miR-155 EXPRESSION UTILIZATION AS A POTENTIAL DIAGNOSTIC BIOMARKER OF HEART FAILURE: A SYSTEMATIC REVIEW

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Abstract

Background: Heart failure (HF) is a complex clinical syndrome with signs and symptoms resulting from any structural dysfunction of ventricular filling or blood ejection. miRNAs were known as essential regulators and tissue-specifically expressed. MicroRNA-155 (miR-155) expression in macrophages is already well known to promote hypertrophy, cardiac inflammation, and failure due to pressure overload. In this systematic review, we aim to identify the role of expression miR-155 as a potential biomarker for HF.

Method: We incorporated search engines from Google Scholar, PubMed, EBSCO Host, and ProQuest to search the articles discussing the level of miR-155 in HF patients. Newcastle Ottawa Scale (NOS) was used to evaluate the bias risk in the case-control research.

Results: A systematic database search reveals 6 relevant studies. This research found that miR-155 levels were significantly higher in HF patients than in the control groups. The treadmill test has an average sensitivity and specificity of 68% and 77%, respectively. Transthoracic echocardiography also had a sensitivity of 82% and a specificity of 69% compared to lower miR-155 sensitivity and specificity. MiR-155's plasma levels in HF are higher than the control group, with a cut-off value of 0.8591, a sensitivity value of 98.5%, and a specificity value of 64.6%. However, miRNA expression patterns do not appear to differ significantly between pf and cf LVAD. On the other hand, transthoracic echocardiography had a sensitivity of 82% and a specificity of 69%. Different sensitivity and specificity could be affected by separate quantitative Reverse Transcription – Polymerase Chain Reaction (qRT-PCR) kits.

Conclusion: Our systematic review showed that miR-155 could be a potential new diagnostic biomarker in HF patients. miR-155 could also be developed into diagnostic strategies for other cardiovascular diseases in the near future.

Keywords: MicroRNAs, miR-155, Heart Failure, Heart Disease, Diagnostic Biomarker

Introduction

Heart failure (HF) is a complicated clinical syndrome with symptoms and signs resulting from any constructional or dysfunctional ventricular filling or blood ejection (1). HF could often be non-specific, resulting in high mortality and high morbidity. Since 1990 to 2017, there was an increased incidence HF by fifty percents of world's populations (2). A study in Malaysia and Singapore reveals the prevalence of HF in Southeast Asian countries is higher by 30-50% than in the rest of the world (3). According to the Acute Decompensated Heart Failure Registry (ADHERE), Southeast Asian HF patients are younger than US patients. This data allows comparisons the incidence of HF patients between Asian and Western countries (2).

Many studies have already concluded that MicroRNAs (miRNAs) could be a potential HF biomarker. MiRNAs are known as essential regulators and are also expressed by heart tissue specifically. Recent data shows that miRNAs are released into the circulatory system, possibly communicating with distant tissues (4). In general, the expression of miRNA is similar to the host gene. Still, recent evidence shows that up to 35% of intron miRNAs

are expressed as accessible transcriptional units under the involvement of their promoter. Most miRNAs were produced by RNA polymerase II transcription, resulting in a primary miRNA transcript (prior-miRNA) with a characteristic of a 3'poly (A) tail and 5'm7G cap structure (5). An alteration of miRNAs could be seen in many various physiological or pathological conditions such as cardiovascular diseases (6).

The expression of miR-155 is upregulated in various inflammatory diseases, i.e., multiple sclerosis and rheumatoid arthritis (7). miR-155, for the first time, was defined as a novel gene called B-cell integration cluster (BIC) (8) that can activate by insertion of proviral in avian leukosis virus-induced lymphomas (9). Later in 2007, miR-155 expression is identified in macrophages, which is activated by inflammation (10, 11). miR-155 expressions in macrophages also promote hypertrophy, cardiac inflammation, and failure due to overload pressure (12, 13), indicating that miR-155 macrophage is responsible for driving adverse cardiac remodeling and failure. Interestingly, several studies indicated a miR-155 essential role in altering cardiac tissue (13-15). From our experience, no studies have specifically examined the relationship between miR-155 as a diagnostic tool in patients with HF. In this systematic review, we aim to identify the importance of miR-155 expression as a potential biomarker for HF.

Materials and Methods

This research did not involve human subjects; therefore, it was exempt from ethical clearance. We incorporated four search engines (Google Scholar, PubMed, EBSCO Host, and ProQuest) to search the articles. The keywords used in the PubMed database search were "miR-155" OR "Micro-RNA" OR "Micro-RNA 155" AND "biomarker" OR "biologic marker" AND ''Heart failure" OR "HF". Modified keywords were used for other databases.

The inclusion criteria were articles that performed empirical studies (primary articles for human studies), observational studies, articles that are written in the English language, full-text articles, articles that reported miR-155 as a potential biomarker in HF patients from January 1st, 2007, until January 1st, 2022, articles published in peer-reviewed and reputable journals, the study subjects were HF patients. The study's exclusion criteria were as follows: 1) literature review studies, meta-analysis, and systematic review studies, 2) the publications that were duplicated, and 3) the lack of sufficient data in the study.

All authors screened searched results from the titles and abstracts of all search results. Full papers were then retrieved for further review if relevant after all the abstracts had been screened. The articles included in this study should report about miR-155 expression as a potential biomarker in HF patients.

Three authors extracted further information independently about the research that has been included, and the fourth author resolved their differences. The extracted data were as follows: 1) Authors identity (i.e., name of the first author and publication year); 2) Research design; 3) Country of study; 4) Subjects; 5) Methods; 6) Outcome; 7) Results; and 8) Conclusion.

We used Newcastle Ottawa Scale (NOS) to assess the risk of bias in this study. NOS used eight subscale items to evaluate participant selection, comparability, and outcome. Case-control studies use up to 9 points from the total number of subscale items. KT and IT made this critical assessment. Disagreements are resolved through discussion. By seniority expertise, the third reviewer's opinion (SL) as senior researcher was used in the final decision.

Results

A total of 962 articles were recorded from four research databases. After removing duplicate records, 782 articles were screened, and 53 articles were assessed for eligibility. This review refers to PRISMA Guidelines 2020 (the Preferred Reporting Items for Systematic Review and Meta-Analyses, Figure 1). Final selection was comprised of six studies were included in the review. All 6 studies are case-control studies and diagnostic markers for HF patients. Many studies were not selected (>10% of initial abstract screening) because most of the studies are not specific to the miR-155 biomarker in HF patients.

The primary demographic characteristics of the chosen studies and a summary of the included studies were presented in Table 1 and 2. In sum of 607 subjects were included in the analysis. Most studies calculate potential confounding factors, and using statistical analysis, miR-155 were not affected by gender or BMI (body mass index) with $p \geq 0.05$.

Quantitative measurement of miR-155

The study by Fan et al. (2013) aims to characterize the level of cardiovascular miRNAs in the circulation of patients with HF caused by Dilated Cardiomyopathy (DCM) and to determine biomarkers value for DCM (16). As a result of this study, the level of plasma of the immune-related miRNAs, miR-155, were not different between the DCM and control groups ($p = 0.437$ and $p = 0.702$, respectively). Another study by Zhang et al. (2019) found different results (17). Two hundred fifty-eight patients were recruited. Quantitative reverse transcription (qRT)-PCR were used to measure their serum miR-155 levels. The left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter and left ventricular posterior wall thickness were measured by ECG.

Potential diagnostic biomarker of miR-155 for HF patients

The study by Ding et al. (2020) used Spearman's correlation coefficient to measure the consistency of the results (18). As a result, six small RNAs (miR-30a-3p, miR-21-5p, miR-155 -5p, miR-30a-5p) are composed of miR-216a-5p and miR-217-5p. A study by Glezeva et al. (2019), which

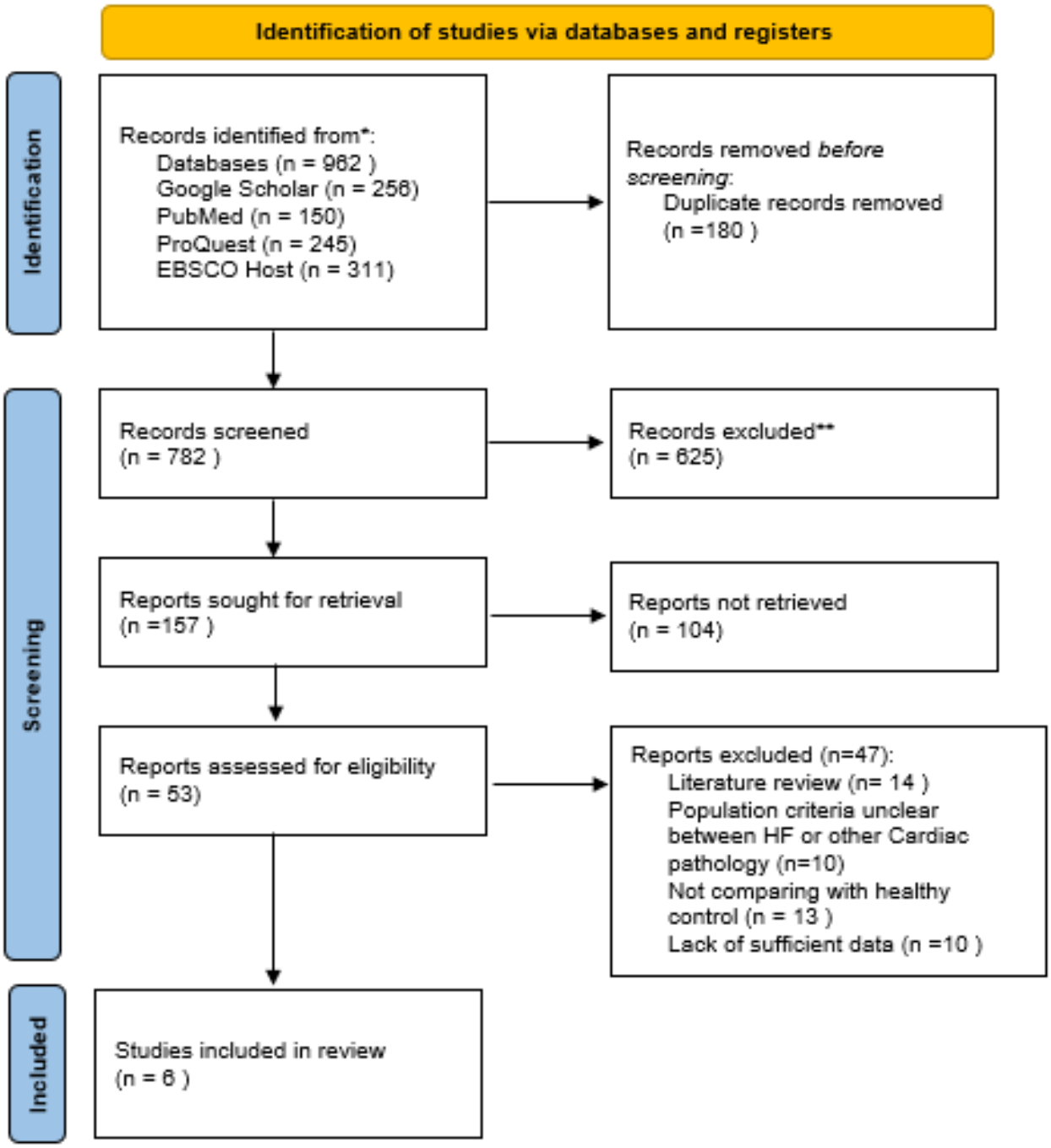

Figure 1: Flowchart of the study selection process

Table 1: Basic demographics of the included studies

Author Identity	Group	Number of subjects	Age (years)[a]	Male (n, %)	Female (n, %)	BMI (kg/m²)[a]
Fan et al. (2013) (16)	HF	45	47.76 ± 12.28	32 (71.1%)	13 (28.9%)	-
	Control	39	47.59 ± 11.85	25 (64.1%)	14 (35.9%)	-
Zhang et al. (2019) (17)	HF	90	64.31 ± 7.99	48 (53.33%)	42 (46.67%)	22.91 ± 3.14
	HF after myocardial infarction	88	62.31 ± 7.39	46 (52.27%)	42 (47.73%)	22.11 ± 3.18
	Control	80	62.91 ± 6.79	41 (51.25%)	39 (48.75%)	22.23 ± 3.16
Ding et al. (2020) (18)	HF	62	62 ± 8.89	40 (64.52%)	22 (35.48%)	26.07 ± 3.36
	Control	62	60 ± 11.80	42 (67.74%)	20 (32.26%)	24.76 ± 3.83
Glezeva et al. (2019) (19)	HF (HOCM)	12	51 ± 6	12 (100%)	0 (0%)	30 [27.5-31.2]
	HF (DCM)	9	52 ± 4	9 (100%)	0 (0%)	26.6 [25.8-33.7]
	HF (ISCM)	9	53 ± 5	9 (100%)	0 (0%)	27.5 [24.9-39.9]
	Control	9	52 ± 7	9 (100%)	0 (0%)	-
Li et al. (2020) (20)	HF	20	43.54 ± 5.72	15	5	-
	Control	20	44.48 ± 6.63	14	6	-
Lok et al. (2015) (21)	HF (tissue sample pf-LVAD)	17	45 ± 3	14 (82%)		25.7 ± 1.8
	HF (tissue sample cf-LVAD)	17	39 ± 3	16 (94.12%)	1 (5.88%)	22.8 ± 0.87
	HF (plasma sample cf-LVAD)	18	45 ± 3	14 (77.78%)	4 (22.22%)	24.3 ± 1.3
	Control	10	-	-	-	-

[a] : Mean ± Standard Deviation
HF: Heart Failure
BMI: Body Mass Index
HOCM : Hypertrophic Obstructive Cardiomyopathy
DCM : Dilated Cardiomyopathy
ISCM : Ischemic Cardiomyopathy
pf-LVAD : Pulsatile Flow Left Ventricular Assist Devices
cf-LVAD : Continuous Flow Left Ventricular Assist Devices

Table 2: Summary of the included studies

Study	Title	Study Design	Country of study origin	Subjects	Methods	Results	Conclusions
Fan et al. (2013) (16)	Circulating microRNAs levels in Chinese heart failure patients due to dilated cardiomyopathy	Case Control	China	45 DCM patients and 39 age- and sex-matched controls	MiR-155 expressions were measured using the qRT-PCR. DCM group patients determined by doppler echocardiography	There is no difference between the DCM group and the control group in plasma miR-155 aspects (p = 0.702).	The plasma concentrations of miR-155, -146a, and -126 associated with immunity were not indicated the significant different between the DCM group and the control group.
Zhang et al. (2019) (17)	The expression of serum microRNA-155 and the clinical role in patients with heart failure after myocardial infarction	Case Control	China	90 HF patients, 88 MI patients, 80 healthy controls	Serum miR-155 levels were measured using qRT-PCR. LVEF left ventricular end-diastolic diameter and left ventricular posterior wall thickness were measured by echocardiography.	The miR-155 levels in HF patients were significantly higher than in MI and controls group. The AUC of miR-155 serum for HF diagnose after MI is 0.941, cutoff value is 1.77, specificity was 92.14%, and the sensitivity is 92.73%,	Patients with post-MI heart failure had elevated levels of miRNA-155 and decreased its cardiac function. The study was conducted by measuring miRNA-155 expression.
Ding et al. (2020) (18)	Combined detection of miR-30a-3p, miR-21-5p, miR-155-5p, miR-30a-5p, miR-216a and miR-217 for early screening of HF	Case Control	China	60 healthy control samples and 62 HF disease samples	MicroRNAs in plasma from samples were measured by qRT-PCR	This study reveals the circulation of miR-155-5p was expressed differently between healthy group and HF group. Plasma levels of miR-155-5p were unaffected by hemolysis.	The results showed that miR-30a-3p, miR-21-5p, miR-30a-5p, miR-216a, miR-155-5p, and miR-217 may be new diagnostic biomarkers for HF and related diseases.
Glezeva et al. (2019) (19)	Targeted DNA methylation profiling of human cardiac tissue indicates new epigenetic traits and deregulation of gene across different HF patient subtypes	Case Control	Ireland	30 male HF patients, and 9 control group patients with non failing hearts	DNA extracted from septal tissue Subsequent gene expression analysis was assessed using qRT-PCR	By comparing each HF subgroup with the non-disorder in control group. We identified 195 distinct methylated regions. One is hypomethylation (miR-155), which has significantly downregulated or upregulated expression levels consistent with the direction of methylation in each HF subgroup.	For the first time, changes in the expression of gene associated with changes in DNA methylation have been identified in pathologically different pathological HF tissues. The methylation susceptibility and disease-related genes / ncRNAs identified in this study show plausible potential as new therapeutic targets and diagnostic for HF and represent a loci with unique cohort that need further investigation.

Table 2: Summary of the included studies (continued)

Study	Title	Study Design	Country of study origin	Subjects	Methods	Results	Conclusions
Li et al. (2020) (20)	ETS2 and microRNA-155 responsible with the regulation of the HF pathogenesis through regulating and targeting the expression of GPR18	Case Control	China	20 matched healthy groups and 20 patients with HF	Dataset GSE84796 was extracted from the GeneExpression Omnibus database and screened for differential expression genes using the Bayesian method of the Limma package. The protein-protein interaction network (PPI) then uses the microRNA expression miR-155	A total of 419 genes were identified, such as 53 downregulated genes and 366 upregulated genes. The up-regulated DEG was significantly enriched in the "natural killer cell-mediated cytotoxicity", "cytokine-cytokine receptor interaction", and "primary immunodeficiency" signaling pathways. In addition, a total of 3 miRNAs and 8 TFs were identified in the TF / miRNA target network. In particular, GPR18 was found to be a target for miR-155. Clinical validation revealed that miR-155 expression levels were significantly reduced in HF samples.	In conclusion, in this study, GPR18 may be the target of miR-155 and ETS2, and by targeting and regulating GPR18, miR-155 cell viability of H9c2 (2-1) cells and suggests that it can regulate apoptosis mechanism.
Lok et al. (2015) (21)	The Expression of MicroRNA in Myocardial Tissue and Plasma of Patients in End-Stage HF during LVAD Support: Comparison of Pulsatile and Continuous Devices	Case Control	Nether-lands	The pulsatile left ventricular assist device (pf-LVAD) was replaced with continuous flow LVAD (cf-LVAD) in 17 patients with end-stage HF	MiRNA were selected (according to microarray data and literature reviews) and validated in myocardial tissue before and after pf and cfLVAD support.	Of the 26 miRs selected, 5 miRs showed similar pattern during support for cf-LVAD and pf-LVAD. MiR-129 and miR-146a were downregulated in patients prior to LVAD support and increased during mechanical support. In contrast, miR-155, miR-221, and miR-222 were upregulated before LVAD and decreased after transplantation.	The different expression of miR after LVAD support, indicates that the different expressions of miRs are partially involved in the functional and morphological changes in the heart observed after support. doing.

HF: Heart Failure
LVEF : Left Ventricular Ejection Fraction
qRT-PCR : quantitative Reverse Transcription – Polymerase Chain Reaction
DCM : Dilated Cardiomyopathy
AUC : Area Under Curve
pf-LVAD : Pulsatile Flow Left Ventricular Assist Devices
cf-LVAD : Continuous Flow Left Ventricular Assist Devices

Table 3: Quality assessment of the included studies

Study	Selection				Comparability	Exposure		Total score
	Is the Case Definition Adequate?	Representativeness of the Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls on the Basis of the Design or Analysis	Ascertainment of Exposure	Non-Response Rate	
Fan et al. (2013) (16)	1	1	1	1	2	1	1	8
Zhang et al. (2019) (17)	1	1	1	1	2	1	1	8
Ding et al. (2020) (18)	1	1	1	1	2	1	1	8
Glezeva et al. (2019) (19)	1	1	0	1	0	1	1	5
Li et al. (2020) (20)	1	1	1	1	2	1	1	8
Lok et al. (2015) (21)	1	1	0	0	0	1	1	4

Interpretation:
0: not mentioned
1: mentioned but with incomplete data
2: mentioned with complete data

Total score:
7-9: low risk of bias
4-6: moderate risk of bias
5-3: high risk of bias
0-2: very high risk of bias

used methylation sequencing from the left ventricular septal tissue, was interesting because it was the first time DNA methylation alterations were identified (19). The methylation susceptibility and disease-related genes/ncRNAs identified in this study represent a unique cohort of loci showing potential as new diagnostic and therapeutic targets for HF. By sequencing gene and non-coding RNA expression in the methylation-sensitive regions identified by methylation sequencing, miR-155 expression was increased 1.63-fold in patients with ISCM due to HF ($p = 0.030$) (19). Lok et al. (2015) study using 26 miRNAs was selected (according to literature studies and microarray data) and validated in myocardial tissue before and after continuous flow (cf)- and pulsatile flow (pf)-LVAD support (20). In this study, 10 healthy controls were found, and all 26 miRNAs were measured.

Levels of miR-155 were upregulated before LVAD and decreased after transplantation. This suggests that misexpressed miRNAs are partially involved in the functional and morphological changes in the heart observed after the support was done. In addition, miRNA expression patterns do not appear to be significantly different between pf- and cf-LVAD. Most cardiac changes and clinical outcomes specific to each device are independent of differences in miRNA expression levels. Li et al. (2020) study found the opposite results (21). Next, a differentially expressed gene (DEG)-encoded protein-protein interaction (PPI) network was built by interacting gene/tool of protein search. A web-based gene was a transcription factor (TF) / miRNA targeting network. It was built according to the set analysis toolkit. Clinical validation revealed that miR-155 expression levels were significantly reduced in HF samples (20, 21).

Diagnostic power of miR-155 in HF patients

In a study by Zhang et al. (2019), miR-155 levels in HF patients were significantly higher than in myocardial infarction and control groups, with a cutoff value of 1.77, specificity was 92.14%, and a sensitivity of 92.73% (17). Followed by another study by Ding et al. (2020), plasma level miR-155 was higher in HF than in controls, with a cutoff value of 0.8591, a sensitivity value of 98.5%, and a specificity value of 64.6% (18).

Quality assessment of case control studies

The quality assessment of included articles is indicated in Table 3. Two studies have moderate risk of bias, and the rest of the studies have low risk of bias (4, 5). One study has mentioned obtaining control samples from hospital controls within the same community as the cases group (i.e., not another city) but derived from a hospitalized

population and the other one has no description of healthy control criteria. One study should have mentioned the history of outcomes for the definition of control. The two studies did not mention cases or controls that were consistent with analytically adjusted design and confounding factors.

Discussion

Six studies (16-21) have been done to understand the involvement of miR-155 in HF. In this clinical science study, miR-155 was found to be a frequent target for a wide range of inflammatory mediators (10).

A quantitative study on humans and rodents involving microRNA sequencing for the circulation of biomarkers found that miRNAs fresh plasma should be preferred over serum for rodent samples because of the sensitivity and specificity. Plasma samples contain miR-related sequences and serum samples contain other non-coding RNA populations (22). Meanwhile, a study detecting miR-155 from peripheral blood found the level of miR-155 in plasma similar to the levels in peripheral blood mononuclear cells (PBMCs), which means miR-155 in plasma may come from PBMCs (23). A steady form of miR-155 can still be detected in serum despite the process of how miR-155 is released in the circulatory system is still questioned (24). MiR-155 can also be found in endothelial cell-derived apoptotic bodies (25).

Cardiac tissue cellular studies were performed on right ventricular septal samples from individuals with acute myocarditis (26). The study found that miR-155 expression was predominantly localized to invasive macrophages and T lymphocytes in myocarditis. The administration of nucleic acid anti-microRNA (LNA-anti-miR) blocked cardiac invasion by monocyte of macrophages, reduces the activation of T lymphocytes, and during acute myocarditis in mice. LNA anti-miR has already been developed as an inhibitor of miR-155 and is called Cobomarsen or MRG-106 (27). Although the biological function and the involvement of miR-155 in inflammation are known, further studies are needed to define the physiological effects of miR-155 inhibition on the targets before considering anti-miR-155 therapy is required.

From all six included studies, all studies declare that no significant differences in the clinical characteristics from the populations were observed, including age, gender, or body mass index (16-21). Another study already investigated miRNAs, which were found to correlate with age (28). MiR-155 levels were found to vary with gender, age, smoking status, and hormone and lipid profiles (29). These results may indicate that the predictive value of miR-155 levels declines with increased age. A study related to miR-155 for predicting long-term mortality in critically ill patients suggests that miR-155 varies with increased age older than 65 years (30). Another experimental study using PBMCs from young group and old group individuals shows that changes in the expression of miRNA decreased sharply with age. The study also found that miR-155 decreased with the increase in age (31).

The cardiopulmonary exercise test is the current gold standard for identifying HF (31). But in the published research articles, the treadmill test has an average sensitivity and specificity of 68% and 77%, respectively. On the other hand, transthoracic echocardiography had a sensitivity of 82% and a specificity of 69%. Meanwhile, studies already found that miR-155 as a diagnostic biomarker for HF sensitivity was 92.73%, and specificity was 92.14% with a cutoff value was 1.77 and the area under the curve (AUC) was 0.941 (23). Using miRNAs as a biomarker for HF compared with a gold standard, Ding et al. (2020) study found a sensitivity value of 98.5% and a specificity value of 64.6% with a cutoff value of 0.8591 (18). Different sensitivity and specificity could be affected by separate qRT-PCR kits. Ding et al. (2020) collected serum from fresh blood and used TaKaRa quantitative PCR kit and Bio-Rad real-time quantitative PCR instrument to process and analyze the samples and repeated three times in the experiment. Meanwhile, Zhang et al. (2019) collected serum from blood mixed with the anticoagulant ethylenediaminetetraacetic acid using SYBR® Green qRT-PCR kit (17, 18). Although the exact cause of different specificities is still not found in all studies. AUC values greater than 0.7 indicate that the miR-155 is effective as a diagnostic and prognostic biomarker in conjunction with existing gold standards. The study found miR-155 was not affected by hemolysis, age, and gender when used to diagnose HF.

This study had some limitations. All studies included were case controls which have lower evidence-based than the randomized controlled trial design studies. Evaluating miR-155 as a diagnostic biomarker for HF required more randomized controlled trials or more extensive prospective studies with larger sample sizes. Small sample sizes could result in small analysis results. Geographical distribution, mainly in China, might not represent overall global dispersion. Further research was needed to investigate the mechanism of miR-155 in as a diagnostic or therapeutic tool in other cardiovascular diseases.

Conclusion

Our systematic review showed that miR-155 could be a potential new diagnostic biomarker in HF patients. Future studies should provide further analysis of the level of miR-155 as a diagnostic biomarker in HF patients by analysing the serum of HF patients and in randomized controlled trial design studies.

Acknowledgement

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

Ethical Clearance

This research did not involve human subjects; therefore, it was exempt from ethical clearance.

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