Meta-Analysis of MiR-122 in Predicting Cardiovascular and Cerebrovascular Diseases

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Abstract

Objective

To evaluate the diagnostic value of MiR-122 in predicting cardiovascular and cerebrovascular diseases systematically.

Methods

Searching China National Knowledge Infrastructure(CNKI), Wanfang Database, VIP Database (VIP), China Biomedical Literature Database (CBM), Clinical Registry, PubMed, Cochrane Library and Embase Library to obtain relevant documents. The time frame is from January 1, 2006 to February 28, 2021. MiR-122 plays a diagnostic role in patients of cardiovascular and cerebrovascular diseases with randomized controlled trials and cross-sectional studies. According to the inclusion and exclusion criteria, the literatures were screened, data extracted and related quality evaluated. Cochrane System Reviewer Manual Version 5.0 was applicable to related quality evaluation and Review Manager 5.3 was used for meta-analysis.

Results

A total of 23 articles were included and 6375 patients altogether. The meta-analysis showed that compared with the control group, MiR-122 was more effective in the patients of myocardial infarction (WMD= -2.33, 95% *CI* [-2.88,-1.78], $P<0.0001$), Angina pectoris and cardiovascular disease (WMD= -0.45, 95% *CI* [-0.61,-0.29], $P<0.00001$). Cerebrovascular diseases also have higher expression levels of MiR-122(WMD=- 0.34, 95% *CI* [-0.53, 0.33], $P<0.00001$). The prognosis of patients with high MiR-122 expression are worse (WMD=-2.20, 95% *CI* [-2.66,-1.75], $P<0.00001$). There are differences between the groups, with statistical significance ($P<0.05$).

Conclusion

MiR-122 has great diagnostic value in predicting cardiovascular and cerebrovascular diseases, and expression is elevated in diseases such as myocardial infarction, angina pectoris and stroke. Thus it has diagnostic value in the prognosis of patients with cardiovascular and cerebrovascular diseases.

Full Text

Despite the continuous advancement of modern medical care, cardio-cerebrovascular disease (CCVD) is still a major cause of the global increase in mortality^[1].According to the statistics, the number of deaths from CCVD has accounted for about one-third of the total deaths in the world since 2015. The World Health Organization estimates that more than 20 million people will die from CCVD in the next 10 years^[2].

CCVD is a general term for cardiovascular and cerebrovascular diseases. It refers to ischemic or hemorrhagic diseases of the heart, brain and systemic tissues caused by hyperlipidemia, blood viscosity, atherosclerosis, and hypertension^[3-4]. CCVD is a common disease that seriously threatens the health of humans, especially middle-aged and elderly people over 50 years old. It has the characteristics of high morbidity, disability and mortality. However, more than 50% of survivors from cerebrovascular accidents cannot take care of themselves completely. The number of people who die from CCVD in the world is as high as 15 million every year, ranking first among various causes of death^[5-6].

The current clinical using CCVD-specific detection markers may be negative in the early detection, and the diagnosis cannot be made quickly and effectively. Therefore, there is an urgent need for new and easy-to-detect early diagnostic markers to reduce mortality and improve prognosis. MiR-122 is a small non-coding RNA molecule consisting of 19 to 25 nucleic acids. More and more studies have shown that MiR-122 may be an important biomarker for the diagnosis and prognosis in CCVD [7]. MiR-122 is extremely stable in the circulation, has a specific tissue source and can be detected with high sensitivity and specificity by using sequence-specific amplification^[8-9]. However, there is still lack of comprehensive studies on the diagnostic value of MiR-122 in CCVD.

Therefore, this study conducted a corresponding meta-analysis of the published randomized controlled trials and cross-sectional research literatures on the impact of MiR-122 in diagnosis, so as to provide evidence-based medicine for the clinical diagnosis of the disease.

1 Materials And Methods

1.1 Inclusion and exclusion criteria

1.1.1 Inclusion criteria

☐Type of research: The types of published literatures are limited to randomized controlled trials and cross-sectional studies, and the languages are limited to Chinese and English; ☐Research objects: The intervention group and control group patients need to be tested for MiR-122 related indicators. At the same time, CCVD patients in the intervention group must be clearly diagnosed. And the gender, race, body mass index and disease course of them are not restricted; ☐Intervention measures: Intervention measures in both group are not limited; ☐Outcome indicators: The outcome indicators including MiR-122 as the main evaluation and research of the literature.

1.1.2 Exclusion criteria

☐The type of study did not clearly explain the test method; ☐The effective outcome could not be extracted from the literature; ☐Repeated papers; ☐The full text could not be obtained; ☐Patients ≥ 70 years old, advanced tumor dissemination throughout the body, abnormal blood coagulation and destruction of the hilar anatomy; ☐The sample size was too small.

1.2 Retrieval strategy

The literature searched randomized controlled trial of the effect for rehabilitation nursing on the quality of life in patients after liver transplantation. It was searched by database: Wanfang database, VIP database (VIP), Clinical Registry, PubMed, Cochrane Library, Embase Library database. The search time limit is from January 1, 2006 to February 28, 2021, tracking and including research-related literature. The Chinese search terms are: ☐Type of disease: "myocardium" or "coronary artery" or "stroke" or "cerebrovascular"; ☐Research method: "randomized controlled" or "clinical" or "retrospective study". English search words are mainly based on the characteristics of major databases. We use corresponding subject terms and keywords to search and we also need to eliminate duplicate documents. English search terms are: ☐disease type: "myocardium" OR "coronary artery" OR "Strock" OR "vessel of brain" OR "cardiac"; ☐"Randomized control" OR "clinical" OR "retrospective study".

1.3 Literature selection and quality evaluation

After the literature search completed, two reviewers would independently screen the literature, and first based on the title, abstract, etc., to exclude articles that were obviously inconsistent with the research content, such as animal experiments, related Content review, etc. Then inspecting the preliminary screening literature and excluding the related literature of self-control experiments. Finally, a full-text screening was performed to eliminate the literature with unclear diagnosis and outcome. In the event that effective information was missing or unknown, it is necessary to communicate and verify with

the author through emails, telephones, etc. If two reviewers disagree on the article, we would ask higher-level experts or professors to distinguish the results before they were adopted. All the literatures in this study were evaluated by referring to the Cochrane Systematic Review Manual, and the publication bias was represented by a funnel chart.

1.4 Statistical methods

The statistical data in this study were all using Cochrane Collaboration RevMan 5.2 software for Meta analysis, and χ^2 test was used for statistical heterogeneity test. If the result is $P \geq 0.10$ and $I^2 \leq 50\%$, it is indicated that there is no obvious heterogeneity between two groups, the fixed-effects model are used to describe the data. If heterogeneity test result is $P < 0.10$, $I^2 > 50\%$, it means that there is heterogeneity. By investigating the source of heterogeneity, performing subgroup and sensitivity analysis on the results at the same time, the final result is described according to whether the fixed effect model is used to show homogeneity and whether the random effect model is used to show homogeneity. The effect model incorporates the effect value; the literature that is not suitable for meta-analysis to describe the data. Analyzing measurement data of continuous variables is expressed by weighted mean difference (WMD) and 95% confidence interval and $P < 0.05$ is considered as statistically significant.

2 Result

2.1 Literature search results

Through database search, 176 articles were initially retrieved, including ten articles from CNKI, VIP database of three articles, three articles in Wanfang, 89 articles in PubMed and 57 articles from other databases. According to the inclusion and exclusion criteria, 23 articles were finally included in the study. As shown in Figure 1.

2.2 The basic data

A total of 23 articles were included, including 6375 patients in all. All participants were mainly from China and European countries; the studies were published between 2012 and 2021. Among all including studies, the observation group was patients with CCVD and control group is a healthy population. The basic features are shown in Table 1.

Table 1
Basic characteristics of the included literature

Author	Year	Country	Sample size (Observation /Control group)	Age (Observation/Control group)	Sex (Male/Total)%	Grouping method
Irene R	2020	Spain	476/487	46.7/45.4	47	Myocardial infarction/Control group
Mikko H	2020	Finland	59/120	46.4 ± 4.0/7.4 ± 3.7	74	Death/Survival group
Yu Wang	2018	China	66/70	43.8 ± 0.9/41.8 ± 1.4	36	Acute myocardial infarction/Control group
Moritz B	2021	Spain	137/905	43.7 ± 0.6/42.3 ± 0.5	44	Acute Coronary Syndrome/Control group
Rafał B	2021	Poland	47/40/55	49.3/50.3/44.6	65	Coronary artery disease/Carotid artery disease/Both
Lobna A	2017	Cairo	80/80/60	49.5 ± 5.7/49.0 ± 5.2/51.6 ± 5.4	45	Acute myocardial infarction with end-stage renal disease/Acute myocardial infarction/Control group
Sandeep S	2020	India	203/192	42.4 ± 0.5/42.3 ± 1.2	52	Stable angina pectoris/Unstable angina pectoris
Lin Meijun	2020	China	28/20	43.3 ± 8.2/42.1 ± 6.4	63	Normal group/ Nasopharyngeal carcinoma radiotherapy group
Hao L	2020	China	34/31/22	47.6 ± 2.2/46.8 ± 4.0	54	Acute myocardial infarction/Unstable Angina/Control group
Hong Chengying	2021	China	16/18	59.1 ± 19.1/66.7 ± 22.1	43	Cardiomyopathy/Control group
Shi Bing	2019	China	10/10	72.6/72.5	54	Heart failure/Control group
Ruixia Z	2019	China	567/552	61.7 ± 10.1/61.9 ± 9.5	66	Stroke/Control group
Xin-Liang Y	2015	China	50/39	63.2 ± 11.4/62.7 ± 10.5	55	Acute myocardial infarction/Control group
Nuno C	2016	Portugal	142/18	62 ± 12	62	Acute myocardial infarction/Control group
N Dayan	2021	America	30/37/148	-	-	Acute Coronary Syndrome with Pre- eclampsia/Acute Coronary Syndrome with Pregnancy Hypertension/Control group

Author	Year	Country	Sample size (Observation /Control group)	Age (Observation/Control group)	Sex (Male/Total)%	Grouping method
Zhang Yan	2016	China	10/10/10/10	60.7 ± 9.9/54.7 ± 8.6/53.2 ± 8.8/60.4 ± 65.5	54	Control/ Diabetes / Coronary heart disease / Diabetes with coronary heart disease group
Wei G	2012	China	255/100	65.2 ± 10.7/63.0 ± 10.7	65	Coronary heart disease/Control group
Xiangdong L	2015	China	287/115	-	46	Unstable Angina/Acute Myocardial Infarction
Gilje	2014	Sweden	35/30	65/72	47	CPC1-2/CPC3-5
Wu Xia	2017	China	40/91/46/45	55.4 ± 5.9/56.6 ± 2.4	51	Control/Acute coronary syndrome/Acute myocardial infarction/Unstable angina
Luo Ting	2021	China	84/90	56.21 ± 6.13/55.96 ± 6.27	55	Ischemic stroke/Control group
Li Linlin	2020	China	49/71/20	69.2 ± 6.4/66.4 ± 5.9	62	Low/Medium /High risk group
Huang Weiwen	2021	China	68/60	39.49 ± 9.93 /38.77 ± 10.19	47	Severe head injury/Control group

2.3 Research methods and bias assessment with scoring

The quality of literatures in this study were scored by BSHS-A, including general health status, social relations, mental function and physical function. The risks of bias were assessed using the Cochrane Handbook recommended by assessment tools and methods for descriptive statistics. We have shown in Figures 2-1 and 2-2.

2.4 Analysis the outcome indicators and heterogeneity

2.4.1 The diagnostic value of Mir-122 in acute myocardial infarction

Eleven studies reported the diagnostic value of MiR-122 in acute myocardial infarction. The heterogeneity is large (the result is $I^2=85\%$, $P<0.00001$), there is no source of heterogeneity in the sensitivity analysis. And subgroup analysis is carried out according to whether the intervention group is combined with other diseases in the experiment. The subgroup of simple myocardial infarction heterogeneity ($I^2=83\%$, $P=0.0001$) with the heterogeneity of other diseases ($I^2=80\%$, $P=0.0001$). The subgroup heterogeneity is still very large, whether it is combined with other diseases is not heterogeneous. There is no source of heterogeneity was found. Therefore, a random effects model was selected to merge the data. The results of Meta analysis showed that MiR-122 was more expressed in patients with myocardial infarction than healthy people (WMD=-2.33, 95% CI[-2.88,-1.78], $P<0.0001$), the forest diagram is shown in Figure 3-1. The funnel chart is obtained by statistical software, as shown in Figure 3-2 below. It can be seen that scatter points are symmetrical and located in the upper middle part. The possibility of published bias is small and no other research is needed.

2.4.2 Diagnostic value of Mir-122 for other heart diseases

Thirteen studies reported on the diagnostic value of Mir-122 for other heart diseases other than myocardial infarction, of which ten were angina, two were heart failure, and one was cardiomyopathy. The heterogeneity was large (the result was $I^2=80\%$, $P<0.00001$), and the sensitivity analysis did not find the source of the heterogeneity. At the same time, the study that excluded heart failure and cardiomyopathy ($I^2=83\%$, $P<0.0001$). The heterogeneity of two subgroups was still significant. The difference is not the main cause of heterogeneity, and no source of heterogeneity has been found. Therefore, a random effects model was chosen to merge the data. The analysis results show that compared with the healthy control group, the expression of Mir-122 in angina pectoris and other heart diseases was higher (WMD=-0.45, 95% CI [-0.61, -0.29], $P<0.00001$). The forest diagram was shown in Figure 4-1. At the same time, the funnel chart is obtained by statistical software, as shown in Figure 4-2 below. It can be seen that the scattered points are symmetrical, concentrated in the upper part and the possibility of publication bias is very small, thus no additional research is needed.

2.4.3 The diagnostic value of Mir-122 in cerebrovascular diseases

Four studies reported the changes in the expression level of Mir-122 in cerebrovascular diseases. Four reports all showed that Mir-122 expression increased in patients with stroke, brain injury and other diseases. The heterogeneity results showed ($I^2=6\%$, $P=0.36$) and a fixed-effect model was used to merge the data. The analysis shows that Mir-122 is better than the control group in the diagnosis value of cerebrovascular diseases (WMD=-0.34, 95% CI [-0.53, 0.33], $P<0.00001$). The forest diagram is shown in Figure 5. This observation is included in four studies, which is relatively few. The funnel chart test efficiency has certain limitations, so the funnel chart is not drawn.

2.4.4 The diagnostic value of Mir-122 in the prognosis of CCVD

Nine studies have reported on the diagnostic value of MiR-122 in the prognosis of patients. The heterogeneity was high ($I^2=99\%$, $P<0.00001$) and the sensitivity analysis did not find the source of the heterogeneity. At the same time, according to whether it is a cardiovascular disease, a subgroup analysis is performed. The cardiovascular disease subgroup heterogeneity ($I^2=99\%$, $P<0.00001$), the heterogeneity of cerebrovascular disease subgroups ($I^2=90\%$, $P<0.00001$), the heterogeneity of the two subgroups is still obvious. Whether it is cardiovascular disease is not the main cause of heterogeneity, so no source of heterogeneity has been found. Therefore, a random effects model was chosen to merge the data. The analysis results show that compared with the control group, patients with high MiR-122 expression have a worse prognosis (WMD=-2.20, 95% CI [-2.66, -1.75], $P<0.00001$). The forest diagram is shown in Figure 6-1. At the same time, the funnel chart is obtained through statistical software, as shown in Figure 6-2. It can be seen that the scattered points are symmetrical and concentrated in the upper point and the possibility of publication bias is very few.

3 Discussion

Past studies have shown that biomarkers in acute myocardial infarction, such as cardiac troponin and creatine kinase MB, do not rise significantly during the early diagnosis^[10]. Nowadays, with the advent of high-sensitivity cardiac troponin test, even within one hour, myocardial infarction can be diagnosed with reasonable accuracy^[11]. Nevertheless, looking for other early biomarkers, especially in different potential molecular mechanisms, may achieve higher sensitivity and specificity in short time. In the early diagnosis of stroke, the same problem is also faced, it is difficult to distinguish between transient ischemic attack and ischemic stroke within the time window of thrombolytic treatment. Although the latest imaging technology can be used in the time window, TIA is diagnosed complexity and high cost. These methods limit widespread and a variety of blood markers are used for the predictive value of TIA^[12-13]. Recently studies have shown that myocardial infarction is highly correlated with the incidence of stroke and can be given by measuring MiR-122^[14-15]. MiR-122 is a non-coding RNA that participates in the post-transcriptional regulation of gene expression by binding to target mRNA^[16]. MiR-122 can regulate lipid metabolism and the pathophysiological process of atherosclerosis in CCVD. The content shows stable changes in the serum of subjects. This feature may have potential value as a therapeutic target^[17].

In this study, the value of MiR-122 in the diagnosis of CCVD was evaluated and analyzed through Meta analysis. It has shown that MiR-122 has a greater diagnostic value for predicting CCVD and its expression is elevated in diseases such as myocardial infarction, angina pectoris and stroke. The differences between the groups are statistically significant. In the evaluation of the diagnostic value of biomarkers, there are three main aspects that can lead to consensus among researchers^[18–19]: 1. The biomarker can quickly diagnose acute and severe cardiovascular and cerebrovascular diseases and detect high-risk patients. 2. The biomarker has high specificity in cardiovascular and cerebrovascular diseases, and is less interfered by other diseases or the patient's own state. 3. The marker is easy to detect and the price is easy to accept. The results of this study have shown that, compared with the control group, MiR-122 is expressed in CCVD patients at a higher level. MiR-122 has a more accurate diagnostic value for the prognosis of patients and fulfills the above-mentioned specificity requirements. The study in Koyama et al.^[20] showed that compared with the control group, the level of miR-122 in patients with acute myocardial infarction was significantly higher. The level of miR-122 in patients with non-ST-segment elevation myocardial infarction was higher than ST-segment elevation myocardium patients with infarction at the peak of eight hours ($P < 0.05$). Other studies have shown that MiR-122 can be obtained by real-time quantitative fluorescence polymerase chain reaction detection in the peripheral blood of patients. Its detection method is simple and quick, and has potential value as a cardio-cerebrovascular biomarker^[21–22].

Although this study has been evaluated objectively, it still has deficiencies. The literature including the research is relatively few and it includes retrospective research, which may have an influence on the credibility of conclusions. Based on the sample estimation of 23 articles, the random allocation method of some articles is not standardized and the allocation concealment, blind method and review are lacking. Due to the lack of original data, it is difficult for us to restore the missing data. Nonetheless, our data shows that the heterogeneity of these studies has been corrected to the greatest extent by combining the data of the random effects model. And the funnel chart also shows that the conclusions are less biased.

In order to evaluate the diagnostic potential of MiR-122 in CCVD, further studies are still needed. Subsequent research should also pay attention to the correlation between MiR-122 and other cardiac biomarkers in various heart disease patients, as well as the correlation with plaque vulnerability. Therefore, it remains to be determined whether the differences in the plasma concentration and elevated dynamics of MiR-122 in the cardi-cerebrovascular systems can be used to identify the underlying pathophysiological mechanisms in different subdivisions. Whether these differences can be used to stratify risk groups accurately.

4 Conclusion

1. MiR-122 is significantly increased in cardiovascular diseases and has great diagnostic value in predicting cardiovascular diseases such as cardiac infarction and angina pectoris.
2. The expression of MiR-122 is elevated in cerebrovascular diseases such as stroke, which has great diagnostic value for the diagnosis of this type of disease.
3. MiR-122 has diagnostic value in the prognosis of patients with CCVD.

Declarations

a. Ethics approval and consent to participate

Not applicable

b. Consent for publication

Not applicable

c.Availability of data and materials

Not applicable

d. Competing interests

There is no conflict of interest in this study. Jiao Kun, Su Ping, Feng Yubao, Li Changqing have all read and approved the submitted manuscript. On behalf of all authors, I declare that our article is original research and has not been published before, and has not considered publishing all or part of the above content in other places.

e. Funding

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f. Authors' contributions

Jiao Kun wrote the main manuscript text, Su Ping carried out literature search and statistics, Feng Yubao prepared figures and table, and Li Changqing reviewed and revised the article. The final manuscript read and approved by all authors.

g. Acknowledgments

Not applicable

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Figures

Figure 1.

Figure 1

Flow chart of literature screening

Figure 2-1

Figure 2-2

Figure 2

2-1 The proportion of literature methodology quality evaluation

2-2 Evaluation the risk of literature bias

Figure 3-1

Figure 3-2

Figure 3

3-1 Forest diagram of the diagnostic value in Mir-122 for acute myocardial infarction

3-2 The funnel chart of the diagnostic value of Mir-122 in AMI

Figure 4-1

Figure 4-2

Figure 4

4-1 Forest diagram of the diagnostic value of Mir-122 for other heart diseases

4-2 Funnel diagram of the diagnostic value of Mir-122 for other heart diseases

Figure 5

A forest plot of the diagnostic value of Mir-122 for cerebrovascular diseases

Figure 6-1

Figure 6-2

Figure 6

6-1 The diagnostic value forest diagram of Mir-122 in the prognosis of CCVD

6-2 Funnel chart of the diagnostic value of Mir-122 in the prognosis of CCVD