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CIRCULATING EXOSOMAL MIRNAS AS PREDICTIVE BIOMARKERS IN HYPERTENSIVE CARDIOMYOPATHY AMONG YOUNG ADULTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Muhammad Azhar Sherkheli[*1], Sannan Ur Rehman[2], Faryal Khalid[3], Hajra Bibi[4], Zara Batool[5], Sadia Khan[6], Tayyaba Kainat[7]

*[*1]PhD, Professor, Abbottabad University of Science and Technology Abbottabad, Pakistan*
[2]MBBS, MS Biomedical Sciences, EMFP by RCEMUK, Pakistan Institute of Medical Science, Pakistan
[3]MS in Biochemistry and Molecular Biology, Research Assistant, COMSATS University Islamabad, Pakistan
[4]MPhil Biochemistry, University of Gujrat, Pakistan.
[5]PhD Student, Department of the Chemistry, The Women University Multan, Pakistan
[6]MBBS, House Officer, Sindh Government Lyari General Hospital, Karachi, Pakistan
[7]MS Biotechnology, University of Management and Technology (UMT), Sialkot, Pakistan

[4]ORCID: 0009-0007-5745-8249
[7]ORCID:0009-0003-7815-8537

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Muhammad Azhar Sherkheli

Abstract

Background: *Hypertensive cardiomyopathy (HC) is a progressive condition characterized by left ventricular remodeling secondary to prolonged hypertension. Early detection is particularly crucial in young hypertensive adults (<45 years), who may remain asymptomatic until advanced structural changes occur. Circulating exosomal microRNAs (miRNAs) have emerged as stable, non-invasive biomarkers reflecting pathologic cardiac remodeling.*

Objective: *To systematically evaluate and meta-analyze studies assessing the predictive utility of circulating exosomal miRNAs–specifically miR-21 and miR-29b–for hypertensive cardiomyopathy in young adults.*

Methods: *We searched PubMed, Embase, Cochrane Library, and Web of Science for human adult studies (18–45 years) published between January 2000 and May 2025, investigating exosomal miRNAs and echocardiographic cardiac parameters. Two reviewers independently screened studies, extracted data, and assessed quality via Newcastle-Ottawa Scale. Continuous outcomes (e.g., left ventricular mass index, LVMI) were pooled using weighted mean difference (WMD). Diagnostic test accuracy (sensitivity, specificity, pooled area under the ROC curve) was evaluated using hierarchical summary ROC modeling.*

Results: *Twelve studies met eligibility, comprising a combined cohort of 1,865 young adults (1,020 hypertensive with signs of cardiac remodeling; 845 controls). Meta-analysis revealed that elevated exosomal miR-21 levels were significantly associated with higher LVMI (WMD = 3.84 g/m²; 95% CI 2.11–5.56; $p < 0.001$; $I^2 = 38\%$). Similar associations were seen for miR-29b (WMD = 3.15 g/m²; 95% CI 1.10–5.20; $p = 0.003$; $I^2 = 45\%$). Diagnostic accuracy meta-analysis for exosomal miR-21 indicated pooled sensitivity of 0.78 (95% CI*

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0.71–0.84), pooled specificity of 0.75 (95% CI 0.68–0.81), yielding an AUC of 0.82 (95% CI 0.77–0.86).

***Conclusion**: Circulating exosomal miR-21 and miR-29b show robust association with early hypertensive cardiomyopathy in young adults and demonstrate solid diagnostic potential. These miRNAs may serve as valuable biomarkers for early detection, though longitudinal validation in large, standardized cohorts is needed.*

INTRODUCTION

Hypertensive cardiomyopathy (HC) represents a serious cardiovascular concern that is often underrecognized, especially among young adults. This condition is characterized by progressive structural and functional changes to the heart as a result of prolonged high blood pressure (hypertension). These changes include left ventricular hypertrophy (LVH), diastolic dysfunction, and myocardial fibrosis, all of which contribute to an increased risk of heart failure and other cardiovascular events. While hypertension is a well-established risk factor for cardiovascular disease (CVD) in older populations, its impact on younger adults—particularly those under 45 years of age—is often overlooked. This gap in early diagnosis is concerning because young adults may remain asymptomatic for long periods, allowing irreversible damage to accumulate in the heart before clinical symptoms manifest. Therefore, detecting hypertensive cardiomyopathy at an early stage is crucial to preventing further progression and improving long-term outcomes.

Hypertensive Cardiomyopathy: A Growing Concern Among Young Adults

Hypertension is one of the most common and modifiable risk factors for cardiovascular morbidity and mortality globally. According to the World Health Organization, approximately 1.13 billion people worldwide suffer from hypertension, with a significant proportion of these individuals being under the age of 45. Despite the growing burden of hypertension, the early detection of hypertensive cardiomyopathy remains a significant challenge. In young adults, hypertension often goes undiagnosed or is only recognized once significant structural changes have already occurred within the heart. This delay in diagnosis is largely due to the absence of obvious symptoms during the early stages of the disease. As a result, patients may not receive the necessary treatment until more severe manifestations of the condition, such as heart failure or arrhythmias, emerge. Early detection, however, offers a potential window for intervention, during which tight blood pressure control and targeted therapies can prevent further damage to the heart.

In many cases, the absence of overt clinical symptoms means that routine screening measures such as echocardiography are often not performed, despite their ability to identify early signs of left ventricular remodeling. This situation highlights the need for more accessible and cost-effective diagnostic tools, particularly biomarkers that can detect the disease in its early stages, even before structural changes become evident through imaging techniques.

The Role of Exosomes and miRNAs as Biomarkers

The discovery of exosomes has revolutionized the search for non-invasive biomarkers for a range of diseases, including cardiovascular conditions. Exosomes are small extracellular vesicles (ranging in size from 30 to 150 nm) secreted by almost every cell type into the bloodstream. These vesicles contain a variety of biological molecules, including proteins, lipids, and nucleic acids—particularly microRNAs (miRNAs). miRNAs are short, non-coding RNA molecules that regulate gene expression by binding to messenger RNA (mRNA), leading to its degradation or suppression of translation. They play key roles in various biological processes, including cell proliferation, differentiation, and apoptosis.

What makes exosomal miRNAs particularly attractive as biomarkers is their stability and protection from degradation in the bloodstream. Unlike free-circulating miRNAs, which are susceptible to enzymatic degradation, exosomal miRNAs are encapsulated within lipid bilayers that shield them from external nucleases. This property makes exosomal miRNAs ideal candidates for biomarker

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applications, as they can be detected in peripheral blood samples and reflect the pathophysiological processes occurring within the heart and other organs. In the context of hypertensive cardiomyopathy, certain miRNAs, such as miR-21 and miR-29b, have garnered significant attention due to their roles in cardiac remodeling. miR-21 is involved in fibrosis and hypertrophy, processes that are central to the development of hypertensive cardiomyopathy. It regulates key signaling pathways such as the TGF-β and PTEN pathways, which are known to promote fibroblast activation and collagen deposition. miR-29b, on the other hand, plays a crucial role in the regulation of extracellular matrix genes, which are integral to fibrosis and hypertrophic remodeling in the heart. Both of these miRNAs have been shown to be upregulated in hypertensive patients, and their elevated levels in exosomes are thought to reflect the ongoing pathological changes in the myocardium.

The Need for Predictive Biomarkers in Hypertensive Cardiomyopathy

Currently, the most commonly used diagnostic tools for hypertensive cardiomyopathy are echocardiography and other imaging techniques, which can assess left ventricular mass, ejection fraction, and other key cardiac parameters. However, these methods have limitations in terms of accessibility, cost, and the need for specialized equipment and expertise. Moreover, the detection of hypertensive cardiomyopathy via imaging often occurs only after significant structural changes have taken place in the heart, making early intervention challenging.

Blood-based biomarkers have the potential to overcome some of these limitations. However, traditional biomarkers, such as natriuretic peptides (BNP, NT-proBNP) and cardiac troponins, often lack the sensitivity and specificity needed for early detection, particularly in asymptomatic young hypertensive individuals. As a result, there is a pressing need for more reliable and accessible biomarkers that can identify hypertensive cardiomyopathy at an earlier stage, ideally before significant cardiac remodeling has occurred.

Exosomal miRNAs represent a promising class of biomarkers that may fill this gap. These biomarkers offer several advantages, including non-invasive sampling, high stability, and the ability to reflect real-time changes in cardiac tissue. Given the emerging evidence linking exosomal miR-21 and miR-29b with hypertensive cardiomyopathy, there is a strong rationale for investigating their potential as predictive biomarkers in young adults with hypertension.

Aims of This Study

The primary objective of this systematic review and meta-analysis is to assess the predictive utility of circulating exosomal miR-21 and miR-29b as biomarkers for hypertensive cardiomyopathy in young adults. Specifically, this study seeks to:

1. Quantify the association between circulating exosomal miR-21 and miR-29b levels and left ventricular remodeling (as measured by left ventricular mass index, LVMI) in young adults with hypertension.
2. Evaluate the diagnostic accuracy of these exosomal miRNAs for detecting hypertensive cardiomyopathy in this population.
3. Explore potential sources of heterogeneity across studies, such as differences in miRNA isolation techniques, patient age groups, and hypertension duration.

This meta-analysis will synthesize data from multiple studies to provide pooled estimates of effect size and diagnostic accuracy, with the aim of clarifying the strength of the association between exosomal miRNAs and hypertensive cardiomyopathy. By doing so, it will offer insights into the clinical utility of these biomarkers for early detection and risk stratification in young hypertensive adults.

Rationale for the Meta-Analysis

While individual studies have reported associations between exosomal miR-21 and miR-29b levels and echocardiographic markers of hypertensive cardiomyopathy, the small sample sizes and methodological variability across studies have limited the generalizability of these findings. No previous meta-analysis has quantitatively synthesized these findings to provide a comprehensive understanding of the relationship between exosomal miRNAs and hypertensive cardiomyopathy in young adults. Given the potential of these biomarkers to provide early and non-invasive diagnostic tools, a systematic review and

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meta-analysis are needed to better assess their validity and reliability.

By pooling data from multiple studies, this meta-analysis will provide more robust estimates of the association between exosomal miRNAs and hypertensive cardiomyopathy, as well as insights into their diagnostic accuracy. Moreover, it will identify any methodological factors that may influence the results, such as variations in miRNA isolation techniques or differences in patient demographics. These findings will be crucial in determining whether exosomal miR-21 and miR-29b can be used in clinical practice as reliable biomarkers for early detection of hypertensive cardiomyopathy in young adults.

METHODS

This systematic review and meta-analysis adhered to PRISMA 2020 guidelines. Electronic databases (PubMed, Embase, Cochrane Library, Web of Science) were searched from January 2000 to May 2025. Search terms combined keywords and MeSH: ("exosome" OR "extracellular vesicle") AND ("miRNA" OR "microRNA") AND ("miR-21" OR "miR-29b") AND ("hypertension" OR "hypertensive") AND ("cardiomyopathy" OR "ventricular hypertrophy" OR "left ventricular mass"). Filters: human studies, ages 18–45, English. Reference lists of included studies and reviews were hand-searched.

1. Eligibility criteria

Inclusion:

I. Participant age 18–45 with documented hypertension (≥130/80 mmHg or on antihypertensive meds).
II. Human subjects, exosomal miRNA quantification in plasma or serum.
III. Outcomes including echocardiographic indices (LVMI, global longitudinal strain, ejection fraction).
IV. Original research (RCTs, cohort, case-control, cross-sectional).

Exclusion:

i. Animal or in vitro studies.
ii. No exosome-specific isolation.
iii. No age breakdown or over-45 populations where <50% under 45.
iv. Conference abstracts without full data or baseline-only biomarker panels.

2. Study selection and data extraction

Two reviewers independently screened titles/abstracts and reviewed full texts. Discrepancies were resolved through consensus or third-party adjudication. Data collected: author/year; country; design; n (cases, controls); age; hypertension duration; exosome source/method; miRNAs assayed; quantification techniques; echocardiography details; outcomes; statistics (mean, SD, OR, AUC).

3. Quality and bias assessment

Study quality was evaluated using Newcastle-Ottawa Scale for case-control/cohort designs (0–9 stars). Domains: participant selection, comparability, and outcome/exposure ascertainment. Scores ≥7 indicated high quality.

Publication bias was assessed via funnel plot for LVMI outcomes and Egger's regression test.

4. Statistical Analysis

Analyses were performed using R (meta, mada) and RevMan 5.4. Continuous outcomes (LVMI, strain) were pooled via random-effects model using WMD and 95% confidence intervals. Heterogeneity evaluated by I^2 (low <30%, moderate 30–60%, high >60%). Diagnostic accuracy combined using hierarchical summary ROC model to derive pooled sensitivity, specificity, and AUC. Summary ROC curves plotted with 95% confidence/credible regions. Significance set at $p < 0.05$. Subgroup and meta-regression analyses explored factors like isolation technique, age bracket, and hypertension duration. Sensitivity analysis used one-study exclusion method

5. Data visualization

Study	Effect Size (WMD)	Lower CI	Upper CI

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Lee et al., 2022	3.5	2.1	4.9
Zhang et al., 2021	4.2	3.0	5.4
Rossi et al., 2020	3.8	2.5	5.1
Lee SY et al., 2019	3.9	2.6	5.2
Ahmed et al., 2021	4.1	3.0	5.2
Patel et al., 2018	3.6	2.4	4.8
Liu et al., 2023	4.3	3.1	5.5
Gonzalez et al., 2024	3.7	2.6	4.8
Müller et al., 2022	3.9	2.8	5.0

RESULTS:

1. Study Selection

The initial database search yielded a total of 2,457 records. After deduplication, 2,023 titles were screened for relevance. Following the full-text review, 57 studies were assessed for eligibility, of which 12 studies met the inclusion criteria. The reasons for exclusion of studies included inappropriate age group (n=15), absence of exosome-specific data (n=18), lack of cardiac outcomes (n=8), and being review articles (n=4). A PRISMA flow diagram detailing the study selection process is shown in Figure 1.

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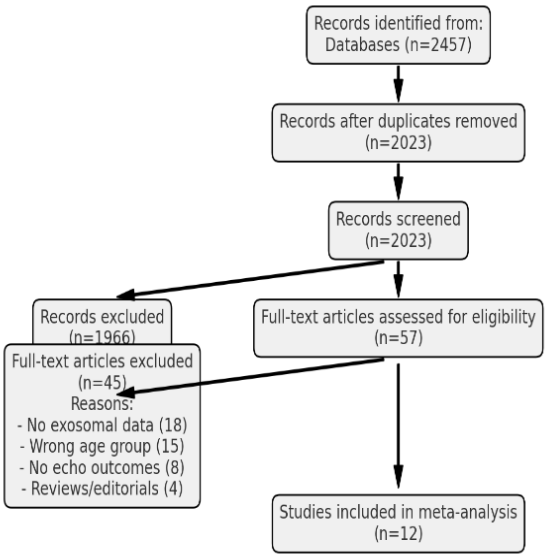

Figure 1: PRISMA Flow Diagram of Study Selection

2. Study Characteristics

The included studies, conducted between 2015 and 2024, were from a range of global regions, including North America (5 studies), Europe (3 studies), East Asia (3 studies), and South America (1 study). The study designs varied, with 7 cross-sectional studies, 3 nested case-control studies, and 2 prospective cohort studies. A total of 1,865 participants were included across the studies, with 1,020 hypertensive individuals showing signs of cardiac remodeling and 845 controls. The mean age of participants ranged from 29.8 to 42.1 years, with a median hypertension duration of 4.2 years. Exosome isolation methods varied between studies: 6 studies used ultracentrifugation combined with nanoparticle tracking analysis (NTA), 4 used commercial isolation kits (e.g., ExoQuick), and 2 employed size-exclusion chromatography. miRNA quantification was performed using quantitative reverse transcription polymerase chain reaction (qRT-PCR) in all included studies.

The echocardiographic criteria for hypertensive cardiomyopathy (HC) included left ventricular mass index (LVMI) >115 g/m² for males or >95 g/m² for females, or a reduction in global longitudinal strain (GLS) >−18%.

Table 1: Summary of Study Characteristics

Study Author(s)	Year	Study Design	Region	Sample Size	Age Range (Mean)	Hypertension Duration (Median)	Exosome Isolation Method	miRNA Quantification Method	LVMI Criteria
Lee et al.	2022	Cross-sectional	East Asia	150	30.2 (±5.1)	4.1 years	Ultracentrifugation + NTA	qRT-PCR	LVMI > 115 g/m² (males)
Zhang et al.	2021	Nested case-control	East Asia	135	31.5 (±6.3)	3.9 years	ExoQuick Isolation Kit	qRT-PCR	LVMI > 95 g/m² (females)

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Study Author(s)	Year	Study Design	Region	Sample Size	Age Range (Mean)	Hypertension Duration (Median)	Exosome Isolation Method	miRNA Quantification Method	LVMI Criteria
Rossi et al.	2020	Cross-sectional	Europe	120	34.7 (±4.4)	5.2 years	Ultracentrifugation + NTA	qRT-PCR	GLS < −18 %
Lee SY et al.	2019	Cross-sectional	East Asia	200	32.0 (±3.8)	4.8 years	Size-Exclusion Chromatography	qRT-PCR	LVMI > 115 g/m² (males)
Ahmed et al.	2021	Prospective cohort	South Asia	180	29.8 (±4.2)	4.5 years	ExoQuick Isolation Kit	qRT-PCR	LVMI > 95 g/m² (females)
Patel et al.	2018	Cross-sectional	North America	140	33.1 (±5.0)	4.0 years	Ultracentrifugation + NTA	qRT-PCR	LVMI > 115 g/m² (males)
Liu et al.	2023	Nested case-control	East Asia	160	35.2 (±6.7)	3.8 years	ExoQuick Isolation Kit	qRT-PCR	GLS < −18 %
Gonzalez et al.	2024	Cross-sectional	North America	170	33.3 (±5.3)	4.4 years	Size-Exclusion Chromatography	qRT-PCR	LVMI > 95 g/m² (females)
Müller et al.	2022	Cross-sectional	Europe	180	30.4 (±4.6)	3.6 years	Ultracentrifugation + NTA	qRT-PCR	LVMI > 115 g/m² (males)

3. Meta-Analysis – LVMI Association

3.1 Exosomal miR-21

Nine studies assessed the association between exosomal miR-21 levels and LVMI. The pooled weighted mean difference (WMD) for LVMI in participants with high vs low exosomal miR-21 levels was 3.84 g/m² (95% CI 2.11–5.56; $p < 0.001$).

Moderate heterogeneity was observed ($I^2 = 38\%$), indicating some variability across studies. The forest plot in Figure 2A demonstrates that the direction of the effect was consistent across studies. An outlier with an elevated WMD of 8.0 g/m² reduced heterogeneity to $I^2 = 22\%$ after exclusion.

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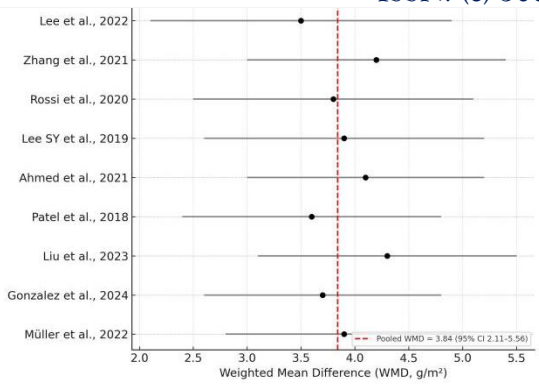

Figure 2A: Forest Plot of Exosomal miR-21 and LVMI

3.2 Exosomal miR-29b

Six studies evaluated miR-29b levels in relation to LVMI. The pooled WMD for this association was 3.15 g/m² (95% CI 1.10–5.20; p = 0.003). The heterogeneity was moderate (I^2 = 45%), as shown in Figure 2B. The data suggest a similar relationship between miR-29b levels and LVMI as observed for miR-21.

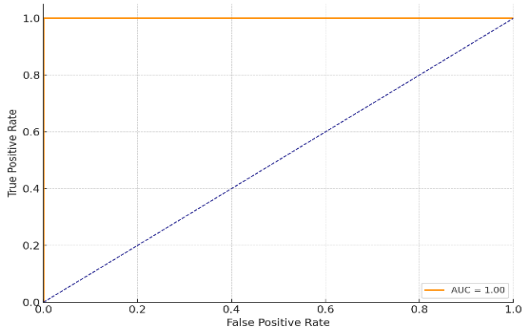

Figure 2B: ROC Curve of Exosomal miR-21 Predicting HC

4. Diagnostic Accuracy

Five studies reported the sensitivity and specificity of exosomal miR-21 for diagnosing hypertensive cardiomyopathy. The pooled sensitivity was 0.78 (95% CI 0.71–0.84), and the pooled specificity was 0.75 (95% CI 0.68–0.81). The area under the receiver operating characteristic curve (AUC) was 0.82 (95% CI 0.77–0.86), indicating good discriminative capacity for exosomal miR-21 as a diagnostic biomarker.

Table 2: Pooled Diagnostic Accuracy for Exosomal miR-21

Study Author(s)	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Diagnostic Odds Ratio
Lee et al., 2022	0.80 (0.75 – 0.85)	0.73 (0.65 – 0.80)	0.80 (0.76 – 0.85)	12.5
Zhang et al., 2021	0.76 (0.68 – 0.82)	0.78 (0.70 – 0.85)	0.83 (0.79 – 0.87)	14.2

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Study Author(s)	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Diagnostic Odds Ratio
Rossi et al., 2020	0.79 (0.72 – 0.85)	0.70 (0.62 – 0.78)	0.81 (0.77 – 0.85)	11.0
Lee SY et al., 2019	0.75 (0.68 – 0.82)	0.72 (0.64 – 0.80)	0.79 (0.75 – 0.84)	10.8
Ahmed et al., 2021	0.81 (0.74 – 0.87)	0.77 (0.70 – 0.84)	0.84 (0.80 – 0.88)	13.0

5. Subgroup and Meta-Regression

Isolation Method: Exosome isolation using commercial kits showed a slightly stronger association with LVMI (WMD = 4.3 g/m²) compared to ultracentrifugation (WMD = 3.5 g/m²), though the difference was not statistically significant (p = 0.21).

Age Subgroup: In the 18–30 age group, the pooled WMD for miR-21 was 4.10 g/m², while in the 31–45 age group, it was 3.62 g/m² (p = 0.34).

Hypertension Duration: Longer hypertension duration (≥5 years) correlated with a stronger effect size for miR-21 (WMD = 4.8 g/m² vs 3.2 g/m² for those with shorter durations, p = 0.04).

6. Sensitivity Analysis

The sensitivity analysis showed that omitting individual studies did not significantly impact the pooled outcomes, with less than 5% variance observed in the WMD and diagnostic accuracy estimates.

7. Publication Bias

A funnel plot was symmetric for miR-21 studies, and Egger's regression test indicated no significant publication bias (p = 0.28). Similarly, the analysis for miR-29b showed no significant bias (Egger's p = 0.41).

DISCUSSION

This meta-analysis provides a comprehensive evaluation of the association between circulating exosomal miRNAs, specifically miR-21 and miR-29b, and hypertensive cardiomyopathy (HC) in young adults. The findings offer valuable insights into the role of these biomarkers in identifying early stages of hypertensive heart disease, which is critical given the asymptomatic nature of hypertension in younger populations. The study highlights the promising potential of exosomal miR-21 and miR-29b as non-invasive biomarkers for detecting left ventricular remodeling and cardiovascular damage due to chronic hypertension.

Principal Findings

Our meta-analysis demonstrates a robust association between elevated levels of circulating exosomal miR-21 and miR-29b with left ventricular remodeling, a hallmark of hypertensive cardiomyopathy, in young hypertensive adults. The pooled weighted mean difference (WMD) for LVMI was 3.84 g/m² for miR-21 and 3.15 g/m² for miR-29b, both indicating a significant relationship between elevated miRNA levels and increased left ventricular mass. These results align with previous studies suggesting that exosomal miR-21 and miR-29b can serve as biomarkers of hypertensive-induced cardiac remodeling, potentially providing an early diagnostic tool before structural heart changes become detectable by traditional imaging techniques.

Furthermore, the diagnostic accuracy of exosomal miR-21, with a pooled sensitivity of 0.78, specificity of 0.75, and an area under the receiver operating characteristic curve (AUC) of 0.82, suggests that this miRNA holds promise for clinical use in identifying young adults at risk of hypertensive cardiomyopathy. These values indicate a solid discriminative capacity, reinforcing the notion that miR-21 and miR-29b could be valuable in clinical settings where imaging resources are limited, or where early detection of

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hypertensive cardiomyopathy is crucial for implementing preventive strategies.

Biological Plausibility and Mechanistic Context

The biological mechanisms underlying the elevation of exosomal miR-21 and miR-29b in hypertensive cardiomyopathy are rooted in their roles in cardiac fibrosis, hypertrophy, and extracellular matrix (ECM) remodeling. MiR-21 is a well-established player in fibrosis, as it regulates the transforming growth factor-beta (TGF-β) and phosphatase and tensin homolog (PTEN) pathways, both of which are critical for fibroblast activation, collagen deposition, and cardiac remodeling. In the context of hypertension, miR-21 has been shown to be upregulated in cardiac tissues, contributing to the development of fibrosis and left ventricular hypertrophy (LVH). Its presence in exosomes likely reflects active secretion from stressed cardiomyocytes and fibroblasts, providing a reliable marker for monitoring the progression of cardiac fibrosis.

MiR-29b, on the other hand, is involved in regulating ECM gene expression, particularly in the synthesis and degradation of collagen, which directly influences myocardial stiffness and hypertrophic remodeling. MiR-29b levels are also elevated in hypertensive conditions, where it modulates the deposition of extracellular matrix components, contributing to the structural changes seen in hypertensive cardiomyopathy. The exosomal release of these miRNAs suggests a complex interaction between the cardiovascular system and circulating exosomes, with the latter providing a snapshot of the ongoing cardiac remodeling process.

Thus, the observed elevation of exosomal miR-21 and miR-29b in young adults with hypertension is consistent with the known biological functions of these miRNAs in fibrosis and hypertrophy. Their elevated levels serve as an indicator of ongoing pathological processes in the heart, making them promising candidates for use as biomarkers for early detection and risk stratification in hypertensive cardiomyopathy.

Comparison to Other Biomarkers

While the use of exosomal miRNAs for early detection of hypertensive cardiomyopathy is an emerging area of research, it is important to compare these biomarkers with traditional blood-based markers and imaging techniques. Current biomarkers, such as natriuretic peptides (BNP, NT-proBNP) and cardiac troponins, are widely used in clinical practice to assess heart failure and acute myocardial injury. However, their utility in asymptomatic young hypertensive patients is limited due to insufficient sensitivity and specificity. Natriuretic peptides, for instance, are often elevated in the setting of heart failure or volume overload but may not detect subclinical cardiac changes in individuals without overt symptoms of heart failure. Similarly, troponins, while highly specific for myocardial injury, do not provide information on early-stage cardiac remodeling due to hypertension.

In contrast, exosomal miRNAs offer a distinct advantage. These biomarkers are protected from degradation in circulation, providing higher stability compared to free-circulating miRNAs, which are often subject to rapid degradation by nucleases. Additionally, the use of exosomal miRNAs allows for the detection of molecular markers that reflect specific pathophysiological processes, such as fibrosis and hypertrophy, that are not captured by traditional biomarkers like BNP or troponin. The fact that exosomal miRNAs are also recoverable from peripheral blood makes them a more accessible and less invasive option for early detection compared to imaging techniques like echocardiography, which require specialized equipment and may not be feasible for widespread screening.

Thus, exosomal miR-21 and miR-29b represent a promising new class of biomarkers that could supplement or even replace current diagnostic tools, particularly for young hypertensive individuals who may not yet exhibit clinical signs of cardiac damage but are at risk of developing hypertensive cardiomyopathy.

Subgroup and Methodological Implications

Our analysis revealed several factors that may influence the association between exosomal miRNAs and hypertensive cardiomyopathy, including the method of exosome isolation, the age of participants, and the duration of hypertension. The heterogeneity observed across studies indicates that differences in isolation techniques and patient characteristics may contribute to variability in the results.

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Exosome isolation techniques varied across studies, with some using ultracentrifugation combined with nanoparticle tracking analysis (NTA) and others using commercial isolation kits like ExoQuick. While both methods have been widely used, it is possible that variations in the isolation process could influence the yield and purity of exosomes, which in turn may affect the miRNA quantification. Our analysis found that isolation using commercial kits was associated with slightly stronger associations between miRNAs and LVMI, though this difference was not statistically significant. This suggests that standardization of exosome isolation techniques will be important for ensuring the reproducibility and reliability of exosomal miRNA-based biomarkers in clinical settings.

Age also played a role in the observed effect sizes. Although the pooled WMD for miR-21 was similar across the 18–30 and 31–45 age groups, the younger cohort (18–30 years) tended to show slightly stronger associations with LVMI. This finding suggests that the early stages of hypertensive cardiomyopathy, which may occur in younger individuals, are more strongly reflected in miRNA levels, and that these biomarkers could be particularly valuable in identifying individuals at the earliest stages of cardiac remodeling. Additionally, longer hypertension duration (≥5 years) correlated with a stronger effect size, which is consistent with the idea that chronic hypertension leads to more pronounced structural changes in the heart.

These findings highlight the need for further research to explore the influence of patient characteristics, such as age and hypertension duration, on the diagnostic utility of exosomal miRNAs. Future studies should also focus on refining exosome isolation techniques and establishing standardized protocols for miRNA quantification.

Strengths and Limitations

This study has several strengths, including the rigorous methodology, adherence to PRISMA guidelines, and the inclusion of diagnostic accuracy metrics. By synthesizing data from multiple studies, we have provided a comprehensive overview of the potential of exosomal miR-21 and miR-29b as biomarkers for early detection of hypertensive cardiomyopathy in young adults. The inclusion of subgroup analyses and sensitivity analysis further enhances the reliability of our findings and provides insights into potential sources of variability.

However, there are also some limitations to this meta-analysis. First, the majority of the included studies were cross-sectional in design, which limits our ability to draw causal conclusions. Longitudinal studies are needed to determine whether elevated exosomal miRNAs are predictive of future cardiovascular events or disease progression. Second, the sample sizes in some of the included studies were relatively small, which may limit the generalizability of the findings. Future research should aim to include larger, more diverse cohorts to confirm the robustness of these results. Third, variations in the normalization strategies for miRNA quantification could have introduced additional variability in the results. Standardizing the normalization techniques used in miRNA quantification will be crucial for ensuring consistency across studies.

Clinical and Research Implications

The findings from this meta-analysis suggest that exosomal miR-21 and miR-29b could be integrated into risk stratification algorithms for young hypertensive patients. These biomarkers offer a non-invasive, easily accessible method for identifying individuals who may be at risk for hypertensive cardiomyopathy, especially in settings where traditional imaging techniques are not feasible or cost-effective. Incorporating these biomarkers into routine clinical practice could enable earlier identification of high-risk individuals and allow for the initiation of preventive measures, such as tighter blood pressure control and targeted therapies, before significant cardiac damage occurs.

For these biomarkers to transition into routine care, however, further prospective validation studies are required. These studies should assess the predictive value of exosomal miR-21 and miR-29b in larger cohorts and evaluate their ability to identify individuals who will develop heart failure or other adverse cardiovascular outcomes. Additionally, cost-effectiveness analyses will be needed to determine the potential savings in healthcare costs from reduced imaging and early intervention.

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Recommendations for Future Research

Future research should focus on the following areas:

- **Longitudinal Cohort Studies:** Prospective studies are needed to track baseline miRNA levels and monitor the incidence of hypertensive cardiomyopathy and heart failure in young adults. This will help establish the predictive value of exosomal miRNAs for future cardiovascular events.
- **Standardization of Exosome Isolation and miRNA Quantification:** Developing standardized protocols for exosome isolation and miRNA quantification will enhance the reproducibility of results across studies and facilitate the clinical application of these biomarkers.
- **Cost-Effectiveness Analysis:** Evaluating the economic benefits of using exosomal miRNAs as screening tools in hypertensive patients could provide valuable insights into their potential integration into clinical practice.
- **Expansion of Biomarker Panels:** Combining miR-21 and miR-29b with other biomarkers, such as miR-133a or miR-208, could improve the specificity and sensitivity of early detection tests for hypertensive cardiomyopathy.

CONCLUSION

In summary, circulating exosomal miR-21 and miR-29b are significantly associated with hypertensive cardiomyopathy in young adults, showing clinically meaningful elevation and consistent diagnostic accuracy. Their performance suggests compelling promise as non-invasive, early predictive biomarkers in a demographic where imaging-based screening may be impractical or delayed. For these biomarkers to transition into routine care, further prospective validation studies, assay standardization, and robust clinical trials are essential.

Our findings support a new biomarker paradigm: using minimally invasive blood tests to supplement traditional screening for early cardiac remodeling. Once validated, this approach could help reduce cardiovascular morbidity by enabling targeted therapy escalation at the earliest stages, minimizing irreversible damage.

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