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Meta-analysis of the association between miR-499 gene polymorphism and hepatocellular carcinoma HCC genetic susceptibility

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► ***Original article***

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Keywords: *Hepatocellular carcinoma, genetic susceptibility, miR-499 polymorphism, meta-analysis, liver cancer.*

ABSTRACT

Background: The link between the miR-499(rs3746444) gene polymorphism and genetic predisposition to hepatocellular carcinoma (HCC) was thoroughly assessed in this study. ***Materials and Methods:*** This study used Rev-Man 5.41 statistical software to conduct a meta-analysis of case-control studies that investigated the relationship between genetic susceptibility to HCC and the miR-499 gene or the rs3746444 locus polymorphism. The articles were searched in PMC, PubMed, and other databases. ***Results:*** In this analysis, 15 publications were used, with 4901 normal individuals serving as the control group and 3366 HCC patients as members of the experimental group. The findings showed that the risk of getting HCC was higher in those with the AA (95%CI (0.64, 0.94), I2 = 71%, P = 0.009) or AG (95%CI (1.01, 1.40), I2 = 58%, P = 0.04) genotypes. The risk of HCC was minimal when the genotype was GG (95%CI (0.79, 1.50), I2=56%, P = 0.60). A statistical difference was found between the G allele (95%CI (1.13, 1.69), I2 = 60%, P=0.002), while no significant difference was found between the two groups with respect to the A allele (95%CI (0.56, 1.15), I2 = 79%, P = 0.23). ***Conclusions:*** There was a strong link between the polymorphism of miR-499 gene and the genetic predisposition to hepatocellular cancer. Therefore, the polymorphism of the miR-499 gene can be utilized as a predictor of liver cancer occurrence, which is highly relevant for the early detection and management of liver cancer.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a cancer that poses a major risk to human health, with one of the highest rates of morbidity and mortality among malignant tumors [1]. Hepatocellular carcinoma constitutes over 85% - 90% of primary liver cancer on a global scale, with around 45% of HCC-related deaths occurring in greater China. This illness has a significant financial burden on patients, payers, and society. It also significantly lowers the quality of life for those who are impacted [2]. The development of HCC is related to many factors, including environmental factors and genetic factors. Hepatocellular carcinoma (HCC) can develop for a variety of reasons. Some of these include viruses like hepatitis B and C, drinking too much alcohol, metabolic liver disorders like non-alcoholic fatty liver disease, and ingesting toxins like aflatoxin and aristolochic acid [3].

Genetic susceptibility to HCC refers to an individual's susceptibility to certain genetic factors that make it more susceptible to HCC. Hereditary carcinogenesis is characterized by genetic diversity. Hereditary colorectal cancer (HCC) is more common in a number of rare hereditary disorders, including iron regulation gene mutations, alpha 1-antitrypsin deficiency, glycogen storage diseases, porphyria (involving hydroxymethylbilane synthase and uroporphyrinogen decarboxylase), tyrosinemia (involving fumarylacetoacetate hydrolase), and Wilson disease (involving ATPase copper-transporting beta) [4]. The development of HCC is influenced by genetic factors, particularly by variations in or mutations to specific genes [5]. Recent research has highlighted the significance of microRNAs (miRNAs) as a family of gene regulatory molecules that contribute significantly to the initiation and progression of HCC [6]. The progression and evolution of HCC are influenced by miRNAs, which are short noncoding RNAs that function as regulators as well as players. Autophagy, drug resistance, angiogenesis, invasion, metastasis, epithelial-mesenchymal transition (EMT), and proliferation are all processes that are fundamentally regulated by microRNAs (miRNAs) in hepatocellular carcinoma (HCC) [7].

Various types of microRNAs impact the progression of HCC. In instance, miRNA-499 has been recognized as a key biomarker for gauging the

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outcome of HCC [8]. Previous research demonstrated that the reduced expression of miR-499 encourages the proliferation of HCC cells through histone deacetylases (HDAC1-3), implying that miR-499 may function as a tumor suppressor [9]. A highly expressed miRNA gene called miR-499 is found at chromosome location 1P3C1 in humans. A number of malignancies, including HCC, lung cancer, breast cancer, and others, have significantly higher expression levels of miR-499 [10]. Several malignancies' prognoses and responses to treatment are correlated with miR-499 gene expression levels, according to studies [11]. The target gene's mRNA is bound by the miR-499 gene's regulatory mechanism, which then degrades the mRNA and lowers the target gene's expression [12]. Research has demonstrated that a wide range of regulatory variables, including transcription factors, hormones, medications, and other substances, influence the expression of the miR-499 gene. Additionally, other miRNAs also control the expression of the miR-499 gene [13].

More and more research has linked variations in the miR-499 gene to an increased risk of hereditary colorectal cancer (HCC) [14]. According to a Chinese study, there is a strong correlation between the Glanzmann thrombasthenia (GT) variation of the miR -499 gene and the risk of HCC, but the Torque teno (TT) variant is associated with a decreased risk [15]. The TT genotype of miR-499 was associated with a decreased risk of HCC development in another investigation [16]. Furthermore, connected to hereditary vulnerability to HCC, certain investigations have linked the expression level of the miR-499 gene. For instance, a Taiwanese study discovered a positive correlation between the expression level of miR-499 and the risk of HCC [17]. The risk of HCC was significantly associated with miR-499 expression level, according to another study [18]. Therefore, polymorphisms in the miR-499 gene may have a role in hereditary vulnerability to HCC. The purpose of a meta-analysis is to identify the reliability and correlation of study results by comparing them to those of other studies.

This study aimed to examine the correlation between genetic susceptibility to HCC and polymorphisms in the miR-499 gene using meta-analysis. We integrate the latest and most comprehensive data, unveiling distinct risk patterns associated with different miR-499 genotypes. By considering both genetic variants and miR-499 expression levels, we actively contribute to a concise and comprehensive understanding of HCC susceptibility.

MATERIALS AND METHODS

Document inclusion criteria

Research on the link between HCC risk and variations in the miR-499 gene was the focus of this investigation. The subjects were adults (older than 18 years); the study must include indicators such as gene polymorphism (such as SNP, single nucleotide polymorphism) or expression level; the study must have a control group; after the eligible studies are selected, statistical processing is required for these studies.

Selection criteria of study

(1) Random sequence generation; (2) Allocation concealment; (3) Blinding of outcome assessment; (4) Consistency of indicators; (5) Acupuncture stimulation was used after operation in the intervention group; (6) No other bias.

Methods

Retrieval strategy

Keywords: Hepatocellular carcinoma; Genetic susceptibility; miR-499 gene; Meta-analysis. Databases: PMC, PubMed and other databases.

Quality evaluation

The entire text was reviewed independently by two expert researchers, who then meticulously filtered the references using the inclusion and exclusion criteria. Any references that met the inclusion criteria were double-checked. In case of disagreement, discuss the decision or a third researcher ruling.

Statistical analysis

Rev-Man 5.41 was utilized to conduct the meta-analysis. The combined effect will be estimated by using standardized mean differences and their 95% CI. The random effects model was employed for analysis when $P \leqslant 0.1$ and $I2 \geqslant 50\%$ indicated that the studies were heterogeneous. The fixed effects model was employed for analysis when $P > 0.1$ and $I2 < 50\%$, indicating that no heterogeneity was found among the studies.

RESULTS

Study characteristics

A total of 55 pertinent literature sources were acquired based on the search technique. Following a review of the titles, abstracts, and full texts of the literature, 15 literatures [19–33] were ultimately included in accordance with the inclusion and exclusion criteria. For details on the studies experimental and control group sizes, as well as the first author and publication year, refer to table 1.

The publication bias analysis

The findings of the evaluation of the 15 included literatures are displayed in figure 1. Since there is only one red dot in the figure, the 15 literary works have a high overall quality that satisfies the quality level.

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Table 1. Basic characteristics of the included literature.

Included literature	Number of samples Experimental\Control group		Indicators
Yu Xiang 2012 [19]	100	100	AA, AG, GG, A allele, G allele
Y.F. Shan 2013 [20]	185	172	AA, AG, GG
X.H. Wang 2014 [21]	152	304	AA, AG, GG, G allele
Kyung Tae Min 2011 [22]	446	502	AA, AG, GG
Xinhong Li 2015 [23]	266	266	AA, AG, GG
Fteah AM 2019 [24]	75	75	AA, AG, GG, A allele, G allele
Mohamed Abdel-Hamid 2018 [25]	50	50	AA, AG, GG, A allele, G allele
L.H. Zhang 2016 [26]	175	302	AA, AG, GG
Pingping Yan 2015 [27]	274	328	AA, AG, GG
JIAN-TAO KOU 2014 [28]	271	532	AA, AG, GG
Juan Zhou 2012 [29]	186	483	AA, AG, GG, A allele, G allele
Sheng Zhang 2020 [30]	584	923	AA, AG, GG, G allele
Zhaleh Farokhizadeh 2019 [31]	100	120	AA, AG, GG, A allele, G allele
Jia-Hui Qi 2014 [32]	314	407	AA, AG, GG, A allele, G allele
Yin-Hung Chu 2014 [33]	188	337	AA, AG, GG

Note: Guanine (G), Adenine (A).

Meta-analysis results

Mean age of the two groups of patients

The analysis was based on the sample size and average age of the two patient groups. Figure 2-5 shows the patient count and average age for the two groups, with SE representing the standard error, RD the risk difference, and SMD the standard mean difference. According to the data, there were 4901 instances in the control group and 3366 cases in the experimental group; nevertheless, there was no statistically significant difference between the two groups (95% CI (- 0.00,0.00), P = 1.00). The two groups did not vary statistically significantly (95% CI (- 0.00,0.15), P = 0.06), and the participants' mean age varied from 35 to 65 years old.

Number of males

Before treatment, there was no discernible change in the proportion of men in the two groups. The number of males in the two groups was counted to observe the influence of gender on HCC genetic susceptibility. In figures 6 and 7, you can see the outcomes. As can be seen from the figures, the proportion of males in the two groups is similar (95% CI (0.99, 1.22), I^2 = 41%, P = 0.08). Therefore, gender is not a factor affecting HCC genetic susceptibility.

The proportion of AA and AG genotypes in HCC patients

Compared to healthy controls, people with HCC had a much greater prevalence of AA and AG genotypes. The common genotypes of miR-499 locus were AA, AG and GG, and their role in HCC genetic susceptibility was explored, as shown in figure 8-10. The results indicated that individuals with AA (95% CI (0.64, 0.94), I^2 = 71%, P = 0.009) or AG (95% CI (1.01, 1.40), I^2 = 58%, P = 0.04) genotypes were at greater risk of developing HCC. When the genotype was GG (95% CI (0.79, 1.50), I^2 = 56%, P = 0.60), the risk of HCC was low. There is a link between genotype and the likelihood of developing HCC.

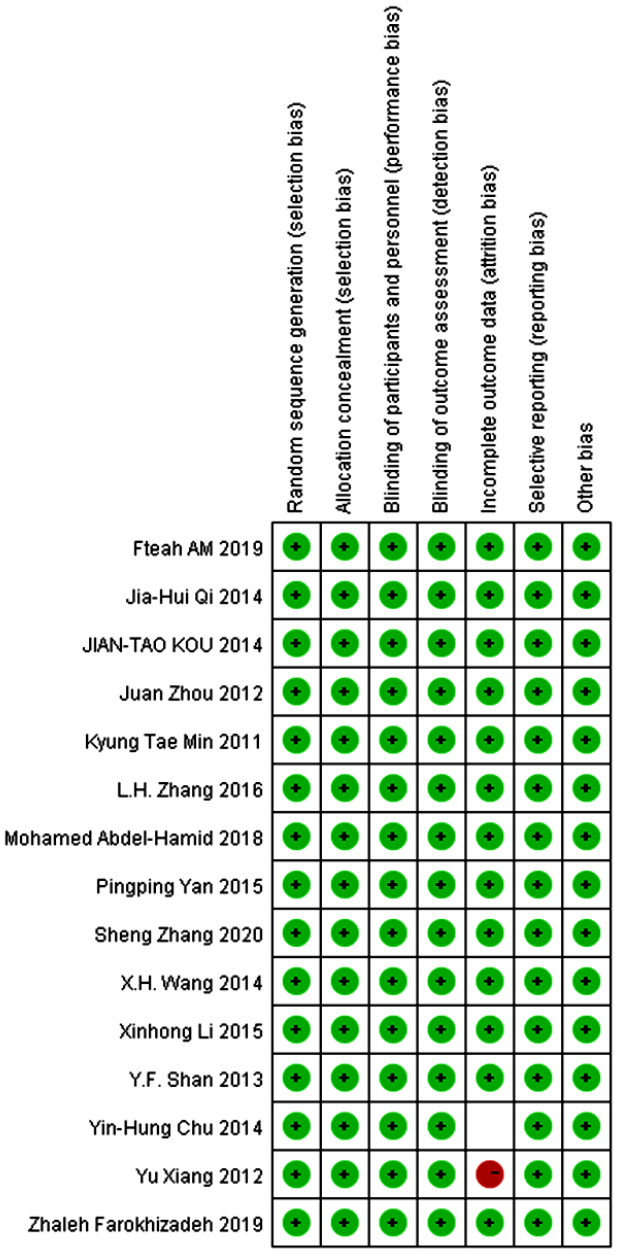

Figure 1. The publication bias analysis.

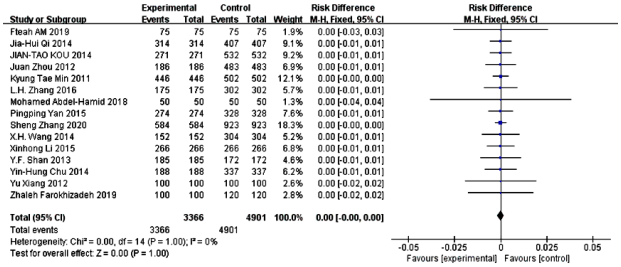

Figure 2. The forest plot of sample number.

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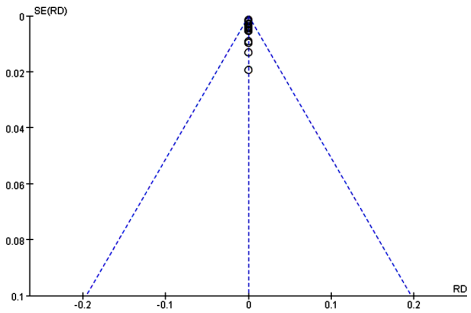

Figure 3. The bias analysis of sample number.

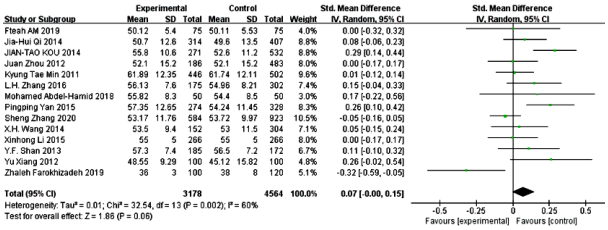

Figure 4. The forest plot of mean age.

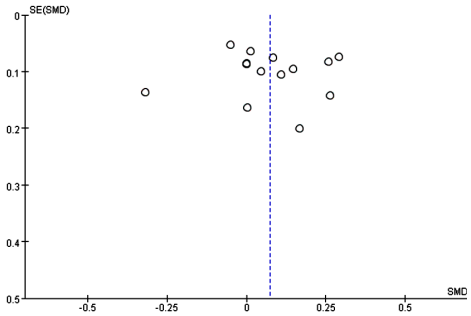

Figure 5. The bias analysis of mean age.

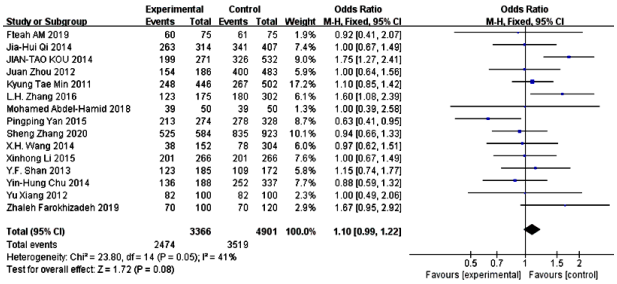

Figure 6. The forest plot of the number of males.

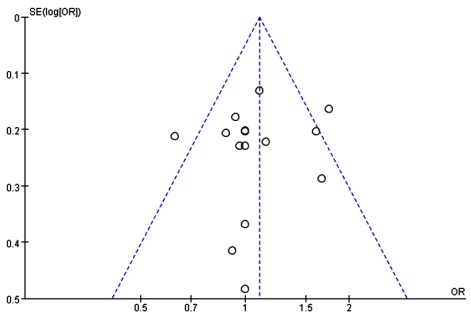

Figure 7. The bias analysis of the number of males between the two groups.

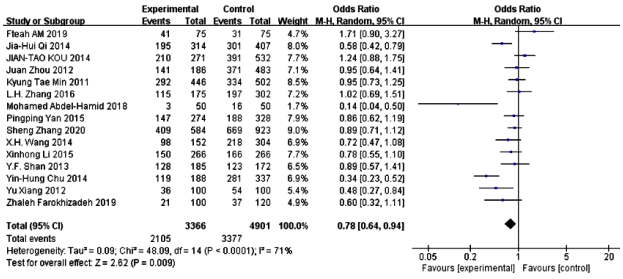

Figure 8. The forest map of AA.

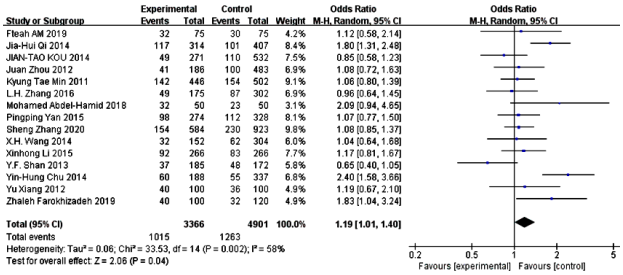

Figure 9. The forest map of AG.

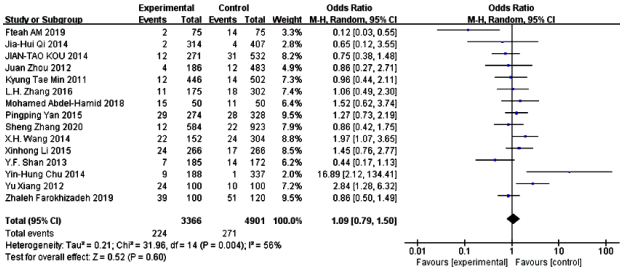

Figure 10. The forest map of GG.

Effects of G and A allele

G allele significantly increased the risk of disease compared to an A allele. Figures 11 and 12 portray the outcomes of the comparison of A and G's effects on HCC risk under the allele model. Comparing the two groups with the A allele, the results showed no statistical difference (95% CI (0.56, 1.15), I2 = 79%, P = 0.23). However, when looking at the G allele, there was a statistical difference (95% CI (1.13, 1.69), I2 = 60%, P = 0.002). Therefore, compared with A allele, G allele can significantly increase the risk of disease.

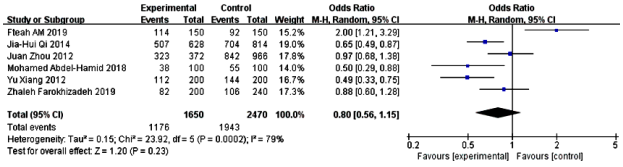

Figure 11. The forest map of A allele.

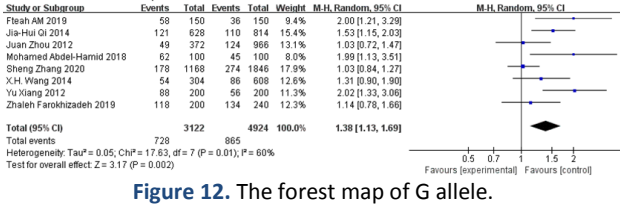

Figure 12. The forest map of G allele.

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DISCUSSION

The result of this research shows unbiased of 14 out of 15 literatures, as could be observed in figure 1. The number and average age of patients are not different, as well as the number of males. Also, males used in the study do not differ from the control, therefore were not considered to influence HCC genetic susceptibility in terms of gender (figure 6 and 7). HCC is usually caused by malignant transformation of liver cells under the influence of long-term hepatitis virus infection, alcoholism, smoking and other factors [34]. HCC usually presents with liver enlargement, pain, jaundice, cirrhosis and other symptoms, which can be life-threatening if left untreated [35]. There are a lot of elements that interact in a complicated way to cause HCC to start and progress. One of the major contributors to HCC development is heredity, and there may be a correlation between HCC and certain gene variants [36].

Improving the study's reliability and precision, evaluating confidence intervals for correlation coefficients, and determining the link between miR-499 gene polymorphism and HCC genetic susceptibility can all be accomplished using meta-analysis [37]. In meta-analysis, attention should be paid to evaluation of research quality and interpretation of results to avoid bias and uncertainty [38]. Multiple factors may interact in the complex link between miR-499 gene polymorphism and HCC etiology, according to various studies. For example, the miR-499 gene may be involved in the regulation of cell cycle regulatory networks, thereby influencing the occurrence of HCC. Furthermore, the miR-499 gene could potentially have a role in controlling signaling pathways, like the Notch and Wnt/β-catenin pathways, which could impact the development of HCC [39].

This study found that the risk of getting HCC was higher in persons with the AA (95%CI (0.64, 0.94), I2 = 71%, P = 0.009) or AG (95%CI (1.01, 1.40), I2 = 58%, P = 0.04) genotypes. When the genotype was GG (95% CI (0.79, 1.50), I^2 = 56%, P = 0.60), the risk of HCC was low. The A allele did not differ significantly between the two groups (95% CI (0.56, 1.15), I2 = 79%, P = 0.23), whereas the G allele did differ statistically (95% CI (1.13, 1.69), I2 = 60%, P = 0.002). Since the GG genotype was much less common in HCC cases, the combined miR-499 (AA+AG) genotypes were much more common, which is consistent with earlier studies that found a statistically significant difference in the frequency of miR-499 (rs3746444) genotypes [40]. Additional findings from Egypt's National Liver Institute-Menoufia University corroborated the association between the GG or G allele genotype and an elevated risk of HCC [41]. The results in the present study showed that there was no significant difference between the two groups and A allele, while there was statistical difference between G allele (figures 11 and 12). Therefore, compared with A allele, G allele can significantly increase the risk of disease. But another study found that if the rs738409 C > G polymorphism is found in people at risk for liver cirrhosis, PNPLA3 genotyping and more extensive surveillance may help [42]. Overall, multiple studies have shown that miR-499 gene polymorphisms and expression levels are associated with genetic susceptibility to HCC. Thus, it is important for the early detection and treatment of liver cancer because the miR-499 gene polymorphism can be utilized as an indication to predict the occurrence of liver cancer [43]. Furthering our understanding of the pathophysiology of liver cancer and providing new ideas for early diagnosis and treatment of liver cancer can be achieved through the research of the miR-499 gene and its regulatory mechanism.

CONCLUSION

Hepatocellular carcinoma (HCC) genetic vulnerability is strongly associated with miR-499 gene polymorphism, according to a meta-analysis of fifteen trials. The unbiased results, independent of gender influences, consistently reveal elevated HCC risk for individuals with AA or AG genotypes, emphasizing the noteworthy impact of the G allele. These findings align with previous research and highlight miR-499's potential as a predictive biomarker for HCC. The identified molecular mechanisms involving cell cycle networks and signaling pathways further contribute to our understanding of HCC pathogenesis. Overall, the study supports the clinical relevance of miR-499 gene polymorphism in early diagnosis and intervention for liver cancer, suggesting a promising avenue for future research and clinical applications.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

Authors' contributions: All authors contributed to the work equally.

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