Systematic Review and Meta-Analysis

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Upregulated miR-328-3p and its high risk in atrial fibrillation

A systematic review and meta-analysis with meta-regression

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Abstract

Background: Several studies have shown miR-328-3p increased in atrial fibrillation (AF), but some researches indicated no difference or even decreased. This inconsistent result confuses researchers, and it is urgent to know the truth. This study is to assess the association between miR-328-3p levels in plasma/atrial tissue and patients with AF.

Methods: PubMed, EMBASE, Scopus, Web of Science, and ProQuest were searched from inception to February 1, 2021. The standardized mean differences (SMD) with their 95% confidence interval (CI) were calculated to evaluate the association between miR-328-3p levels and AF.

Results: Twelve studies met the inclusion criteria and were used for our meta-analysis. Overall, the levels of miR-328-3p were higher in patients with AF than in the control group (SMD = 0.69, 95% CI [0.10, 1.28], $P = .022$). After adjustment, the overall SMD was 0.82 (95% CI [0.22, 1.42], $P = .007$). Sensitivity analysis indicated that the results were stable, and the trim-fill analysis showed that the results were credible. Subgroup analyses showed that AF patients, $n \geq 30$, various of comorbidity, articles published earlier, and Asia groups had higher levels of expression of miR-328-3p.

Conclusions: High levels of miR-328-3p are significantly associated with an increased risk of AF. It implies that miR-328-3p played an important role in diagnosis and may serve as a potential momentous, and useful biomarker to identify AF.

Abbreviations: 95% CI = 95% confidence interval, AF = atrial fibrillation, NOS = The Newcastle-Ottawa Quality Assessment scale, SD = standard deviation, SMD = standardized mean differences.

Keywords: atrial fibrillation, meta-analysis, meta-regression, miRNA-328-3p, systematic review

1. Introduction

Atrial fibrillation (AF) is the most common persistent arrhythmias in adults, globally, 46.3 million individuals in 2016.[1] It can lead to stroke, heart failure, dementia, and even death, with a high rate of disability and fatality, thus exerts a great deal of burden in the world at large.[2] The pathogenesis and maintaining mechanism of AF is the result of many aspects,[3] atrial electrical remodeling, structural remodeling, autonomic nerve remodeling, calcium ion homeostasis disorders, etc. Interestingly, binge drinking is associated with the occurrence of AF.[4] Previous studies have confirmed that multiple miRNAs are involved in the regulation of atrial remodeling and changes in miRNA expression can increase the risk of AF.[5]

MicroRNAs (miRNAs) are a class of short non-coding endogenous RNAs that regulate gene expression post-transcriptionally in major cardiac physiological and pathological processes, for instance, myocardial infarction, atrial remodel, arrhythmia, contractility, hypertrophy,[1,6–9] and relevant to the development and maintenance of AF. However, the full spectrum of miRNA function remains elusive. Recently, some studies have proved that miR-328-3p has a potential role as a disease biomarker and therapeutic target. Lu et al[10] found that miR-328-3p increased in patients with AF. But it is strongly conflicted, with some papers reporting that it has a weak correlation even irrelevance with AF patients.[11–13]

Considering these contradictory findings, we performed a meta-analysis of case-control studies between miR-328-3p with AF. This study synthesized data from existing literatures to evaluate the expressions of miR-328-3p in patients with AF. Meanwhile, we explored the difference between circulation and atrial tissue concerning AF, as well as the study region and sample size.

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Data Availability: The data supporting the conclusions of this study are available from the corresponding author upon request.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Methods

This meta-analysis was performed according to the Cochrane systematic review guidelines and the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement.[14] The study protocol has been published previously in PROSPERO (CRD42021225803). All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

2.1. Search strategy

For this systematic review and meta-analysis, we searched articles in 4 electronic databases including PubMed (https://pubmed.ncbi.nlm.nih.gov/), EMBASE (https://www.embase.com), Scopus (https://www.scopus.com/home.uri), Web of Science (www.webofknowledge.com/), and ProQuest (https://www.proquest.com/). "Atrial fibrillation" and ("microRNA-328" or "miRNA-328" or "miR-328") were selected as the subject headings for searching literature, recorded between the inception of each database and February 1, 2021. All the English publications were searched without any restriction of countries or article type. The reference list of all selected articles will independently be screened to identify additional studies left out in the initial search.

2.2. Inclusion and exclusion criteria

Studies were included if case-control studies evaluated the association between the miR-328-3p expression level and AF risk, patients diagnosed with AF in the case group and healthy people or patients without AF in the control group, detailed miRNA expression level data were extracted for the calculation of standardized mean difference (SMD) and 95% confidence interval (CI), applied miRNA expression analysis including miRNA sequencing experiments or quantitative real-time polymerase chain reaction (RT-qPCR) technologies, if serial studies from the same group of people were reported, included the latest study, and the search was limited to the language or date publication.

The following types of articles were excluded: studies are unrelated to miR-328-3p expression level and atrial fibrillation risk; case studies, case series, intervention studies, qualitative studies, systematic reviews, expert comments, abstracts, conference papers, meta-analysis, and repetition of previous publications; the same article of previous publications; the information provided in the original literature is not enough to calculate the statistical index SMD value.

2.3. Data extraction

Studies will be identified by 2 reviewers independently. Disagreements will be resolved by discussion or consensus with a third investigator. If the detailed data of miRNA expression level was not reported directly, only statistical graphs without specifying the specific values of mean and standard deviation (SD), data were extracted from the statistical graph by utilizing Adobe Photoshop 2020 (Adobe Inc., San Jose, CA).[15] When the literature merely provided median and interquartile range, the mean and the SD were calculated by the formula given by Hozo et al.[16] Data was extracted from included studies as follows: name of the first author, year of publication, study country, characteristics of case and control groups, sample size, age, gender, specimen type, detection method, the mean and SD of miR-328-3p in each group, etc.

2.4. Quality assessment

The Newcastle-Ottawa Quality Assessment scale (NOS) was used to assess the quality of studies incorporated in this meta-analysis.[17] Each study was evaluated based on the following 3 aspects: the selection of participants, comparability of the groups, and ascertainment of exposure. The lowest score was 0 and the highest was 9, and a NOS score ≥ 5 indicated that the study was reliable. Any studies with <7 stars in NOS were defined as high risk of bias and those with ≥ 7 stars were regarded as low risk of bias. Any discrepancies between reviewers were resolved by mutual consensus.

2.5. Data analysis

Analyses were performed in STATA version 12.0 (StataCorp., College Station, TX). All reported probabilities were 2-sided, and statistical significance was regarded as $P < .05$. A forest plot with SMD and corresponding 95% CI was used to assess the strength of association between miR-328-3p expression levels and AF risk for continuous outcomes. Statistical heterogeneity was investigated by Q test and I^2 statistics and according to the statistical value of consistency checking, a meta-analysis model was chosen.[18] When $P < .1$ or $I^2 > 50\%$, which indicated that there is heterogeneity among the research results, the DerSimonian–Laird random-effects model was utilized.[19] Otherwise, the inverse-variance fixed-effect model was applied.[20]

2.6. Meta-regression and subgroup analysis

To explore the sources of heterogeneity, the meta regression[21] and subgroup analyses[22] were performed according to the year of publication, the variance of comorbidity between AF and control groups, specimen type (peripheral blood plasma and atrial tissue), study region (Asia, America, and Europe) and sample size of AF group ($n < 30$, $n \geq 30$).

2.7. Sensitivity and publication bias

Sensitivity analysis,[23] 1 study at a time was removed and the rest were analyzed, was used to explore the extent to which our results and conclusions alter as a result of changes in data or analytical methods. Egger linear regression test[24] was used to evaluate the symmetry of funnel plots to explore the latent publication bias. Duval trim and fill method[25] was used to assess the potential impact of small sample studies, and visualized the outcome through funnel plots.

3. Results

3.1. Search results and study characteristics

A total of 255 citations were identified from PubMed, Embase, Scopus, Web of Science, and ProQuest during the initial search. According to the titles and abstracts, 84 duplicate records were removed and 151 studies were excluded. Of the 37 remaining literatures, 12 were eventually included in the meta-analysis after satisfying the study criteria (Fig. 1). These eligible studies included a total of 3084 subjects with 555 AF patients and 2529 controls. In the study of Soeki et al,[26] specimens were isolated from the blood of periphery and left atrial appendage, respectively. Consequently, we served this study as 2 independent studies. Overall, 7 studies explored plasma, 5 studies explored atrial tissue, and 1 explored whole blood. The study characteristics of the included studies were shown in Table 1.

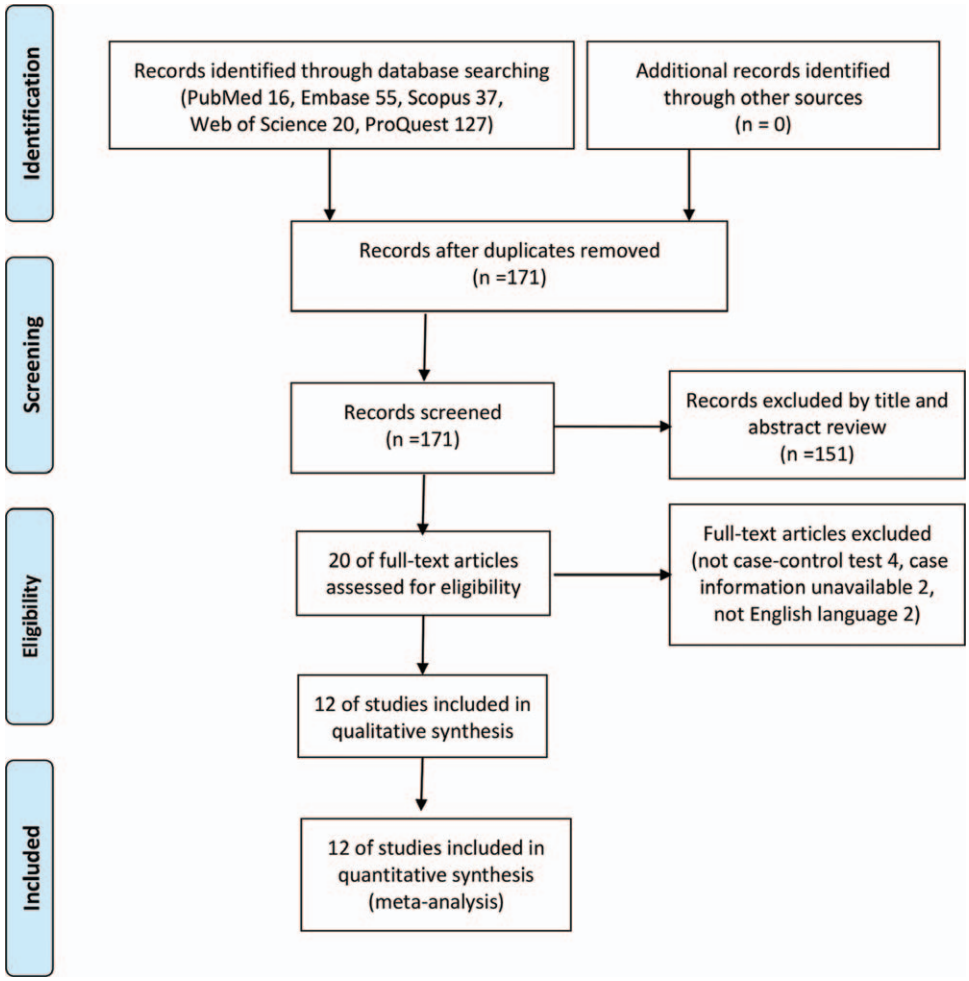

Figure 1. Flow diagram of literature search and selection.

3.2. Quality evaluation

As presented in Table 1 and Table 2, a total of 12 articles were included, all of which were case-control designs. According to the NOS quality scale, all documents were reliable, 4 studies had a high risk of bias and 8 studies had a low risk of bias.

3.3. Meta-analysis

As shown in Fig. 2, miRNA expression was found to be significantly higher in patients with AF than the controls, and the overall SMD of the randomized effect model was 0.69 (95% CI [0.10–1.28], $P = .022$; Heterogeneity: $I^2 = 94.8\%$, $P < .001$). The

Table 1

Characteristics of the included studies.

First Author				Sample size		Age			Gender (male/female)			
(Ref. No.)	Year	Country	Sample type	SR	AF	SR	AF	*P*-value	SR	AF	Methods	NOS
Liu et al[12]	2014	China	LAA	6	6	47.5±8.4	49.4±11.9	.79	3/3	2/4	Microarray	7
da Silva et al[43]	2018	Brazil	Plasma	15	21	55.0±12	57.7±10.5	.8	7/8	15/6	RT-qPCR	8
Liu et al[13]	2016	China	Plasma	40	40	52.3±11	53.9±13.4	.56	29/11	29/11	RT-qPCR	8
Lu et al[11]	2010	China	RAA	10	12	38.8±11.3	55.6±7.4	.00	5/5	4/8	RT-qPCR	5
McManus et al[14]	2014	American	whole blood	2185	153	65.6±8.7	72.7±8.2	.00	932/1253	93/60	RT-qPCR	5
Soeki et al[27]	2016	Japan	Plasma	10	30	65±3	63±2	.02	6/4	22/8	RT-qPCR	7
Zhelankin et al[45]	2020	Russian	Plasma	30	30	47.3±5.6	67.6±10	<.01	15/15	15/15	RT-qPCR	6
Masè et al[46]	2019	Italy	RAA	21	9	74.1±10.1	74±4.4	.98	18/3	6/3	RT-qPCR	6
Biliczki et al[47]	2019	Germany	Atrial tissue	8	14	55±11	70±9	.00	5/3	9/5	RT-qPCR	8
Xu et al[28]	2021	China	Plasma	96	109	60.3±5.1	62.6±7.7	.01	39/57	40/69	RT-qPCR	7
Sieweke et al[44]	2020	Germany	Plasma	60	21	58.2±19	71.8±11.3	.00	42/18	14/7	RT-qPCR	7
Galenko et al[48]	2019	American	Plasma	48	110	57.8±11.5	63.3±10.5	.00	21/27	66/44	RT-qPCR	7

AF = atrial fibrillation, LAA = left atrial appendage, NOS = The Newcastle-Ottawa Quality Assessment Scale score, RAA = right atrial appendage, RT-qPCR = quantitative real-time polymerase chain reaction, SR = sinus rhythm.

Table 2

Quality assessment based on the Newcastle-Ottawa scale.

Study	Selection	Comparability	Outcome	Total score	Quality
Liu et al, 2014	◆◆◆	◆◆	◆◆	7	High
da Silva et al, 2018	◆◆◆◆	◆◆	◆◆	8	High
Liu et al, 2016	◆◆◆◆	◆◆	◆◆	8	High
Lu et al, 2010	◆◆◆	–	◆◆	5	Low
McManus et al, 2014	◆◆◆	–	◆◆◆	6	Low
Soeki et al, 2016	◆◆◆◆	◆	◆◆	7	High
Zhelankin et al, 2020	◆◆◆◆	◆	◆	6	Low
Masè et al, 2019	◆◆◆	◆	◆◆	6	Low
Biliczki et al, 2019	◆◆◆◆	◆◆	◆◆	8	High
Xu et al, 2021	◆◆◆◆	◆	◆◆	7	High
Sieweke et al, 2020	◆◆◆◆	◆	◆◆	7	High
Galenko et al, 2019	◆◆◆◆	◆	◆◆	7	High

Selection, representativeness of studies (score 0–4); Comparability, comparability of studies (score 0–2); Outcome, assessment of outcome and follow up (score 0–3). Low, high risk of bias (total score 0–6); High, low risk of bias (total score 7–9).

result showed the miR-328-3p expression level may be predictive and serve as a diagnostic tool for AF.

3.4. Evaluation of heterogeneity

Significant heterogeneity between studies was found using the chi-square test, and McManus et al,[13] Soeki et al,[26] Lu et al,[10] Xu et al[27] were the potential source of heterogeneity by visual inspection of the Galbraith plot (Fig. 3A). McManus' study was a community-based cohort contained numerous subjects from the Framingham Offspring Study. However, the difference in age, current smoking, medication history, and comorbidity (for instance, myocardial infarction, heart failure, and diabetes mellitus) between the AF group and controls were statistically significant. Moreover, 107 new-onset AF patients were omitted, which leads to considerable selection bias. And most importantly, the whole blood was chosen to isolate miR-328-3p, neither plasma nor atrial tissue. The composition of human peripheral blood was complexed in which there were blood cells, serum, exosomes, and so on. Each type of blood cell contains a unique miRNA profile.[28] Considering the above 3 defects, we excluded this study in the next subgroup analysis. Analyzing the other

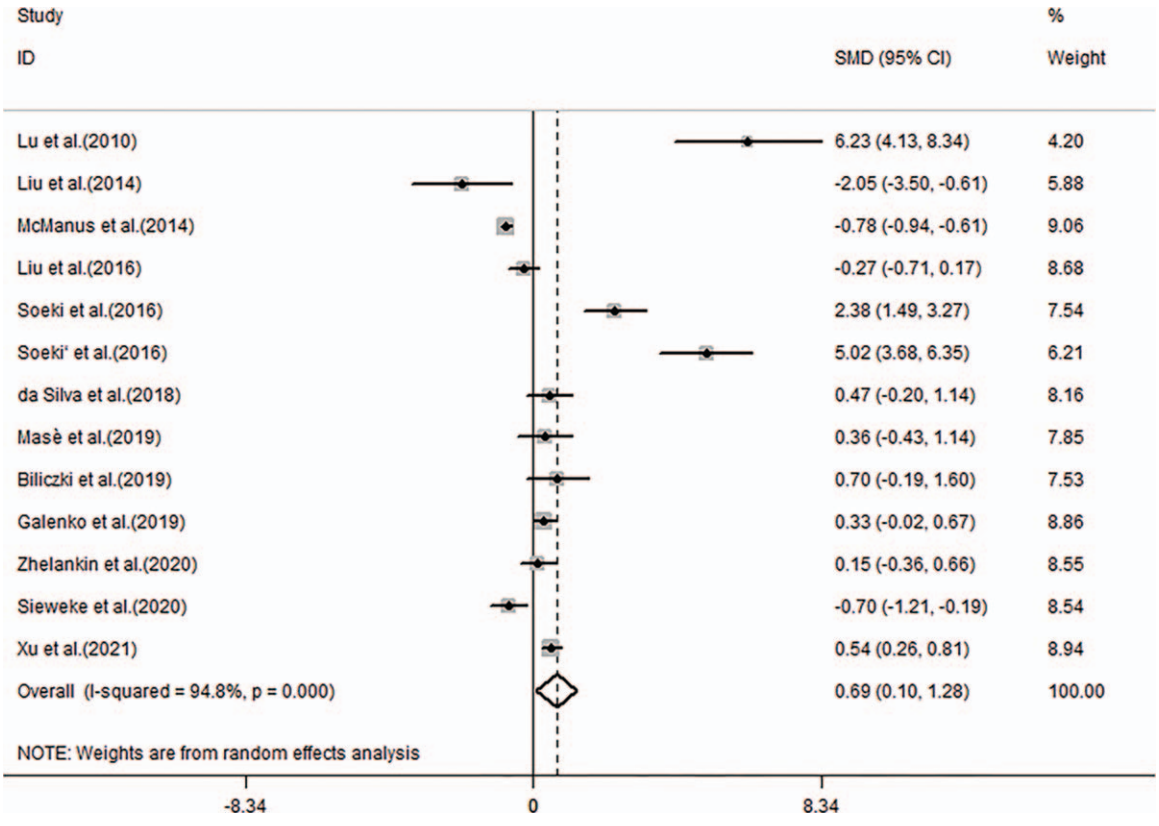

Figure 2. Forest plot of standardized mean difference with corresponding 95% CI of studies on the association between miR-328-3p level and atrial fibrillation. 95% CI = 95% confidence interval.

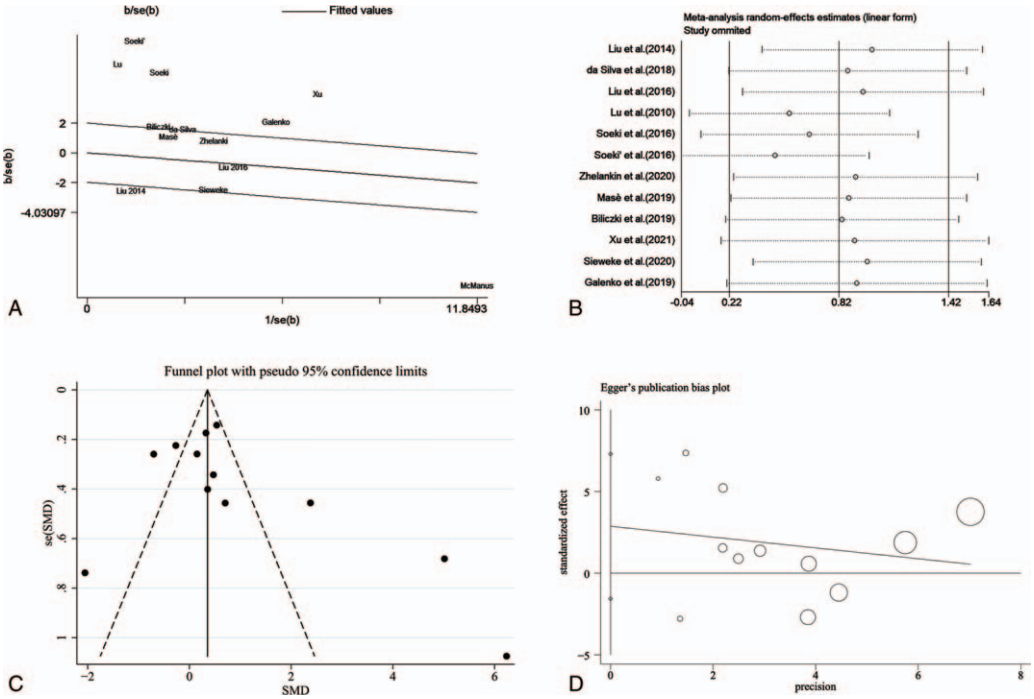

Figure 3. The results of sensitivity analysis and publication bias. (A) Heterogeneity analysis with a Galbraith plot. (B) Sensitivity analyses of miR-328-3p level difference between AF and control group by excluding one study at a time. (C) The funnel plot of miR-328-3p level difference between AF and controls. The SMD effect size was estimated using random-effects model. (D) Egger test to detect publication bias. AF = atrial fibrillation, SMD = standardized mean difference.

3 pieces of literature repeatedly, we did not find any shortcoming which results in clinical heterogeneity. In short, except for McManus et al,[13] there was only statistical heterogeneity, but no clinical heterogeneity.

3.5. Meta-regression and subgroup analysis

Since the heterogeneity was still very high after the deletion of McManus et al,[13] meta-regression and subgroup analyses were performed to investigate potential sources of between-study variability in terms of year of publication, comorbidity, specimen type, study region, and sample size. To avoid data dredging and get better goodness of fit, there was only a single covariate incorporated into the meta-regression model that used the restricted maximum of likelihood (REML) method at every turn. The adjusted R^2 (the value meant that the current model could explain the study heterogeneity size) and *P*-value of comorbidity, year of publication, region and specimen type covariate were 30.13%, 18.93%, 4.92%, 2.77% and 0.047, 0.096, 0.243, 0.274, respectively (Table 3).

Subsequently, we divided the patients into different subgroups according to preset plan and the results of meta-regression. The overall SMD was 0.82 (95% CI [0.22, 1.42], $P = .007$; $I^2 = 91.8$, $P < .001$) after omitted McManus et al[13] prudently. Subgroup analyses showed that the AF patients, $n \geq 30$, various of comorbidity, atrial tissue, articles published earlier, and Asia groups had higher levels of miR-328-3p when compared with controls (Table 4).

3.6. Sensitivity analyses and publication bias

From the results of the sensitivity analysis, the combined results did not significantly change the overall results, indicating the results were relatively stable (Fig. 3B). Visual inspection of the funnel plot found the graph is seemingly asymmetrical (Fig. 3C), which suggested that there may be some publication bias among

Table 3

The results of meta regression.

Covariates	Coef.	S.E.	95% CI	τ^2	Adjusted R^2	*P*-value
Comorbidity	2.53	1.11	(0.05, 5.01)	3.082	30.13%	.047
Year of publication	–0.37	0.2	(–0.82, –0.08)	3.577	18.93%	.096
Region	0.88	0.71	(–.070, 2.45)	4.195	4.92%	.243
Specimen type	0.76	0.65	(–0.70, 2.22)	4.289	2.77%	.274
Sample size	0.3	0.68	(–1.22, 1.81)	4.823	–9.32%	.672
Detection method	0.38	1.61	(–3.21, 3.96)	4.94	–11.98%	.818

REML estimate of between-study variance.τ^2 = study between the component of variation size, adjusted R^2 = the current covariate can explain the size of heterogeneity, CI = confidence interval, Coef. = regression coefficients, SE = standard error of regression coefficients.

Table 4

Subgroup analysis of miRNA-328-3p expression levels in AF.

Stratification group	N	References	Random-effects model		Heterogeneity test		
			SMD (95% CI)	*P*	*Q*	I^2 (%)	*Ph*
Overall	12	ALL	0.82 (0.22, 1.42)	.007	134.27	91.8	<0.001
Comorbidity							
Consistent	7	[12,13,28,43,45,46,48]	0.15 (–0.20, 0.50)	.398	19.81	69.7	0.003
Variance	5	[11,27,27,44,47]	2.60 (0.38, 4.81)	.022	109.58	96.3	<0.001
Year of publication							
2010~2018	6	[11,12,13,27,27,43]	1.84 (0.10, 3.57)	.038	112.65	95.6	<0.001
2019~2021	6	[28,44,45,46,47,48]	0.21 (–0.17, 0.59)	.287	18.75	73.3	0.002
Specimen type							
Plasma	7	[13,27,28,43,44,45,48]	0.34 (–0.14, 0.81)	.167	45.25	86.7	<0.001
Atrial tissue	5	[11,12,27,46,47]	1.96 (–0.36, 4.28)	.098	78.28	94.9	<0.001
Sample size							
<30	6	[11,12,43,44,46,47]	0.58 (–0.58, 1.74)	.33	53.76	90.7	<0.001
≥30	6	[13,27,27,28,45,48]	1.10 (0.35, 1.86)	.004	75.19	93.3	<0.001
Study region							
Asia	6	[11,12,13,27,27,28]	1.77 (0.41, 3.13)	.011	112.65	95.6	<0.001
America	2	[43,48]	0.36 (0.05, 0.66)	.022	0.14	0	0.704
Europe	4	[44,45,46,47]	0.06 (–0.54, 0.67)	.837	10.65	71.8	0.014

AF = atrial fibrillation, CI = confidence interval, SMD = standard mean difference, N = number of literatures, I^2 = the variation in SMD attributable to heterogeneity; *Ph* = *P* value of *Q* test for heterogeneity test.

the included studies. However, as shown in Fig. 3D, the Egger test results ($t = 1.44$, $P = .179$) was inconsistent with the funnel plot. And then, we evaluated the effect of publication bias on the results through trim and fill analysis. The trim and fill analysis showed data unchanged, which suggested that there was no publication bias and the results were relatively robust.

4. Discussion

AF is the leading cause of stroke and atrial appendage thrombus formation worldwide results in a major public health-care burden. In the United States, the annual incremental cost of AF was an estimated $26.0 billion, and arising from an estimated 0.7 million additional cardiovascular-specific inpatient admissions and 3.2 million additional hospital days.[29] Ambulatory electrocardiographic (ECG) monitoring is the most widely used method to detect cardiac arrhythmias in the outpatient ambulatory setting, but it often fails.[30] There are growing evidence that a large amount of morbidity and mortality associated with subclinical arrhythmias is often missed by conventional 24-hour monitoring.[31] The AF detection rate is correlated with the duration of ECG monitoring and decreases over the monitoring period.[32] Gladstone et al[33] demonstrated 30-day ECG monitoring strategy was superior to 24-hour ECG monitoring. However, extended ECG monitoring for AF detection is resource-consuming and potentially compromises patients. Therefore, a novel predictor, easy to detect, and quantitative non-invasive affordable test, would be an urgent need to forecast the occurrence of AF and prevent cardiogenic stroke, as well as for prognostic purposes.

Circulating microRNAs are easily detectable, generally stable, and tissue-specific. Hsa-miRNA-328-3p (5′-CUGGCCCUCU-CUGCCCUUCCGU-3′) belongs to the miRNA-328 family, which is located on chromosome chr16:67202327-67202348. miR-328-3p plays an important role in the occurrence and maintenance of AF[34] and is expected to become a marker for the diagnosis and prognosis of AF. It reported that miR-328-3p targets the genes encoding L-type Ca^{2+} channel proteins to reduce I_{CaL} density and increased AF vulnerability by shortening atrial action potential duration, which served as a mechanism underlying the atrial arrhythmogenic potential.[10] Furthermore, through translational inhibition of SERCA2a, miR-328-3p enhances the level of intracellular Ca^{2+}, activates the calcineurin/NFATc3 signaling pathway, and promotes cardiac hypertrophy.[35] After cardiac surgery, the expression of miR-328-3p is significantly higher in postoperative AF patients (POAF), compared with non-POAF patients.[27] The increased expression of miR-328-3p may contribute to the prognosis assessment of clinical AF. It has also been reported that miR-328-3p takes inhibitory effect in AF by regulating the expression of lncRNA and circRNA. TCONS_00075467, a novel lncRNA, was down-regulated by higher expression of miR-328-3p in cardiomyocytes of AF. The decreased abundance of TCONS_00075467 restrained the expression of CACNA1C in cardiomyocytes, which induced intracellular calcium overload, and activated the occurrence of electrical remodeling and the initiation of AF.[36]

It is worth noting that miR-328-3p has been implicated in many other pathological conditions. Several studies have demonstrated that miR-328-3p has antitumor activity.[37–39] In human cervical cancer tissues and cells, miR-328-3p was significantly down-regulated. Further research found that miR-328-3p repressed cell proliferation and colony formation of cervical cancer cells in vitro and inhibited the growth of cervical cancer xenografts in vivo.[37] Han et al[38] showed that miR-328-3p suppresses the survival of esophageal cancer cells and Shi et al[39] showed that miR-328-3p mediates the anti-tumor effect in osteosarcoma. Interestingly, miR-328-3p plays an oncogenic role and can promote tumor cell migration and invasion in glioma.[40] Therefore, miR-328-3p seems to exert the context-dependent effects on tumorigenesis. It is well known that miRNAs act in concert with argonaute (AGO) proteins, leading to post-transcriptional gene silencing. Eiring et al[41] showed that miR-328-3p has a second function, acting as a decoy by binding to hnRNP E2, independently of Ago proteins, and lifting its translational repression of an mRNA involved in myeloid cell differentiation.

Previous studies have reported contradictory results on the levels of miR-328-3p in patients with AF. In this study, meta-

analysis combined with 12 records, 4 studies showed increased miR-328-p expression levels in AF patients,[10,26,27,42] whereas 2 studies showed decreased,[13,43] the remaining 6 studies showed no significant change with only slightly increased[44–47] or decreased[11,12] between AF and controls. The overall results of this meta-analysis manifest that the expression level of miR-328-3p in AF patients was significantly higher than that in the control group through the random-effect model, indicating a high level of miR-328-3p may be a risk factor for AF. The NOS scale was used to analyze the quality of the included literature, and the results showed that all the studies had high scores, indicating the high quality of the included literature. The funnel plot looks asymmetrical, while Egger test and trim-fill analysis showed the outcome was stable and credible.

Bearing in mind the high heterogeneity observed in the meta-analysis, we conducted meta-regression and subgroup analyses. The results of meta-regression indicated that various comorbidity may lead to differences between studies. Five studies were partly variance in comorbidity included rheumatic heart disease, Wolff–Parkinson–White syndrome, valvular disease, and stroke. Additionally, we also noticed that the relative quantitative detection of RT-qPCR may not applicable for merging, the selection of internal reference is related to the authenticity and reliability of the relative quantitative results, which may lead to some deviation.[48] When stratified by year of publication, miR-328-3p levels were significantly higher in articles published between 2010 and 2019 than 2019 to 2021. It indicated that the risk of miR-328-3p in AF is higher in the earlier researches than the latest, but the total sample from 2010 to 2018 is only 40% of the sample from 2019 to 2021 which may cause some bias. When stratified by sample size, AF patients from the $n \geq 30$ group manifested higher miR-328-3p levels and the merging result was more stable. This shows that small sample studies are sometimes unstable. When stratified by specimen type, AF patients from the atrial tissue group showed higher miR-328-3p levels. Interestingly, the closer to the myocardium, the higher expression levels of miR-328-3p (plasma of periphery blood < plasma of left atrial appendage blood < atrial tissue). The regional distribution of miR-328-3p illustrated that the potential mechanism of changing the profile of circulating plasma miRNAs in AF is the secretion of exosomes by atrial cardiomyocytes. These exosomes contain a specific miRNA signature altered in AF.[49] When stratified by study region, AF patients from the Asia group showed higher miR-328-3p levels, however, the heterogeneity is relatively high, and the confidence interval of the results is wider, suggesting that the quality of research in Asia needs to be further strengthened. To conclude, sample size, specimen type, and study region were associated with miR-328-3p levels in AF patients.

Patients were divided into new-onset AF and well-controlled AF in da Silva et al,[42] and they found that expression of miR-328-3p is higher in patients with acute new-onset AF compared with patients with well-controlled AF ($P < .05$), whereas the expression levels of well-controlled AF is like healthy controls. This discovery has been a great inspiration for future research. However, the reliability of the results is worthy of further demonstration by large sample sizes and multi-region studies.

5. Limitations

Nevertheless, this study has several disadvantages. Firstly, heterogeneity was substantial among studies although we performed subgroup analyses to explore the source of it. Secondly, we did not study the difference of the expression of miR-328-3p between paroxysmal and persistent AF. Thirdly, we pooled Soeki et al[26] as 2 independent studies and omitted McManus et al,[13] which may lead to a certain bias. Lastly, the studied population presented inhomogeneities in comorbidities, for example, valvular disease and rheumatic heart disease, which may have acted as confounding factors, contributing to the variability of miRNA expression.

6. Conclusions

In summary, our study reveals that a higher level of miR-328-3p is a potential risk factor for AF. In addition, the levels of miR-328-3p in atrial tissue are higher than in peripheral blood plasma. These results may pave the way for future experimental studies and are expected to become an important target for the diagnosis of AF. Furthermore, more large sample studies that applied absolute quantitative detection methods are needed to better clarify the effect of miR-328-3p in AF.

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Author contributions

Haitao Huang and Can Chen contributed to the conception or design of the work. Haitao Huang, Hao Chen, and Xiao Liang conducted the literature search. Haitao Huang, Xiaoxin Chen, and Xiuting Chen conducted screening and extraction of data. Haitao Huang and Hao Chen conducted statistical analyses, Haitao Huang, Can Chen, and Xiao Liang wrote the draft. All authors reviewed the manuscript, gave their final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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