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The role of MicroRNAs in arrhythmogenic right ventricular cardiomyopathy: A systematic review

Short title: MicroRNAs in ARVC: A systematic review

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ABSTRACT:

Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare inherited heart condition with structural and functional abnormalities of the right ventricle. Microribonucleic acids (miRNAs, miRs) could be a solution in detecting ARVC earlier, more commonly, and in a less invasive way.

Aims: We aimed to systematically review the current knowledge about the role of miRNAs in ARVC.

Methods: Primary original research written in English assessing miRNAs in ARVC were included. Systematic reviews, meta-analyses, reviews, case reports, letters to editors, commentaries, conference abstracts, guidelines/statements, expert opinions, pre-prints, and book chapters were excluded at the screening stage. Five databases were searched: Embase, Medline Ultimate, PubMed, Scopus, and Web of Science, last on October 4, 2024. Eventually,

13 original studies relevant to the discussed area were included. The quality of research was assessed with the Newcastle–Ottawa Scale.

Results: MiR-216a was consistently increased in mice ARVC models and in patients suffering from this disease. Based on the reviewed literature, miR-1, miR-21, and miR-122 are other most important miRNAs in the ARVC. Nevertheless, the research that has already been performed on these miRNAs gives evidence only for their diagnostic potential. Bioinformatic analyses revealed that the following miRNAs are the most important ones involved in ARVC: let-7b, miR-10b-5p, miR-15a-5p, miR-21-5p, miR-29b-3p, miR-122-5p, miR-144-3p, miR-149-5p, miR-182-5p, miR-186-5p, miR-320a, miR-494-3p, and miR-590-3p.

Conclusions: Creating a miRNA panel that could identify ARVC patients with high sensitivity and specificity would be helpful. Currently, there are many gaps in the existing knowledge, which makes miRNA in ARVC an attractive field for future investigation.

Key words: arrhythmias, arrhythmogenic cardiomyopathy, biomarkers, microRNAs, systematic review

WHAT'S NEW?

To the best of our knowledge, it is the first systematic review to summarize the current state of the art regarding the role of miRNAs in arrhythmogenic right ventricular cardiomyopathy (ARVC). After searching five databases, we identified 13 relevant original articles. Consistent findings include increased expression of miR-216a in mice ARVC models and patients suffering from this disease. MiR-1 and miR-21 are other miRNAs worth highlighting in terms of ARVC. Creating a miRNA panel that could identify ARVC patients with high sensitivity and specificity would help decrease the rate of fatal events among people suffering from this disease.

INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare inherited heart condition with structural and functional abnormalities of the right ventricle (RV) [1], which is often the cause of life-threatening ventricular arrhythmias and RV failure. Sudden cardiac death could be the first clinical manifestation of the disease when occurring in its early concealed phase [2]. The disease can also affect the left ventricle (LV), which may worsen the prognosis. Recent studies suggest that LV dysfunction is present in up to 60% of cases [3]. Although the broader term "arrhythmogenic cardiomyopathy", which includes forms with predominant or isolated

LV involvement (arrhythmogenic left ventricular cardiomyopathy), has gained increased recognition in recent years, the 2023 European Society of Cardiology Guidelines for the management of cardiomyopathies have preserved the traditional phenotype of ARVC, classifying most forms of arrhythmogenic LV cardiomyopathy within the non-dilated left-ventricular cardiomyopathy category [4]. According to this approach, in this systematic review, we use the term ARVC due to the predefined search strategy and to remain consistent with the terms used in the reviewed studies.

For many years, the diagnosis of ARVC has been based on multiparametric clinical criteria developed by the International Task Force Criteria in 2010, including structural, histological, electrocardiographic, arrhythmic, and familial/genetic features. The probability of ARVC (definite, borderline, or possible) is determined according to the presence of major and minor criteria. RV abnormalities, such as regional dyskinesia and dilation of the RV, local RV aneurysms, and fibrofatty replacement of myocardium on endomyocardial biopsy, are considered one of the major criteria. Characteristic findings on electrocardiography include epsilon waves and inverted T-waves in V1–V3, as well as ventricular tachycardia with a left bundle branch block morphology [5]. Identification of pathogenic variants associated with the disease and ARVC confirmed in a first-degree relative are also listed as major factors. Due to the absence of a single diagnostic test, the diagnosis remains challenging, especially in the early stages of the disease [6[.

Epidemiology

The prevalence of ARVC varies depending on the geographical location, ranging from about 1:2000 to 1:5000. The disease is slightly more common in males [7]. According to some studies, 3%–4% of sudden deaths are caused by ARVC. It is reported to be the most frequent reason for sudden death in the group of young Italian individuals, especially connected with high-intensity sports [2]. There are several known pathogenic variants in desmosomal genes that can be identified in individuals with ARVC [8]. In 30%–50% of the cases, ARVC is related to family history [9].

Problems in clinical practice

Patients suffering from ARVC have an increased risk of sudden cardiac death, which refers primarily to young adults and athletes [10]. Usually, it does not appear with any symptoms and can lead to an unexpected death at a young age. Despite the latest criteria for diagnosing ARVC, the disease still causes many diagnostic challenges [11]. Characterization of pathological,

clinical, and imagining findings is not specific and can resemble other causes of ventricular tachycardia. Although magnetic resonance imaging is recommended in patients with suspected ARVC, it can be nondiagnostic in the case of early stages of the disease. On the other hand, invasive tests like biopsy are not commonly performed. It explains why so much research aims to find new paths for diagnosing ARVC [12]. Biomarkers could be a solution in detecting ARVC earlier, more commonly, and in a less invasive way.

MicroRNAs as novel biomarkers

Microribonucleic acids (miRNAs, miRs) are small, non-coding ribonucleic acids with about 22 nucleotides [13]. Their role is to regulate gene expression through binding to messenger RNAs (mRNAs) [14]. Such a complementary binding may inhibit the translation process or cause mRNA degradation [15]. MiRNAs can be found in tissues and various body fluids such as blood, pericardial fluid, urine, or saliva [16, 17]. The expression levels of miRNAs are altered in multiple diseases, e.g., cardiovascular [18–21], muscular [22], or neurologic [23] conditions. They can also serve as a valuable tool for therapy monitoring [24]. Recently, they have become very promising biomarkers in many diseases.

We aimed to systematically review the current knowledge about the role of miRNAs in ARVC. We aimed to answer the following questions: 1) Can miRNAs differentiate patients with ARVC from healthy people? 2) Can miRNAs differentiate patients with ARVC from patients with other arrhythmias?

METHODS

This systematic review was conducted according to the PRISMA 2020 Statement [25] (Supplementary material, *Table S1*).

Primary original research, both clinical and preclinical, and bioinformatic analyses written in English assessing miRNAs in ARVC were included. Systematic reviews, meta-analyses, reviews, case reports, letters to editors, commentaries, conference abstracts, guidelines/statements, expert opinions, preprints, and book chapters were excluded at the screening stage. Five databases were searched: Embase, Medline Ultimate, PubMed, Scopus, and Web of Science, by the query: “("miRNA" OR "microRNA" OR "miR" OR "microribonucleic acid") AND ("Arrhythmogenic right ventricular dysplasia" OR "Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy" OR "ARVD" OR "ARVC" OR "Arrhythmogenic Right Ventricular Cardiomyopathy" OR "Arrhythmogenic Cardiomyopathy")” which yielded a total of 339 records. Each database was last searched on

October 4, 2024. For each screening stage, we used 2 screeners working together (not independently). Final decisions in arguable cases were reached by a consensus between the 2 screeners. Data from each included work was extracted by 2 extractors working together (not independently).

The following data was extracted from each included research: study characteristics (sample sizes, methodology used, year of publication), the changes in miRNA levels between compared groups, results of receiver operating characteristic (ROC) analysis (area under the curve [AUC]).

After removing 190 duplicates, the remaining 149 records were screened by title and abstract. It yielded 18 records that met the inclusion/exclusion criteria. All 18 studies were retrieved in complete form. The complete data reports were evaluated for eligibility, excluding 5 studies due to inappropriateness. Eventually, 13 original studies relevant to the discussed area were included (Figure 1). The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized case-control studies [26] (Supplementary material, *Table S2*).

We divided the studies into the following parts: (i) preclinical research evaluating the role of miRNAs in ARVC, (ii) clinical patient-based research assessing the role of miRNAs in ARVC, (iii) bioinformatic analyses investigating the role of miRNAs in ARVC. The results of the included studies were reported in a narrative form.

RESULTS

Preclinical research evaluating the role of miRNAs in ARVC

Mazurek et al. created a mouse model overexpressing miR-130a and compared it to littermate control mice. They found that transgenic mice developed RV dilation. The electrocardiogram of transgenic mice showed features of an arrhythmogenic phenotype due to the presence of premature ventricular contractions [27].

Further, Rainer et al. [28] assessed miRNA profiles in cardiac stromal cells (CStCs) derived from ARVC patients and healthy controls. They performed an RT-qPCR validation, which showed an upregulation of miR-29b-3p in CStCs derived from ARVC patients compared to controls [28].

Again, Calore et al. [29] performed a study with a murine model for ARVC. They created transgenic mice with the overexpression of human desmoglein-2, either wild-type or truncated. For further analysis, line with the overexpression of the truncated desmoglein-2 — Tg-hQ13, served as a model for ARVC. The authors first evaluated which miRNAs presented

altered expression levels in heart tissue and found that 24 miRNAs were changed in Tg-hQ13 compared to non-transgenic mice (of which 18 were upregulated and six were downregulated). Afterwards, they validated the four most deregulated miRNAs with real-time PCR. MiR-217-5p and miR-708-5p were upregulated, while miR-499-5p was downregulated in Tg-hQ13 mice compared to Tg-hWT40 and non-transgenic mice. On the other hand, miR-216a-5p was upregulated in Tg-hQ13 mice but only when compared to non-transgenic mice (not when compared to Tg-hWT40). In silico, the analysis of predicted target genes for miR-217-5p, miR-708-5p and miR-499-5p identified the following potentially involved pathways: the regulation of the Wnt/b-catenin signaling, adherens junctions, and gap junctions [29].

Another preclinical research was conducted by Khudiakov et al. [30]. They differentiated induced pluripotent stem cells from an ARVC patient and a healthy donor into the cardiomyocytes. Then, they compared the intracellular and extracellular levels of several miRNAs. They found that miR-1, miR-21, miR-133a, miR-208a, miR-378a, and miR-494 were increased in the supernatant compared to the precipitate fraction. Furthermore, miR-21, miR-29b-2, and miR-378a were increased in the supernatant fraction from the ARVC cells compared to the supernatant fraction from the healthy donor cells. MiR-1 and miR-133a were increased in the supernatant and precipitate fractions from ARVC cells compared to the corresponding fractions from the healthy donor cells. Nevertheless, there was no difference in the intracellular levels of miR-1, miR-21, miR-29b-2, miR-133a, and miR-378a between the ARVC cells and the healthy donor cells [30] . The research discussed in this subsection with additional data is summarized in Table 1.

Clinical patient-based research assessing the role of miRNAs in ARVC

Zhang et al. [31] investigated the miRNA levels in heart samples of ARVC patients. They included ARVC patients undergoing heart transplantation and compared them to healthy controls without any heart disease who died in an accident. First, they examined 1078 various miRNAs in pooled participant samples and found that 24 were significantly dysregulated. In a validation step, in which they assessed all 24 miRNAs individually in each sample, they discovered that miR-21-3p, miR-21-5p, miR-34a-5p, miR-212-3p, miR-216a, miR-584-3p, miR-1251, miR-3621, miR-3674, miR-3692-3p, miR-4286, and miR-4301 were upregulated while miR-135b, miR-138-5p, miR-193b-3p, miR-302b-3p, miR-302c-3p, miR-338-3p, miR-451a, miR-491-3p, miR-575, miR-4254, miR-4643 were downregulated in ARVC patients. The authors also performed a ROC analysis, and almost all miRNAs showed high AUC values

except miR-3674 (AUC 0.585) and miR-451a (AUC 0.653). All other miRNAs had AUC values higher than 0.750 [31].

Sommariva et al. [32] measured miRNA levels in plasma samples from ARVC patients, idiopathic ventricular tachyarrhythmia (IVT) patients, and healthy controls. During the first step, they screened 377 miRNAs in samples from ARVC patients and healthy controls and found that five miRNAs were significantly dysregulated. Next, they measured these miRNA expression levels in all study participants. MiR-302a was the only one that differed between the groups. It had lower expression levels in ARVC patients than in healthy controls and IVT patients. The authors performed a ROC analysis to assess the ability of miR-302a to discriminate ARVC from IVT patients. It had poor performance, with an AUC of only 0.69. Moreover, their AUC did not increase substantially when the miR-302a expression level was added to the global/regional dysfunction criterion or electrocardiogram abnormalities. Interestingly, no correlation between miR-302a level and ARVC severity was found [32].

Yamada et al. [33] recruited patients with ventricular arrhythmia: (i) patients with definite ARVC diagnosis, (ii) patients with borderline/possible ARVC diagnosis, (iii) patients with IVT, and also healthy controls. In the first step, they screened 84 miRNAs, known to be dysregulated in cardiovascular diseases, in patients with definite ARVC diagnosis and healthy controls. They found an altered expression of 17 miRNAs. However, they chose only those miRNAs with four times higher/lower expression levels for the validation step, which was valid for 11 miRNAs. Then, they measured the expression level of these miRNAs in all patients and found that miR-144-3p, miR-145-5p, miR-185-5p, and miR494 had higher levels in definite ARVC patients than other groups. Moreover, in the ROC analysis evaluating the discrimination of patients with definite diagnoses of ARVC from other patients with ventricular arrhythmia, miR-494 had an AUC value of 0.891. Furthermore, they divided patients with definite diagnoses of ARVC who underwent ablation into those who experienced a recurrence of ventricular arrhythmia and those who did not. The first group had higher levels of miR-494 than the latter. MiR-494 was a predictor of ventricular arrhythmia recurrence with an AUC of 0.832 [33].

Bueno Marinas et al. [34] conducted a multi-stage research including not only ARVC patients and healthy controls but also non-affected family members of ARVC probands carrying a desmosomal pathogenic variant (ARVC gen+phen−), hypertrophy cardiomyopathy patients, dilated cardiomyopathy patients, Brugada syndrome patients, and myocarditis patients. They first compared screening with microarrays and RNA sequencing methods in heart tissue and blood samples. Then, they validated 13 candidate miRNAs with qPCR. MiR-122-5p, miR-182-

5p, and miR-183-5p were upregulated, while miR-133a-3p, miR-133b, and miR-142-3p were downregulated in ARVC patients compared to healthy controls. In ROC analysis, all six miRNAs performed well in discriminating ARVC patients from healthy controls (AUC values range: 0.707 to 0.9692). Furthermore, a panel consisting of these six miRNAs was evaluated in ROC analysis to differentiate ARVC patients from healthy controls, ARVC gen+phen−, hypertrophy cardiomyopathy patients, dilated cardiomyopathy patients, Brugada syndrome patients, and myocarditis patients. In each scenario, the AUC value was higher than 0.8 [34].

Khudiakov et al. [35] included patients suffering from ARVC and compared them to patients with post-infarction ventricular tachycardia. They performed an RNA sequencing which showed the upregulation of miR-122-5p, miR-206, miR-1-3p and downregulation of miR-3679-5p, miR-21-5p in ARVC patients compared to the latter group. They found a correlation between RNA-seq and qPCR results for miR-1-3p, miR-21-5p, miR-122-5p, and inconsistency for miR-206, miR-3679-5p. The authors mapped differentially expressed miRNAs against databases with biological processes, and it resulted in the following terms: cell cycle, heart and muscle development, inflammation, hormone-mediated signaling pathway, T-helper 17 cell differentiation, muscle development, skeletal muscle cell differentiation, cell death, cell proliferation, and cardiogenesis [35].

Sacchetto et al. [36] measured miRNA plasma concentration in ARVC patients and healthy controls. First, they performed a pilot study using microarrays. They assessed the expression level of 754 miRNAs and found five differentially expressed miRNAs: miR-505, miR-20b, miR-590-5p, miR-520c-3p, and miR-185-5p. These miRNAs were then validated with qPCR. MiR-20b was downregulated, while miR-185-5p was upregulated in patients suffering from ARVC compared to healthy controls. Moreover, the authors conducted an in-silico analysis to look for the predicted target genes for miR-185-5p. Interestingly, the genes found were involved in regulating cell adhesion and in Wnt and Hippo pathways [36].

Bonet et al. [37] performed small RNA-seq analysis to identify differentially expressed miRNAs between patients with a definite diagnosis of ARVC and unrelated ARVC subjects who died from conditions other than cardiac diseases as a control group. They found eight differentially expressed miRNAs: miR-135a-5p, miR-140-3p, and miR-145-5p were upregulated while miR-486-5p, miR-486-3p, miR-125a-5p, let-7e-5p, and let-7d-3p were downregulated in patients with a definite ARVC diagnosis [37]. All studies discussed in this subsection, along with additional data, are summarized in Table 2.

Bioinformatic analyses investigating the role of miRNAs in ARVC

Lu et al. [38] performed a bioinformatic analysis using RNA-sequencing datasets from the Gene Expression Omnibus database. It included ARVC patients and healthy controls — the samples were collected from the right and left ventricular myocardium. The authors made a weighted gene co-expression network analysis. They also looked for long non-coding RNAs (lncRNAs) differentially expressed between ARVC patients and healthy controls. Then, they sought for lncRNA–mRNA pairs and miRNA overlap. They found 258 lncRNA–mRNA pairs with significant miRNA overlaps. The authors also conducted a lncRNA-miRNA-mRNA network analysis, in which the top 3 miRNAs were miR-590-3p, miR-186-5p, and miR-15a-5p [38].

Li et al. [39] conducted another bioinformatic analysis. They analyzed differentially expressed mRNAs, lncRNAs, and miRNAs in ARVC patients. They found altered mRNAs and lncRNAs using the Gene Expression Omnibus database. Meanwhile, deregulated miRNAs were taken from a study by Bueno Marinas et al. [34], which we discussed earlier. First, the authors constructed a miRNA-mRNA network in which they identified 12 downregulated miRNAs targeting 17 upregulated mRNAs and eight upregulated miRNAs targeting 55 downregulated mRNAs. Furthermore, they created a lncRNA-miRNA-mRNA network, in which the following miRNAs could be found: let-7b, miR-10b-5p, miR-21-5p, miR-29b-3p, miR-122-5p, miR-144-3p, miR-149-5p, miR-182-5p, miR-320a, miR-494-3p [39]. Both studies discussed in this subsection with additional data are summarized in Table 3.

DISCUSSION

Not so many studies have been conducted to date investigating the role of miRNAs in ARVC. Nevertheless, the research has been done in both clinical and preclinical scenarios. Overlapping findings include increased expression of miR-216a in mice ARVC models and in patients suffering from this disease. MiR-1 and miR-21 are other miRNAs that are worth being highlighted. The levels of miR-1 were consistently increased in (i) supernatant and precipitant fractions of cardiomyocyte culture derived from induced pluripotent stem cell from ARVC patient, (ii) pericardial fluid of ARVC patients compared to post-infarction ventricular tachyarrhythmia patients. Meanwhile, miR-21 was increased in (i) precipitant fraction of cardiomyocyte culture derived from induced pluripotent stem cell from ARVC patient, (ii) heart samples of ARVC patients compared to healthy controls but decreased in the pericardial fluid of ARVC patients compared to post-infarction ventricular tachyarrhythmia patients. Furthermore, miR-122 was increased in the pericardial fluid of ARVC patients compared to post-infarction ventricular tachyarrhythmia patients and in the whole blood of ARVC patients compared to healthy controls.

Two fascinating bioinformatic analyses have already been undertaken. Their main aim was not the assessment of miRNAs in ARVC, but some exciting findings regarding this aspect were also presented. Mainly, it regarded miRNAs involved in the lncRNA-miRNA-mRNA network, particularly: let-7b, miR-10b-5p, miR-15a-5p, miR-21-5p, miR-29b-3p, miR-122-5p, miR-144-3p, miR-149-5p, miR-182-5p, miR-186-5p, miR-320a, miR-494-3p, and miR-590-3p.

Importantly, presented studies often used different laboratory techniques for miRNA measurements. This disenables drawing firm conclusions and making direct, head-to-head comparisons. However, it does not prevent hypothesizing with the aim of conducting further research in the field. Figure 2 presents a comprehensive summary of the current knowledge about the role of miRNAs in ARVC. In order to enable more in-depth interpretation, we have prepared a table demonstrating the top 3 predicted target genes (based on https://mirdb.org) of all miRNAs altered in ARVC (Table 4).

Limitations of the study

We must disclose a limitation of our article: Different study types were included in this systematic review. However, this allowed us to thoroughly present and discuss all available research in the field. The small amount of research in the field allowed us to discuss and summarize all the existing knowledge thoroughly.

CONCLUSIONS

Although the results were sometimes conflicting, a few studies showed that some miRNAs can differentiate patients with ARVC from healthy people, presenting high AUC values in the ROC analysis. Similarly, the researchers discovered several promising miRNAs that could discriminate between patients with ARVC and other arrhythmias.

Creating a miRNA panel that could identify ARVC patients with high sensitivity and specificity would be helpful in decreasing the rate of fatal events among people suffering from this disease. Moreover, it could create a basis for novel therapeutics if some miRNA alterations were causal for ARVC development and progression. Altogether, there are many gaps in the existing knowledge, which makes miRNA in ARVC an attractive field for investigation.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

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REFERENCES

1. Basso C, Corrado D, Bauce B, et al. Arrhythmogenic right ventricular cardiomyopathy. Circ Arrhythm Electrophysiol. 2012; 5(6): 1233–1246, doi: 10.1161/CIRCEP.111.962035, indexed in Pubmed: 23022706.
2. Gemayel C, Pelliccia A, Thompson PD. Arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol. 2001; 38(7): 1773–1781, doi: 10.1016/s0735-1097(01)01654-0, indexed in Pubmed: 11738273.
3. Altmayer S, Nazarian S, Han Y. Left ventricular dysfunction in arrhythmogenic right ventricular cardiomyopathy (ARVC): Can we separate ARVC from other arrhythmogenic cardiomyopathies? J Am Heart Assoc. 2020; 9(23): e018866, doi: 10.1161/JAHA.120.018866, indexed in Pubmed: 33222587.
4. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J. 2023; 44(37): 3503–3626, doi: 10.1093/eurheartj/ehad194, indexed in Pubmed: 37622657.
5. Haugaa KH, Haland TF, Leren IS, et al. Arrhythmogenic right ventricular cardiomyopathy, clinical manifestations, and diagnosis. Europace. 2016; 18(7): 965–972, doi: 10.1093/europace/euv340, indexed in Pubmed: 26498164.
6. Casian M, Papadakis M, Jurcut R. Arrhythmogenic right ventricular cardiomyopathies (ARVC): Diagnostic challenges from imaging to genetics. Pol Heart J. 2024 [Epub ahead of print], doi: 10.33963/v.phj.102391, indexed in Pubmed: 39240923.
7. Krahn AD, Wilde AAM, Calkins H, et al. Arrhythmogenic right ventricular cardiomyopathy. JACC: Clin Electrophysiol. 2022; 8(4): 533–553, doi: 10.1016/j.jacep.2021.12.002, indexed in Pubmed: 35450611.

8. Basso C, Corrado D, Marcus F, et al. Arrhythmogenic right ventricular cardiomyopathy. Lancet. 2009; 373(9671): 1289–1300, doi: 10.1016/s0140-6736(09)60256-7, indexed in Pubmed: 19362677.
9. Corrado D, Basso C, Thiene G. Arrhythmogenic right ventricular cardiomyopathy: An update. Heart. 2009; 95(9): 766–773, doi: 10.1136/hrt.2008.149823, indexed in Pubmed: 19366719.
10. Corrado D, Basso C, Judge DP. Arrhythmogenic cardiomyopathy. Circ Res. 2017; 121(7): 784–802, doi: 10.1161/CIRCRESAHA.117.309345, indexed in Pubmed: 28912183.
11. Mizia-Stec K, Burchardt P, Mazurkiewicz Ł, et al. Position statement of Polish Cardiac Society experts on cardiomyopathy. Pol Heart J. 2024; 82(10): 1040–1053, doi: 10.33963/v.phj.102977, indexed in Pubmed: 39377635.
12. Calkins H, Corrado D, Marcus F. Risk stratification in arrhythmogenic right ventricular cardiomyopathy. Circulation. 2017; 136(21): 2068–2082, doi: 10.1161/CIRCULATIONAHA.117.030792, indexed in Pubmed: 29158215.
13. Starega-Roslan J, Krol J, Koscianska E, et al. Structural basis of microRNA length variety. Nucleic Acids Res. 2011; 39(1): 257–268, doi: 10.1093/nar/gkq727, indexed in Pubmed: 20739353.
14. Du T, Zamore PD. Beginning to understand microRNA function. Cell Res. 2007; 17(8): 661–663, doi: 10.1038/cr.2007.67, indexed in Pubmed: 17694094.
15. Moreno-Moya JM, Vilella F, Simón C. MicroRNA: Key gene expression regulators. Fertil Steril. 2014; 101(6): 1516–1523, doi: 10.1016/j.fertnstert.2013.10.042, indexed in Pubmed: 24314918.
16. Kuosmanen SM, Hartikainen J, Hippeläinen M, et al. MicroRNA profiling of pericardial fluid samples from patients with heart failure. PLoS One. 2015; 10(3): e0119646, doi: 10.1371/journal.pone.0119646, indexed in Pubmed: 25763857.
17. Layne TR, Green RA, Lewis CA, et al. microRNA detection in blood, urine, semen, and saliva stains after compromising treatments. J Forensic Sci. 2019; 64(6): 1831–1837, doi: 10.1111/1556-4029.14113, indexed in Pubmed: 31184791.
18. Grodzka O, Procyk G, Gąsecka A. The role of MicroRNAs in myocarditis — what can we learn from clinical trials? Int J Mol Sci. 2022; 23(24), doi: 10.3390/ijms232416022, indexed in Pubmed: 36555663.

19. Grodzka O, Procyk G, Wrzosek M. A narrative review of preclinical in vitro studies investigating microRNAs in myocarditis. Curr Issues Mol Biol. 2024; 46(2): 1413–1423, doi: 10.3390/cimb46020091, indexed in Pubmed: 38392209.
20. Krauze A, Procyk G, Gąsecka A, et al. The role of microRNAs in aortic stenosis-lessons from recent clinical research studies. Int J Mol Sci. 2023; 24(17), doi: 10.3390/ijms241713095, indexed in Pubmed: 37685901.
21. Procyk G, Grodzka O, Procyk M, et al. MicroRNAs in myocarditis-review of the preclinical in vivo trials. Biomedicines. 2023; 11(10): 2723, doi: 10.3390/biomedicines11102723, indexed in Pubmed: 37893097.
22. Kiełbowski K, Bakinowska E, Procyk G, et al. The role of microRNA in the pathogenesis of Duchenne muscular dystrophy. Int J Mol Sci. 2024; 25(11): 6108, doi: 10.3390/ijms25116108, indexed in Pubmed: 38892293.
23. Grodzka O, Słyk S, Domitrz I. The role of microRNA in migraine: A systemic literature review. Cell Mol Neurobiol. 2023; 43(7): 3315–3327, doi: 10.1007/s10571-023-01387-9, indexed in Pubmed: 37432603.
24. Procyk G, Klimczak-Tomaniak D, Sygitowicz G, et al. Circulating and platelet micrornas in cardiovascular risk assessment and antiplatelet therapy monitoring. J Clin Med. 2022; 11(7): 1763, doi: 10.3390/jcm11071763, indexed in Pubmed: 35407371.
25. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021(372): n71, doi: 10.1136/bmj.n71, indexed in Pubmed: 33782057.
26. GA Wells BS, D O'Connell, J Peterson, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.
27. Mazurek SR, Calway T, Harmon C, et al. MicroRNA-130a regulation of desmocollin 2 in a novel model of arrhythmogenic cardiomyopathy. Microrna. 2017; 6(2): 143–150, doi: 10.2174/2211536605666161109111031, indexed in Pubmed: 27834139.
28. Rainer J, Meraviglia V, Blankenburg H, et al. The arrhythmogenic cardiomyopathy-specific coding and non-coding transcriptome in human cardiac stromal cells. BMC Genomics. 2018; 19(1): 491, doi: 10.1186/s12864-018-4876-6, indexed in Pubmed: 29940860.
29. Calore M, Lorenzon A, Vitiello L, et al. A novel murine model for arrhythmogenic cardiomyopathy points to a pathogenic role of Wnt signalling and miRNA dysregulation. Cardiovasc Res. 2019; 115(4): 739–751, doi: 10.1093/cvr/cvy253, indexed in Pubmed: 30304392.

30. Khudiakov AA, Smolina NA, Perepelina KI, et al. Extracellular microRNAs and mitochondrial DNA as potential biomarkers of arrhythmogenic cardiomyopathy. Biochemistry (Mosc). 2019; 84(3): 272–282, doi: 10.1134/S000629791903009X, indexed in Pubmed: 31221065.
31. Zhang H, Liu S, Dong T, et al. Profiling of differentially expressed microRNAs in arrhythmogenic right ventricular cardiomyopathy. Sci Rep. 2016; 6: 28101, doi: 10.1038/srep28101, indexed in Pubmed: 27307080.
32. Sommariva E, D'Alessandra Y, Farina FM, et al. MiR-320a as a potential novel circulating biomarker of arrhythmogenic cardiomyopathy. Sci Rep. 2017; 7(1): 4802, doi: 10.1038/s41598-017-05001-z, indexed in Pubmed: 28684747.
33. Yamada S, Hsiao YW, Chang SL, et al. Circulating microRNAs in arrhythmogenic right ventricular cardiomyopathy with ventricular arrhythmia. Europace. 2018; 20(FI1): f37–f45, doi: 10.1093/europace/eux289, indexed in Pubmed: 29036525.
34. Bueno Marinas M, Celeghin R, Cason M, et al. A microRNA expression profile as non-invasive biomarker in a large arrhythmogenic cardiomyopathy cohort. Int J Mol Sci. 2020; 21(4): 1536, doi: 10.3390/ijms21041536, indexed in Pubmed: 32102357.
35. Khudiakov AA, Panshin DD, Fomicheva YV, et al. Different expressions of pericardial fluid micrornas in patients with arrhythmogenic right ventricular cardiomyopathy and ischemic heart disease undergoing ventricular tachycardia ablation. Front Cardiovasc Med. 2021; 8: 647812, doi: 10.3389/fcvm.2021.647812, indexed in Pubmed: 33816578.
36. Sacchetto C, Mohseni Z, Colpaert RMW, et al. Circulating miR-185-5p as a potential biomarker for arrhythmogenic right ventricular cardiomyopathy. Cells. 2021; 10(10): 2578, doi: 10.3390/cells10102578, indexed in Pubmed: 34685557.
37. Bonet F, Campuzano O, Córdoba-Caballero J, et al. Role of miRNA-mRNA interactome in pathophysiology of arrhythmogenic cardiomyopathy. Biomedicines. 2024; 12(8): 1807, doi: 10.3390/biomedicines12081807, indexed in Pubmed: 39200271.
38. Lu W, Li Y, Dai Y, et al. Dominant myocardial fibrosis and complex immune microenvironment jointly shape the pathogenesis of arrhythmogenic right ventricular cardiomyopathy. Front Cardiovasc Med. 2022; 9: 900810, doi: 10.3389/fcvm.2022.900810, indexed in Pubmed: 35845067.
39. Li H, Song S, Shi A, et al. Identification of potential lncRNA-miRNA-mRNA regulatory network contributing to arrhythmogenic right ventricular cardiomyopathy. J Cardiovasc Dev Dis. 2024; 11(6): 168, doi: 10.3390/jcdd11060168, indexed in Pubmed: 38921668.

Table 1. Summary of preclinical research evaluating the role of miRNAs in ARVC.

Ref.	Year	Population	Comparison	miRNA	Methodology	Study design	Outcome
[27]	2017	17 transgenic mice overexpressing miR-130a	14 control littermate mice	miR-130a	Mice examined with TTE and surface ECG	Animal model study	Right ventricular dilation in mice overexpressing miR-130a the presence of PVCs in mice overexpressing miR-130a (11.52 ± 5.36 PVC/min) and no PVCs in control mice
[28]	2018	CStCs derived from 8 ARVC pts	CStCs derived from 5 HCs	miR-520c-3p, miR-29b-3p, miR-1183	miRNA in CStCs by qRT-PCR	*In vitro* study	↑ miR-29b-3p in CStCs derived from ARVC pts
[29]	2019	5 Tg-hQ13 mice	5 Tg-hWT40 5 non-transgenic mice	Real-time PCR	miRNA in heart tissue by Illumina HiSeq 2000	Animal model study	24 miRNAs altered in Tg-hQ13 compared to

				validation: miR-499-5p, miR-216a-5p, miR-217-5p, miR-708-5p	platform and real-time PCR		non-transgenic mice (18 upregulated and 6 downregulated) ↑ miR-217-5p, miR-708-5p and ↓ miR-499-5p in Tg-hQ13 mice compared to both Tg-hWT40 and non-transgenic mice ↑ miR-216a-5p in Tg-hQ13 mice compared to non-transgenic mice (but not when compared to Tg-hWT40)
[30]	2019	Cardiomyocytes derived from iPSC	Cardiomyocytes derived from iPSC	miR-1, miR-21, miR-29b-2,	Extracellular and intracellula	*In vitro* study	↑ miR-1, miR-21, miR-133a, miR-208a,

		lines from ARVC pt	lines from HCs	miR-30c, miR-133a, miR-208a, miR-378a, miR-494	r miRNA by qPCR		miR-378a, and miR-494 in the supernatant compared to the precipitate fraction ↑ miR-21, miR-29b-2, and miR-378a in the supernatant fraction from the ARVC cells compared to the supernatant fraction from the HC cells ↑ miR-1 and miR-133a in the supernatant and precipitate fractions from ARVC cells compared to the correspondin

							g fractions from the HC cells no difference in the intracellular levels of miR-1, miR-21, miR-29b-2, miR-133a, and miR-378a between the ARVC cells and the HC cells

Abbreviations: ↑, increased; ARVC, arrhythmogenic right ventricular cardiomyopathy; CStCs, cardiac stromal cells; ECG, electrocardiogram; HCs, healthy controls; iPSC, induced pluripotent stem cell; miR/miRNA, microRNA; pts, patients; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; ref., reference; RNA, ribonucleic acid; TTE, transthoracic echocardiography

Table 2. Summary of clinical patient-based research assessing the role of miRNAs in ARVC.

Ref.	**Year**	**Population**	**Comparison**	**miRNA**	**Methodology**	**Study design**	**Outcome**

[31]	2016	24 ARVC pts undergoing HTx	24 HCs (autopsies or donors w/o heart disease)	1078 various human microRNAs	miRNA in heart samples by S-Poly(T) Plus method	Case-control study	AUC value for differentiating ARVC from HCs was presented in [] below: ↑ miR-21-3p [0.936], miR-21-5p [0.944], miR-34a-5p [0.819], miR-212-3p [0.910], miR-216a [0.798], miR-584-3p [0.781], miR-1251 [0.978], miR-3621 [0.849], miR-3674 [0.585], miR-3692-3p [0.861], miR-4286 [0.778], miR-4301 [0.799] in ARVC pts ↓ miR-135b [0.936], miR-138-5p [0.758], miR-193b-3p [0.946], miR-302b-3p [0.991], miR-

							302c-3p [0.992], miR-338-3p [0.970], miR-451a [0.653], miR-491-3p [0.837], miR-575 [0.922], miR-4254 [0.838], miR-4643 [0.966] in ARVC pts
[32]	2017	36 ARVC pts	53 HCs 21 IVT pts	377 various miRNAs in screening RT-qPCR validation: miR-223, miR-320, miR-483-5p, miR-126, miR-301	miRNA in plasma by microarrays and RT-qPCR	Case-control study	↓ miR-302a in ARCV pts compared to HCs ↓ miR-302a in ARCV pts compared to IVT pts ROC analysis of miR-302a in ARVC vs IVT pts: AUC = 0.69 no correlation between miR-302a and ARVC severity

[33]	2018	28 definite ARVC pts	11 borderline/possible ARVC pts 23 IVT pts 33 HCs	84 cardiac-related miRNAs in screening real-time PCR validation: hsa-let-7e, miR-122-5p, miR-144-3p, miR-145-5p, miR-185-5p, miR-195-5p, miR-494, miR-107, miR-142-3p, miR-150-5p, miR-378a-3p	miRNA in plasma by microarrays and real-time PCR	Case-control study	↑ miR-144-3p, miR-145-5p, miR-185-5p, and miR-494 in definite ARVC pts compared to other groups ROC analysis definite ARVC vs IVT + borderline/possible ARVC pts: miR-144-3p: AUC = 0.728, miR-145-5p: AUC = 0.619, miR-185-5p: AUC = 0.740, and miR-494: AUC = 0.891 ↑ miR-494 in definite ARVC pts with recurrent VA after ablation compared to definite ARVC pts w/o recurrence, miR-494 as a predictor of VA recurrence: AUC = 0.832

[34]	2020	90 ARVC pts	20 HCs 17 non-affected family members of ARVC probands carrying a desmosomal pathogenic variant (ARVC *gen+phen−*) 20 HCM pts 20 DCM pts 13 BrS pts 13 myocarditis pts	Real-time PCR validation: miR-21-5p, miR-122-5p, miR-133a-3p, miR-133b, miR-142-3p, miR-144-3p, miR-149-5p, miR-182-5p, miR-183-5p, miR-184, miR-208a-3p, miR-320a, miR-494-3p,	miRNA in heart tissue and whole blood by microarrays, RNA-seq, and qPCR	Case-control study	↑ miR-122-5p, miR-182-5p, miR-183-5p, and ↓ miR-133a-3p, miR-133b, miR-142-3p in ARVC pts compared to HCs ROC analysis (AUC) for ARVC pts vs HCs: miR-122-5p (0.9146), miR-133a-3p (0.845), miR-133b (0.858), miR-142-3p (0.9692), miR-182-5p (0.7371), miR-183-5p (0.707) ROC analysis (AUC) for 6-miRNA panel ARVC pts vs: HCs (0.995), HCM pts (0.804), DCM pts (0.917), ARVC

							gen+phen− (0.825), BrS pts (0.981), myocarditis (0.978)
[35]	2021	6 ARVC pts	3 post-infarction VT pts	145–411 microRNAs per sample in RNA-seq qPCR validation: miR-1-3p, miR-21-5p, miR-122-5p, miR-206, miR-3679-5p	miRNA in pericardial fluid by small RNA-seq and qPCR	Case-control study	RNA-seq: ↑ miR-122-5p, miR-206, miR-1-3p and ↓ miR-3679-5p, miR-21-5p in ARVC pts compared to post-infarction VT pts correlation between RNA-seq and qPCR for miR-1-3p, miR-21-5p, miR-122-5p, and inconsistency for miR-206, miR-3679-5p

[36]	2021	37 ARVC pts	30 HCs	754 miRNAs in a pilot study by microarray 5 miRNA in qPCR validation: miR-505, miR-20b, miR-590-5p, miR-520c-3p, miR-185-5p	miRNA in plasma by microarrays and qPCR	Case-control study	↓ miR-20b and ↑ miR-185-5p in ARVC pts compared to HCs ROC analysis of miR-185-5p in ARVC vs HCs: AUC = 0.854
[37]	2024	4 definite ARVC pts	4 unrelated ARVC subjects who died from other conditions than cardiac disease	Small RNA-seq analysis	miRNA libraries in RV myocardial samples by NEXTFLEX small RNA-seq kit v3	Case-control study	↑ miR-135a-5p, miR-140-3p, miR-145-5p, and ↓ miR-486-5p, miR-486-3p, miR-125a-5p, let-7e-5p, let-7d-3p in definite ARVC pts compared to controls

Abbreviations: ↑, increased; ↓, decreased; ARVC, arrhythmogenic right ventricular cardiomyopathy; AUC, area under the ROC curve; BrS, Brugada Syndrome; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HCs, healthy controls; HTx, heart transplantation; IVT, idiopathic ventricular tachyarrhythmia; pts, patients; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; ref., reference; RNA, ribonucleic

acid; ROC, receiver operating characteristic; RV, right ventricle; VA, ventricular arrhythmia; VT, ventricular tachycardia; w/o—without.

Table 3. Summary of bioinformatic analyses investigating the role of miRNAs in ARVC.

Ref.	Year	Population	Comparison	miRNA	Methodology	Study design	Outcome
[38]	2022	15 ARVC pts	11 HCs	the interacted miRNAs of lncRNAs and mRNAs searched in the RNAinter database	RNA-seq in ventricular myocardium data from the GEO database	bioinformatic analysis	198 differentially expressed lncRNAs between ARVC pts and HCs 934 lncRNA–mRNA pairs among which 258 pairs with significant miRNA overlaps top-3 miRNAs from lncRNA-miRNA-mRNA network analysis: miR-590-3p, miR-

							186-5p, miR-15a-5p
[39]	2024	27 ARVC pts	17 HCs	lncRNA-miRNA-mRNA network construction	GEO database, results from Bueno Marinas [34]	bioinformatic analysis	miRNA-mRNA network: 12 downregulated miRNAs targeting 17 upregulated mRNAs and 8 upregulated miRNAs targeting 55 downregulated mRNAs let-7b, miR-10b-5p, miR-21-5p, miR-29-b-3p, miR-122-5p, miR-144-3p, miR-149-5p, miR-182-5p, miR-320a, miR-

		494-3p included in the lncRNA-miRNA-mRNA network

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; GEO, Gene Expression Omnibus; HCs, healthy controls; lncRNAs, long non-coding RNAs; miR/miRNA, microRNA; mRNAs, messenger RNAs; pts, patients; ref., reference; RNA, ribonucleic acid.

Table 4. Top 3 predicted target genes (based on https://mirdb.org) of all miRNAs altered in arrhythmogenic right ventricular cardiomyopathy. Bolded miRNAs are mice miRNAs; all others are human

miRNA	**Top 3 predicted targets**
miR-1-3p	3-hydroxyacyl-CoA dehydratase 3, monocyte to macrophage differentiation associated, solute carrier family 44 member 1
miR-10b-5p	Cell adhesion molecule 2, transcription factor AP-2 gamma, CCR4-NOT transcription complex subunit 6
miR-15a-5p	Pappalysin 1, fatty acid synthase, unc-80 homolog, NALCN channel complex subunit
miR-20b	Ectonucleotide pyrophosphatase/phosphodiesterase 5 (putative), FYVE and coiled-coil domain containing 1, dynein cytoplasmic 1 light intermediate chain 2
miR-21-3p	Serine/threonine kinase 38 like, protocadherin 19, TSC22 domain family member 2
miR-21-5p	YOD1 deubiquitinase, PR/SET domain 11, Fas ligand
miR-29b-2	POU class 2 homeobox 2, leucine rich repeat transmembrane neuronal 2, WNK lysine deficient protein kinase 1
miR-29b-3p	Collagen type V alpha 3 chain, collagen type V alpha 1 chain, tet methylcytosine dioxygenase 1
miR-34a-5p	Hyperpolarization activated cyclic nucleotide gated potassium channel 3, family with sequence similarity 76 member A, MDM4, p53 regulator

miR-122-5p	Heterogeneous nuclear ribonucleoprotein U, cytoplasmic polyadenylation element binding protein 1, CD40 ligand
miR-125a-5p	StAR related lipid transfer domain containing 13, FRAS1 related extracellular matrix 1, protein phosphatase 4 regulatory subunit 3A
miR-130a	SKI/DACH domain containing 1, myeloblastosis oncogene-like 1, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
miR-133a-3p	BicC family RNA binding protein 1, mastermind like transcriptional coactivator 1, polypyrimidine tract binding protein 1
miR-133b	BicC family RNA binding protein 1, LHFPL tetraspan subfamily member 6, polypyrimidine tract binding protein 1
miR-135a-5p	Leucine zipper tumor suppressor 1, synaptotagmin 2, small integral membrane protein 13
miR-135b	Leucine zipper tumor suppressor 1, synaptotagmin 2, small integral membrane protein 13
miR-138-5p	V-set and transmembrane domain containing 2 like, UPF2, regulator of nonsense mediated mRNA decay, required for meiotic nuclear division 5 homolog A
miR-140-3p	Iduronate 2-sulfatase, ADAM metallopeptidase domain 10, activin A receptor type 2B
miR-142-3p	Zinc finger E-box binding homeobox 2, transcription activation suppressor family member 2, RPTOR independent companion of MTOR complex 2
miR-144-3p	Ubiquitin conjugating enzyme E2 D1, transportin 1, gamma-aminobutyric acid type A receptor alpha1 subunit
miR-145-5p	Fascin actin-bundling protein 1, abhydrolase domain containing 17C, Fli-1 proto-oncogene, ETS transcription factor
miR-149-5p	Cache domain containing 1, elongator acetyltransferase complex subunit 5, VPS53, GARP complex subunit
miR-182-5p	Protein kinase cAMP-activated catalytic subunit beta, regulator of G protein signaling 17, basonuclin 2
miR-183-5p	Profilin 2, myocyte enhancer factor 2C, potassium two pore domain channel subfamily K member 10
miR-185-5p	SMG7, nonsense mediated mRNA decay factor, solute carrier family 16 member 2, suppressor of glucose, autophagy associated 1
miR-186-5p	RUN and FYVE domain containing 3, zinc finger CCCH-type containing 11A, zinc finger protein 644
miR-193b-3p	Mitogen-activated protein kinase 10, phosphatidylinositol glycan anchor biosynthesis class A, DDB1 and CUL4 associated factor 7

miR-206	3-hydroxyacyl-CoA dehydratase 3monocyte to macrophage differentiation associated solute carrier family 44 member 1
miR-208a	Stanniocalcin 1, receptor accessory protein 1, EYA transcriptional coactivator and phosphatase 4
miR-212-3p	Cyclin dependent kinase 19, translocase of inner mitochondrial membrane 9, LEM domain containing 3
miR-216a-5p	Zinc finger and BTB domain containing 2, synovial sarcoma, X 2 interacting protein, mitogen-activated protein kinase 1 interacting protein 1-like
miR-217-5p	Enhancer of zeste 2 polycomb repressive complex 2 subunit, TPase, Na+/K+ transporting, beta 1 polypeptide, glycoprotein m6a
miR-302a	YOD1 deubiquitinase, large tumor suppressor kinase 2, carnitine O-octanoyltransferase
miR-302b-3p	YOD1 deubiquitinase, large tumor suppressor kinase 2, carnitine O-octanoyltransferase
miR-302c-3p	YOD1 deubiquitinase, large tumor suppressor kinase 2, carnitine O-octanoyltransferase
miR-320a	YOD1 deubiquitinase, cyclin dependent kinase like 5, one cut homeobox 2
miR-338-3p	Cbl proto-oncogene, galectin like, RAB14, member RAS oncogene family
miR-378a	Kallikrein related peptidase 4, nuclear receptor subfamily 2 group C member 2, NK3 homeobox 1
miR-451a	Odd-skipped related transcription factor 1, cut like homeobox 2, proteasome subunit beta 8
miR-486-3p	Retrotransposon Gag like 5, coiled-coil domain containing 97, phospholipase C beta 1
miR-486-5p	B-TFIID TATA-box binding protein associated factor 1, small nuclear ribonucleoprotein D1 polypeptide, small nuclear ribonucleoprotein D1 polypeptide
miR-491-3p	Ubiquitin conjugating enzyme E2 D3, protocadherin 7, solute carrier family 5 member 7
miR-494-3p	Family with sequence similarity 169 member A, solute carrier family 1 member 2, ArfGAP with GTPase domain, ankyrin repeat and PH domain 1
miR-499-5p	Post-GPI attachment to proteins 1, myelin basic protein expression factor 2, repressor, SRY (sex determining region Y)-box 6
miR-575	NudE neurodevelopment protein 1 like 1, DENN domain containing 5A, DENN domain containing 5A
miR-584-3p	Coiled-coil glutamate rich protein 1, ELK3, ETS transcription factor, CCR4-NOT transcription complex subunit 2
miR-590-3p	3'(2'), 5'-bisphosphate nucleotidase 1, listerin E3 ubiquitin protein ligase 1, zinc finger DHHC-type containing 21
miR-708-5p	SNF2 histone linker PHD RING helicase, RIKEN cDNA 4931406P16 gene, vaccinia related kinase 3

miR-1251	Zinc finger protein 99, dual specificity tyrosine phosphorylation regulated kinase 1A, centrosomal protein 350
miR-3621	Ubiquitin specific peptidase 19, chromosome 4 open reading frame 19, zinc finger protein 484
miR-3674	Zinc finger CCHC-type containing 14, claudin 4, microtubule associated protein 10
miR-3679-5p	Monoamine oxidase B, basal cell adhesion molecule (Lutheran blood group), CD2 associated protein
miR-3692-3p	Zinc finger protein 773, ZFP1 zinc finger protein, zinc finger protein 189
miR-4254	KH and NYN domain containing,SPOUT domain containing methyltransferase 1,SEL1L, ERAD E3 ligase adaptor subunit
miR-4286	Zinc finger and BTB domain containing 7B, mannosidase alpha class 2A member 2, ssemaphorin 4F
miR-4301	Lymphoid enhancer binding factor 1, transportin 1, caprin family member 2
miR-4643	Suppressor of cytokine signaling 6, solute carrier family 6 member 19, RAB6B, member RAS oncogene family
let-7b	StAR related lipid transfer domain containing 13, high mobility group AT-hook 2, immunoglobulin superfamily DCC subclass member 3
let-7d-3p	Mex-3 RNA binding family member C, BEN domain containing 2, prostaglandin I2 synthase
let-7e-5p	StAR related lipid transfer domain containing 13, high mobility group AT-hook 2, immunoglobulin superfamily DCC subclass member 3

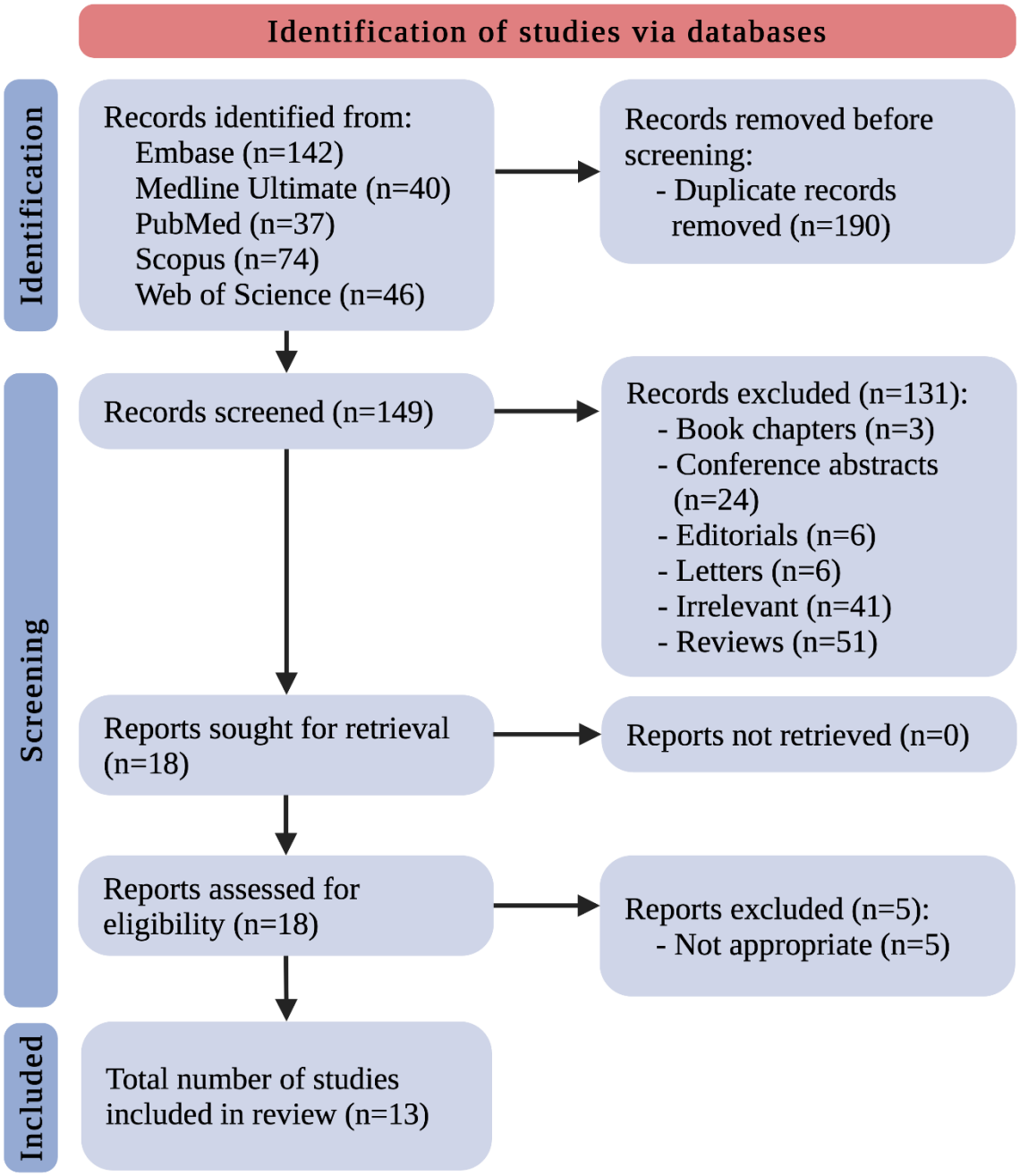

Figure 1. The flowchart for the selection process

Abbreviations: n, number of studies

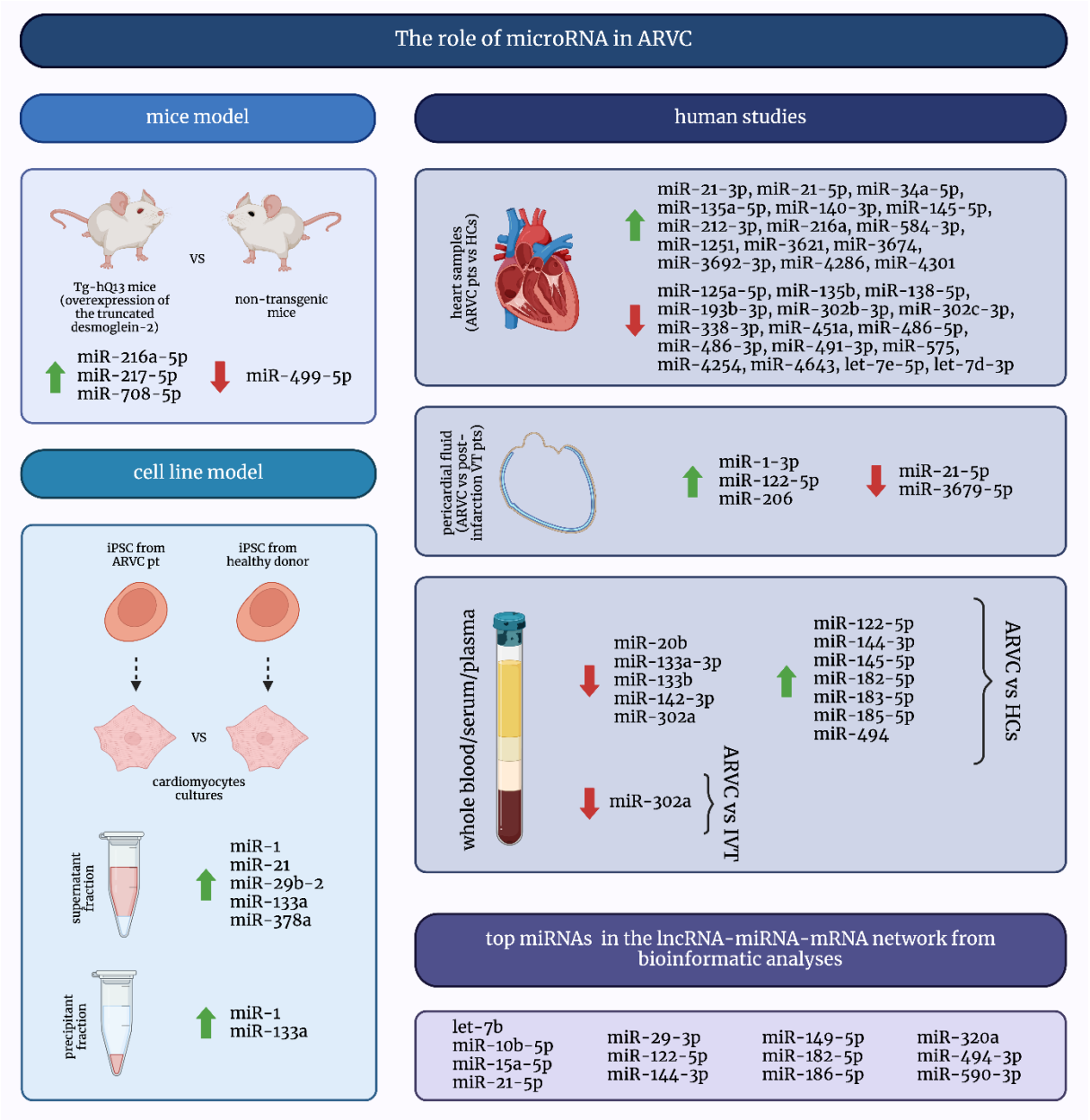

Figure 2. A central figure summarizing the role of microRNAs in arrhythmogenic right ventricular cardiomyopathy

Abbreviations: ↑, increased; ↓, decreased; ARVC, arrhythmogenic right ventricular cardiomyopathy; HCs, healthy controls; iPSC, induced pluripotent stem cell; IVT, idiopathic ventricular tachyarrhythmia; lncRNAs, long non-coding RNAs; miR/miRNA, microRNA; mRNAs, messenger RNAs; VT, ventricular tachycardia