Association of MBOAT7-TMC4 rs641738 with the risk of hepatocellular carcinoma and persistent infection of hepatitis B virus: a case-control study and meta-analysis

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Research article

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Abstract

Background: Recent studies reported that a hot genetic variant, rs641738 within the membrane bound O-acyltransferase domain containing 7(MBOAT7) and transmembrane channel-like 4 (TMC4) , was associated with several liver diseases. However, results are still conflicting. We conducted this study to explore the role of MBOAT7-TMC4 rs641738 in the risk of hepatocellular carcinoma (HCC) and persistent hepatitis B virus (HBV) infection.

Methods: We first performed a case-control study by including 779 HCC cases and 1412 cancer-free controls. Controls are consisted of 678 HBV persistent carriers and 734 spontaneously recovered subjects. Rs641738 was genotyped by MassARRAY platform. Results were analyzed by multivariate logistic regression analysis under five genetic models. Second, we conducted a systematic review and meta-analysis to further explore the role of this variant in HCC risk.

Results: Results suggested no association between MBOAT7-TMC4 rs641738 and HCC risk in most genetic models (All P > 0.05), although a marginally significant association was observed in TT vs. CC (P = 0.037) and recessive model (P = 0.044). Further meta-analysis including 2135 HCC cases and 4388 controls supported that this variant was not related to HCC risk, even in the TT vs. CC and recessive models. Besides, we identified that this variant also had no influence on persistent HBV infection. Conclusion: Our work highlights that MBOAT7-TMC4 rs641738 is not associated with the risk of HCC or persistent HBV infection. This study provides some clues to identify the “truth” of potential disease-related genetic factors in the post-genome era.

Background

Hepatocellular carcinoma (HCC) is a common cancer with rapid progress and high mortality in the world, especially in China [1]. As the fourth common cancer in China, it was estimated to have 466100 new cases in 2015[2]. Environmental factors such as infection of hepatitis B virus (HBV) are confirmed to be a crucial pathogenesis of HCC[3]. Increasing evidence has revealed that genetic factors also play an important role in the development of HCC [4].

HCC is a complicated disease with high genetic heterogeneity. Candidate gene researches and genome-wide association studies (GWASs) have found hundreds of genes and loci associated with HCC risk. How to identify the “truth” of these genetic factors is becoming an urgent issue in the post-genome era. In 2015, a GWAS study reported a genetic variant near the *membrane bound O-acyltransferase domain containing 7(MBOAT7)* gene, rs641738, C>T, increasing the risk of alcohol-related cirrhosis [5]. Later it is also reported to be located in the *transmembrane channel-like 4 (TMC4)* gene. In 2016, Thabet demonstrated that *MBOAT7-TMC4* rs641738 could be a risk factor of hepatic inflammation and liver fibrosis[6]. Subsequent studies further investigated the association between this variant and HCC risk, but led to a conflicting conclusion [7–9].

Here, we first conducted a case-control study including 779 HCC cases and 1412 cancer-free controls, aiming to explore the effects of *MBOAT7-TMC4* rs641738 on HCC risk in a Chinese population. Then we performed a systematic review and meta-analysis to further explore the role of this variant and validate our results.

Methods

Study Subjects

This case-control study included 779 HCC cases and 1412 cancer-free controls. Cases were pathologically confirmed and enrolled between January 2014 and June 2016 at Tongji Hopital of Huazhong University of Science and Technology (HUST), central China. Controls are consisted of 678 hepatitis B virus (HBV) persistent carriers and 734 spontaneously recovered subjects, who were recruited from a health screening in the same hospital during the same period as the cases were included. HBV persistent carriers were people who were positive for both of HBsAg and HBcAb, but negative for anti-HCV. Spontaneously recovered subjects were people who were negative for both of HBsAg and anti-HCV, but positive for both of HBcAb and HBsAb. All subjects were unrelated Han Chinese from Wuhan and the surrounding regions. Cases and controls were frequency-matched for sex and age. At recruitment, a 2-ml peripheral blood sample and a written informed consent were collected from each subject, and demographic information (i.e., sex, age, smoking and drinking status) were also obtained by questionnaire. Definitions of smoking and drinking status have been detailed previously [10, 11]. This study was approved by the institutional ethics committee of Tongji Hospital, Tongji Medical College of HUST.

Serological Testing

Enzyme-linked-immunosorbent assay (ELISA) was applied to detect serum HBsAg, HBsAb, HBcAb and anti-HCV (IMX; Abbott Diagnostics, USA). There were three positive controls, two negative controls and one blank control in each reaction plate. About 5% of the samples were randomly chosen for repetition, and results were 100% concordant.

Genotyping

Genomic DNA was extracted from leucocyte pellets of 2-ml peripheral blood by the coagulated blood DNA mini-extraction kit (DP6101, BioTeke Corporation, China). *MBOAT7-TMC4* rs641738 was genotyped by the Sequenom MassARRAY iPLEX Platform (SEQUENOM, CA, USA). All assays were conducted using 384-well plate with positive and negative controls for each plate, without the information of the disease status of samples. We randomly selected 5% of the samples as duplicate sets, and got a 100% concordance rate. The average call rate of this variant was 99.7%.

Statistical Analysis

A goodness-of-fit χ^2 test was applied to assess the Hardy-Weinberg equilibrium (HWE) in controls. Differences between cases and controls are examined by independent t test, ANONVA analysis or Pearson's χ^2 test according to the category of variables. The risk of HCC or HBV persistent infection was estimated by odds ratio (OR) and 95% confidence interval (CI), using a multivariate logistic regression analysis after adjusting for age, sex, smoking and drinking status. A two-tailed *P* value < 0.05 was considered statistically significant. All the analyses above were performed by IBM SPSS Statistics version 20.0 (Chicago, IL, USA). In addition, we calculated the statistical power of this study by Power V3.0[12]. Based on our sample size to detect an OR of 1.30, a power of 0.95 was estimated for *MBOAT7-TMC4* rs641738.

Meta-analysis

This meta-analysis was performed according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA)[13].

Literature search, Study Selection and Data Extraction

A comprehensive literature search was conducted through PubMed, Embase and Web of Science up to August, 2019 without any restrictions. The search items included "*MBOAT7*",, "*TMC4*",, "rs641738", and "hepatocellular carcinoma". References from identified publications were also reviewed for obtaining potential relevant studies.

The inclusion criteria was as follows: (1) a case-control or cohort study to evaluate the association between *MBOAT7-TMC4* rs641738 and HCC risk, and (2) providing ORs and 95%CIs, or allele frequency and/or genotypes of this variant. A study was excluded if it met one of the following criteria: (1) review, meta-analysis, comment or conference abstract; (2) insufficient data to estimate OR and 95%CI; (3) a deviation from HWE in controls; and (4) studies with overlapped data. If a study contained overlapped data with another, we kept the one with larger sample size.

Data was extracted from each included study as follows: first author, publication year, country, ethnicity, gender, age, sample size, genotype distribution, genotyping method, adjustment, and HWE information. Two authors independently conducted the work above. Disagreement was resolved by discussion. The quality of each included study was evaluated by the Newcastle-Ottawa scale (NOS)[14]. Quality evaluation was not an exclusion criterion for eligible studies (Additional file 1).

Statistical Analysis for Meta-analysis

We used ORs and 95%CIs to estimate the association between *MBOAT7-TMC4* rs641738 and HCC risk. Multivariate-adjusted OR and 95%CI was preferentially extracted if available, otherwise unadjusted OR and 95%CI was calculated instead. Between-study heterogeneity was examined by Q test and I^2 statistic. If $P < 0.10$ or $I^2 > 50$ %, it was considered a significant heterogeneity and applied the random-effects model; otherwise the fixed-effects model was used. To evaluate the quality, we also performed the sensitivity analysis and publication test [15, 16]. The meta-analysis was conducted via Stata 12.0 software (College Station, TX, USA).

Results

Subject Characteristics

A total of 779 HCC cases, 678 HBV persistent carriers and 734 spontaneously recovered subjects were included in this study. Demographic characteristics are summarized in Table 1. In these three groups, the male proportion of the three groups was 70.6%, 68.7% and 68.1%, respectively; and the mean age was 53.20 ± 12.49, 52.27 ± 11.45 and 52.28 ± 12.89 years, respectively. There was no significant difference among the three groups on sex (P = 0.551), age (P = 0.240), smoking (P = 0.071) and drinking status (P = 0.091). Genotypes of *MBOAT7-TMC4* rs641738 in all groups did not deviate from HWE (HCC: P = 0.485; HBV persistent carriers: P = 0.133; spontaneously recovered subjects: P = 0.769).

Association of *MBOAT7-TMC4* rs641738 with Risk of HCC and Persistent HBV Infection

We performed four comparisons under five genetic models and showed the results in Table 2. In the comparison of HCC cases vs. all controls, we found that after adjusting for sex, age, smoking and drinking status, *MBOAT7-TMC4* rs641738 did not confer any increased risk of HCC risk in dominant, additive or allelic model (All P > 0.05). Although this variant seemed a risk factor of HCC in two models, the results were marginally significant (TT vs. CC: P = 0.037; Recessive: P = 0.044). Similar results were also observed in the further comparison of HCC vs. HBV persistent carriers. When we set spontaneously recovered subjects as controls, we observed that *MBOAT7-TMC4* rs641738 was not associated with HCC risk (All P > 0.10). To explore whether this variant influences the risk of persistent HBV infection, we conducted a further comparison between HBV persistent carriers and spontaneously recovered subjects. Results suggested that this variant was also unrelated to persistent infection or clearance of HBV (All P > 0.30).

Meta-analysis of the Association between *MBOAT7-TMC4* rs641738 and HCC Risk

In addition, we conducted a systematic review and meta-analysis to further examine our results. Initially, we got 87 records by searching PubMed, Embase and Web of Science, and excluded 79 records by title and abstract review. After assessing the full-text articles, we further excluded five studies due to deviation from HWE (n = 1)[9], insufficient data to estimate ORs (n = 1)[17], or having overlapped data (n = 3)[18–20]. Finally, we included three eligible articles [6–8] and this study for meta-analysis (Additional file 2).

A total of 2135 HCC cases and 4388 controls were included. Characteristics are detailed in Table 3. We first applied a meta-analysis under the allelic model (Figure 1). Pooled results demonstrated that *MBOAT7-TMC4* rs641738 was not associated with HCC risk (OR = 1.10, 95%CI = 0.99–1.23, $P_{hetergeneity}$ = 0.453, I^2 = 0%), which was stable suggested by the sensitivity analysis (Additional file 3). Egger's or Begg's test did not suggest any publication bias. Considering that marginally significant results were observed in our study, we further applied meta-analyses in the TT vs. CC and recessive models. As shown in Table 4, pooled results in these models also consistently and stably showed that there was no association between *MBOAT7-TMC4* rs641738 and HCC risk.

Discussion

In this study, we conducted a case-control study including 799 HCC cases and 1412 controls to investigate the effect of *MBOAT7-TMC4* rs641738 on HCC risk. Although this variant showed a marginally significant association in TT vs. CC (P = 0.037) and recessive model (P = 0.044), the other genetic models all demonstrated non-significant results. We further performed a systematic review and meta-analysis to explore the role of *MBOAT7-TMC4* rs641738 in the susceptibility to HCC. A total of 2135 HCC cases and 4388 controls were included. Results consistently suggested that *MBOAT7-TMC4* rs641738 was not associated with HCC risk, even in the TT vs. CC and recessive models. In addition, our study revealed that this variant was also not related to persistent HBV infection in all genetic models. To the best of our knowledge, it is the first study to investigate the association between *MBOAT7-TMC4* rs641738 and the risk of HCC and persistent HBV infection in Asians.

The rs641738 variant is mapped to the 500-bp downstream of *MBOAT7* and likewise located at exon 1 of the *TMC4* gene. Therefore, previous studies refer to it as *MBOAT7* or *MBOAT7-TMC4* variant. This variant was first identified as a risk locus for alcohol-related cirrhosis [5], then reported to be associated with nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) [21] and liver fibrosis

[6]. In 2016, Thabet first investigated the association of *MBOAT7-TMC4* rs641738 with HCC risk, but did not fond a significant result[6]. Subsequently, Donati contradicted the conclusion and showed that this variant predisposed to HCC in NAFLD subjects [9]. However, the significant association was not confirmed by later studies [6–8]. Even in the NAFLD cohort, *MBOAT7-TMC4* rs641738 did not show any association with the risk of Matteoni type 4 or NASH-HCC [17]. Additionally, a recent meta-analysis revealed that this variant was not related to the susceptibility of NAFLD [22]. In view of a small sample size of the previous studies, we performed this case-control and meta-analysis, and finally confirmed that *MBOAT7-TMC4* rs641738 was not associated with HCC risk.

Persistent HBV infection is a crucial risk factors contributing to HCC in China. However, studies about the effect of *MBOAT7-TMC4* rs641738 on HBV infection is limited up to date. Here, we also explored the association between *MBOAT7-TMC4* rs641738 and persistent HBV infection. Results exhibited that this variant was not related to spontaneous clearance of HBV, which was in concordance with a previous report from a Moroccan cohort[23]. Interestingly, Thabet reported that *MBOAT7-TMC4* rs641738 influenced hepatic inflammation and fibrosis in patients with persistent HBV infection [24]. A possible explanation is that this variant's effect on liver disease is not associated with HBV, or it is not the causal variant.

Nowadays, the role of *MBOAT7-TMC4* rs641738 in liver diseases is still conflicting. *MBOAT7* encodes a lysophosphatidylinositol acyltransferase involved in phospholipid metabolism. *TMC4* encodes a member protein of the calcium-dependent chloride channels, which are widely expressed in epithelia of many tissues, and exist in both plasma membrane and intracellular compartments [25]. Some studies showed that rs641738 reduced mRNA and hepatic MBOAT7 expression, but some studies refuted it[9, 24, 26]. Similar contradictions are also reported in fibrosis and NAFLD[23, 24, 26]. In fact, the exact biological mechanisms of *MBOAT7* and *TMC4* on liver diseases remain elusive. So whether and how *MBOAT7-TMC4* rs641738 influences liver diseases is doubtful. Nonetheless, our study and a recent meta-analysis support that this variant is not associated with the risk of HCC and NAFLD, respectively.

There are some limitations in our study. First, this is a hospital-based case-control study, which might be influenced by selection bias. However, our multivariate analysis, power calculation and subsequent meta-analysis ensured accuracy of our conclusion. Second, our meta-analysis only included four studies due to limited number of relevant studies, which were not performed further stratified analyses according to factors including age, sex, smoking or other lifestyle habits. Even so, the results of meta-analysis were reliable because of robustness, no publication bias and low heterogeneity.

Conclusion

In summary, our case-control study and meta-analysis highlight that *MBOAT7-TMC4* rs641738 is not associated with HCC risk. Besides, our work also suggests no relationship of this variant with persistent HBV infection in a Chinese population. Further studies are required to validate our results.

Abbreviations

MBOAT7, membrane bound O-acyltransferase domain containing 7; TMC4, transmembrane channel-like 4; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; GWAS, genome-wide association study; HUST, Huazhong University of Science and Technology; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analyses; NOS, Newcastle-Ottawa scale; SD, standard deviation; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional ethics committee of Tongji Hospital, Tongji Medical College of HUST (Wuhan, China). All procedures were in accordance with the approved guidelines and principles of Helsinki Declaration and its later amendments or comparable ethical standards of 1975. All participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are available from the corresponding author upon reasonable request. But those clinical data are not available for authors have an ethical and legal responsibility to respect participant's rights to privacy and to protect their identity.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PW finished the main part experiment and data analysis, and drafted this manuscript; YZ and YG finished the sample collection. YZ, LL and YG finished the literature search and selection. LL and RZ did part of the data collection and analysis. NS designed the project and reviewed the manuscript. LL and NS acquired the funding. All authors have read and approved this manuscript.

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Tables

Table 1. The characteristics of the included subjects

riables	HCC, N (%)	HBV persistent carriers, N (%)	Spontaneously recovered subjects, N (%)	χ^2/F	*P*
al	779	678	734		
x				1.191	0.551
Male	550 (70.6)	466 (68.7)	500 (68.1)		
Female	229 (29.4)	212 (31.3)	234 (31.9)		
e (mean ±)	53.20 ± 12.49	52.27 ± 11.45	52.28 ± 12.89	1.428	0.240
oking status				5.280	0.071
Smokers	301 (38.6)	243 (35.8)	242 (33.0)		
Non-smokers	478 (61.4)	435 (64.2)	492 (67.0)		
nking status				4.803	0.091
Drinkers	270 (34.7)	265 (39.1)	291 (39.6)		
Non-drinkers	509 (65.3)	413 (60.9)	443 (60.4)		

Table 2. The effects of *MBOAT7-TMC4* rs641738 on persistent HBV infection and HCC

es	HCC, N (%)	HBV persistent carriers, N (%)	Spontaneously recovered subjects, N (%)	Adjusted OR (95% CI), P^a	Adjusted OR (95% CI), P^b	Adjusted OR (95% CI), P^c	Adjusted OR (95% CI), P^d
	426 (54.7)	380 (56.1)	420 (57.7)	Reference	Reference	Reference	Reference
	295 (37.9)	264 (39.0)	264 (36.3)	1.05 (0.87-1.27), 0.604	1.00 (0.82-1.24), 0.981	1.10 (0.89-1.37), 0.370	1.11 (0.89-1.38), 0.366
	58 (7.4)	33 (4.9)	44 (6.0)	1.47 (1.02-2.12), 0.037	1.64 (1.04-2.57), 0.033	1.35 (0.89-2.05), 0.164	0.85 (0.53-1.36), 0.491
nt				1.10 (0.92-1.32), 0.280	1.07 (0.87-1.32), 0.541	1.14 (0.93-1.40), 0.219	1.07 (0.87-1.32), 0.529
ve				1.44 (1.01-2.06), 0.044	1.64 (1.05-2.55), 0.029	1.29 (0.86-1.95), 0.218	0.81 (0.51-1.29), 0.383
				1.13 (0.98-1.31), 0.094	1.13 (0.95-1.33), 0.172	1.13 (0.96-1.34), 0.138	1.02 (0.85-1.21), 0.851
nodel (T				1.13 (0.98-1.30), 0.095	1.12 (0.95-1.33), 0.175	1.14 (0.96-1.34), 0.135	1.02 (0.86-1.21), 0.853

[a] HCC vs. (HBV persistent carriers + spontaneously recovered subjects), adjusted for sex, age, smoking and drinking status.

[b] HCC vs. HBV persistent carriers, adjusted for sex, age, smoking and drinking status.

[c] HCC vs. spontaneously recovered subjects, adjusted for sex, age, smoking and drinking status.

[d] HBV persistent carriers vs. spontaneously recovered subjects, adjusted for sex, age, smoking and drinking status.

Table 3. The characteristics of the included studies

	Country	Ethnicity	Male, N (%)	Age (mean ± SD or mean [25th, 75th percentile])	Cases/ Controls	Genotype (CC/TC/TT)		Genotyping method	Adjustment	HWE	NOS score
						Case	Control				
t)	Multi-country	Caucasian	Case: NA; Control: 1101 (64.5)	Case: NA; Control: 44.9 (38-52)	75/1706	24/35/16	16/531/822	TaqMan	Age, gender, BMI and Child-Pugh score	0.288	9
el)	Switzerland	Mixed	Case: 679 (90); Control: 817 (70)	Case: 61 ± 10; Control: 55 ± 10	751/1165	203/363/185	185/314/583	TaqMan	Age, gender, BMI, and type II diabetes mellitus	0.934	7
yot)	Thailand	NA	Case: 424 (0.8); Control: 77 (73.3)	HBV-HCC: 62.1 ± 7.8, HCV-HCC: 62.2 ± 7.5, NBNC-HCC: 63.3 ± 9.3; Control: 50.7 ± 4.6	530/105	279/213/38	38/66/34	TaqMan	No	0.818	6
	China	Chinese	Case: 550 (70.6); Control: 966 (68.4)	Case: 53.2 ± 12.5; Control: 52.3 ± 12.2	779/1412	426/295/58	58/800/528	Massary	Age, sex, smoking and drinking status	0.403	7

Table 4. Meta-analysis of the association between *MBOAT7-TMC4* rs641738 and HCC risk under other genetic models

Genetic model	OR (95%CI)	$P_{hetergeneity}$	I^2 (%)	Sensitivity analysis	P_{egg}	P_{begg}
Recessive	1.17 (0.98-1.38)	0.623	0	Stable	0.529	0.734
TT vs. CC	1.18 (0.97-1.43)	0.472	0	Stable	0.548	0.734

Figures

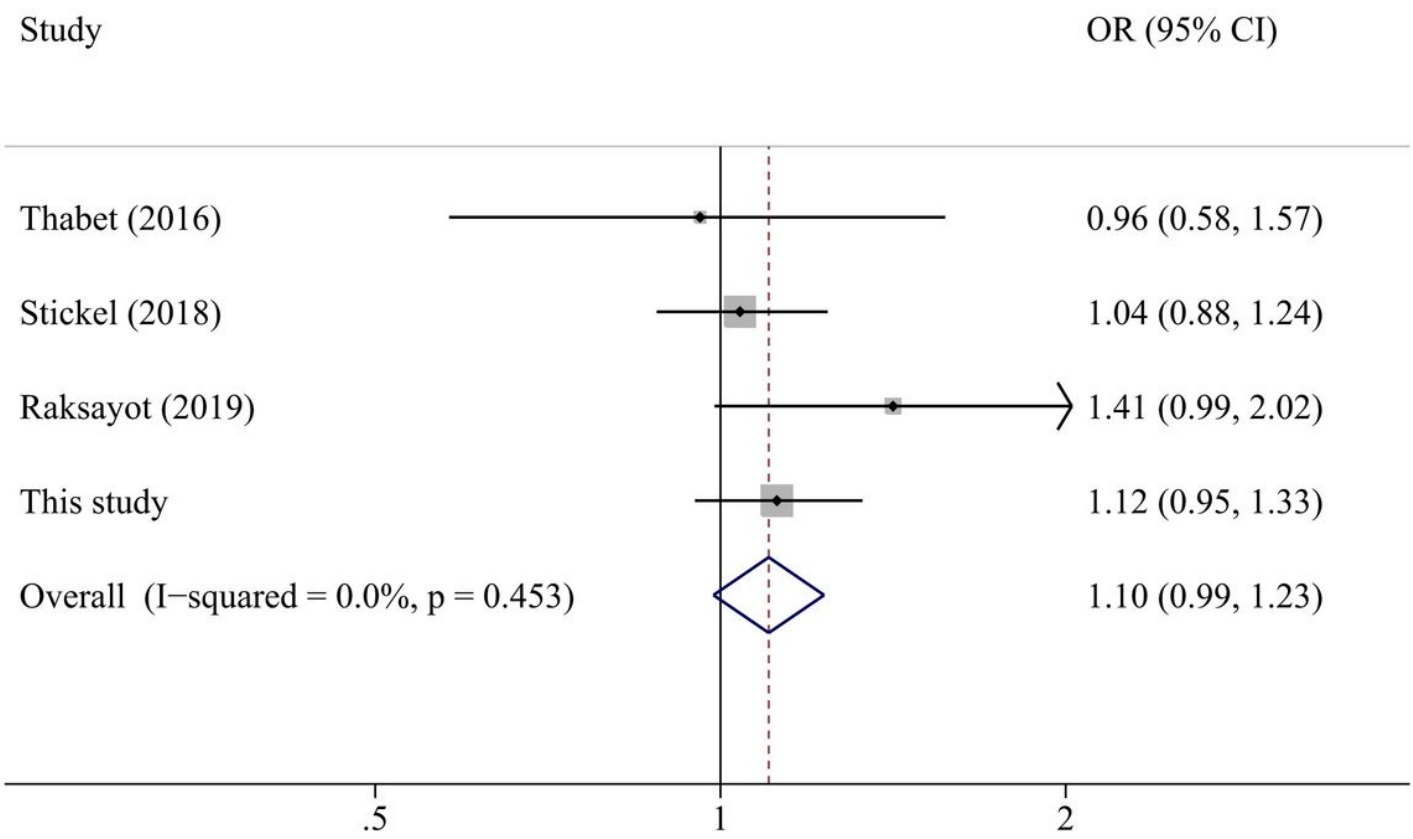

Figure 1

The forest plot of the association between MBOAT7-TMC4 rs641738 and HCC risk under the allelic model.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile3.tif
- Additionalfile1.docx
- Additionalfile2.tif