134-5p were decreased by 7-fold and 5-fold in STEMI patients compared with those in healthy subjects. Moreover, circulating miR-183-5p, miR-15a-5p, and miR-134-5p exhibited high AUC values and had significant power to differentiate NSTEMI and STEMI patients from healthy controls. These dysregulated miRNAs could be potential clinical biomarkers for the assessment of ACS patients.[35] The expression of circulating miR-587 in UA patients was evidently upregulated compared with that in control subjects. Additionally, in ACS patients with three vessel lesions, the miR-587 level was markedly elevated compared with that in patients with double and single vessel lesions. Additionally, the creatine kinase isoenzyme (CK-MB) level and Gensini score of ACS patients were positively associated with miR-587 expression. Moreover, an increased level of circulating miR-587 was closely correlated with the severity of CAD lesions and could be used as a blood-based marker for the diagnosis and prognosis of ACS patients.[36]

Serum miR-483-5p expression was highly elevated in ACS patients compared with that in healthy subjects and was correlated with the Gensini and SYNTAX scores. An increased occurrence of MACEs was observed in patients with elevated miR-483-5p levels during a 6-month follow-up after PCI treatment. Additionally, upregulated miR-483-5p effectively differentiated ACS patients from healthy participants and suggested that circulating miR-483-5p can be a useful non-invasive biochemical marker for the assessment of ACS patients and prediction of MACE onset after PCI management.[37]

In patients with ACS, serum miR-122-5p expression was remarkably higher than that in control subjects, and the expression level could significantly differentiate between UA and AMI patients according to the high AUC value. Based on the Gensini score, elevated serum miR-122-5p was positively associated with the severity of coronary artery lesions in UA patients. In addition, elevated expression of serum miR-122-5p was observed in ACS patients with coronary artery stenosis severity of more than 80%. A high level of serum miR-122-5p is a new biomarker for ACS patients and could be useful for assessment of the severity of coronary artery stenosis.[38]

A multicenter prospective study reported that plasma miR-4286 expression was significantly upregulated in ACS patients and the TG level was positively correlated with the circulating miR-4286 level. The results suggested that an elevated plasma miR-4286 level was directly related to an increased incidence of ACS (Table 2).[39]

The role of miRNAs as biomarkers of AMI

Recently, Liu et al. demonstrated that exosomal plasma miR-4516 and miR-203 levels were significantly elevated in AMI patients compared with those in healthy individuals and showed high AUC values with a high diagnostic accuracy for the evaluation of AMI patients. Moreover, exo-miR-4516 was positively associated with the SYNTAX score, and the plasma SFRP1 level was directly correlated with LDL and cTnI levels. The results also suggested that upregulated exo-plasma miR-4516, miR-203, and SFRP1 levels could be used in combination to predict the severity of AMI.[40]

In patients with STEMI, serum miR-30d-5p, miR-146a-5p, and miR-23a-3p

Table 2. Role of circulating (plasma/serum) miRNAs in ACS.

miRNAs	Expression	Role	Associated with	Important target genes	References
miR-497	Upregulated	Diagnostic	Endothelial injury, TNF-α, ICAM-1, IL-1β	TRAF6	3,31
miR-143, miR-145	Downregulated	Diagnostic	Gensini score, degree of coronary artery stenosis		32
miR-361-5p	Upregulated	Diagnostic, prognostic	Endothelial dysfunction	VEGF	33
miR-137, miR-106b-5p	Upregulated	Diagnostic	Inflammatory mediator, severity of myocardial ischemia	Nourin, ANAPC11, FTHL-17	34
miR-183-5p	Upregulated	Diagnostic	Three-vessel CAD	Claudin-5 protein	35
miR-134-5p, miR-15a-5p	Downregulated	Diagnostic	Plasma troponin I		35
miR-587	Upregulated	Diagnostic, prognostic	Creatine kinase isoenzyme and severity of CAD		36
miR-483-5p	Upregulated	Diagnostic, prognostic	Major cardiovascular risk factors	PLA2G5	37
miR-122-5p	Upregulated	Diagnostic	Severity of coronary artery lesions	SIRT6	38
miR-4286	Upregulated	Diagnostic	Triglyceride levels and incidence of ACS	PI3K	39

miRNA, microRNA; ACS, acute coronary syndrome; CAD, coronary artery disease; TNF, tumor necrosis factor; IL, interleukin.

expression levels were downregulated by 1.581-fold, 4.048-fold, and 4.857-fold compared with those in control subjects. Moreover, downregulated serum miR-23a-3p levels were significantly inversely associated with the APACHE II and Global Registry of Acute Coronary Events risk scores. Therefore, these miRNAs could be used as blood-based clinical markers for severity assessment and may have potential diagnostic and prognostic value in STEMI patients.[41]

The plasma expression levels of miR-26a-1, miR-146a, and miR-199a-1 in patients with AMI (before and after PCI) were markedly upregulated compared with those in healthy controls, and their AUC values could significantly distinguish between AMI patients and healthy subjects. Moreover, miR-26a-1, miR-146a, and miR-199a-1 expression levels were directly associated with high sensitivity-cTnT and N-terminal pro b-type natriuretic peptide levels in patients with AMI before and after PCI, indicating these elevated miRNAs may be considered as risk factors and new blood-based biomarkers for the early diagnosis of AMI and provide useful molecular information for the pathogenesis of AMI.[42]

Patients in the STEMI group exhibited significantly higher expression levels of miR-223-3p, miR-142-3p, miR-146a-5p, miR-125a-5p, miR-486-5p, and miR-155-5p

than those in controls. Patients with higher levels of miR-223-3p, miR-142-3p, and miR-146a-5p demonstrated an increased risk of developing MACEs during 1 year of follow-up. Additionally, the expression of miR-125a-5p was negatively correlated with aging, and miR-142-3p expression was inversely related to sex. Moreover, the relative expression levels of miR-223-3p and miR-146a-5p were positively correlated with the left ventricular global longitudinal strain values but negatively associated with the two-dimensional left ventricular ejection fraction values and myocardial work indices (global work index, global constructive work, and global work efficiency). These results suggest that upregulated plasma levels of miR-223-3p, miR-142-3p, and miR-146a-5p have significant prognostic value for AMI patients.[43]

The serum miR-96-5p level was significantly decreased and BCL2L13 expression was markedly upregulated in AMI patients compared with those in healthy subjects. Low levels of miR-96-5p also presented a good AUC value with high sensitivity and specificity and could clearly differentiate AMI patients from healthy participants. Furthermore, expression of a miR-96-5p mimic remarkably reduced oxidative stress and cellular apoptosis and evidently improved H9c2 cellular viability by targeting BCL2L13, indicating downregulation of serum miR-96-5p as a potential non-invasive diagnostic biomarker. Additionally, overexpression of miR-96-5p may be considered a new molecular target for the treatment of AMI patients.[44]

Circulating miR-21-5p and miR-126 expression levels were remarkably higher in the infarct-related artery total occlusion (IR-ATO) AMI group than those in the control group and exhibited a significant correlation with cTnI and CK-MB. ROC curve analysis revealed a strong diagnostic accuracy for IR-ATO AMI and suggested that miR-21-5p and miR-126 may also be promising prognostic clinical biomarkers for AMI and IR-ATO patients.[45] The expression of serum miR-499 was significantly increased and the serum miR-22 level was markedly reduced in AMI patients compared with those in healthy controls and the non-myocardial infarct group, and these two miRNAs showed significant AUC values with high sensitivity and specificity for the diagnosis of AMI patients. MiR-499 expression showed considerable positive correlations, whereas miR-22 exhibited strong negative correlations with total cholesterol, CK, and CK-MB levels. In addition, serum miR-499 was evidently higher and miR-22 was noticeably lower in the MACE group than in the non-MACE group, suggesting that these two miRNAs have strong clinical significance for the diagnosis of AMI.[46]

Significantly upregulated serum miR-32-5p expression was observed in AMI patients; inversely, marked downregulation of serum KLF2 mRNA was found in patients with AMI compared with that in healthy participants. Additionally, elevated serum miR-32-5p expression was positively correlated with cTnI, heart-type fatty acid binding protein, Von Willebrand factor (vWF), IL-1β, IL-6, and TNF-α levels and showed a high AUC value, indicating that elevated serum miR-32-5p may serve as a useful diagnostic biomarker and molecular target for the treatment of AMI (Table 3).[47]

Therapeutic role of miRNAs in AMI treatment

Recently, Boxhammer et al. reported that miR-30d-5p expression was significantly downregulated in the ischemic myocardium of a rat model of myocardial infarction compared with that in healthy myocardium. AMI rats treated with miR-30d-5p mimic after 72 hours and after 6 weeks showed a significantly reduced infarct area size in the left ventricle. Furthermore, in HUVECs

Table 3. Role of circulating miRNAs in AMI.

miRNAs	Expression	Role	Associated with	Important target genes	References
miR-4516, miR-203	Upregulated	Diagnostic	SYNTAX score, LDL and cTnI	SFRP1	[40]
miR-23a-3p	Downregulated	Diagnostic, prognostic	APACHE II and GRACE risk scores	MnSOD, NF-κB target genes	[41]
miR-26a-1, miR-146a, miR-199a-1	Upregulated	Diagnostic	Hs-cTnT, NT-proBNP, and pathogenesis of AMI	Irak1 and Traf6	[42]
miR-223-3p, miR-146a-5p	Upregulated	Prognostic	LV GLS and LVEF		[43]
miR-96-5p	Downregulated	Diagnostic, therapeutic	Oxidative stress, apoptosis	BCL2L13	[44]
miR-21-5p	Upregulated	Prognostic	cTnI and creatine kinase isoenzyme		[45]
miR-499	Upregulated	Diagnostic	TC, creatine kinase isoenzyme. and major cardiovascular events		[46]
miR-32-5p	Upregulated	Diagnostic, therapeutic	H-FABP, IL-1β, IL-6, TNF-α	KLF2	[47]

miRNA, microRNA; AMI, acute myocardial infarction; LDL, low-density lipoprotein; cTnI, cardiac troponin-I; Hs-cTnT, high sensitivity cardiac troponin T; TC, total cholesterol; LV GLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide; GRACE, Global Registry of Acute Coronary Events; IL, interleukin; TNF, tumor necrosis factor; H-FABP, heart-type fatty acid binding protein.

and cardiomyocytes transfected with a miR-30d-5p mimic, gap closures were markedly increased and the cardiomyocyte apoptosis rate was remarkably reduced 20 hours post-scratching. These results indicate that mimic miR-30d-5p may significantly enhance infarct healing and could be a novel therapeutic target for the prevention of ischemic cardiomyopathy after AMI.[48] Serum expression levels of let-7e-5p, let-7g-5p, and miR-26a-5p were distinctly downregulated during the acute onset of NSTEMI compared with those in healthy participants and were inversely correlated with the pro-inflammatory cytokine TNF-α and the chemokines MCP-3 and MDC. Moreover, HUVECs transfected with let-7e-5p mimic or inhibitor showed markedly enhanced cellular adhesion and angiogenesis capacity, suggesting that let-7e-5p is essentially involved in NSTEMI pathogenesis and may constitute a potential therapeutic target for AMI.[49]

Our previous study found that plasma miR-375 expression in STEMI and NSTEMI patients and in mouse AMI models was significantly downregulated in relation to that in controls. Additionally the AUC values were increased with remarkable sensitivity and specificity and clearly distinguished STEMI and NSTEMI patients from healthy volunteers. Furthermore, hypoxia-reoxygenation-induced H9c2 cells treated with mimic miR-375 demonstrated reductions of the apoptosis rate and caspase-3 activity and showed markedly improved cardiomyocyte viability through upregulation of its target protein, NLK. These results suggested that downregulation of plasma miR-375 may serve as a promising clinical

biomarker for the early detection of AMI, and overexpression of miR-375 could be considered a new molecular target for the management of AMI patients.[50]

Zhang et al. demonstrated that miR-27a-5p is markedly decreased in H9c2 cells exposed to hypoxia for 24 hours and in the myocardium of a rat AMI model. This result was associated with increased HIF-1α protein expression, cell membrane damage, apoptosis and necrosis, and proapoptotic gene expression (caspase-3, BAX, Faslg, and P53) but decreases in expression of the antiapoptotic gene Bcl-2 and cell viability. Overexpression of miR-27a-5p remarkably reduced hypoxia-induced cardiomyocyte injury, cell membrane damage, and cellular apoptosis, decreased the level of autophagy, and significantly improved cellular viability through inhibition of expression of its target gene, Atg7. These results suggested that mimic miR-27a-5p plays a significant cardioprotective role against hypoxia-induced H9c2 cell injury and may be an innovative target for the treatment of ischemic heart disease.[51]

MiR-150 expression was prominently downregulated in the infarcted myocardium region after AMI in a rat model, and the myocardial fibrosis-related proteins col1α1, col1α2, col3, and α-SMA were significantly elevated. Moreover, overexpression of miR-150 remarkably decreased the expression levels of col1α1, col1α2, col3, and α-SMA in the border area of the infarcted myocardium, reduced the collagen volume fraction and apoptosis rate, and inhibited myocardial fibrosis but significantly enhanced ventricular remodeling and cardiac function after AMI. These results indicated that upregulation of miR-150 has a significant impact on the clinical outcomes of AMI.[52]

Wang et al. found that miR-29b levels in the infarct border zone of a rat AMI model were markedly decreased, but COL1A1 and α-SMA levels were remarkably upregulated. Furthermore, expression of a miR-29b mimic significantly downregulated COL1A1 and α-SMA expression levels and reduced the collagen volume fraction and myocardial fibrotic level but markedly improved cardiac function by upregulating SH2B3 gene expression, suggesting overexpression of miR-29b might be a novel therapeutic target after AMI.[53] Xue et al. also reported that overexpression of miR-29b-3p significantly inhibited the proliferation, migration, and differentiation of TGF-β1-mediated cardiac fibrosis after AMI in rats. They suggested that mimic miR-29b-3p has a significant anti-fibrotic effect on cardiac fibrosis by targeting FOS and might be helpful for post myocardial infarction management.[54]

The relative expression of miR-206 in infarcted myocardial areas and in hypoxia-induced cardiomyocytes was significantly decreased compared with that in controls. Overexpression of miR-206 in rat hearts injected with a miR-206 agomir resulted in a marked reduction of the myocardial infarct size compared with that in control rats. Mimic miR-206 expression remarkably decreased the apoptosis rate in hypoxia-exposed neonatal rat cardiomyocytes through downregulation of protein tyrosine phosphatase 1B expression, suggesting that a high level of miR-206 is a significant cardioprotective therapeutic strategy in AMI treatment.[55]

The cardiac-enriched miR-210 level was significantly increased in a rat model of AMI. Overexpression of miR-210 markedly promoted angiogenesis with amplified microvessel density in the infarcted myocardium area, enhanced left ventricular fractional shortening and the left ventricular ejection fraction ratio, improved cardiac contractility and left ventricular remodeling after AMI, and significantly enhanced cardiac function by suppressing β-MHC and elevating HGF expression. The results suggested that a miR-210 agonist could be a molecular therapeutic tool for AMI treatment.[56]

miRNAs are critically regulated in angiogenesis, and angiogenesis plays an essential role in tissue repair after myocardial infarction. Recently, Bestepe et al. revealed that miR-409 expression was significantly upregulated in ACS patients and a mouse model of AMI compared with that in control groups. Moreover, inhibition of miR-409 in endothelial cells subjected to ischemia-reperfusion (I/R) resulted in significant elevation of pro-angiogenic factors including VEGF and fibroblast growth factor, increased endothelial cell proliferation and migration via upregulation of its target mRNA, DNAJB9, and increased protein expression through p38 mitogen-activated protein kinase pathways. In addition, in miR-409-3p knockout mice, the left ventricular ejection fraction was amplified by 28% and the infarct area was diminished by 33.8% compared with that in control mice. These results suggest that miR-409 has a substantial effect on the angiogenic endothelial cell response to cardiomyocyte ischemia and could be a new molecular target for therapeutic intervention for AMI.[57]

Cardiac miR-1 levels in rat hearts exposed to I/R were significantly increased, but after administration of telmisartan (12 mg/kg/day for 3 weeks) miR-1 expression was remarkably downregulated, Cnx43, KCNQ1, and Bcl-2 levels were markedly upregulated, cardiomyocyte injury was significantly reduced, and cellular viability was improved. These results suggested that miR-1 has a cardioprotective effect against myocardial damage through telmisartan by modulation of its targets, Cnx43, KCNQ1, and Bcl-2l.[58]

MiR-21 was downregulated in a rat model of AMI, oxidative stress-induced cardiomyocytes, and infarct areas of a mouse I/R model. However, a miR-21 mimic significantly attenuated apoptosis, caspase-3 activity, and the myocardial infarct size and markedly enhanced angiogenesis, cellular viability, and cardiac function after AMI through suppression of PDCD4 expression. These results indicated miR-21 as a potential therapy for AMI (Table 4).[59]

Role of miRNAs in cardiovascular-related aging

Aging is a complex multisystem physiological process characterized by progressive degeneration of human tissues or organs, a subsequent decline in cellular repair capacity, and loss of function. Globally, approximately 20% of people will be 65 years or older by 2030. Biological aging is a non-modifiable major risk factor for CVDs including atherosclerosis, hypertension, CHD, myocardial infarction, cardiac hypertrophy, heart failure, peripheral arterial diseases, and stroke. Recently, several basic and clinical studies demonstrated that various miRNAs are differentially expressed during aging, critically regulate the aging process, and have a potential for use as aging biomarkers and therapy.[60]

Lee et al. reported that the peripheral circulating hsa-miR-409-3p expression level was remarkably higher in people older than 65 years than in those younger than 30 years among both healthy male and female individuals. In senescent human endothelial progenitor cells (EPCs), hsa-miR-409-3p expression was significantly upregulated compared with that in young EPCs, markedly inhibited angiogenesis through targeting of protein phosphatase 2 catalytic subunit alpha (PPP2CA) gene expression, and was controlled by the PP2A/p38 signaling pathways. The results suggested that hsa-miR-409-3p might be an innovative biomarker for human aging.[61] Carini et al. found that circulating miR-101-3p and miR-142-5p expression levels were evidently downregulated in a group of frail individuals more than

Table 4. Therapeutic role of miRNAs in AMI.

miRNAs	Expression	Important target genes	Function/Effects	References
miR-30d-5p	Mimic	p53/pp53	Reduced infarct size of the left ventricle and cardiomyocyte apoptosis	48
let-7e-5p	Mimic	TNF-α, MCP-3, and MDC	Improved angiogenesis capacity	49
miR-375	Mimic	NLK	Reduced apoptosis and enhanced cardiomyocyte viability	50
miR-27a-5p	Mimic	Atg7	Cardioprotective role via preventing cardiomyocyte injury	51
miR-150	Mimic	col1α1, col1α2, col3, and α-SMA	Inhibited myocardial fibrosis and enhanced cardiac function	52
miR-29b	Mimic	SH2B3, FOS	Markedly improved cardiac function, anti-fibrotic role in cardiac fibrosis	53,54
miR-206	Mimic	Protein tyrosine phosphatase 1B	Reduced myocardial infarct size and cardioprotective effects	55
miR-210	Inhibition	β-MHC and HGF	Enhanced LVEF, improved cardiac contractility, and ventricular remodeling	56
miR-409	Inhibition	DNAJB9 and mitogen-activated protein kinase	Increased LVEF, reduced infarct size, and improved angiogenesis.	57

miRNA, microRNA; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction.

70 years old compared with those in controls.[62] Additionally, these two miRNAs showed excellent AUC values and significantly discriminated frail patients from control subjects. Furthermore, these two miRNAs could potentially regulate cellular aging processes through their targets and could be new biomarkers for aging-related frailty syndrome patients.[20] High expression of circulating miR-34a, miR-34b, and miR-34c was observed in CAD patients, and these three miRNAs were significantly associated with aortic stiffening. Elevated levels of miR-34a and miR-34c were negatively correlated with SIRT1 or JAG1, NOTCH2, CTNNB1, and ATF1. Inhibition of miR-34a/b/c ameliorated atherosclerotic plaque formation in an atherosclerotic mouse model through elevation of Sirt1 and Jag1 expression, indicating that miR-34a/b/c have potential clinical roles in human arterial aging and atherosclerotic vascular disease.[63]

MiR-34a and IL-6 expression levels were increased in 21-month-old mice, human aortic smooth muscle cells (HASMCs) of different ages, and cells that had undergone senescence. Expression of a miR-34a mimic significantly accelerated HASMC senescence and calcification through activation of the senescence-associated secretory phenotype and augmented IL-6 secretion, suggesting that miR-34a is directly associated with vascular inflammation.[64] Circulating miR-23a levels were markedly higher in a middle-aged group (45–60 years old) than in a young (20–35 years old) group of participants, and animal studies showed that miR-23a significantly increased with aging. Upregulation of miR-23a remarkably inhibited cell proliferation and restricted

the WI-38 cell cycle through downregulation of its target, FOXO3a. Therefore, miR-23a plays an essential role in regulating cellular senescence and the human aging process.[65]

Endothelial cell senescence and endothelial barrier dysfunction are significantly induced by advanced glycation end-products (AGEs) through downregulation of the transepithelial electrical resistance and elevation of p-MLC/MLC and MLCK expression. Expression of a miR-1-3p mimic decreased the MLCK signal, enhanced AGE-influenced endothelial barrier function impairment, and decreased oxidative stress and endothelial cell senescence associated with aging.[66] The miR-146a expression level was remarkably increased in post-myocardial infarction aged mouse model hearts, and matrix metalloprotease (MMP)2/16 levels were evidently decreased in cardiomyocytes, leading to elevated MLCK3 and MLC2 expression. MiR-146a knockout mice were unable to control the MMP2/16-MLCK3-p-MLC2 pathway in senescent cardiomyocytes and subsequently exhibited decreased cardiac function in post-myocardial infarction hearts. In aging mice, miR-146a failed to regulate the MMP2/16-MLCK3-p-MLC2 axis and enhanced myocardial ischemic injury.[67]

Cellular anti-aging activity is crucially controlled by nicotinamide adenine dinucleotide (NAD^+). MiR-146a expression was elevated in senescent cells, and AMPK activation was decreased. Furthermore, inhibition of miR-146a upregulated metformin-mediated NAMPT expression, NAD^+ synthesis, and SIRT activity and markedly protected against cellular senescence, suggesting miR-146a as a new molecular target for the prevention of aging and aging-associated diseases.[21]

In older mice (24–25 months), miR-29a expression was highly increased in the heart compared with that in younger mice (2–3 months). Expression of a miR-29a mimic in cardiac muscle greatly reduced cellular proliferation and migration and prevented aging-related cardiac fibrosis through downregulation of SERPINH1 gene expression. Therefore, miR-29a has prospective therapeutic value in preventing cardiac aging.[68] In senescent endothelial cells, the miR-217 level was highly upregulated, and expression of a miR-217 mimic considerably decreased proliferation, migration, and angiogenesis during endothelial cell growth through enhancement of senescence-associated β-galactosidase (SA-β-gal). Inhibition of miR-217 evidently diminished SA-β-gal via targeting the SIRT1/p53 signaling pathway, providing a new molecular mechanism for the development of vascular endothelial cell senescence.[69] In centenarians (mean age 101.80 years old) miR-142-3p expression was more strongly upregulated than that in elderly control participants (mean age 72.5 years old) with no family history of longevity. Moreover, expression of a miR-142-3p mimic improved genotoxicity-related stress resistance and impaired cell cycle growth in IMR90 cells. Additionally, miR-142-3p mimic-injected mice exhibited greatly diminished insulin/insulin-like growth factor signaling and distinctly modified longevity-linked phenotypes, including enhanced stress resistance, augmented diet/aging-associated glucose intolerance, and longevity-related changes in the metabolic profile. These results suggest miR-142-3p as a potential therapeutic option to prevent human aging or aging-related disease and promote human longevity.[70]

Circulating miR-17 and miR-126-3p expression levels in geriatric (>65 years old) hospitalized patients were highly downregulated during 31 days, 1 year, and 2 years of follow-up and were significantly associated with the neutrophil-to-lymphocyte ratio, estimated glomerular filtration rate, and cardiovascular

multimorbidity and mortality. Decreased miR-17 and miR-126-3p levels have a strong clinical impact on evaluation of an increased risk of short- and medium-term mortality in older patients. Therefore, these miRNAs may have diagnostic and prognostic biomarker value for aged people.[71] Circulating miR-126-3p expression progressively increased from 18 years to 99 years of age in healthy subjects, but it was significantly decreased in centenarians (100–111 years old) compared with that in younger subjects. Moreover, increased miR-126-3p expression was observed in senescent endothelial cells compared with that in younger cells. MiR-126-3p might have diagnostic or prognostic significance for bio-positive aging and age-related diseases.[72] Plasma miR-3162-3p levels in elderly (>65 years old) UA patients were exceptionally increased and showed the best accuracy, highest discrimination power, and remarkable sensitivity and specificity for the diagnosis of older UA patients (Table 5).[73]

Our previous study found that plasma miR-21 progressively increased with aging among healthy subjects, and higher expression was observed in the 70 to

Table 5. Role of miRNAs in aging and aging-related cardiovascular diseases.

miRNAs	Expression	Role	Important target genes	Effects	References
miR-146a	Upregulated in aged mouse heart	Molecular target for the prevention of aging-related cardiovascular diseases	SIRT	Inhibition of miR-146a and markedly protected against cellular senescence	[12]
miR-409-3p	Upregulated in older adults	Biomarker for human aging	PPP2CA gene	Inhibited angiogenesis in senescent human endothelial progenitor cells	[61]
miR-23a levels	Elevated with aging	Cellular senescence and human aging	FOXO3a	Inhibited cell proliferation through downregulation of its target, FOXO3a	[65]
miR-29a	Increased in aged mouse heart	Therapeutic role in preventing cardiac aging	SERPINH1	Overexpression of miR-29a prevented aging-related cardiac fibrosis	[68]
miR-142-3p	Upregulated in 101.80-year-old individuals	Prevent human aging and promote human longevity		miR-142-3p mimic-injected mice showed reduced insulin/IGF-1 signaling and regulated longevity-linked phenotypes	[70]
miR-17, miR-126-3p	Downregulated in >65-year-old individuals	Diagnostic, prognostic		Associated with eGFR, neutrophil-to-lymphocyte ratio, cardiovascular multimorbidity and mortality	[71]
miR-21	Upregulated in individuals ≥65 years old	Prevents aging-associated oxidative stress	p53, γ-H2AX, PTEN, PI3K, Nrf2	Reduced oxidative stress damage in senescent $CD4^+$ T cells	[74–76]

miRNA, microRNA; eGFR, estimated glomerular filtration rate.

84-year-old group than that in the 30 to 49-year-old group. Moreover, in the 70- to 84-year-old and 50- to 69-year-old groups, circulating miR-21 levels were markedly elevated in both stable angina and UA patients compared with those in younger (30- to 49-year-old) stable angina and UA patients. Additionally, miR-21 showed outstanding AUC values for the diagnosis of stable angina and UA patients. Therefore, miR-21 plays an important role in cardiovascular aging.[74]

Increased expression of circulating miR-21 was found in older hypertensive patients ($\geq$65 years), and echocardiographic reports showed markedly increased septal thickness and left ventricular mass indices in aged hypertensive patients compared with those of normal subjects. Furthermore, miR-21 expression in cardiomyocytes isolated from aged mice (50 weeks old) was significantly higher than that in younger mice (12 weeks old) and was strongly related to the S100a8/NF-κB/NFAT signaling pathway. Additionally, miR-21 levels and cardiac-correlated proteins such as myosin heavy chain 7, atrial natriuretic peptide, lactic dehydrogenase, and cTnl were significantly upregulated in aged cardiomyocytes compared with those in young cardiomyocytes. Furthermore, elevated miR-21 expression augmented pressure overloaded-associated cardiac hypertrophy in the aging population.[75]

Mesenchymal stem cell (MSC)-derived exosomes have a potential role in aging-related diseases. Human placenta MSC-derived exosomal (hPMSC-exo) treatment of senescent $CD4^+$ T cells resulted in significant reduction of oxidative stress-induced damage (ROS and 8-hydroxy-2′-deoxyguanosine), aging-associated protein expression (p53 and γ-H2AX), and senescence-associated secretory phenotype expression (IL-6 and OPN). The hPMSC-exo-miR-21 evidently reduced PTEN expression, elevated p-PI3K and p-AKT expression and Nrf2 nuclear translocation, and markedly prevented aging-associated oxidative stress-induced damage of senescent $CD4^+$ T cells through targeting of the PTEN/PI3K-Nrf2 axis.[76]

Conclusion

MiRNA-based basic and clinical research is progressing rapidly. However, most research is related to the pathophysiology, diagnosis, and prognosis of various CVDs. Although many studies have reported that cardiac-enriched circulating miRNAs have a significant clinical impact as biomarkers for ischemic heart disease, further large multicenter clinical studies are needed to explore their advantages and side effects before use in clinical practice. Recently, several AMI animal models showed that some miRNAs, including miR-590, miR-199a, miR-210, and miR-34a, significantly protected against cardiomyocyte injury and improved cardiac function. Therefore, these miRNAs should be used as novel therapeutic targets for the treatment of AMI patients, but this research is still in the primary stage and requires more extensive animal studies and human clinical trials before the findings are applied to humans. Aging is an irreversible cause of cellular degeneration, and several mimics and inhibitory miRNAs strongly regulate cellular aging processes and delay cellular death. They may be used as new molecular targets for aging and aging-related CVDs, but more advanced basic and clinical experiments are needed prior to their use in medical practice.

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References

1. Martin SS, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2024 Update: a report from the American Heart Association. *Circulation* 2024; 149: e347–e913.
2. Harold EB, Anandita K, Charles G, et al. Ten things to know about ten cardiovascular disease risk factors – 2022. *Am J Prev Cardiol* 2022; 6: 100342.
3. Ali Sheikh MS, Alduraywish A, Almaeen A, et al. Therapeutic value of miRNAs in coronary artery disease. *Oxid Med Cell Longev* 2021; 2021: 8853748.
4. Szydełko J and Matyjaszek-Matuszek B. MicroRNAs as biomarkers for coronary artery disease related to type 2 diabetes mellitus—from pathogenesis to potential clinical application. *Int J Mol Sci* 2023; 24: 616.
5. González-López P, Álvarez-Villarreal M, Ruiz-Simón R, et al. Role of miR-15a-5p and miR-199a-3p in the inflammatory pathway regulated by NF-κB in experimental and human atherosclerosis. *Clin Transl Med* 2023; 13: e1363.
6. Lu X, Yang B, Yang H, et al. MicroRNA-320b modulates cholesterol efflux and atherosclerosis. *J Atheroscler Thromb* 2022; 29: 200–220.
7. Jayawardena E, Medzikovic L, Ruffenach G, et al. Role of miRNA-1 and miRNA-21 in acute myocardial ischemia-reperfusion injury and their potential as therapeutic strategy. *Int J Mol Sci* 2022; 23: 1512.
8. Huang JP, Chang CC, Kuo CY, et al. Exosomal microRNAs miR-30d-5p and miR-126a-5p are associated with heart failure with preserved ejection fraction in STZ-induced type 1 diabetic rats. *Int J Mol Sci* 2022; 23:7514.
9. Zhang X, Wang X, Wu J, et al. The diagnostic values of circulating miRNAs for hypertension and bioinformatics analysis. *Biosci Rep* 2018; 38: BSR20180525.
10. Zhang HG, Zhang QJ, Li BW, et al. The circulating level of miR-122 is a potential risk factor for endothelial dysfunction in young patients with essential hypertension. *Hypertens Res* 2020; 43: 511–517.
11. Koch L. microRNAs as systemic regulators of ageing. *Nat Rev Genet* 2023; 24: 415.
12. Gong H, Chen H, Xiao P, et al. miR-146a impedes the anti-aging effect of AMPK via NAMPT suppression and NAD^+/SIRT inactivation. *Signal Transduct Target Ther* 2022; 7: 66.
13. Abdelmaksoud NM, Sallam AM, Abulsoud AI, et al. Unraveling the role of miRNAs in the diagnosis, progression, and therapeutic intervention of Alzheimer's disease. *Pathol Res Pract* 2024; 253: 155007.
14. Li J, Chen W, Yi Y, et al. miR-219-5p inhibits tau phosphorylation by targeting TTBK1 and GSK-3β in Alzheimer's disease. *J Cell Biochem* 2019; 120: 9936–9946.
15. Yin Z, Herron S, Silveira S, et al. Identification of a protective microglial state mediated by miR-155 and interferon-γ signaling in a mouse model of Alzheimer's disease. *Nat Neurosci* 2023; 26: 1196–1207.
16. Baethge C, Goldbeck-Wood S and Mertens S. Sanra-a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev* 2019; 4: 5.
17. Vancheri C, Morini E, Prandi FR, et al. Downregulation of circulating Hsa-miR-200c-3p correlates with dyslipidemia in patients with stable coronary artery disease. *Int J Mol Sci* 2023; 24: 1112.

18. Mishra S, Rizvi A, Pradhan A, et al. Circulating microRNA-126 &122 in patients with coronary artery disease: Correlation with small dense LDL. *Prostaglandins Other Lipid Mediat* 2021; 153: 106536.
19. Abdallah HY, Hassan R, Fareed A, et al. Identification of a circulating microRNAs biomarker panel for non-invasive diagnosis of coronary artery disease: case-control study. *BMC Cardiovasc Disord* 2022; 22: 286.
20. Coban N, Erkan AF, Ozuynuk-Ertugrul AS, et al. Investigation of miR-26a-5p and miR-19a-3p expression levels in angiographically confirmed coronary artery disease. *Acta Cardiol* 2023; 78: 945–956.
21. Li H, Gao F, Wang X, et al. Circulating microRNA-378 levels serve as a novel biomarker for assessing the severity of coronary stenosis in patients with coronary artery disease. *Biosci Rep* 2019; 39: BSR20182016.
22. Ling H, Guo Z, Du S, et al. Serum exosomal miR-122-5p is a new biomarker for both acute coronary syndrome and underlying coronary artery stenosis. *Biomarkers* 2020; 25: 539–547.
23. Li J, Chen Z, Wang X, et al. LncRNA UCA1, miR-26a, and miR-195 in coronary heart disease patients: Correlation with stenosis degree, cholesterol levels, inflammatory cytokines, and cell adhesion molecules. *J Clin Lab Anal* 2022; 36: e24070.
24. Zhu X, Hu J, and Xie L. The interplay of long noncoding RNA HULC with microRNA-128-3p and their correlations with lipid level, stenosis degree, inflammatory cytokines, and cell adhesion molecules in coronary heart disease patients. *Ir J Med Sci* 2022; 191: 2597–2603.
25. Coban N, Ozuynuk AS, Erkan AF, et al. Levels of miR-130b-5p in peripheral blood are associated with severity of coronary artery disease. *Mol Biol Rep* 2021; 48: 7719–7732.
26. Xu L, Fu T, Wang Y, et al. Diagnostic value of peripheral blood miR-296 combined with vascular endothelial growth factor B on the degree of coronary artery stenosis in patients with coronary heart disease. *J Clin Ultrasound* 2023; 51: 520–529.
27. Babaee M, Chamani E, Ahmadi R, et al. The expression levels of miRNAs- 27a and 23a in the peripheral blood mononuclear cells (PBMCs) and their correlation with FOXO1 and some inflammatory and anti-inflammatory cytokines in the patients with coronary artery disease (CAD). *Life Sci* 2020; 256: 117898.
28. Lv F, Liu L, Feng Q, et al. Long non-coding RNA MALAT1 and its target microRNA-125b associate with disease risk, severity, and major adverse cardiovascular event of coronary heart disease. *J Clin Lab Anal* 2021;35: e23593.
29. Ali Sheikh MS. The mir-21 inhibition enhanced HUVEC cellular viability during hypoxia-reoxygenation injury by regulating PDCD4. *Mediators Inflamm* 2022; 2022: 9661940.
30. Kramna D, Riedlova P and Jirik V. MicroRNAs as a potential biomarker in the diagnosis of cardiovascular diseases. *Medicina (Kaunas)* 2023; 59: 1329.
31. Chen T, Zhang X, Qian W, et al. Serum miR-497-5p serves as a diagnostic biomarker for acute coronary syndrome and predicts the occurrence of major adverse cardiovascular events after percutaneous coronary intervention. *Bioengineered* 2022; 13: 8266–8276.
32. Meng L, Yu X, Han H, et al. Circulating miR-143 and miR-145 as promising biomarkers for evaluating severity of coronary artery stenosis in patients with acute coronary syndrome. *Clin Biochem* 2023; 111: 32–40.
33. Zhang W, Chang G, Cao L, et al. Dysregulation of serum miR-361-5p serves as a biomarker to predict disease onset and short-term prognosis in acute coronary syndrome patients. *BMC Cardiovasc Disord* 2021; 21: 74.
34. Elgebaly SA, Christenson RH, Kandil H, et al. Nourin-dependent miR-137 and miR-106b: novel early inflammatory diagnostic biomarkers for unstable angina patients. *Biomolecules* 2021; 11: 368.
35. Tong KL, Mahmood Zuhdi AS, Wan Ahmad WA, et al. Circulating MicroRNAs in young patients with acute coronary syndrome. *Int J Mol Sci* 2018; 19: 1467.

36. Qiu H, Zhang Y, Zhao Q, et al. Platelet miR-587 may be used as a potential biomarker for diagnosis of patients with acute coronary syndrome. *Clin Lab* 2020; 66. DOI: 10.7754/Clin.Lab.2019.190703.
37. Zhao Y, Song X, Ma Y, et al. Circulating mir-483-5p as a novel diagnostic biomarker for acute coronary syndrome and its predictive value for the clinical outcome after PCI. *BMC Cardiovasc Disord* 2023; 23: 360.
38. Ling H, Guo Z, Du S, et al. Serum exosomal miR-122-5p is a new biomarker for both acute coronary syndrome and underlying coronary artery stenosis. *Biomarkers* 2020; 25: 539–547.
39. Shen M, Xu X, Liu X, et al. Prospective study on plasma microRNA-4286 and incident acute coronary syndrome. *J Am Heart Assoc* 2021;10: e018999.
40. Liu P, Wang S, Li K, et al. Exosomal microRNA-4516, microRNA-203 and SFRP1 are potential biomarkers of acute myocardial infarction. *Mol Med Rep* 2023; 27: 124.
41. Bukauskas T, Mickus R, Cereskevicius D, et al. Value of serum miR-23a, miR-30d, and miR-146a biomarkers in ST-elevation myocardial infarction. *Med Sci Monit* 2019; 25: 3925–3932.
42. Xue S, Zhu W, Liu D, et al. Circulating miR-26a-1, miR-146a and miR-199a-1 are potential candidate biomarkers for acute myocardial infarction. *Mol Med* 2019; 25: 18.
43. Scărlătescu AI, Barbălată T, Sima AV, et al. miR-146a-5p, miR-223-3p and miR-142-3p as potential predictors of major adverse cardiac events in young patients with acute ST Elevation myocardial infarction—added value over left ventricular myocardial work indices. *Diagnostics (Basel)* 2022; 12: 1946.
44. Ding H, Chen W and Chen X. Serum miR-96-5p is a novel and non-invasive marker of acute myocardial infarction associated with coronary artery disease. *Bioengineered* 2022; 13: 3930–3943.
45. Mi XL, Gao YP, Hao DJ, et al. Prognostic value of circulating microRNA-21-5p and microRNA-126 in patients with acute myocardial infarction and infarct-related artery total occlusion. *Front Cardiovasc Med* 2022; 18: 947721.
46. Wang X, Tian L and Sun Q. Diagnostic and prognostic value of circulating miRNA-499 and miRNA-22 in acute myocardial infarction. *J Clin Lab Anal* 2020; 34: 2410–2417.
47. Dai Y, Yan T and Gao Y. Silence of miR-32-5p promotes endothelial cell viability by targeting KLF2 and serves as a diagnostic biomarker of acute myocardial infarction. *Diagn Pathol* 2020; 15: 19.
48. Boxhammer E, Paar V, Wernly B, et al. MicroRNA-30d-5p— a potential new therapeutic target for prevention of ischemic cardiomyopathy after myocardial infarction. *Cells* 2023; 12: 2369.
49. Mompeón A, Pérez-Cremades D, Paes AB, et al. Circulating miRNA fingerprint and endothelial function in myocardial infarction: comparison at acute event and one-year follow-up. *Cells* 2022; 11: 1823.
50. Ali Sheikh MS. Overexpression of miR-375 protects cardiomyocyte injury following hypoxic-reoxygenation injury. *Oxid Med Cell Longev* 2020; 2020: 7164069.
51. Zhang J, Qiu W, Ma J, et al. miR-27a-5p attenuates hypoxia-induced rat cardiomyocyte injury by inhibiting *Atg7*. *Int J Mol Sci* 2019; 20: 2418.
52. Tian HB, Li SH, Hu KQ, et al. MicroRNA-150 alleviates acute myocardial infarction through regulating cardiac fibroblasts in ventricular remodeling. *Eur Rev Med Pharmacol Sci* 2019; 23: 7611–7618.
53. Wang Y, Jin BJ, Chen Q, et al. MicroRNA-29b upregulation improves myocardial fibrosis and cardiac function in myocardial infarction rats through targeting SH2B3. *Eur Rev Med Pharmacol Sci* 2019; 23: 10115–10122.
54. Xue Y, Fan X, Yang R, et al. miR-29b-3p inhibits post-infarct cardiac fibrosis by targeting FOS. *Biosci Rep* 2020; 40: BSR20201227.
55. Yan Y, Dang H, Zhang X, et al. The protective role of MiR-206 in regulating cardiomyocytes apoptosis induced by ischemic injury by targeting PTP1B. *Biosci Rep* 2020; 40: BSR20191000.
56. Fan ZG, Qu XL, Chu P, et al. MicroRNA-210 promotes angiogenesis in acute

myocardial infarction. *Mol Med Rep* 2018; 17: 5658–5665.
57. Bestepe F, Fritsche C, Lakhotiya K, et al. Deficiency of miR-409-3p improves myocardial neovascularization and function through modulation of DNAJB9/p38 MAPK signaling. *Mol Ther Nucleic Acids* 2023; 32: 995–1009.
58. Trotta MC, Ferraro B, Messina A, et al. Telmisartan cardioprotects from the ischaemic/hypoxic damage through a miR-1-dependent pathway. *J Cell Mol Med* 2019; 23: 6635–6645.
59. Chen CH, Hsu SY, Chiu CC, et al. MicroRNA-21 mediates the protective effect of cardiomyocyte-derived conditioned medium on ameliorating myocardial infarction in rats. *Cells* 2019; 8: 935.
60. Jiapaer Z, Su D, Hua L, et al. Regulation and roles of RNA modifications in aging-related diseases. *Aging Cell* 2022; 21: e13657.
61. Lee YN, Wu YJ, Lee HI, et al. Hsa-miR-409-3p regulates endothelial progenitor senescence via PP2A-P38 and is a potential ageing marker in humans. *J Cell Mol Med* 2023; 27: 687–700.
62. Carini, G, Mingardi, J, Bolzetta, F, et al. miRNome profiling detects miR-101-3p and miR-142-5p as putative blood biomarkers of frailty syndrome. *Genes* 2022; 13: 231.
63. Gatsiou A, Georgiopoulos G, Vlachogiannis NI, et al. Additive contribution of microRNA-34a/b/c to human arterial ageing and atherosclerosis. *Atherosclerosis* 2021: 327: 49–58.
64. Zuccolo E, Badi I, Scavello F, et al. The microRNA-34a-induced senescence-associated secretory phenotype (SASP) favors vascular smooth muscle cells calcification. *Int J Mol Sci* 2020; 21: 4454.
65. Wang S, Sun Y, Yao L, et al. The role of microRNA-23a-3p in the progression of human aging process by targeting FOXO3a. *Mol Biotechnol* 2024; 66: 277–287.
66. Cheng M, Yang Z, Qiao L, et al. AGEs induce endothelial cells senescence and endothelial barrier dysfunction via miR-1-3p/MLCK signaling pathways. *Gene* 2023; 851: 147030.
67. Dong M, Chen D, Zhu Y, et al. Impaired regulation of MMP2/16-MLCK3 by miR-146a-5p increased susceptibility to myocardial ischaemic injury in aging mice. *Cardiovasc Res* 2023; 119: 786–801.
68. Rusu-Nastase EG, Lupan AM, Marinescu CI, et al. MiR-29a increase in aging may function as a compensatory mechanism against cardiac fibrosis through SERPINH1 downregulation. *Front Cardiovasc Med* 2022: 8: 810241.
69. Wang Z, Shi D, Zhang N, et al. MiR-217 promotes endothelial cell senescence through the SIRT1/p53 signaling pathway. *J Mol Histol* 2021; 52: 257–267.
70. Wang X, Jung HJ, Milholland B, et al. The regulation of insulin/IGF-1 signaling by miR-142-3p associated with human longevity. *bioRxiv* 2023; 20: 2023.05.19.541542.
71. Marchegiani F, Recchioni R, Di Rosa M, et al. Low circulating levels of miR-17 and miR-126-3p are associated with increased mortality risk in geriatric hospitalized patients affected by cardiovascular multimorbidity. *Geroscience* 2024; 46: 2531–2544.
72. Accardi G, Bono F, Cammarata G, et al. miR-126-3p and miR-21-5p as hallmarks of bio-positive ageing; correlation analysis and machine learning prediction in young to ultra-centenarian Sicilian population. *Cells* 2022; 11: 1505.
73. Cui Y, Song J, Li S, et al. Plasmatic microRNA signatures in elderly people with stable and unstable angina. *Int Heart J* 2018; 59: 43–50.
74. Ali Sheikh MS. Diagnostic role of plasma microRNA-21 in stable and unstable angina patients and association with aging. *Cardiol Res Pract* 2020; 2020: 9093151.
75. Chang WT, Shih JY, Lin YW, et al. miR-21 upregulation exacerbates pressure overload-induced cardiac hypertrophy in aged hearts. *Aging (Albany NY)* 2022; 14: 5925–5945.
76. Xiong Y, Xiong Y, Zhang H, et al. hPMSCs-derived exosomal miRNA-21 protects against aging-related oxidative damage of $CD4^+$ T cells by targeting the PTEN/PI3K-Nrf2 axis. *Front Immunol* 2021; 12: 780897.