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Single nucleotide polymorphism of rs2596542 and the risk of hepatocellular carcinoma development

A meta-analysis

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Abstract

Background: Major histocompatibility complex class I-related chain A (MICA) is considered as a tumor antigen, and its expression is affected by its genetic polymorphisms. However, the relationship between rs2596542 polymorphisms in MICA promoter region and hepatocellular carcinoma (HCC) is not fully elucidated so far. This study aims to explore the relationship between single nucleotide polymorphism of rs2596542 and the risk of HCC development through meta-analysis.

Methods: MEDLINE, Web of Science, and EMBASE databases were systematically searched to identify relevant studies. A meta-analysis was performed to examine the association between MICA rs2596542 polymorphism and susceptibility to HCC. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.

Results: Fourteen case–control studies involving 4,900 HCC cases and 19,519 controls were included. The MICA rs2596542C allele was significantly associated with decreased risk of HCC based on allelic contrast (OR = 0.76, 95% CI = 0.69–0.83, $P < .001$), homozygote comparison (OR = 0.57, 95% CI = 0.48–0.69, $P < .001$), and a recessive genetic model (OR = 0.77, 95% CI = 0.65–0.91, $P < .001$), whereas patients carrying the MICA rs2596542TT genotype had significantly higher risk of HCC than those with the CT or CC genotype (TT vs CT + CC, OR = 1.57, 95% CI = 1.36–1.81, $P < .001$). Subgroups analyses based on the ethnic or the source of control groups found very similar findings.

Conclusion: The C allele in MICA rs2596542 is a protective factor for hepatocarcinogenesis, whereas the T allele is a risk factor. Further large and well-designed studies are needed to confirm this conclusion.

Abbreviations: CI = confidence interval, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MICA = major histocompatibility complex class I-related chain A, NKG2D = natural killing group 2 member D, OR = odds ratios.

Keywords: hepatocellular carcinoma, major histocompatibility complex class I-related chain A, polymorphisms

1. Introduction

Hepatocellular carcinoma (HCC) is a significant cause of cancer morbidity and mortality worldwide.[1] Moreover, more than half of patients are already developed with an intermediate or advanced stage of HCC when their first diagnosis of HCC.[2] Therefore, treatment options are limited. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcohol consumption, obesity pandemic, cryptogenic cirrhosis, or post-nonalcoholic steatohepatitis cirrhosis are risk factors of HCC development.[3–4] However, not all individuals with one or all of these 3 risk factors seem to have the same risk of HCC development. Large numbers of basic researches have shown that HCC that exhibits a high degree of genetic heterogeneity including the multiple molecular pathways may contribute to the subsets of hepatocellular neoplasms. In addition, the host and environmental factors may interact synergistically in HCC pathogenesis and disease progression.

The major histocompatibility complex class I-related chain A (MICA), mapping to chromosome 6p21.33, is a tumor-specific antigen with extensive history of polymorphisms.[5] MICA is not only expressed in normal tissues or cells including an intestinal epithelial cells, but also it is highly expressed in epithelial-derived primary tumors.[6] The MICA molecule is a ligand of the natural killing cell surface activating receptor, natural killing group 2 member D (NKG2D) molecule, which can effectively mediate natural killing cell killing of tumor cells by the binding activation of proteins.[7] However, many membrane-positive MICA tumors release a soluble MICA molecule (sMICA) which then inhibits the function of natural killing cells in the serum.[8] Furthermore, the expression of MICA is also induced by several stress factors including viral infection.

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Previously, it was reported that genetic variation at −1878 (rs2596542C/T) in MICA gene promoter region is associated with chronic HBV infection.[9] Other studies also reported that rs2596542 polymorphisms in MICA are associated with the development of different cancers and autoimmune diseases.[10–12] In recent decade, several studies have reported the role of rs2596542 polymorphisms in MICA and it involves in the development of HCC. However, previously reported results were inconsistent and inconclusive. Therefore, we performed this meta-analysis to investigate the association of rs2596542 polymorphisms and the risk of HCC development.

2. Methods

2.1. Ethics committee and institutional review board

This is a meta-analysis. Ethical approval was not necessary.

2.2. Literature search

MEDLINE, Web of Science, and EMBASE databases were systematically searched from inception to July 2018. The search phrase or MeSH term ("carcinoma, hepatocellular" or "Hepatocellular carcinoma" or HCC or hepatoma) AND (MICA or "MHC class I polypeptide-related sequence A" or "Human Major Histocompatibility Complex class I polypeptide-related sequence A") were used to search literature from these 3 databases (Supplemental Table 1, http://links.lww.com/MD/C877).

2.3. Literature selection

A study was included in the meta-analysis if it satisfied the following criteria: information involved genotype and allele frequencies of rs2596542 in virus-induced liver cirrhosis, chronic hepatitis C or B, and HCC; case–control studies; there is sufficient data to calculate the odds ratio (OR) and the corresponding 95% confidence interval (95% CI); study with the higher quality and more comprehensive outcomes in repeatedly published studies; and English literature. Exclusion criteria include exclusion of letters, notes of conference meetings, reviews, and so on; exclusion of data cannot be extracted. In the case of multiple studies with the same or overlapping data published by the same researchers, we selected the most recent study with the largest number of participants.

All of retrieved literatures were stepwise screened from the title, abstract, and full text according to the preset inclusion and exclusion criteria. Two investigators were assigned and asked to conduct this work at the same time. If there were inconsistencies in the discussion reported, then the third investigator was assigned for their feedback and their opinion about the literature selection for present meta-analysis review paper.

Literature searches and identification of eligible articles based on the inclusion criteria were carried out independently by 2 authors. Then each of these authors independently extracted data about the first author's name; year of publication; country of origin; ethnicity, numbers, and genotypes of cases and controls; source of controls (hospital- or population-based); frequency of T allele; genotyping method; and Hardy–Weinberg equilibrium (HWE) of controls and the discrepancies were resolved by consensus.

2.4. Statistical analysis

The outcomes of this meta-analysis were binary variables, referred to the susceptibility analysis of MICA rs2596542 polymorphisms for HCC development, and were combined from OR and 95% CI. The heterogeneity between different studies was examined using a $\chi^2 Q$ test and I^2 index. When the Q test showed significant heterogeneity ($P < .10$ and/or $I^2 > 50\%$), a random-effect model was performed. Otherwise, the fixed-effect model was preceded.

The HWE in the control population was judged by χ^2 test. A $P < .05$ was considered to be an unbalanced state. Publication bias was diagnosed by Egger linear regression method and funnel plot. A $P < .05$ in the Egger linear regression indicated the potential publication bias. An asymmetric or incomplete funnel diagram also shows publication bias. To assess the sensitivity (stability) of results in this meta-analysis, we compared the differences between the combined effects through removing the included studies one by one. Reversed results after elimination were considered as unstable. Statistical analyses were conducted using RevMan 5.3 software. Publication bias was assessed by Begg funnel plots. P value of Begg test was performed by STATA (version 11.0). All P values were calculated through bilateral test.

3. Results

3.1. Description of studies

A total of 236 potentially relevant publications up to January 17, 2019 were systematically identified through PubMed, Web of Science, and Embase databases. Of these, 215 (90%) were excluded because they did not satisfy the inclusion criteria, or they failed to provide sufficient information to determine whether the criteria were satisfied. Two articles reporting a relationship between the rs2596542 polymorphisms in MICA gene and chronic hepatitis B[9,13] were excluded because the participants in this article did not have HCC. One study that did not report sufficient information about gene polymorphism was also excluded.[14] Two publications had the same first author and were based on the same participants with HCC, so they were considered as one study.[15–16] The articles by Hai et al involved 2 independent case–control studies and were considered separately.[17] In the end, 14 studies[16–28] were included in this meta-analysis based on our literature search strategy and inclusion criteria (PRISMA Flow Diagram).

We established a database according to the information extracted from each of this study. Detailed characteristics of the 14 studies are listed in Table 1. Overall, 4,900 HCC cases and 19,519 controls were retrieved. Subjects of 2 studies were from Italy,[18–19] 4 from China,[16,20–21,25] 5 from Japan,[17,22–23,26] and the other 3 from Swiss,[24] Egypt,[27] and Germany,[28] respectively. All studies had a case–control design. The distribution of genotypes among controls showed HWE in all of these included studies.

Six studies[18,21,23,25,27–28] included a healthy control population (population-based control) and these 6 studies involved a total of 1035 HCC cases and a total of 4149 healthy controls. The number of cases in the hospital-based control was 4639. Of the total number of 19,519 control subjects considered in this meta-analysis, 15,370 (78.7%) were with cirrhosis and/or infected with HBV or HCV.

3.2. Test of heterogeneity

Table 2 shows the relationship between the rs2596542 polymorphisms in MICA and the development of HCC risk. The statistical heterogeneity of rs2596542 polymorphisms in MICA allelic contrast, homozygote comparison, and dominant

Table 1

Main characteristics of all studies included in the meta-analysis.

Study	Country	Genotyping method	Source of control	Cases/Controls	No. of cases			No. of controls		
					CC	CT	TT	CC	CT	TT
Augello 2018	Italy	PCR-RFLP	LC and healthy	154/337	37	64	49	71	183	81
Burza 2016	Italy	PCR-RFLP	LC	192/199	56	91	45	66	98	35
Chen 2013	China	TaqMan	CHB	506/772	264	200	42	425	293	54
Huang 2017	China	TaqMan	CHC	58/647	31	19	8	329	273	45
Jiang 2011	China	PCR-RFLP	Healthy	141/141	64	49	28	76	38	27
Li 2016	China	PCR-RFLP	Healthy	120/124	48	57	15	65	52	7
Hai 2017a	Japan	TaqMan	CHC	142/575	57	58	27	246	269	60
Hai 2017b	Japan	TaqMan	CHC	115/523	48	45	22	250	223	50
Kumar 2011	Japan	PCR-RFLP	CHC	1394/5486	543	486	365	2950	1478	1058
Kumar 2012	Japan	PCR-RFLP	CHB and healthy	407/6356	42	159	206	699	2733	2924
Lo 2013	Japan	PCR-RFLP	CHC and LC	1394/1629	558	660	176	850	681	98
Lange 2013	Swiss	PCR-RFLP	CHC	64/1860	6	24	34	253	871	736
Mohamed 2017	Egypt	PCR-RFLP	LC and healthy	47/94	6	32	9	28	51	15
Tong 2013	Germany	PCR-RFLP	CHB, LC and healthy	166/776	62	74	27	344	350	82

CHB = chronic hepatitis B, CHC = chronic hepatitis C, LC = liver cirrhosis, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

and recessive genetic models was analyzed for all 14 studies. Statistically significant heterogeneity was observed in all studies for the total population and the Asia ethnic subgroup. Therefore, random-effect models were used to analyze the OR.

3.3. Quantitative data synthesis

Table 2 shows the summary ORs for the rs2596542 polymorphisms in MICA and HCC risk on the basis of 4,900 HCC cases and 19,519 controls. We observed an association between rs2596542 polymorphisms in MICA and HCC risk in the total population based on all 14 studies. Given the ethnic differences in the allele frequency of this sequence variant, we evaluated the effect of the rs2596542 polymorphisms in MICA separately in the Asia and in the Europe. Moreover, the subgroup analyses based on the source of control groups were also performed.

Calculation of overall OR in the total population using the random-effect model showed that the rs2596542 polymorphisms in MICA was strongly associated with decreased risk of HCC based on allelic contrast (OR = 0.76, 95% CI = 0.69–0.83, $P < .001$; $I^2 = 60\%$) (Fig. 1), homozygote comparison (OR = 0.57, 95% CI = 0.48–0.69, $P < .001$; $I^2 = 48\%$) (Fig. 2), and the recessive genetic model (OR = 0.77, 95% CI = 0.65–0.91, $P < .001$; $I^2 = 71\%$) (Fig. 3). The association of the rs2596542 polymorphisms in MICA with HCC risk was also observed in the total population using the dominant genetic model (OR = 1.57, 95% CI = 1.36–1.81, $P < .001$; $I^2 = 42\%$) (Fig. 4). Moreover, the subgroup analyses based on the ethnic or the source of control groups were also found similar findings (Table 2).

Table 2

Overall and stratified meta-analyses of the association between rs2596542 polymorphisms in major histocompatibility complex class I-related chain A and risk of hepatocellular carcinoma.

Genotype comparison	OR [95% CI]	Z (P)	Heterogeneity of study design			Analysis model
			χ^2	df (P)	I^2 (%)	
Total (4,639 cases, 19,254 controls)						
C-allele vs T-allele	0.76 [0.69–0.83]	13.18 (<.001)	32.27	13 (.002)	60	Random
CC vs TT	0.57 [0.48–0.69]	6.16 (<.001)	24.89	13 (.02)	48	Random
CC vs CT + TT	0.77 [0.65–0.91]	3.04 (<.001)	37.72	11 (<.001)	71	Random
TT vs CT + CC	1.57 [1.36–1.81]	6.29 (<.001)	22.44	13 (.05)	42	Random
Subgroups						
Asian (4,277 cases, 16,253 controls)						
C-allele vs T-allele	0.75 [0.66–0.85]	12.83 (<.001)	27.50	8 (<.001)	71	Random
CC vs TT	0.56 [0.45–0.70]	5.02 (<.001)	21.12	8 (.007)	62	Random
CC vs CT + TT	0.74 [0.62–0.88]	3.38 (.007)	28.14	8 (<.001)	72	Random
TT vs CT + CC	1.61 [1.32–1.96]	4.65 (<.001)	21.82	8 (.005)	63	Random
European (623 cases, 3266 controls)						
C-allele vs T-allele	0.79 [0.69–0.90]	3.40 (<.001)	2.25	4 (.69)	0	Fixed
CC vs TT	0.63 [0.48–0.84]	3.16 (.002)	2.70	4 (.61)	0	Fixed
CC vs CT + TT	0.80 [0.65–1.00]	1.97 (.05)	6.17	4 (.19)	35	Fixed
TT vs CT + CC	1.54 [1.22–1.93]	3.70 (<.001)	0.61	4 (.96)	0	Fixed
Healthy control (1035 cases, 4149 controls)						
C-allele vs T-allele	0.84 [0.76–0.94]	3.05 (.002)	6.22	5 (.29)	20	Fixed
CC vs TT	0.77 [0.61–0.97]	2.20 (.03)	5.36	5 (.37)	7	Fixed
CC vs CT + TT	0.86 [0.71–1.03]	1.68 (.09)	5.79	5 (.33)	14	Fixed
TT vs CT + CC	1.27 [1.08–1.50]	2.85 (.004)	3.21	5 (.67)	0	Fixed

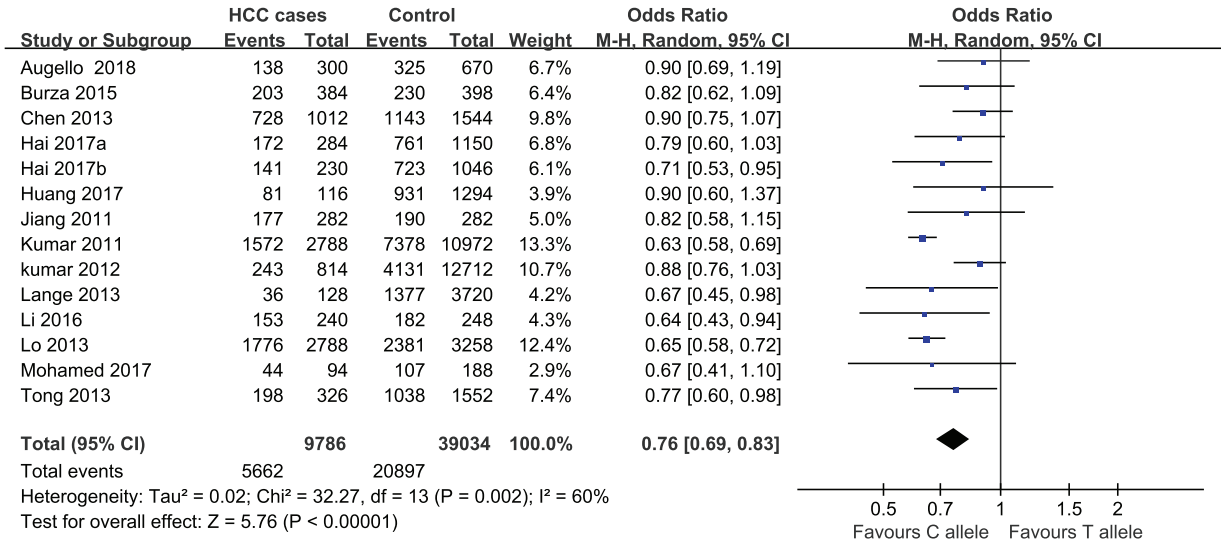

Figure 1. Meta-analysis of the association of the rs2596542 polymorphisms in MICA with HCC risk in the total population using the allelic contrast.

3.4. Sensitivity analysis and publication bias

The results were not altered after excluding studies one by one based on allelic contrast (Supplemental Fig. 1 to 14, http://links.lww.com/MD/C877), homozygote, dominant, or recessive genetic model comparison. Publication bias was assessed by Begg funnel plots. The shape of the funnel plots appeared to be asymmetrical for allele contrast, homozygous comparison, and recessive and dominant genetic models, suggesting the presence of publication bias (Fig. 5). All *P* values of Begg test performed by STATA were <0.001 for allele contrast, homozygous comparison, recessive, and dominant genetic models.

4. Discussion

HCC involves complex, heterogeneous, and multistep malignant tumorigenesis.[29–30] The development of HCC involves the host and environmental factors, as well as the modulation of molecular signaling pathways that were implicated in malignant transformation of hepatocytes and tumor progression.[31] Moreover, populations show large variability in single-nucleotide polymorphisms frequencies.

This systematic review included 14 studies involving 4,900 HCC cases and 19,519 controls. The results of these 14 studies were inconsistent about the association of polymorphism of rs2596542C/T and development of HCC, which may be attributed to ethnicity-related variations. Our meta-analysis based on the total population found the T allele and the TT genotype of MICA rs2596542 polymorphism could raise the risk of an onset of HCC developments it was correlated with the occurrence of HCC. Collectively, the higher frequency of rs2596542 CC genotype in healthy or liver cirrhosis controls compared with HCC arms suggests a protective role of CC

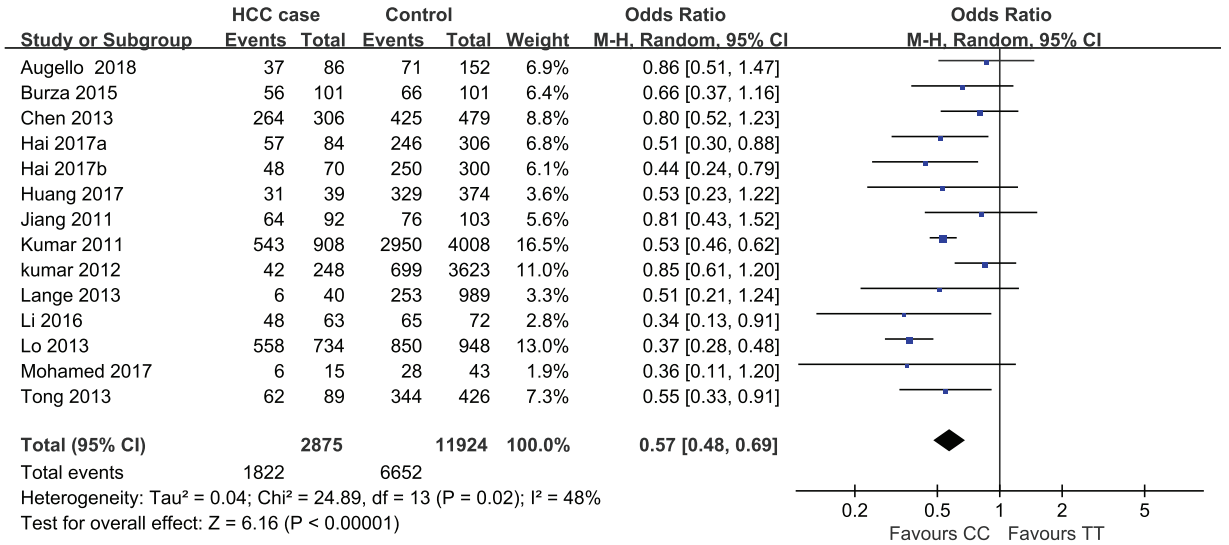

Figure 2. Meta-analysis of the association of the rs2596542 polymorphisms in MICA with HCC risk in the total population using the homozygote comparison.

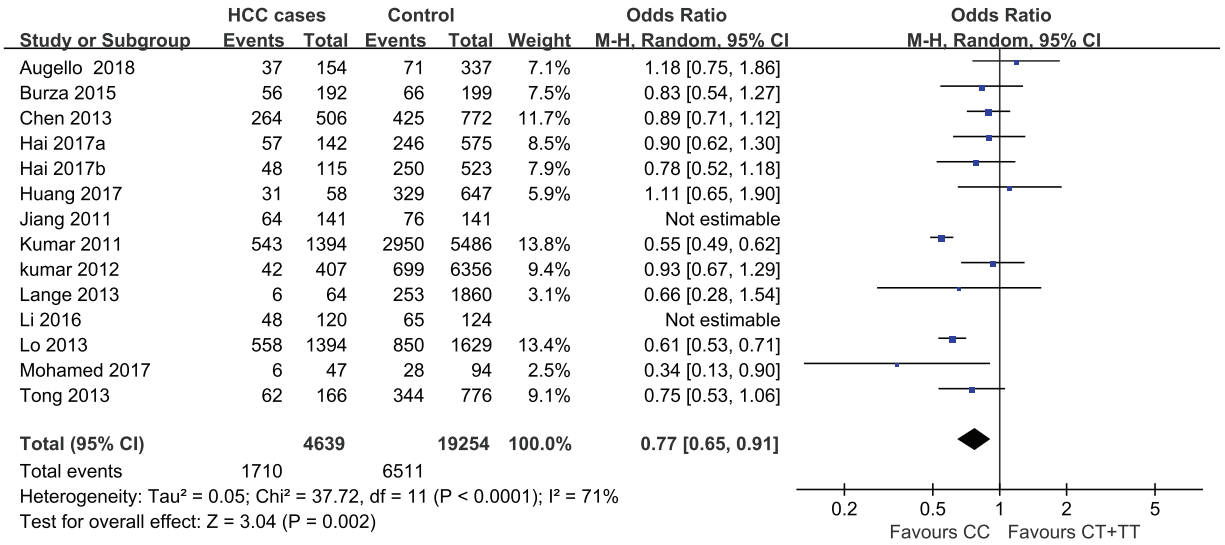

Figure 3. Meta-analysis of the association of the rs2596542 polymorphisms in MICA with HCC risk in the total population using the recessive genetic model.

genotype against the development of HCC. Moreover, the subgroup analyses based on the ethnic or the source of control groups were found similar findings.

Even the molecular mechanism by which single-nucleotide polymorphisms in MICA region are associated with HCC occurrence remains unknown, polymorphism in the MICA gene has been significantly associated with risk of various malignancies,[10–12] including the development of HCC.[16–28] The expression of MICA is induced by several stress factors including viral infections.[32] MICA belongs to the nonclassical class I family. It is a membrane protein that acts as a ligand for NKG2D to initiate antitumor effects through natural killer cells and $CD8^+$ T cells to eliminate virus-infected cells.[32] MICA is released into the serum via cleavage at the transmembrane domain by matrix metalloproteinases.[33–34] Previous studies found that the expression levels of soluble MICA (sMICA) are significantly increased in the serum of patients with HCC and chronic liver diseases.[35–36] Moreover, the level of sMICA in patients with chronic liver disease was higher than that of healthy populations.[22,35–36]

MICA protein is expressed on the surface of tumor cells. The membrane-bind MICA protein on the surface of tumor cells can bind to NKG2D as a tumor antigen and causes activation of natural killer cells and $CD8^+$ T cells, resulting in an antitumor response.[37] In addition, the stress response induced by HBV/HCV infection may be accompanied by the upregulation of matrix metalloproteinases expression, resulting in the shedding a light of MICA protein from the cell membrane to sMICA.[38] The production of sMICA may cause a decrease in MICA expression on the cell surface, leading to a decrease in immunostimulatory signals of cytotoxic lymphocytes.[33] In addition, sMICA production suppresses the antitumor effects of immune cells. These may be the mechanisms of MICA and the occurrence of HCC.

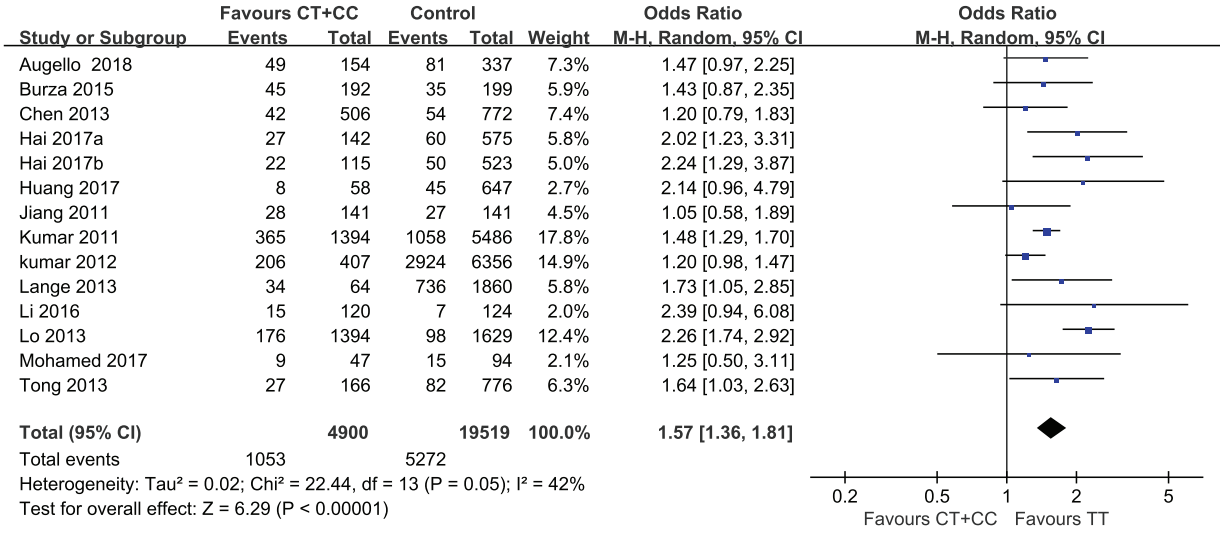

Figure 4. Meta-analysis of the association of the rs2596542 polymorphisms in MICA with HCC risk in the total population using the dominant genetic model.

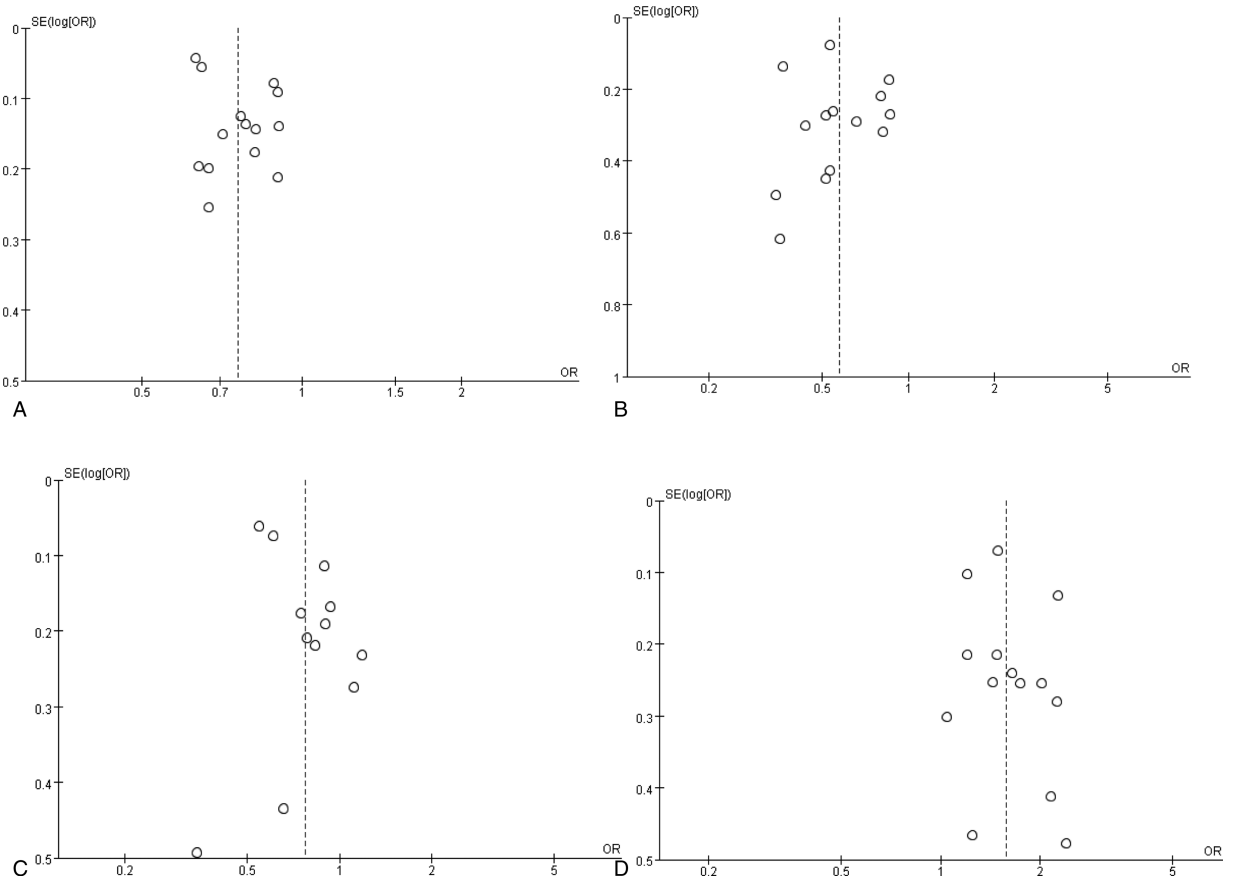

Figure 5. Publication bias: (A) allele contrast; (B) homozygous comparison; (C) recessive genetic models; (D) dominant genetic models.

Results based on the total population and subgroup analyses based on the ethnic or the source of control groups found that T allele of MICA rs2596542 polymorphism is a risk factor of HCC occurrence. Due to included studies involving the healthy controls and different type of liver diseases, such as liver cirrhosis, CHB, and CHC, our results should be interpreted with caution. The impacts of the MICA rs2596542 variant on a particular stage during liver disease progression need to be investigated. Some studies on HCV-related HCC have reported that the MICA rs2596542 variant influences the HCC disease progression from chronic hepatitis.[16–17] Studies on HBV-related HCC also found that MICA polymorphisms were associated with HBV-related HCC and HBV persistence,[20,28] but not from chronic hepatitis B to cirrhosis or from other early stages of HBV infection to liver cirrhosis. Such findings may imply that the effect of MICA rs2596542 variant is an independent of viral factors in liver disease progression. About the association between MICA rs2596542 variant and HCC outcomes, Mohamed et al[27] found that there was no significant association between MICA rs2596542 variant and clinical parameters such as liver enzymes, total bilirubin, alpha fetoprotein, platelets, tumor size, and serum creatinine. Moreover, others also found that MICA rs2596542 variant did not correlate with HCC recurrence following hepatic resection.[39]

Some other limitations of this study also should be considered. Although we systematically searched MEDLINE and EMBASE databases, the number of included studies was still relatively small. Moreover, the results may be affected by additional confounding factors, such as age or sex, tumor status, but most studies either did not report these baseline data or aggregated them in different ways, making it impossible to include them into pooled analysis. And third, publication bias is also a limitation.

In conclusion, this study gives thorough data in regard to the occurrence of HCC and MICA rs2596542 C/T variant. It revealed that possession of T allele of MICA variants leads to an increased risk of chronic liver disease progression. Therefore, MICA rs2596542 C/T genotype could be potential biomarkers for liver disease progression.

Author contributions

X-JK and Z-LD conceived and designed the study. X-JK, D-CM, and YQ searched the literature and extracted data. X-JK and D-CM performed statistical analyses. All authors wrote and reviewed the manuscript.

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Writing – review and editing: Bhavesh K. Ahir.

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