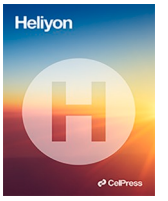
Heliyon 10 (2024) e35201

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Expression profile of circulating miRNAs in patients with atrial fibrillation-dominated cardioembolic stroke: A systematic review and bioinformatics analysis☆

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ARTICLE INFO

Keywords:
miRNAs
Atrial fibrillation
Cardioembolic stroke
Systematic review

ABSTRACT

Background: Cardioembolic stroke is a type of ischemic stroke with high disability and mortality, a high recurrence rate and poor prognosis. miRNAs have been explored as potential noninvasive biomarkers in atrial fibrillation and ischemic stroke, but their expression profile in cardioembolic stroke still needs to be explored. This study will explore the differences in miRNA expression between cardioembolic stroke patients and healthy people through meta-analysis and attempt to analyze the target genes by bioinformatics analysis.

Methods: Literature databases and gene expression databases were searched from the inception date to June 2022. The study reported the circulating miRNA expression profiles in cardioembolic stroke patients and healthy controls. miRNAs with significantly differential expression and their target genes were analyzed.

Results: Three articles and one gene expression dataset were included in the analysis. The results showed that miR-21–5p (SMD: 2.16; 95 % CI: 1.57, 2.75; $p < 0.001$), miR-943, miR-145–3p, and miR-3148 were upregulated in cardioembolic stroke patients compared with controls. The downregulated miRNAs included miR-3136–5p, miR-2277–5p, and miR-2277–3p. The area under the receiver operating characteristic curve of miR-21–5p for cardioembolic stroke was 0.975 (0.933–0.989). For the enrichment results, the target genes of upregulated miRNAs were enriched in the MAPK signaling pathway, Ras signaling pathway, etc. The target genes of downregulated miRNAs were also enriched in the Ras signaling pathway.

Conclusions: This study suggested that circulating miR-21–5p is upregulated in cardioembolic stroke patients compared to healthy controls. The Ras signaling pathway plays an important role in pathogenesis according to enrichment analysis.

☆ Xiangbin Xiao and Ji Liu developed the protocol. Xiangbin Xiao and Zhi Luo carried out the literature search and identified suitable studies. Xiangbin Xiao, Minjian Peng and Hui Yan resolved any conflicts in study inclusion. Dengliang Yi and Zigang Du carried out the analysis. Xiangbin Xiao and Zhi Luo wrote the first draft. Zhi Luo reviewed and edited the protocol and drafts. All authors reviewed and approved the final version of the manuscript.

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https://doi.org/10.1016/j.heliyon.2024.e35201
Received 17 August 2022; Received in revised form 23 July 2024; Accepted 24 July 2024
Available online 25 July 2024

1. Introduction

Stroke is one of the leading causes of death and disability worldwide, with ischemic stroke accounting for approximately 70 % [1]. The etiology of ischemic stroke includes atherosclerosis, occlusion of small cerebral vessels, and cardiac embolism [2]. Cardioembolic stroke accounts for approximately 14%–30 % of ischemic strokes and is associated with higher disability, mortality, early and long-term recurrence and generally worse prognosis than strokes of other etiologies [3,4]. Mortality from cardioembolic stroke has been reported to be as high as 23 % within 30 days and up to 22 % within one year, and more than half of patients die within 1.5 years [5]. Cardioembolic stroke is currently identified as the stroke subtype with the highest morbidity and mortality burden [6]. With the effective intervention of hypertension and hyperlipidemia, the proportion of cardioembolic stroke may further increase [7].

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a prevalence of 1%–2% of the total population [8]. AF is also an important independent risk factor for ischemic stroke, with a 5-fold increased risk of stroke in patients with AF [9]. AF has traditionally been considered an important source of stroke emboli, and the related pathogenesis has been simplified as blood stasis in the fibrillating left atrium, leading to thrombus formation [10]. There is increasing evidence that AF and cardiac emboli are associated with cryptogenic stroke and embolic stroke of undetermined source (ESUS) [11,12], and emboli of undetermined source are likely to originate from occult paroxysmal AF [13,14]. In addition, some cardioembolic strokes may even be the first manifestation of AF [15]. Due to occult paroxysmal AF, relying only on AF diagnosis as a risk factor for cardioembolic stroke is flawed, and more biomarkers need to be explored to help stratify the risk of cardioembolic stroke. Then, more people at high risk of cardioembolic stroke can benefit from empiric anticoagulation [5,16,17].

AF, the most prevalent arrhythmia, can lead to the formation of mobile emboli and an increased risk of stroke. Biomarkers, as indicators that can be objectively quantified, are considered a promising tool to improve stroke classification and identify stroke risk [18]. Identifying biomarkers with differential expression between cardioembolic stroke patients and healthy individuals could enhance early risk assessment and treatment. Moreover, these markers could aid in diagnosing unexplained strokes as potentially cardioembolic.

Alterations in gene expression profiles are considered to be important pathological characteristics in the development of cardiogenic stroke [19]. Epigenetic changes induced by miRNAs may indicate potential biomarkers and therapeutic targets. miRNAs are small noncoding RNA molecules that are highly conserved across species and are involved in the posttranscriptional regulation of gene expression by reducing the stability of the target gene mRNAs or inhibiting translation [20]. miRNA in blood exhibits dynamic expression patterns that are sensitive and specific to various disease states, including central nervous system disorders [21,22]. Its ability to cross the blood-brain barrier and its stability within extracellular vesicles in circulation suggest miRNA's potential as a reliable biomarker [23]. For AF and ischemic stroke, miRNAs have been explored as biomarkers [24], but there is still a lack of comprehensive research on the profile of miRNA expression for cardioembolic stroke.

Current research primarily focuses on the expression of specific miRNA types in cardioembolic stroke patients [25,26]. However, comprehensive transcriptome-based evidence is scarce. This study aims to perform a meta-analysis of studies examining the complete miRNA expression profile, thereby identifying more robust biomarkers for cardioembolic stroke through aggregated data. This biomarker will facilitate the clinical identification of patients with cardioembolic stroke, enabling early diagnosis and even elucidation of stroke etiology. Furthermore, it advances research into the miRNA characteristics of cardioembolic stroke, enhancing insights into the disease's molecular basis and revealing possible therapeutic targets.

2. Material and methods

This study was performed according to The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

2.1. Search strategy

Literature databases were searched, including PubMed, Embase, and the Cochrane Library. Gene expression databases, including Gene Expression Omnibus (GEO) and Arrayexpress, were also searched. The brief search strategy was ((((atrial fibrillation) OR (cardiac)) OR (cardioemboli*)) OR (emboli*)) AND Stroke AND (((((((miR) OR (miRNA)) OR (microRNA)) OR (noncoding RNA)) OR (noncoding RNA)) OR (ncRNA) (untranslated RNA)). Each database was screened from the inception date to June 2022. There were no restrictions in language or ethnicity. The citations of retrieved reviews were also manually scrutinized to avoid omission. Two authors independently searched the database, and if the search results were inconsistent, then the reasons for the inconsistency were discussed, and consistency was reached.

2.2. Inclusion and exclusion criteria

Studies meeting the following criteria were included in the analysis: 1, the study included cardioembolic stroke patients and healthy individuals; 2, the study obtained circulating miRNA expression profiles in cardioembolic stroke patients and healthy controls; and 3, the study reported the raw miRNA expression data or results of differential expression results between the cardioembolic stroke and healthy groups. The exclusion criteria were as follows: 1, the study in which miRNA types have been specified in the study objectives, as such study cannot fully reflect the total miRNA expression profile; 2, duplicate published study; 3, the study conducted in animals or cell lines; and 4, case reports, comments, and reviews. Two authors independently screened the eligible studies, and

disputes were resolved by consultation.

2.3. Data extraction and quality assessment

Data were extracted from the included studies, including the author's name, publication year, study design, research location, sample size, average age, sex, sample source and collection time, and miRNA microarray platform. The results were the raw miRNA microarray expression data or the fold-change results of the miRNA expression profile. When the same dataset was published in multiple journals, the research with the largest amount of information or the latest publication time was retained. Study quality assessment was performed using the Diagnostic Precision Study Quality Assessment tool (QUADAS-2) recommended by the Cochrane Collaboration [27]. The risk of bias of the included studies was also assessed using the modified genetic 8-star Newcastle-Ottawa scale (NOS), which is designed for genetic-based research [28].

2.4. Statistical analysis

The raw miRNA expression data were pooled by meta-analysis, and the heterogeneity between the results was reported. The standardized mean difference (SMD) was used to evaluate the differential expression levels of miRNA between the two groups. Forest

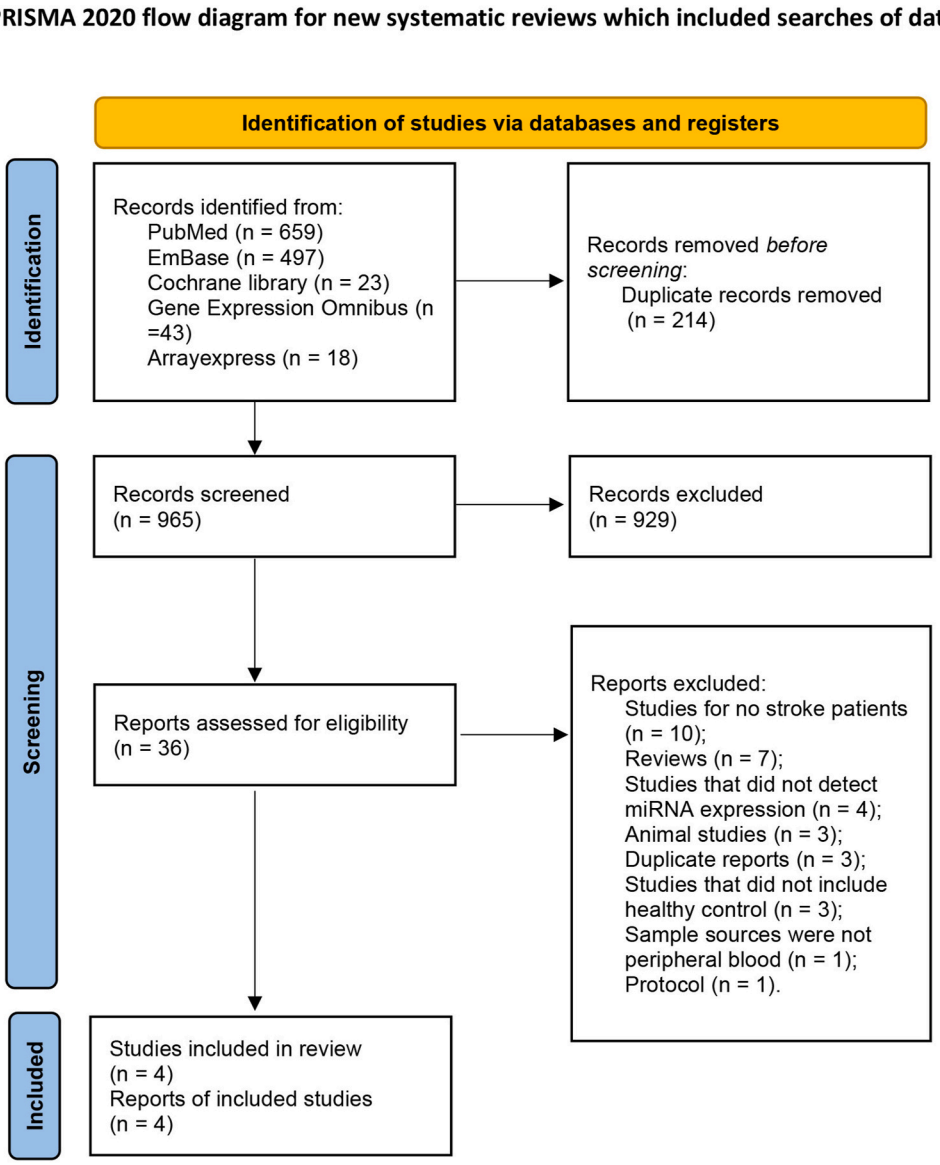

Fig. 1. Flowchart of the study selection process for eligible studies in this systematic review.

Table 1
Characteristics of included studies and datasets in this systematic review.

Study	Design	Location	Sample size	Cardioembolic Stroke	Control	Intervention	Average age of stroke patients	Sex	Sample source	Detection method	Sample collection time	NOS score
Stamova B 2014 [28]	CC	US	46	23(Cardioembolic stroke patients)	23(People without symptomatic vascular diseases)	tPA treatment alone, or in combination with eptifibatide therapy	71.3 ± 8.5	52 % male	Immune Cells	Affymetrix U133 Plus 2.0 whole-genome expression array	<24 h	8
Gui YX 2019 [29]	CC	China	48	28(Cardioembolic stroke patients)	20 (Normal controls)	NA	60 ± 10	43 % male	Serum	The TaqMan Low-Density Array Human miRNA Panel v1.0	<24 h	8
Modak JM 2019 [30]	CC	US	24	16 (Cardioembolic stroke patients)	8 (Outpatients without related risk factors)	NA	74.3 (56, 91)	50 % male	Whole blood	miRCURY LNA™ microRNA Array 7th Gen	24 ± 6 h	7
Zhang C 2017[a]	CC	China	30	20 (Cardioembolic stroke patients)	10 (Health control)	NA	NA	NA	Serum	Exiqon miRCURY LNA microRNA Array; 7th generation	NA	7

Abbreviations: CC: case-control; NA: Not available.
[a] This study is reported as gene expression dataset (GSE60319).

plots were constructed to display effect sizes and their 95 % confidence intervals (CIs). Heterogeneity was assessed by the Q test and inconsistency index (I^2). When I^2>50 % indicated obvious heterogeneity, the random effects model was adopted for pooling; otherwise, the fixed effects model was adopted. Receiver operating characteristic (ROC) curves were plotted for miRNAs with significant differences in expression to clarify the diagnostic value of cardioembolic stroke with area under the curve (AUC) results. The statistical analyses were performed using the R program (Version 4.2.0) with the meta and pROC packages. $p < 0.05$ was considered statistically significant.

2.5. Potential target genes and enrichment analysis

For quality control, miRNA names were converted according to miRbase (https://www.mirbase.org/). To obtain the target genes of miRNAs with significant differences in expression, we selected the target genes reported in both the TargetScan database (https://www.targetscan.org/vert_80/) and mirDB database (http://www.mirdb.org/) for robustness. The default parameters for target gene prediction in the websites were adopted, and no additional restrictions were set. Potential protein–protein interactions among targeted genes were identified by the STRING database (https://cn.string-db.org/). Then, the target genes were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis by the "clusterProfile" package of the R program. In enrichment analysis, no p correction method was used, the p cutoff value was set as 0.05 (default), and the q cutoff value was set as 0.2 (default).

3. Results

After searching the databases, 1179 literature items and 61 gene expression datasets were obtained, and 965 items were left after removing duplicates. After screening titles and abstracts, 929 items were excluded. In addition, 36 articles were obtained for full-text screening. The following articles were excluded: studies for nonstroke patients (n = 10); reviews (n = 7); studies that did not detect miRNA expression (n = 4); animal studies (n = 3); duplicate reports (n = 3); studies that did not include healthy controls (n = 3); sample sources were not peripheral blood (n = 1); and protocols (n = 1). Finally, three articles [25,29,30] and one gene expression dataset (GSE60319) were included in the analysis (Fig. 1).

Among the included studies, two were conducted in China and two in the United States. A total of 148 people were analyzed,

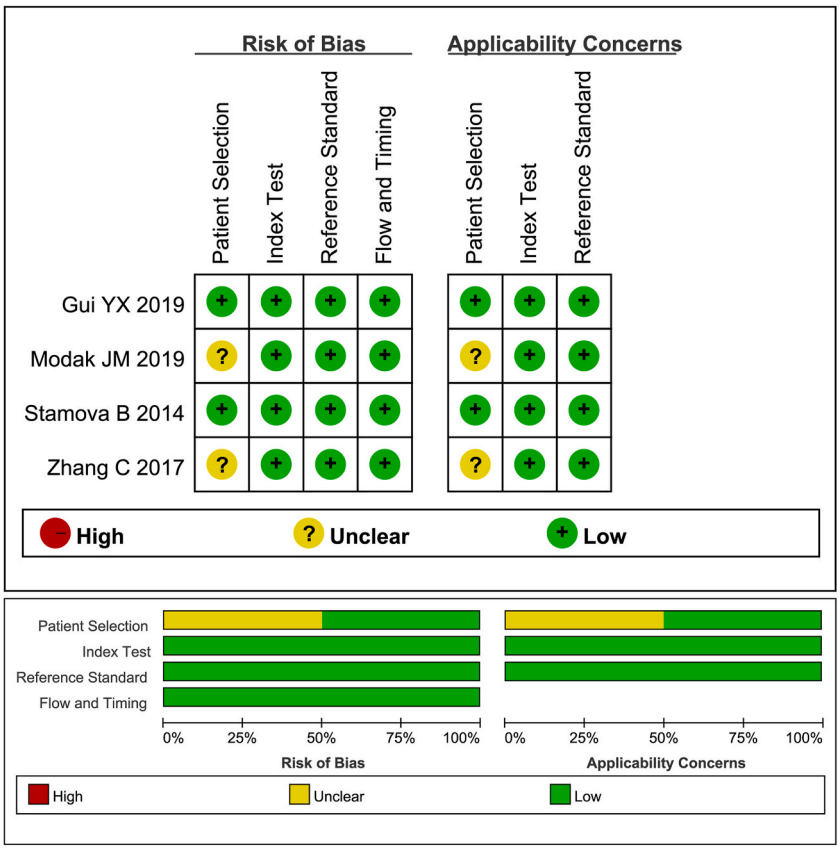

Fig. 2. Methodological quality assessment of included studies.

including 87 cardioembolic stroke patients. The average age was approximately between 60 and 75 years old. The proportions of males and females were similar. The sample sources were whole blood, serum, or peripheral immune cells (Table 1). For study quality assessment, one study excluded patients with non-middle cerebral artery embolic stroke (inappropriate exclusion). One study did not present details of patient inclusion. Therefore, these two articles may have a potential risk of bias in patient selection. The quality of the study design in the index test, reference standard, flow and timing demonstrated a low risk of bias (Fig. 2). Since all included studies used miRNA microarray profiles for high-throughput sequencing, according to the modified NOS scale, the scores of the included studies were 7–8 (Table 1, Supplementary Table 1).

Qualitative results (fold change>2 & $p < 0.05$) showed that miRNAs that were upregulated in more than two studies included miR-21–5p, miR-943, miR-145–3p, and miR-3148. The downregulated miRNAs included miR-3136–5p, miR-2277–5p, and miR-2277–3p. Three probe sites for miR-21 were reported in one study [29]. In the meta-analysis results based on studies reporting raw data, the expression level of miR-21–5p in the peripheral circulation of cardioembolic stroke patients was significantly higher than that of the control population (SMD: 2.16; 95 % CI: 1.57, 2.75; $p < 0.001$) (Fig. 3, A). Additionally, in the subgroup analysis, miR-21–5p was significantly different between the two groups at all three time points (Fig. 3, B). Other quantitative results included miR-943(SMD: 1.56; 95 % CI: 0.91, 2.21; $p < 0.001$), miR-145–3p (SMD: 3.22; 95 % CI: 2.36, 4.09; $p < 0.001$), miR-3148 (SMD: 2.03; 95 % CI: 1.33, 2.73; $p < 0.001$), miR-3136–5p (SMD: 1.26; 95 % CI: 1.89, −0.64; $p < 0.001$), miR-2277–5p (SMD: 1.57; 95 % CI: 2.22, −0.92; $p < 0.001$), and miR-2277–3p (SMD: 6.21; 95 % CI: 7.59, −4.82; $p < 0.001$) (Supplementary Fig. 1).

The diagnostic accuracy of miR-21–5p for cardioembolic stroke was further analyzed by raw data from one study [29]. The results

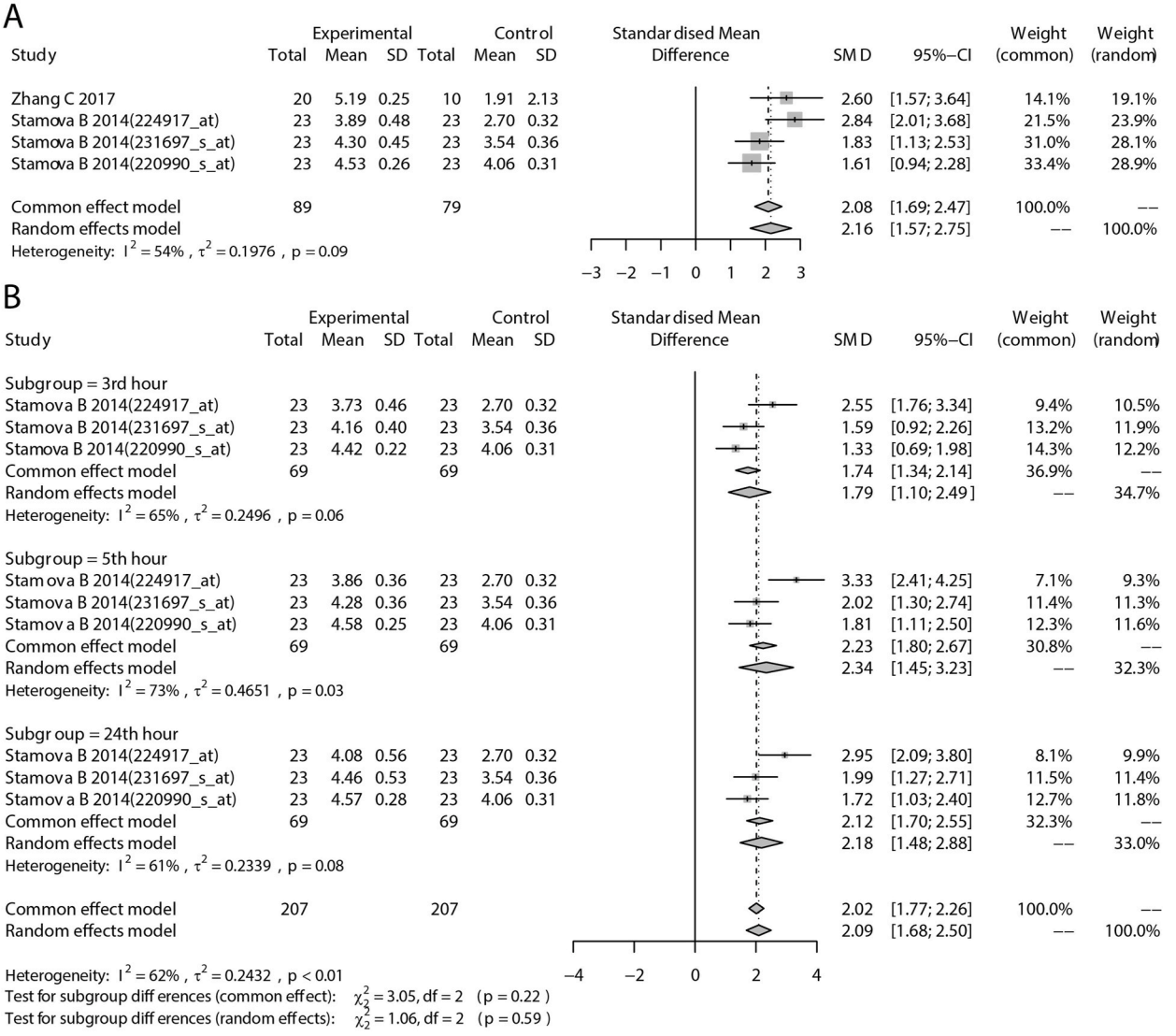

Fig. 3. Forest plots of the expression level of miR-21–5p between cardioembolic stroke patients and controls by meta-analysis and subgroup analysis. A: overall meta-analysis results; B: subgroup analysis according to post-stroke time points at 3, 5, and 24 h.

suggested that the AUC was 0.975 (0.933–0.989). The best cutoff value was 3.781, the specificity was 100 % and the sensitivity was 94.2 %. The overall diagnostic accuracy was 95.65 % (Supplementary Fig. 2).

PPI analysis was performed for the target genes of miRNAs that were confirmed to be significantly differentially expressed in more than two studies. In the results of high confidence, one cure gene was GRB2, which provides a critical linkage between the cell surface growth factor receptor and Ras signaling pathway (Supplementary Fig. 3). No core genes were evident in the target genes of the downregulated miRNAs. Notably, the interactions among GRIN2A, GRIN2B, and RASGRF1 are also related to the Ras signaling

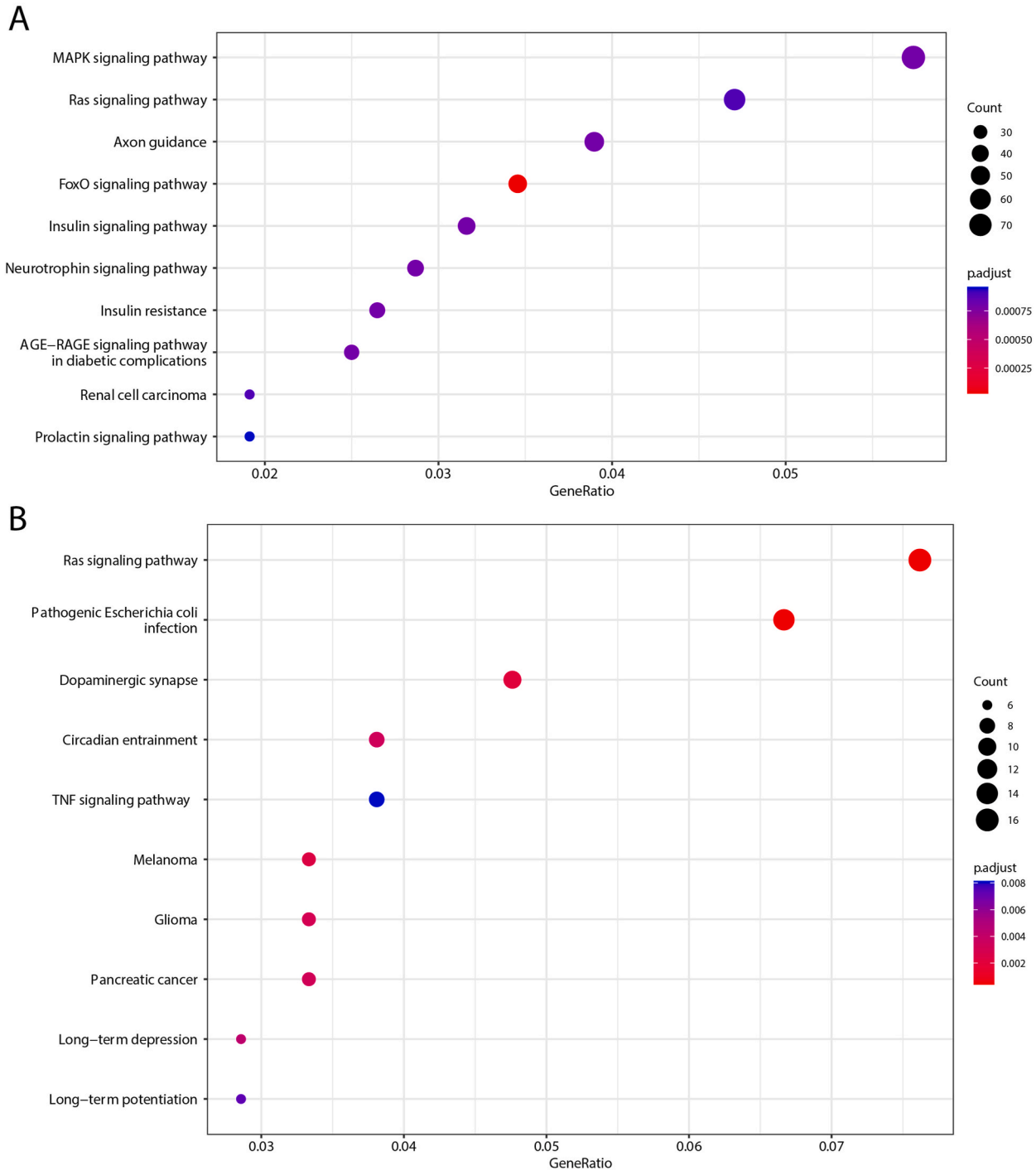

Fig. 4. KEGG enrichment analysis of the target genes of miRNAs that were upregulated (A) and downregulated (B) in cardioembolic stroke patients compared to healthy controls.

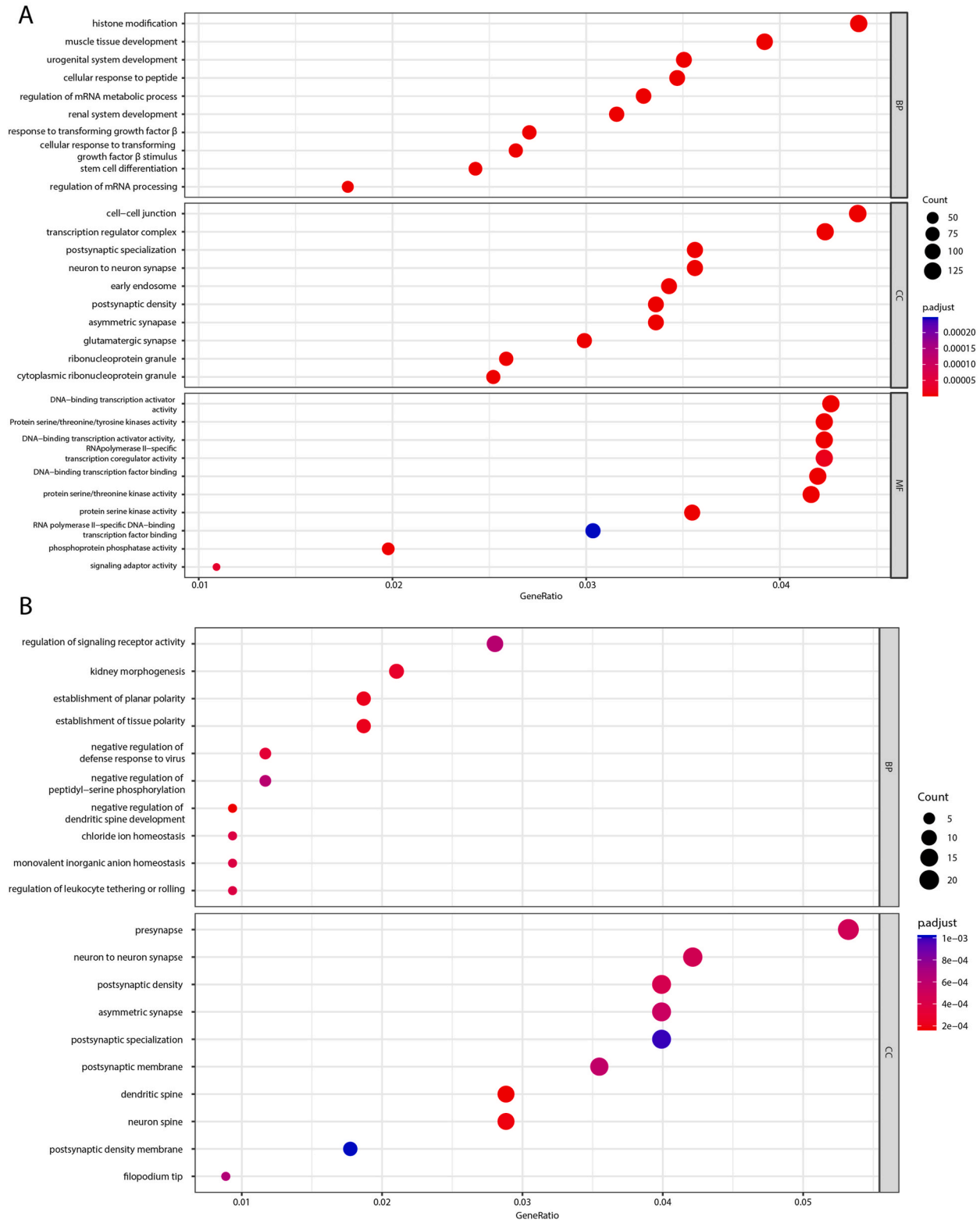

Fig. 5. GO enrichment analysis of the target genes of miRNAs that were upregulated (A) and downregulated (B) in cardioembolic stroke patients compared to healthy controls. BP: biological process; CC: cellular component; MF: molecular function.

pathway (Supplementary Fig. 4).

For the KEGG enrichment results, the target genes of the upregulated miRNAs were enriched in the MAPK signaling pathway, Ras signaling pathway, etc. (Fig. 4A). The target genes of the downregulated miRNAs were also enriched in the Ras signaling pathway (Fig. 4B). In GO enrichment, the target genes of the upregulated miRNAs were mainly enriched in histone modification in the biological process, enriched in cell–cell junction and transcription regulator complex in the cellular component, and enriched in DNA-binding transcription activator activity and protein serine/threonine/tyrosine kinase activity in molecular function (Fig. 5A). The target genes of the downregulated miRNAs were enriched in regulation of signaling receptor activity in biological process and enriched in presynapse and neuron to neuron synapse in cellular component (Fig. 5B).

4. Discussion

Cardioembolic stroke is a type of ischemic stroke with high disability and mortality, a high recurrence rate and poor prognosis. Traditionally, AF is considered to be an important source of cardiogenic emboli, and cryptogenic stroke and ESUS may also be associated with AF. To explore the biomarkers of cardioembolic stroke and potential pathophysiological mechanisms, this study analyzed the circulating miRNA expression profiles between cardioembolic stroke patients and healthy controls by systematic review. The results showed that miRNAs that were upregulated in more than two studies included miR-21–5p, miR-943, miR-145–3p, and miR-3148. The downregulated miRNAs included miR-3136–5p, miR-2277–5p, and miR-2277–3p. Of them, miR-21–5P was reported to be significantly upregulated in three studies.

This study consolidated the evidence of miR-21 as a biomarker of cardioembolic stroke. Current research evidence shows that miR-21 is closely related to AF, and is involved in the progression of ischemic stroke. In AF patients, circulating miR-21 increases and participates in the process of myocardial fibrosis [31]. Compared with patients in sinus rhythm, the miR-21 increased 2.5-fold in left atria from AF patients. The expression of miR-21 is positively correlated with atrial collagen content [32]. The expression of miR-21 in atrial myocytes was also significantly increased in chronic AF patients compared with that in sinus rhythm patients [33]. The level of miR-21 was positively correlated with the degree of myocardial dilatation and the stage of AF [34]. miR-21 was also correlated with echocardiographic parameters that served as predictive biomarkers for AF to help detect paroxysmal AF [35]. As prognostic marker, miR-21 was even significantly associated with AF-free survival in patients after catheter ablation [36]. Therefore, based on the above evidence, we believe that the expression of miR-21 is significantly increased in AF patients and is associated with the degree of myocardial dilation and AF disease stage. MiR-21 can even be used as a prognostic marker for AF-free survival outcome after catheter ablation. AF is the main cause of cardioembolic stroke, and existing evidence has fully confirmed the association between miR-21 and AF.

The association between miR-21–5p and ischemic stroke has been widely studied, but the characteristics of miR-21 in the pathological process of ischemic stroke are still controversial. In the clinic, many studies have supported that miR-21 is elevated in patients with ischemic stroke [37–40]. Some studies suggest that there is no difference in miR-21 levels between ischemic stroke patients and healthy controls [41,42]. A small number of studies believe that miR-21 levels are reduced in ischemic stroke patients [43]. A recent study suggested that neurons dynamically release extracellular vesicles containing miR-21 under hypoxic conditions, which increases circulating miR-21 levels [37]. The level of miR-21 could accurately distinguish subacute phase and recovery phase ischemic stroke patients and the control population [38]. MiR-21 is also significantly higher in ischemic stroke patients than in transient ischemic attack patients [39]. These results suggested that there are dynamic changes in miR-21 levels during the progression of ischemic stroke, and may be related to the severity of stroke. In addition, elevated mIR-21 was also associated with hemorrhagic transformation after cardioembolic stroke. Compared with the population without hemorrhagic transformation, mir-21–5p was significantly increased in the population with hemorrhagic transformation, which may further affect neurological function and survival outcome [22]. Mechanistically, miR-21–5p, as a strong anti-inflammatory and anti-apoptosis molecule, could play a role in reducing inflammation and preventing neuronal death after stroke [44,45]. Different results in clinical practice may be due to differences in the time of stroke onset, type of stroke, and severity.

The KEGG enrichment of the target genes of differentially expressed miRNAs showed that significantly upregulated miRNA target genes were enriched in the Ras signaling pathway. There is evidence that the Ras signaling pathway is involved in heart rate regulation and cardiac remodeling in AF [46–48]. Changes in the gene expression profile regulated by the Ras signaling pathway are involved in the myocardial fibrosis remodeling process during AF [49]. Therefore, in AF and subsequent high cardiogenic stroke risk, both miR-21 and Ras signaling pathways are involved in the process of myocardial fibrosis remodeling and may be involved in the electrophysiological changes of AF.

For ischemic stroke, inhibition of the Ras pathway produces neuroprotective effects that reduce brain edema, improve the integrity of the blood–brain barrier, and reduce cortical and striatal neuronal injury [50]. In an animal model, anti-spasmodic drugs can reduce the size of cerebral infarction and neurological deficits, accompanied by a reduction in Ras signaling pathway activity [51]. The target genes of upregulated and downregulated miRNAs are both enriched in the RAS signaling pathway, which suggests the complex regulatory role of the Ras pathway in ischemic stroke (shown in Supplementary Fig. 5). In photothrombosis-induced ischemic stroke, activation of Ras signaling pathway can protect adult neurons by inducing the production of neurotrophic factors, such as brain-derived neurotrophic factor [52].

Giordano M found that miR-195–5p and miR-451a were significantly increased in acute ischemic stroke and transient ischemia attack patients compared with the healthy population, and the two miRNAs were significantly higher in acute ischemic stroke patients than in transient ischemia attack patients [53]. The two miRNAs were also significantly higher in patients with diabetes than in those without diabetes [54]. The comorbidity of ischemic stroke and diabetes tends to bring more serious symptoms and poor outcomes.

MiR-195, miR-451, and miR-21 had a common predictive target gene, PRICKLE2. PRICKLE2 regulates synaptic formation during brain development [55]. The knockdown of PRICKLE2 in mice causes behavioral and physiological abnormalities [56]. PRICKLE2 can interact with N-methyl-D-aspartate receptor (NMDAR) subunits to promote synaptic development [57]. NMDAR is a key cell surface protein in the Ras pathway. Research on NMDARs in stroke has always been a hot topic [58]. Therefore, it is suggested that miR-21 may target PRICKLE2 together with other miRNAs and then regulate the activity of the Ras signaling pathway through NMDAR. This regulatory axis may be involved in reducing the number of dendritic branches and synapses to bring more serious symptoms and poor outcomes.

This study consolidates the evidence that miR-21 is highly expressed in the circulation of cardioembolic stroke patients. The association of miR-21 in predicting AF-related stroke risk, stroke severity, and neurological outcomes is discussed. Therefore, miR-21 can be used as a biomarker for cardioembolic stroke that helps to determine disease risk and neurological/survival prognosis stratification. Furthermore, after fully exploring the mechanism of miR-21, it is expected to become a preventive and therapeutic target for cardioembolic stroke. There were several limitations in this study. First, the number of studies included in this analysis is relatively small, which makes the results nonrobust. Second, although the main cause of cardioembolic stroke was AF, there were also other causes, such as valvular disease. This study could not separate the results according to the different etiologies. Third, there was a lack of experimental validation of miRNA differential expression and functional enrichment results. Fourth, due to the uncertainty and variability of target gene prediction and the enrichment analysis methods, the results of the enrichment analysis and related interpretations need further elaboration. Fifth, this study is based on retrospective studies but not prospective studies. Therefore, the diagnostic predictive value of miRNA on cardioembolic stroke occurrence still needs to be confirmed by well-designed prospective studies.

In light of the limited number of included studies and the sample sizes, as well as the unclear etiology of cardioembolic stroke in patients, further studies with larger sample size or more diverse gene expression datasets, including patients with a range of etiologies and using a variety of gene chips for detection, are needed to further validate the results of this study.

5. Conclusion

In conclusion, this study suggested that circulating miR-21–5p is upregulated in cardioembolic stroke patients compared to healthy controls. The Ras signaling pathway plays an important role in pathogenesis according to enrichment analysis.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

The datasets analyzed in the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Xiangbin Xiao: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Zhi Luo:** Writing – review & editing, Writing – original draft, Software, Data curation, Conceptualization. **Minjian Peng:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Hui Yan:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Dengliang Yi:** Writing – review & editing, Writing – original draft, Validation, Software, Formal analysis, Conceptualization. **Zigang Du:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Ji Liu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35201.

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