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Original Article

The Investigation of Plasma Micro RNAs as Noninvasive Biomarkers for the Prediction of In-Stent Restenosis

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Abstract

Background: In-stent restenosis (ISR) is a detrimental complication that takes place following coronary stenting. There is strong evidence that micro ribonucleic acids (miRNAs) are involved in inflammation and neointimal formation.

Objectives: The current study aimed to explore the role of some circulating miRNAs in restenosis patients.

Methods: A total of 62 patients were enrolled in this study. According to angiography, the patients were grouped into restenosis and non-restenosis groups. The plasma levels of miR-21, miR-126, miR-143/miR-145, and miR-222 were analyzed with quantitative real-time polymerase chain reaction.

Results: The plasma expression level of miR-21 ($P=0.003$) was significantly higher compared to the control group. In addition, the plasma levels of miR-126 ($P=0.004$), miR-143 ($P=0.003$), and miR-145 ($P=0.008$) were considerably lower in the ISR group compared with the control group. In the ISR group, the plasma level of miR-222 was increased, but this increase was not significant ($P=0.08$).

Conclusion: The results revealed differential changes in the plasma level of miRNAs. Some miRNAs may have critical functions in restenosis pathogenesis, and others may have protective effects. Overall, evidence suggests a predictive role for miRs following interventional therapy.

Keywords: Restenosis, Inflammation, miR-21, miR-126, miR-143, miR-145

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Background

In-stent restenosis (ISR) is defined as the pathological re-narrowing of the stent lumen occuring after implantation. Target lesion revascularization (repeat PCI), is significantly associated with in-stent restenosis and may carry a high risk of adverse out comes compared to de novo interventions (1). According to the data of the National Cardiovascular Data Registry, 10.6% of all PCIs require reinterventions associated with ISR (2). Numerous factors are involved in the incidence of restenosis, including the type of stent (drug-eluting or bare metal), lesion (stent) length > 30 mm, ≥ 3 implanted stents, stent diameter < 3 mm, protocol of medication administration, population of patients, and risk factors associated with cardiovascular diseases (CVDs) (3). Although the exact pathophysiological mechanisms of ISR are not entirely clear, it is believed that inflammation, proliferation of epithelial cells (ECs), and matrix remodeling play a major role in restenosis development (4).

As noted earlier, ISR refers to the re-narrowing of the lumen of a previous stent (5). Angiographically, ISR refers to more than 50% stenosis within or 5 mm adjacent to

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the edge of previous stents. Clinical ISR occurs when patients with a history of angioplasty experience the signs and symptoms of ischemia due to ISR. Vascular smooth muscle cells (VSMCs) and ECs play a key role in the process of ISR (6,7). Most studies have focused on the VSMC proliferation inhibition as a protective strategy against restenosis (8).

Micro ribonucleic acids (miRNAs), a class of small RNAs (18–24 nucleotides), have important biological functions (9). Acting as the master regulators of gene expression, miRNAs play significant roles in various cellular processes, including proliferation, apoptosis, migration, differentiation, and evolution (10). In addition, miRNAs are necessary for the proper evolution of the cardiovascular system (11). Their expression has been reported in circulatory system components (i.e., arterial wall cells, leukocytes, and ECs) and atherosclerotic lesions (6,11).

Recent in vitro and in vivo studies have indicated that changes in blood flow conditions significantly affect the expression of miRs in ECs. These miRs, known as mechanosensitives, regulate the expression of endothelial genes and chemokines. Moreover, they may contribute to vascular integrity, endothelial dysfunction, ischemic angiogenesis, endothelialization, vascular remodeling, and atherosclerosis (12,13).

Regarding the effect of vascular injury on the expression of miRs, it seems that their expression profiles may be beneficial biomarkers for predicting the risk of CVDs (14), including acute myocardial infarction (MI) (15), cardiac remodeling (reconstruction) after ischemia (16), and restenosis (17-19).

Given the increasing number of PCI procedures worldwide, the need for preventing restenosis, and the significant role of miRs in this process, the aim of this research is to investigate the expression profiles of certain miRs in patients with restenosis compared to the control group before PCI as a non-invasive predictor biomarker for ISR.

Materials and Methods

Ethical Protocols

The protocol of the study has been approved by the Ethics Committee of Hamadan University of Medical Sciences, Hamadan, Iran (9807095137, clinical ethics code IR.UMSHA.REC.1398.478). This study was conducted in accordance with the Declaration of Helsinki. All patients signed informed consent forms.

Statistical Analysis

SPSS software (version 21) was used for data analysis. The statistical significance level was considered to be 5%. In the descriptive statistics section, the means and standard deviations were utilized to describe and report quantitative variables, and ratios and percentages were employed for qualitative variables. To compare quantitative variables, if they were normal, the independent t-test was applied to compare the two groups. The analysis of variance and chi-square tests were used to compare more than 2 groups and to check the relationship between qualitative variables, respectively. Finally, Pearson's correlation coefficient was applied to examine the relationship between quantitative variables.

Experimental Design

This study investigated a total of 62 patients (40 males and 22 females) aged between 39 years and 78 years old, who had a history of drug-eluting stent implantation for more than 6 months at Farshchian Heart Center of Hamadan University of Medical Science, from April 2021 to March 2022.

These patients underwent selective coronary angiography due to their clinical signs and symptoms of ischemia, new electrocardiogram changes, positive non-invasive tests (myocardial perfusion scan and stress echocardiography) for evidence of ischemia, or documented vessel involvement in coronary computed tomography. According to their angiography results, they were assigned to two groups, namely, those with (the case group) or without (the control group) ISR.

Patients' data, including demographic data, past medical history, angiographic data, laboratory data, and drug history, were recorded. The patients who had a history of open-heart surgery, angioplasty in less than 6 months, or a history of inflammation or rheumatologic disorders were excluded from the study.

Blood Collection, Plasma Isolation, and Storage

Blood sample from each patient (direct venous puncture) was taken immediately after admission and poured into the serum tube and the ethylenediaminetetraacetic acid tube. Plasma was isolated after centrifugation (1500 g for 10 minutes at room temperature). Plasma samples were aliquoted and stored at -80 ˚C until RNA isolation. The serum high-sensitivity C-reactive protein (hsCRP) levels were measured using the LDN LABOR DIAGNOSTIKA NORD GmbH & Co. KG (LOT 210524), which avoids plasma freeze thawing.

Quantitative Polymerase Chain Reaction

The qPCR technique was employed to measure the plasma level of miRNA expression. RNA was isolated using the RNX-Plus reagent (Sinaclon, IRAN) following the manufacturer's protocols. The quality of the RNAs was assessed using Nanodrop (Thermo Scientific, USA). The RNA integrity was determined through gel electrophoresis. The reverse transcription of the RNAs was performed using the cDNA synthesis protocol, which included adenosine triphosphate, deoxynucleoside triphosphates, polyA, primers, polyA enzyme, *reverse transcription* enzyme, and 1ng -5µg RNA, with nuclease-free H_2O added up to 20 µL in a thermal cycler PCR system (Bio-Rad, USA). The process involved incubation for 60 minutes at 42 ˚C, followed by 5 minutes at 75 ˚C.

The reaction was then stopped at 85 ˚C for 5 minutes and kept at 4 ˚C.

Following enzyme activation at a temperature of 95 ˚C for a duration of 15 minutes, the amplification protocol consisted of denaturation at 95 ˚C for 15 seconds and annealing at 61 ˚C for 40 seconds, repeated for a total of 40 cycles. U6 snRNA was utilized as a reference control in the study, and the average fold changes were calculated using the $2^{-\Delta\Delta CT}$ method.

Micro Ribonucleic Acids-Gene Interaction Networks

Several studies have shown the regulatory function of miRNAs in physiological processes (20,21). To investigate the potential role of miRNAs from phosphodiesterases in coronary artery ISR, in silico prediction methods miRnet (https://www.mirnet.ca), miRDB (https://mirdb.org), and DIANA Tools (http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=mirpath/index) were utilized to predict the interaction of miRNA-gene-ontology (Figure 1) and miRNA-gene-Kyoto Encyclopedia of Genes and Genomes (Figure 2).

The functional annotation of has-miR-21, has-miRNA-126, has-miR-143, has-miR-145, and has-miR-222 target genes and the Kyoto Encyclopedia of Genes and Genomes enrichment analysis were performed using the DAVID and miRDB databases. The annotation included the gene's involvement in biological processes, molecular functions, and cellular components. Additionally, the enrichment analysis identified signal transduction pathways with significant differences. These differences were found to be statistically significant ($P < 0.05$).

MiRNAs play a crucial role in the development of ISR, which involves vessel inflammation and endothelial regeneration. These processes are controlled by various miRNAs. has-miR-21, has-miRNA-126, has-miR-143, and has-miR-145 have an important role in endothelial regeneration, while has-miR-222 is effective in vessel inflammation (22).

Results

Clinical Characteristics of Patients

From April 2021 to March 2022, 62 patients with a history of stent angioplasty were admitted to the Farshchian Heart Center for PCI. Based on angiography results, seventeen patients had developed in-stent restenosis, which presented in three forms: diffuse in-stent restenosis, segmental in-stent restenosis, and complete stent occlusion. The baseline data of patients in the ISR and non-ISR groups are presented in Table 1.

Statistical analysis using a t-test revealed that the incidence of MI ($P=0.043$), statin usage ($P=0.018$), and ESR levels ($P=0.004$) significantly differed between the control and restenosis groups.

The comparison of the two groups indicated significant differences in some variables, including MI, statin utilization, the serum level of hsCRP, and ESR. However, there was no statistical difference in other variables between the two groups.

The Possible Interaction of Micro Ribonucleic Acids

The miRs and their corresponding target genes, which play a crucial role in ISR, were examined based on the Human MicroRNA Disease Database. The has-miR-21, has-miR-126, has-miR-145, and has-miR-222, which were evaluated in this article, are among the effective miRs reported in related databases (Figure 3).

The Plasma Level of Micro Ribonucleic Acids

An analysis of five microRNAs associated with ISR was conducted on a cohort of 62 patients, comprising 17 cases and 45 controls. The expression profiles of these

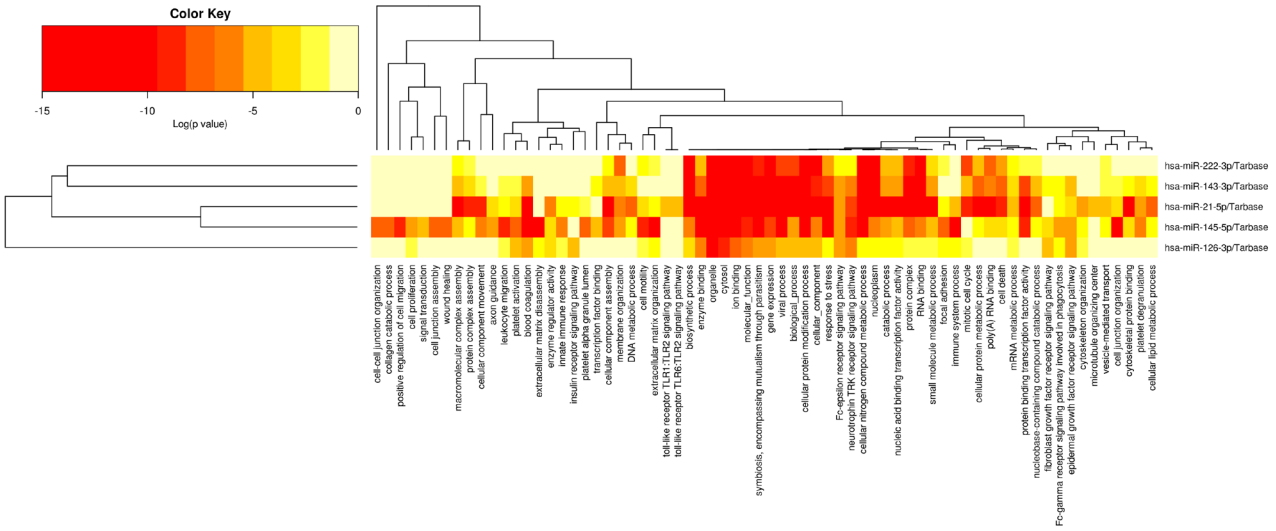

Figure 1. Heat Map Depiction of MicroRNA Involvement in Biological Processes . *Note*. RNAs: Ribonucleic acids. The heat map illustrates how different microRNAs (miRNAs) are associated with various biological processes. Variations in miR expression levels are linked to changes in signaling pathways that regulate critical cellular functions

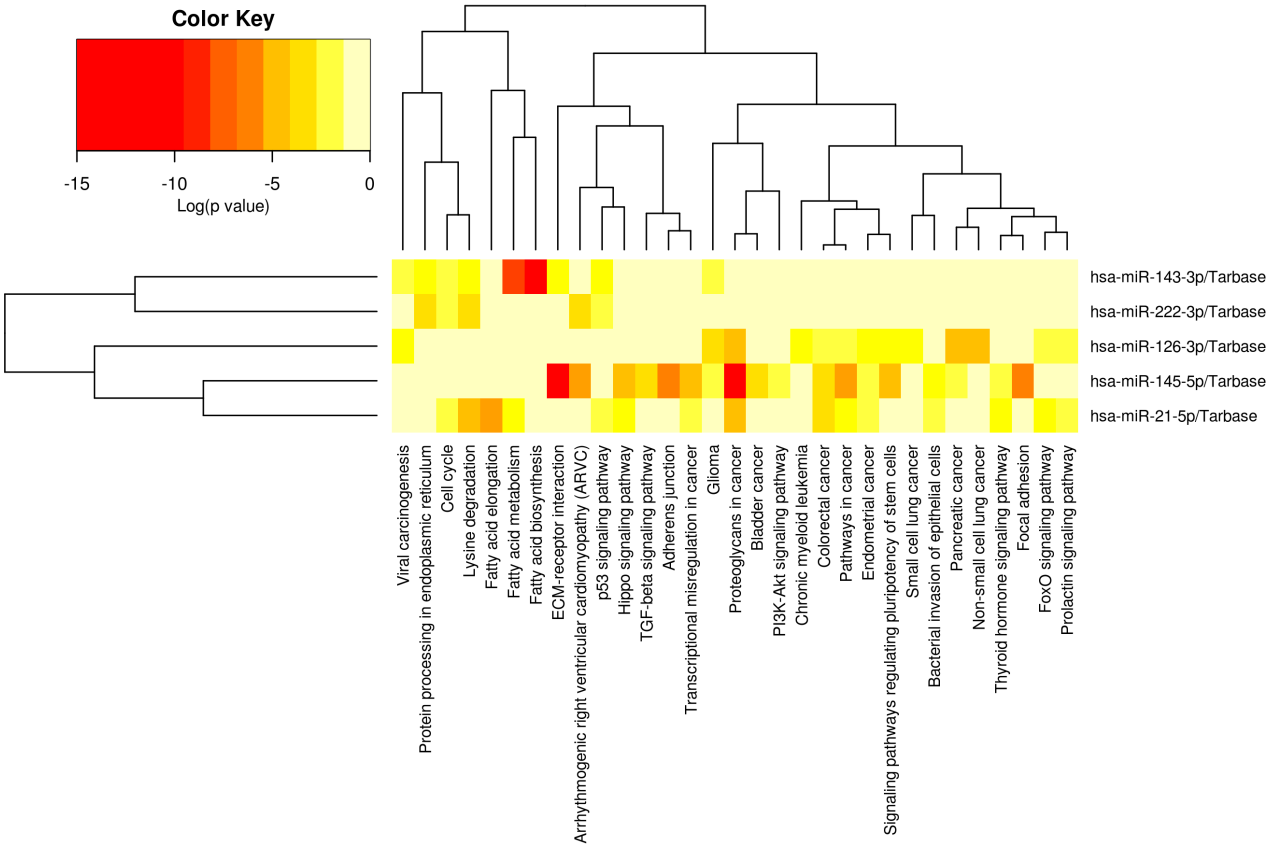

Figure 2. Heat Map Depiction of miRs Involvement in the KEGG Pathway. *Note*. KEGG: Kyoto Encyclopedia of Genes and Genomes; RNAs: Ribonucleic acids. The heat map depicts how miRNAs are associated with various KEGG signaling pathways. It highlights the potential regulatory roles of miRNAs in key biological processes, as reflected by their enrichment across different pathways

Table 1. Demographic Data and Clinical Information of Patients

Parameter	Non-ISR Group (n = 45)	ISR Group (n = 17)	*P* Value
Age (years)	61.35	65.91	0.059
Gender	Male: 28 Female: 17	Male: 11 Female: 6	0.55
Smoking	Yes: 15 No: 30	Yes: 7 No: 10	0.386
DM	Yes: 13 No: 32	Yes: 6 No: 11	0.422
HTN	Yes: 20 No: 25	Yes: 10 No: 7	0.234
MI	Yes: 2 No: 43	Yes: 4 No: 13	0.043
Statins	Yes: 44 No: 1	Yes: 15 No: 2	0.018
P2Y12 inhibitor	Yes: 11 No: 34	Yes: 5 No: 12	0.461
Beta blocker	Yes: 10 No: 35	Yes: 5 No: 12	0.389
ESR	17.73	24.52	0.004
hsCRP (mg/L)	1.63	3.39	0.001

Note. DM: Diabetes mellitus; HTN: Hypertension; MI: Myocardial infarction; ESR: Erythrocyte sedimentation rate; hsCRP: The high-sensitivity C-reactive protein

microRNAs in the plasma were compared between patients with stents and those with ISR, using U6 as a normalization reference. Statistical analysis revealed a significant variance ($P < 0.001$) across all examined genes. Moreover, the overall expression profile significantly differed ($P < 0.05$) from the profiles obtained when using U6 genes individually, except for hsa-miR-222, which did not exhibit this trend.

In summary, our findings (Figure 4) demonstrated that hsa-miR-126, hsa-miR-143, hsa-miR-145, and hsa-miR-222 were downregulated, while hsa-miR-21 was upregulated in the ISR group compared to the control (without ISR) group.

Gene expression levels for each miRNA were visualized separately, comparing the groups as illustrated in Figure 5.

A total of four miRs (the has-miR-21, has-miR-126, has-miR-143, and has-miR-145) exhibited differential expression among the tested groups. Notably, there were gene expression disparities between the control group and the ISR samples. However, no significant expression difference was found in the case of hsa-miR-222. On the other hand, TGFBR2, TCF21, TLR4, TGFB2, ESR1, SMAD3, VEGFR, and VEGFA can be effective in the occurrence of the disease as the target genes of the miRs.

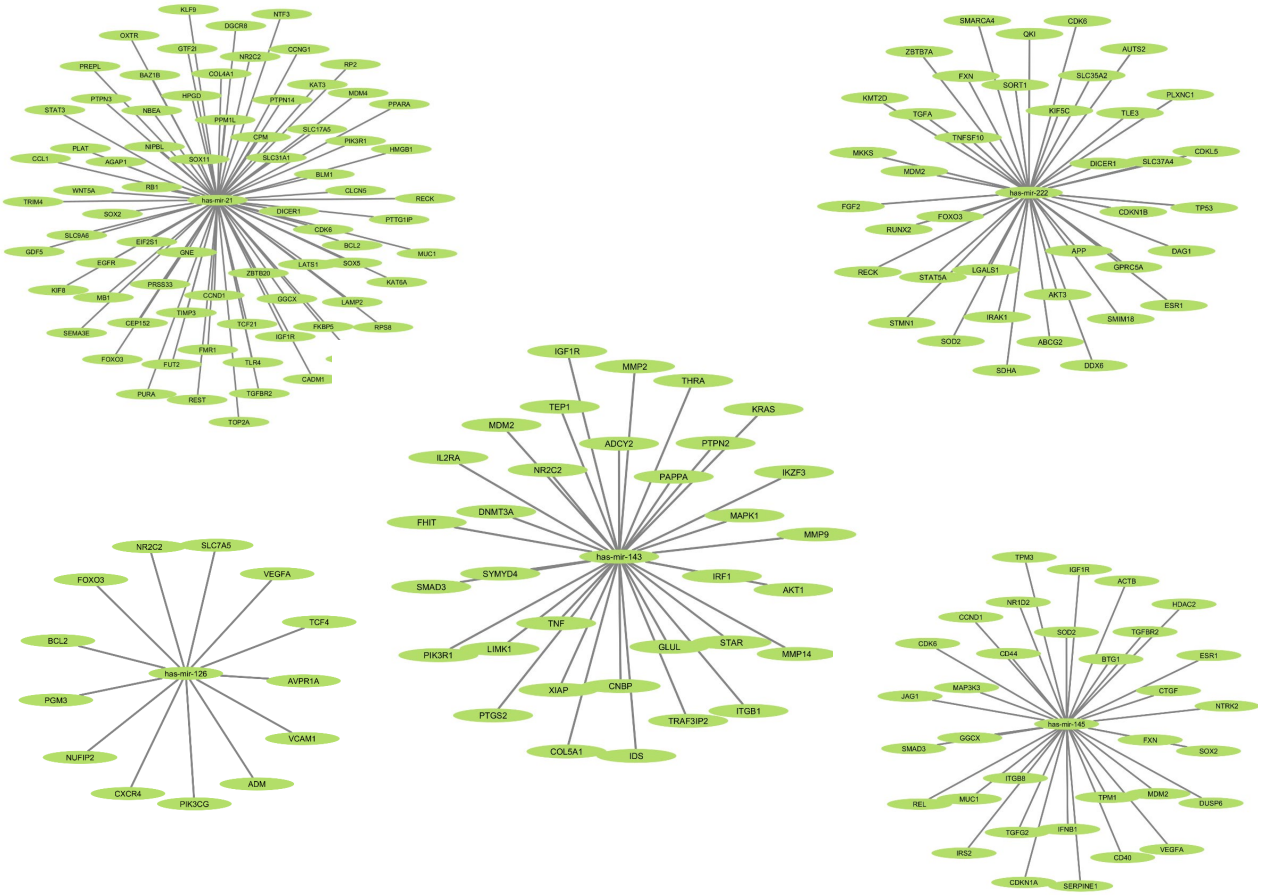

Figure 3. Network Diagrams of the Interactions Between Genes and Regulatory Pathways Targeted by Various MiRNAs. Note. This depicted the interaction of hsa-miR-21, hsa-miR-143, hsa-miR-126, hsa-miR-222, and hsa-miR-145 with targeted genes. Red lines indicate direct or indirect interactions between miRNAs and their associated target gene.

Discussion

In recent years, various studies have been performed to investigate risk prediction, prevention, and novel therapeutic strategies for ISR. In spite of these developments, ISR is the major unfavorable outcome following PCI. From the clinical point of view, ISR characterized by recurrent angina, occurrence of new heart failure and acute MI (1). Increasing evidence underlined miRs as important micro-managers of pathophysiological events in CVDs (23). The current study explored the association between the plasma level of miRs and ISR. It was revealed that the plasma levels of has-miR-21, miR-143/miR-145, and has-miR-126 were precisely associated with the incidence of ISR following drug-eluting stent implantation. In comparison with the control group (non-ISR patients), the plasma level of has-miR21 meaningfully increased in ISR patients. Has-miR-21 is encoded by the *has-miR-21* gene and located on chromosome 17q23.2 (24). Has-miR-21 is important in the cardiovascular system due to its involvement in the differentiation of ECs, migration, and angiogenesis processes (25). Human studies showed the high expression of miR-21 after vascular injuries, indicating its significant role in neointima hyperplasia formation (26). Additionally, some in vitro studies demonstrated the proliferative effect of has-miR-21 on VSMCs. MiR-21 suppression can inhibit neointima hyperplasia formation following angioplasty, stent placement (27,28), or vein grafting (29). It is documented that has-miR-21 has a major role in the occurrence of neointima hyperplasia in the vascular wall via cell proliferation and suppression of cell apoptosis (30). These effects are mediated via protein kinase B and Bcl-2 activation with the suppression of phosphatase and tensin homolog. The has-miR-21 knockdown ceased neointimal lesion formation after the rat carotid artery balloon injury model (26).

MiR-126 is among the most plentiful miRs in ECs, which can regulate the repair of EC (31). This short, stranded non-coding RNA is placed within the intron 7 of the epidermal growth factor-like domain 7 (32). Has-miR-126 is particularly expressed in ECs and has a protective role in vascular endothelium function. Extensive studies have confirmed the association between miR-126 and CVD development (33). Our results revealed the low expression of has-miR-126 in the ISR group-as compared with the control group. The downregulation of has-miR-126 can promote cell adhesion molecule 1 activity and neovascularization. More importantly, has-miR-126 moderates vascular adhesion cytokine-1 expression, which affects atherosclerotic plaque development (1).

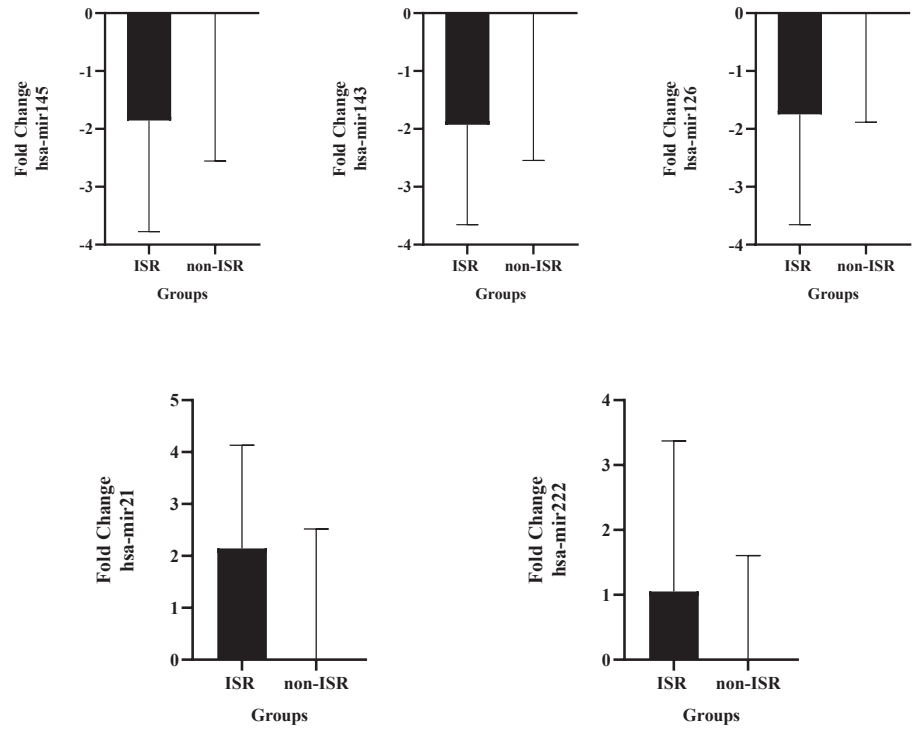

Figure 4. A Signature of Four Differentially Expressed miRNAs Significant for Restenosis Identified Through Statistical Analysis: has-miR-126 (P = 0.0018), has-miR-21 (P = 0.0025), has-miR-143 (P = 0.0055), and has-miR-145 (P = 0.008). *Note*. ISR: In-stent restenosis; MicRNA: Micro ribonucleic acids. Conversely, the expression of hsa-miR-222 was not statistically significant (P = 0.047)

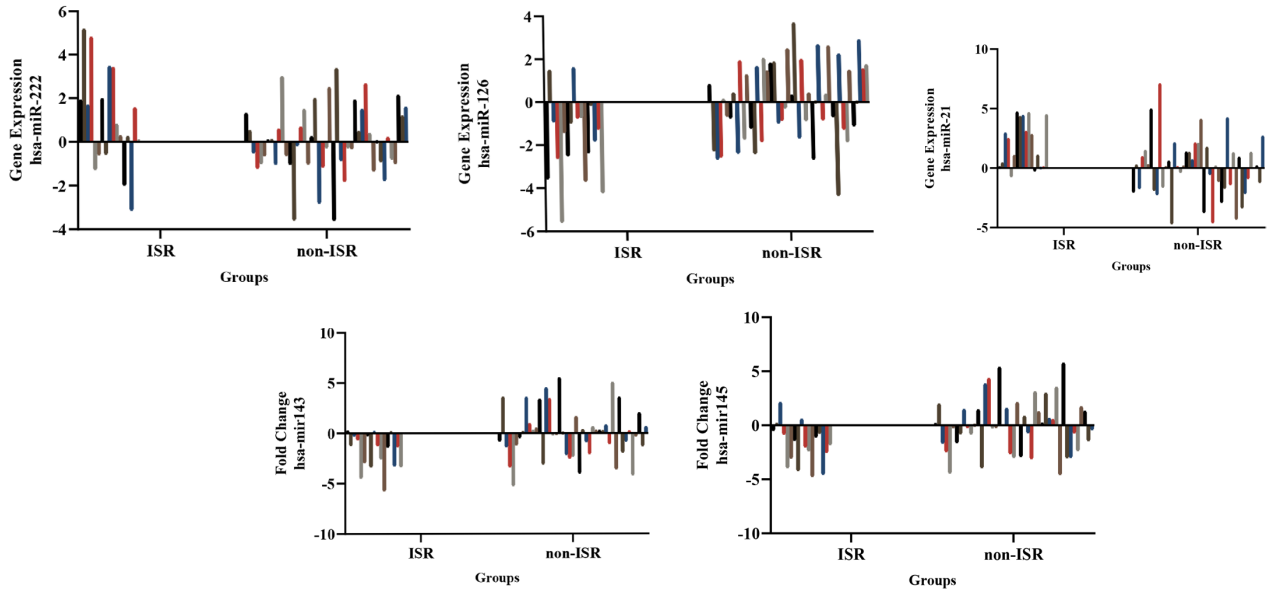

Figure 5. A Comparative Analysis of Gene Expression Levels in the Target Populations. *Note*. It is calculated using the formula $2^{-\Delta\Delta Ct}$ and is presented for 62 samples: The control group (without ISR, shown in blue) and the in-stent restenosis group (displayed in red). This indicated the differences observed between the groups. Each group has been analyzed separately to ensure clarity and to emphasize the distinct expression patterns within the studied populations.

In vivo studies indicated that the stents conjugated with has-miR-126 nanoparticles importantly suppressed neointimal hyperplasia development.

In line with our study, Yuan et al reported a lower plasma level of miR-143/miR-145 in ISR patients compared with non-ISR patients (34). Pathological hypertrophy and in-stent nonatherosclerotic lesions are common events in ISR incidents (35). The high and specific expression of miR-143/miR-145 in VSMCs has been proven. MiR-143 and miR-145 have prominent functions in VSMC proliferation and migration and in arteries (36). In addition, they are involved in cardiac chamber function and formation (37). Human and empirical studies confirmed the association between miR-143/miR-144 and CVD (38). Variable plasma levels of hsa-mir-143/hsa-miR-145 have been observed across different

cardiovascular diseases, including coronary ortery disease (39) and acute MI (40). It is suggested that miR-143/miR-145 may be a prognostic biomarker for CVDs (38).

Based on our results, there were no significant differences in has-miR-222 expression between the ISR group and the control group. Has-miR-222 plays a noticeable role in cardiomyocyte growth (41), cardiomyocyte maturation (42), and cell proliferation. In vivo studies indicated the role of has-miR-222 in neointima formation following vascular injury (43). It has been reported that has-miR-222 targeting may be a beneficial approach for CVDs (44).

The recognition and management of ISR risk factors are required to enhance the probability of ISR diagnosis and determine the best treatment strategy and effective prophylactic programs for ISR (45). Vascular inflammation after PCI results from several complicated interactions, such as the proliferation of smooth muscle cells, extracellular deposition, and other cellular and molecular events (46). In fact, vascular inflammation is one of the main reasons for ISR (47). It is well known that hsCRP is a suitable biomarker in chronic inflammation (48). The results of the current study revealed high serum levels of hsCRP in the ISR group compared with the non-ISR group ($P<0.001$). In agreement with this study, Zhu et al showed that a higher level of hsCRP was associated with the increased risk of ISR (49).

Conclusion

Our findings confirmed that some miRNAs, including has-miR-126 and miR-143/1miR-45, were significantly downregulated in restenosis patients. At the same time, the plasma level of has-miR-21 meaningfully increased in the ISR group. It is suggested that miRNAs have a prognostic biomarker role in differentiating restenosis pathologies. The expression profiling of miRNA may provide novel information about biomarkers for the prediction of ISR. Despite the important convenience of plasma miRNA measurement, more clarification about clinical usability is necessary. Our study had some limitations, including a small sample size. Further, it was impossible to perform experimental assessments on miR targets. Accordingly, more studies with larger sample sizes are required to confirm these results.

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Authors' Contribution

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Competing Interests

None declared.

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