Systematic Review and Meta-Analysis

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Association of interleukin-6 gene polymorphisms with the risk of hepatocellular carcinoma

An up-to-date meta-analysis

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Abstract

Background: This study was aimed to evaluate the association between interleukin-6 (IL-6) gene polymorphisms and the risk of hepatocellular carcinoma (HCC) in a meta-analysis.

Methods: A literature search was performed for case-control studies published during May, 1993 to May, 2020 focusing on IL-6 gene polymorphisms (–174G > C, –572G > C, and –597G > A) and HCC susceptibility by using PubMed, Cochrane Database, EMBASE, Web of science, and China National Knowledge Infrastructure. From 128 full-text articles, 11 were included in this meta-analysis. I^2 index was used to assess heterogeneity and Newcastle-Ottawa Scale was utilized for quality assessment.

Results: For IL-6 –174G > C polymorphism, in codominant (GG vs CC: odds ratios [OR] = 2.78, 95% confidence intervals [CI] = 1.25–6.19, $P = .01$, $I^2 = 16\%$) and recessive (GG+GC vs CC: OR = 2.76, 95% CI = 1.29–5.90, $P = .009$, $I^2 = 3\%$) models, IL-6 –174G>C polymorphism was significantly associated with the risk of HCC. In dominant (GG vs CC+GC: OR = 1.80, 95% CI = 0.92–3.54, $P = .09$, $I^2 = 86\%$) and allele (G vs C: OR = 1.49, 95% CI = 0.95–2.32, $P = .08$, $I^2 = 68\%$) models, IL-6 –174G>C polymorphism had no impact on the risk of HCC. However, in non-Italian Caucasian population, IL-6 –174G>C polymorphism was significantly related to the occurrence of HCC in both dominant (GG vs CC+GC: OR = 3.26, 95% CI = 2.29–4.65, $P < .00001$, $I^2 = 0\%$) and allele (G vs C: OR = 2.48, 95% CI = 1.48–4.15, $P = .0006$) models. Such correlations also could be observed when healthy individuals were selected as controls. For IL-6 –572G>C and –597G>A polymorphisms, no significant association was observed in all models, regardless of the source of control and population subgroups. No publication bias could be calculated when Begg and Egger tests were employed.

Conclusion: This meta-analysis indicated that IL-6 –174G>C polymorphism was significantly related with the risk for HCC, especially in non-Italian Caucasian population. No significant association was observed for the correlation between IL-6 –572G>C and –597G>A polymorphisms and HCC susceptibility.

Abbreviations: CI = confidence intervals, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, IL-6 = interleukin-6, NOS = Newcastle-Ottawa Scale, OR = odds ratios.

Keywords: hepatocellular carcinoma, interleukin-6, polymorphisms, susceptibility

1. Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cancer and also is the fourth leading cause of cancer-related death worldwide.[1,2] The risk factors for HCC include cirrhosis, hepatitis B virus (HBV) or hepatitis C virus infection, alcohol addiction, metabolic liver disease, and exposure to dietary toxin such as aflatoxins and aristolochic acid.[2] Recently, multi-omics technologies, such as miRNome[3] and proteome,[4] shed new light on the pathogenesis of HCC, which may be beneficial for the diagnosis, prognosis, and treatment of patients with HCC. Current therapeutic options, such as surgery, chemotherapy, liver transplantation, and radiofrequency ablation, only benefits a small percentage of patients. Immunotherapy is an effective and promising treatment approach for HCC. Many studies seek to evaluate the efficacy of immunotherapy, including immune checkpoint inhibitors,[5] cancer vaccines,[6] and adoptive cell transfer,[7] yielding some encouraging results. However, further studies need to focus on overcoming the resistance of immunotherapy.

A persistent, nonspecific, and ineffective activation of the immune system within the chronically inflamed liver is thought to

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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promote carcinogenesis.[8] For example, in a recent study, Toll-like receptor 3 polymorphisms were reported to be a novel risk factor for hepatitis C virus-related HCC.[9] Furthermore, cirrhosis caused by chronic inflammation was present in approximately 80% to 90% patients with HCC.[10] The primary trigger for inflammation which is related with hepatocarcinogenesis is death of epithelial cells, and subsequently multiple inflammatory pathways (e.g., Interleukin [IL]-6, tumor necrosis factor-α, nuclear factor kappa B) contribute to the inflammation-mediated hepatocarcinogenesis.[11]

Interleukin-6 (IL-6) is a multifunctional potent pleiotropic inflammatory cytokine and a major driver of hepatocyte repair and replication, which is also a critical mediator of HCC development.[10] In diethylnitrosamine induced mouse model of HCC, IL-6 was demonstrated to play very critical roles in both malignant transformation of HCC progenitor cells and HCC growth.[8,12] IL-6 can signal through 2 distinct pathways: the IL-6 classic and the IL-6 trans-signaling pathway. Bergmann and colleagues found that only IL-6 trans-signaling is essential to promote HCC development via preventing DNA-damage-induced hepatocyte apoptosis and inducing endothelial cell proliferation to promote tumor angiogenesis.[13] Moreover, in patients with HCC, increased IL-6 levels could be observed.[14,15] Single nucleotide polymorphisms of non-coding promoter sequence in IL-6 gene will impact the expression of IL-6, which was considered to be associated with the susceptibility of HCC. Although a meta-analysis published in 2014 demonstrated that IL-6 –174G>C, not –572G>C, polymorphism was related with HCC susceptibility,[16] controversial results also published thereafter.[17–19] Accordingly, an up-to-date meta-analysis is needed to perform. The aim of this study is to evaluate the association between IL-6 gene polymorphisms and HCC development with more studies and larger participant samples. Furthermore, subgroup analysis may discover potential relationships between IL-6 gene polymorphisms and HCC development, which may be beneficial for basic or clinical research in the future.

2. Subjects and methods

2.1. Literature search

A systemic literature search was performed by 2 authors independently for studies published during May, 1993 to May, 2020 using PubMed, Cochrane Database, EMBASE, Web of science, and China National Knowledge Infrastructure. The search terms were: "interleukin-6" or "IL-6", "hepatocellular carcinoma" or "liver cancer" or "hepatocellular cancer", and "SNPs" or "polymorphism". The resulting articles were examined and unrelated articles were excluded. Additionally, articles in the reference list were manually searched for potentially relevant studies. When more than one of the same patient population was included in different publications, only the most recent or complete study was used. This study was approved by the ethics committee of the First Hospital of Jilin University.

2.2. Inclusion and exclusion criteria

Preferred Reporting Items for Systematic Reviews and Meta-Analyses was adopted to report our results. An article was considered relevant if it reported original data from case-control study, regardless of language, investigating the correlations between IL-6 polymorphisms and HCC susceptibility. Controls were healthy individuals, patients with hepatitis B or C virus infection, or patients with hepatitis cirrhosis. The reasons for exclusion from our studies were: studies with insufficient genotyping data of patients or control group; duplicated publication; review articles; experiment researches; studies without control group. If disagreements exist between the 2 reviewers regarding inclusion of a study, consensus was used to resolve such problem. Eleven studies of full-text articles were selected for inclusion in this meta-analysis, and the selection process of studies in this analysis was shown in Figure 1.

2.3. Data extraction and quality assessment

The date was extracted by 2 reviewers independently from all eligible studies according to the inclusion and exclusion criteria above, and the quality of each study was assessed by using the Newcastle–Ottawa Scale (NOS), and 9 points represent the highest quality in this scale. Disagreements was resolved by a third reviewer.

2.4. Data analysis

Review Manager (RevMan) 5.3 (The Cochrane Collaboration, the Nordic Cochrane Centre, Copenhagen, Denmark.) (Cochrane database) was utilized to analyze the data of included studies. The results were reported as odds ratios (OR) with 95% confidence intervals (CI). Heterogeneity between studies was assessed by using the I^2 statistic: values of 25%, 50%, and 75% represent mild, moderate, and severe heterogeneity, respectively. Based on results of the heterogeneity test, a fixed effect model was used if $P>.10$, while a random effects model was performed if $P \leq .10$. Begg and Egger test were employed to evaluate the publication bias across studies with Stata software (version 16.0). (Stata Corporation, College Station, TX, USA) A $P<.05$ was considered statistically significant.

3. Results

3.1. Characteristics of included studies

The characteristics of included studies were summarized in Table 1. Two studies were from Egypt,[19,20] 2 from China,[18,21] 2 from Italy,[14,22] 1 from Israel,[23] 1 from Korea,[24] 1 form Japan,[25] 1 from India,[17] and the remaining 1 from USA.[26] For –172G>C, –572G>C, –597G>A polymorphisms of IL-6, the number of included studies were 5, 7, and 2, respectively. Eventually, 2013 patients and 3217 control were included in this meta-analysis. All studies had a NOS score ≥7, with an average of 7.36 (Table 1).

3.2. Correlations of IL-6 polymorphisms and HCC susceptibility

3.2.1. For IL-6 –174G>C polymorphism. In codominant (GG vs CC: OR = 2.78, 95% CI = 1.25–6.19, $P=.01$, $I^2=16\%$) (Fig. 2A) and recessive (GG+GC vs CC: OR = 2.76, 95% CI = 1.29–5.90, $P=.009$, $I^2=3\%$)(Fig. 2C) models, IL-6 –174G>C polymorphism was significantly associated with the risk of HCC. However, in dominant (GG vs CC+GC: OR = 1.80, 95% CI = 0.92–3.54, $P=.09$, $I^2=86\%$)(Fig. 2B) and allele (G vs C: OR = 1.49, 95% CI = 0.95–2.32, $P=.08$, $I^2=68\%$)(Fig. 2D) models, IL-6 –174G>C polymorphism had no impact on the

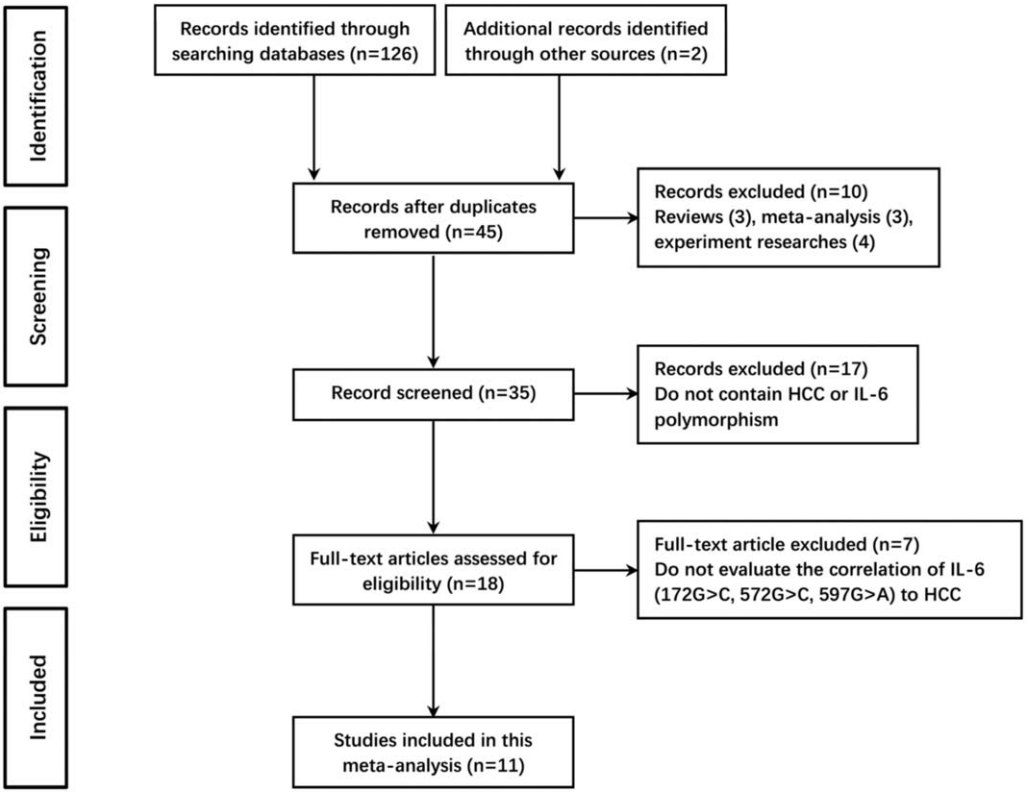

Figure 1. Flow chart of literature selection in this meta-analysis.

risk of HCC. Considering the high heterogeneity in these 2 models, a subgroup analysis was performed to evaluate the association between IL-6 –174G>C polymorphisms and HCC susceptibility. Finally, we found that in the non-Italian Caucasian population, IL-6 –174G>C polymorphism was significantly related with the occurrence of HCC in both dominant (Fig. 3) and allele models (Fig. 4) without heterogeneity.

Taken the control group containing patients with hepatitis or cirrhosis into account, we performed a subgroup analysis with

Table 1

Characteristics of the included studies.

Author, yr	Country	Ethnicity	Number		Source of control	Determination of polymorphism	NOS scores
			Patients	Control			
Ben-Ari et al 2003	Israel	Caucasians	10	125	Healthy control HBV patients	PCR	7
Park et al 2003	Korea	Non-Caucasians	221	475	Liver cirrhosis patients	PCR-RFLP	7
Migita et al 2005	Japan	Non-Caucasians	48	188	HBV patients	PCR	8
Falleti et al 2009	Italy	Caucasians	66	389	Healthy control Liver cirrhosis patients	PCR-RFLP	9
Ognjanovic et al 2009	USA	Caucasians	117	121	Healthy control HBV/HCV patients	Taq Man	8
Giannitrapani et al 2011	Italy	Caucasians	105	193	Healthy control Liver cirrhosis patients	PCR-RFLP	7
Bei et al 2014	China	Non-Caucasians	720	784	Healthy control HBV patients	RT-PCR	7
Saxena et al 2014	India	Caucasians	61	342	Healthy control HBV patients	PCR-RFLP	7
Tang et al 2014	China	Non-Caucasians	505	395	HBV patients	RT-PCR	7
Madkour et al 2017	Egypt	Caucasians	60	105	Healthy control HCV patients	Taq Man	7
Badawy et al 2019	Egypt	Caucasians	100	100	Healthy control	PCR-RFLP	7

NOS = Newcastle-Ottawa Scale, PCR = polymerase chain reaction, PCR-RFLP = PCR restriction fragment length polymorphism, RT-PCR = real-time PCR.

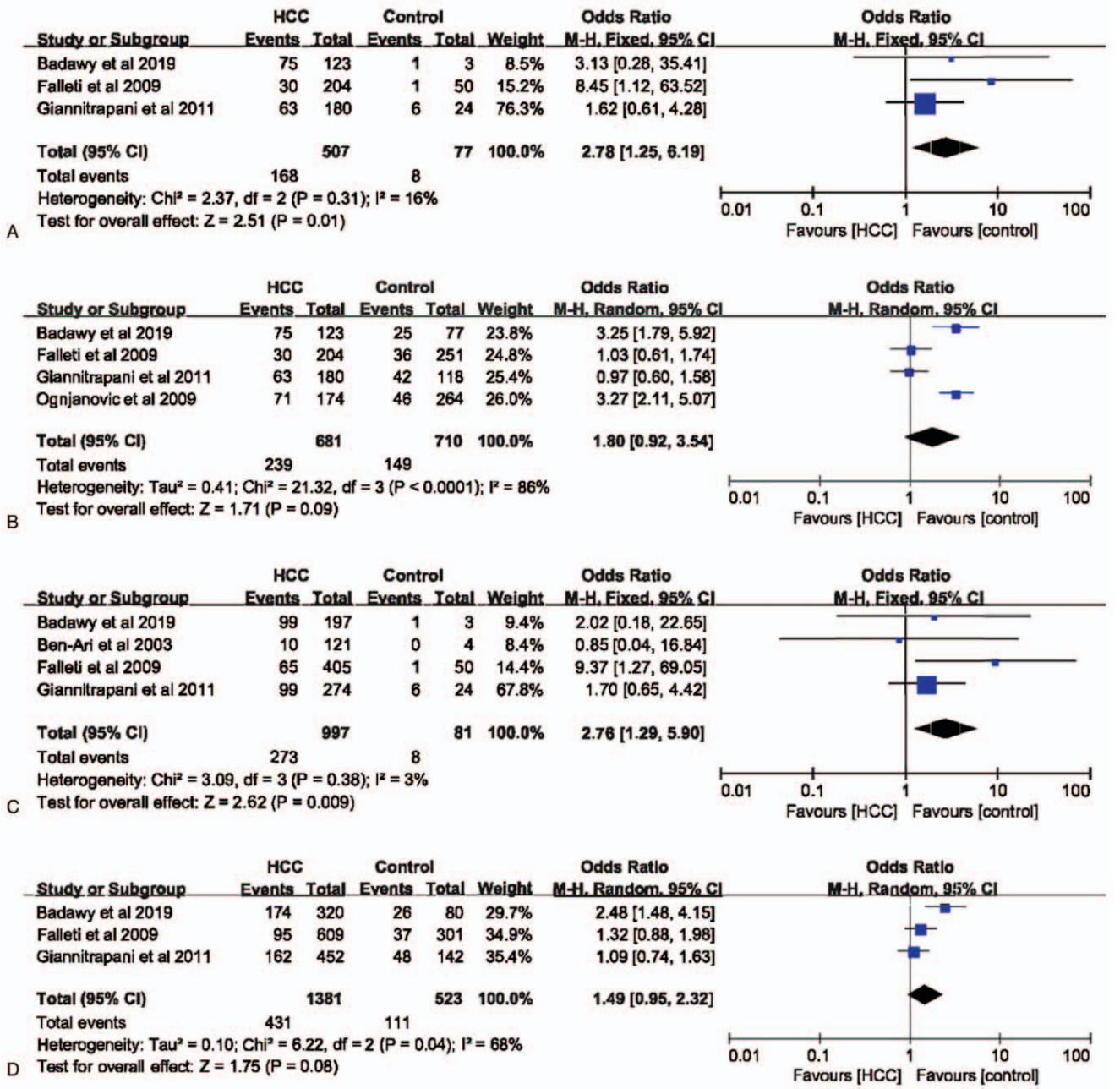

Figure 2. The association between interleukin-6 gene −174G>C polymorphism and hepatocellular carcinoma susceptibility based on overall controls. A. Codominant model; B. Dominant model; C. Recessive model; D. Allele model.

healthy individuals as controls. In codominant (GG vs CC: OR = 3.49, 95% CI = 1.48–8.21, $P = .004$, $I^2 = 0\%$), recessive (GG+GC vs CC: OR = 3.07, 95% CI = 1.37–6.88, $P = .006$, $I^2 = 3\%$), and allele (G vs C: OR = 1.64, 95% CI = 1.15–2.34, $P = .007$, $I^2 = 45\%$) models, IL-6 −174G>C polymorphism was significantly associated with the risk of HCC, which was absent in dominant model (GG vs CC+GC: OR = 1.68, 95% CI = 0.89–3.17, $P = .11$, $I^2 = 73\%$) (Fig. 5). Similarly, in non-Italian Caucasian population subgroup, −174G>C polymorphism of IL-6 gene was significantly related with HCC incidence in dominant model (supplemental Fig. 1, http://links.lww.com/MD/F369).

3.2.2. For IL-6 −572G>C polymorphism. IL-6 −572G>C polymorphism was not significantly associated with the risk of HCC in dominant (GG vs CC+GC: OR = 1.13, 95% CI = 0.89–1.45, $P = .32$, $I^2 = 22\%$), recessive (GG+GC vs CC: OR = 1.08, 95% CI = 0.94–1.25, $P = .27$, $I^2 = 11\%$), allele (G vs C: OR = 1.08, 95% CI = 0.97–1.21, $P = .18$, $I^2 = 37\%$), and codominant (GG vs CC: OR = 1.01, 95% CI = 0.74–1.37, $P = .97$, $I^2 = 0\%$) models (Fig. 6). In a subgroup analysis with healthy individuals as controls, IL-6 −572G>C polymorphism had no influence on the risk of HCC in all models as well (Fig. 7). Furthermore, in both Caucasians and non-Caucasians populations, IL-6 −572G>C

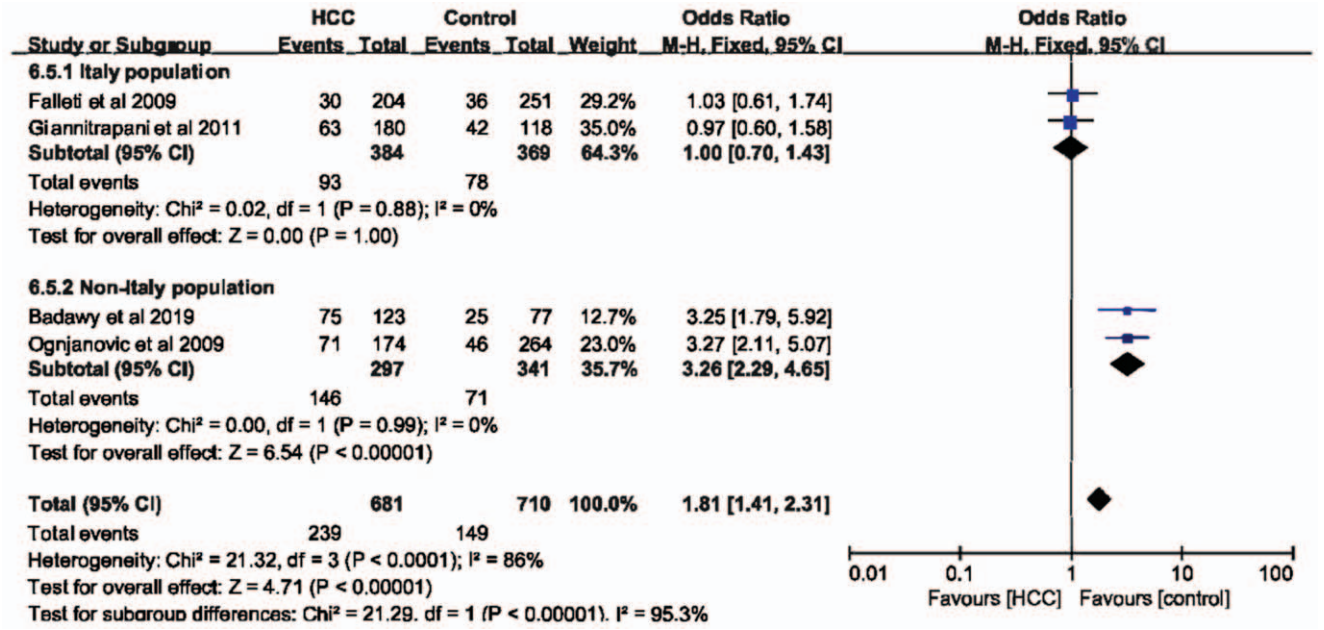

Figure 3. The association between interleukin-6 gene –174G>C polymorphism and hepatocellular carcinoma susceptibility in Italy and non-Italy populations in dominant model based on overall controls.

polymorphism had no impact on HCC susceptibility (supplemental Figs. 2–5, http://links.lww.com/MD/F371, http://links.lww.com/MD/F374, http://links.lww.com/MD/F376, http://links.lww.com/MD/F377).

3.2.3. For IL-6 –597G>A polymorphism. IL-6 –597G>A polymorphism was not significantly related with the risk of HCC in dominant (GG vs AA+GA: OR = 0.95, 95% CI = 0.59–1.54, $P = .84$, $I^2 = 37\%$), recessive (GG+GA vs AA: OR = 1.49, 95% CI = 0.13–17.35, $P = .75$, $I^2 = 87\%$), allele (G vs A: OR = 1.03, 95% CI = 0.55–1.94, $P = .93$, $I^2 = 78\%$), and codominant (GG vs AA: OR = 1.41, 95% CI = 0.11–17.60, $P = .79$, $I^2 = 87\%$) models (Fig. 8). In subgroup analysis with healthy individuals as controls, IL-6 –597G>A polymorphism had no influence on the risk of HCC in all models (Fig. 9).

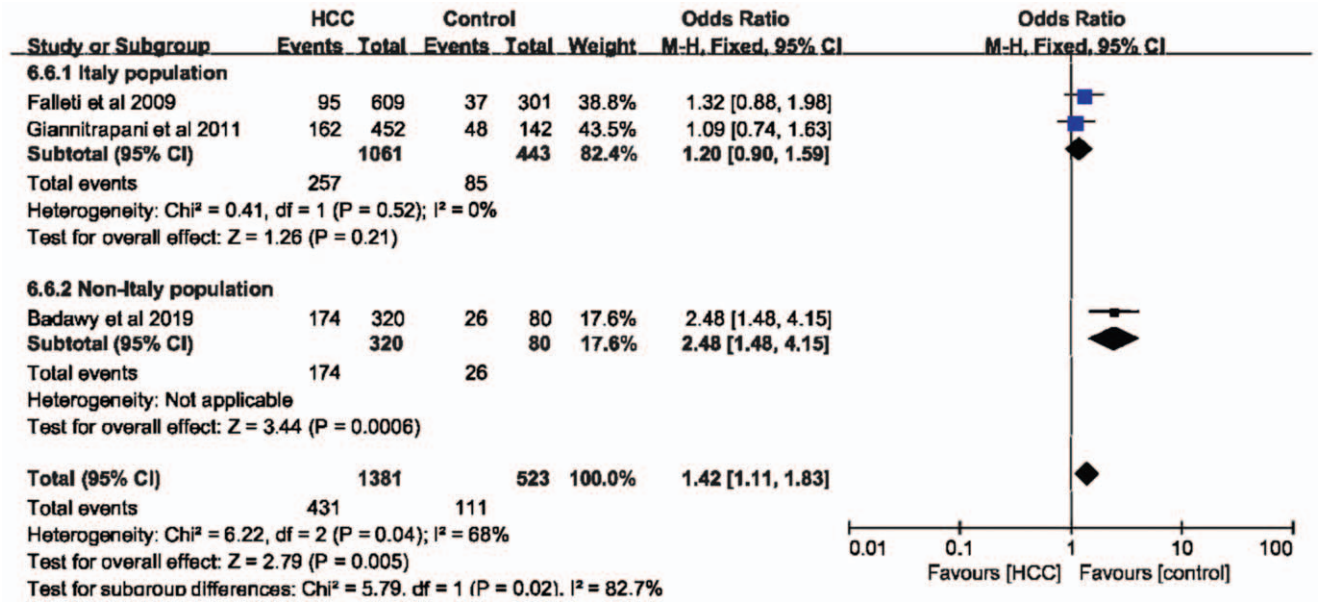

Figure 4. The association between interleukin-6 gene –174G>C polymorphism and hepatocellular carcinoma susceptibility in Italy and non-Italy populations in allele model based on overall controls.

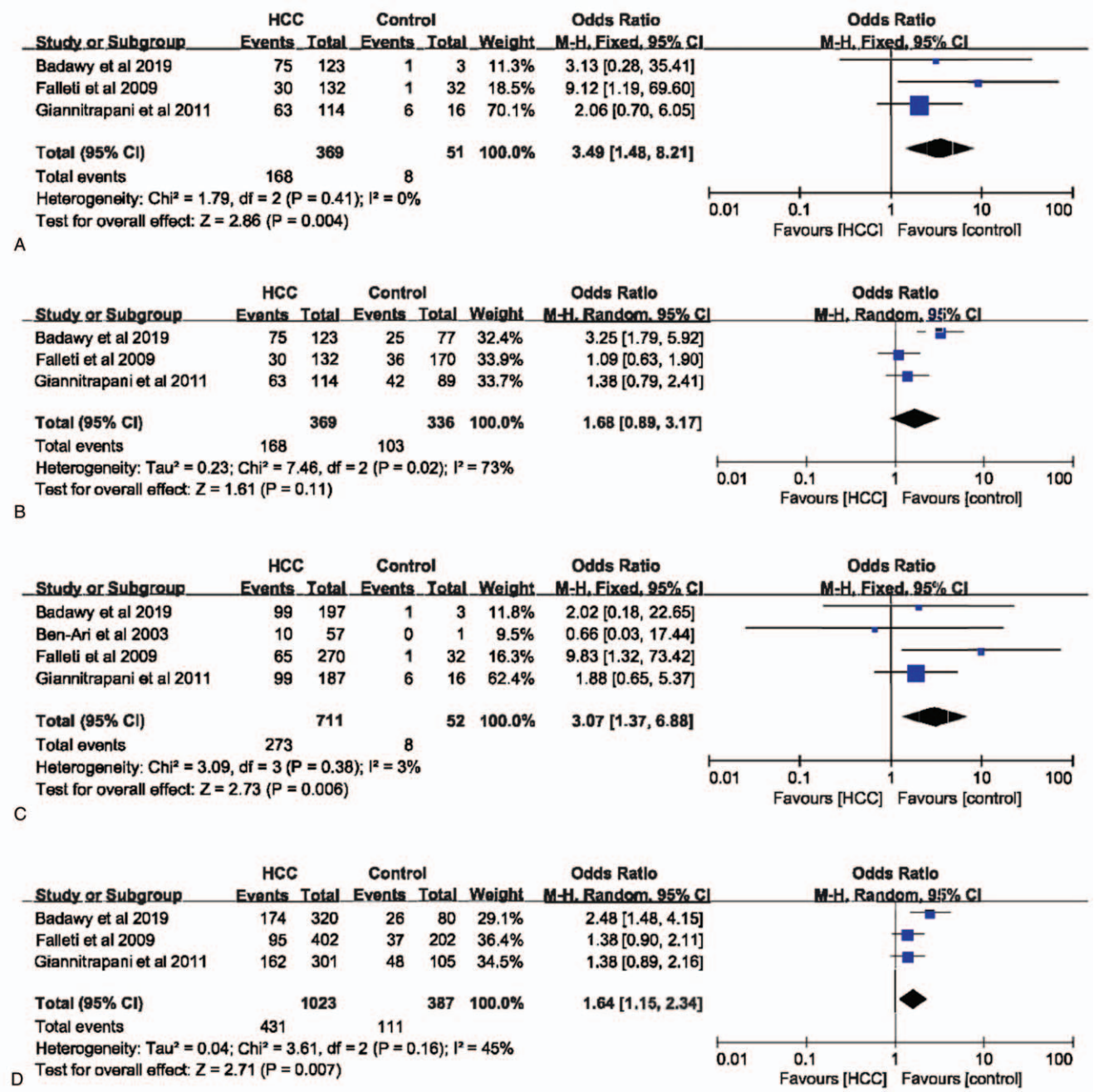

Figure 5. The association between interleukin-6 gene –174G>C polymorphism and hepatocellular carcinoma susceptibility based on normal controls. A. Codominant model; B. Dominant model; C. Recessive model; D. Allele model.

3.3. Publication bias

Begg and Egger tests were used to evaluate the publication bias for the studies included in this study. The subsequent results showed no significant publication bias in both Begg and Egger test (Table 2).

4. Discussion

Inflammation is closely associated with the development and progression of cancer, and often common pathways could be observed in both disease statuses.[27,28] Therefore, targeting inflammation represents an attractive strategy both for cancer prevention and for cancer prevention and therapy.[27] IL-6, one of the major cytokines in the tumour microenvironment, is an important factor which is found at high concentrations and known to be deregulated in many types of cancer.[15,29–31] A number of studies have attempted to associate IL-6 gene polymorphisms with the susceptibility of HCC, mainly involving –174G>C, –572G>C, and –597G>A polymorphisms within the promoter sequence.[14,17–26] However, the conclusion was

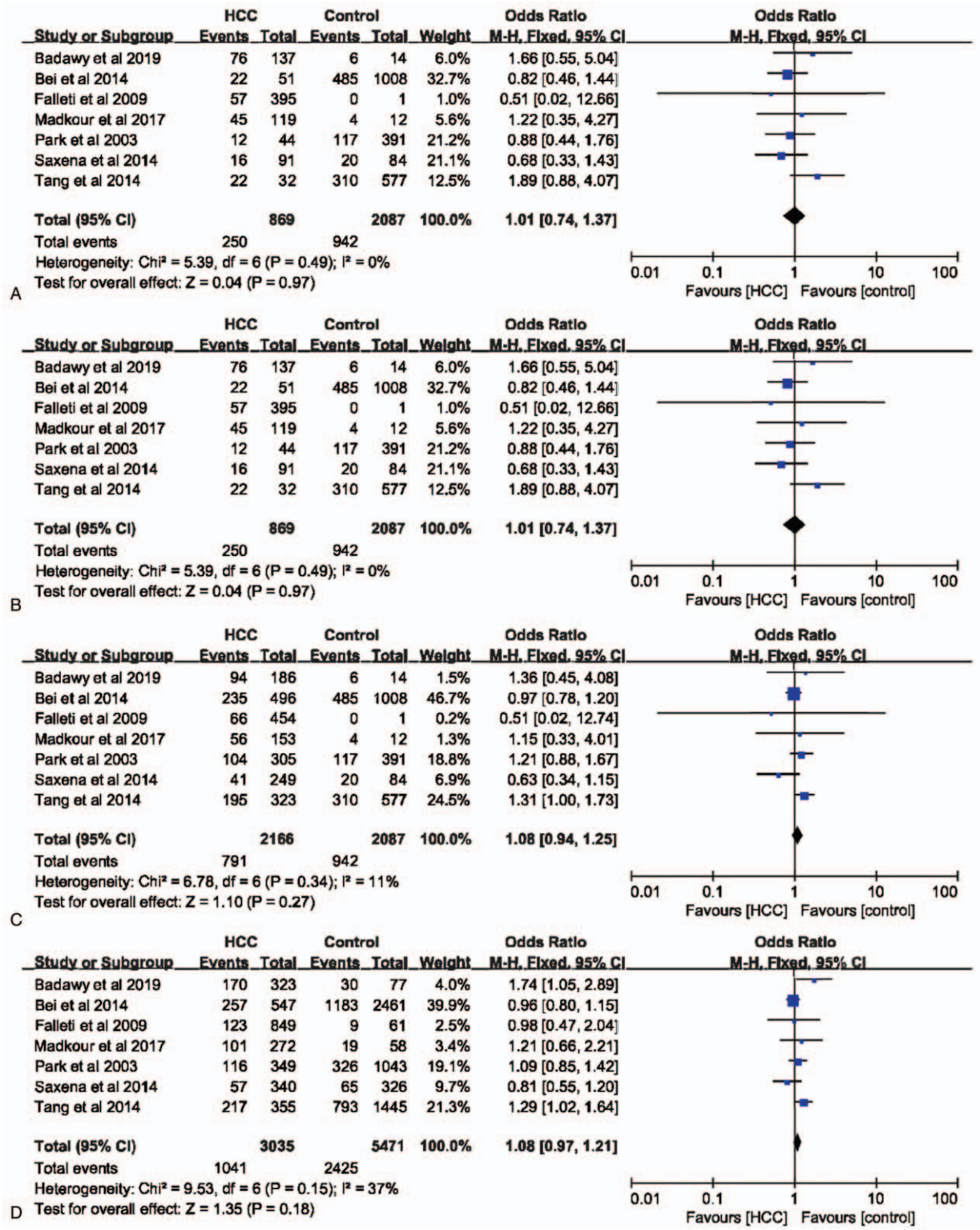

Figure 6. The association between interleukin-6 gene –572G>C polymorphism and hepatocellular carcinoma susceptibility based on overall controls. A. Codominant model; B. Dominant model; C. Recessive model; D. Allele model.

controversial. With the increase of publications in recent years, it is possible to perform an up-to-date meta-analysis.

In codominant and recessive models, IL-6 –174G>C polymorphism was associated with HCC susceptibility with almost no heterogeneity, which was consistent with previous report.[16] In dominant and allele models, IL-6 –174G>C polymorphism had no influence on the risk of HCC. However, the heterogeneity was moderate or severe. Hence, we performed a subgroup

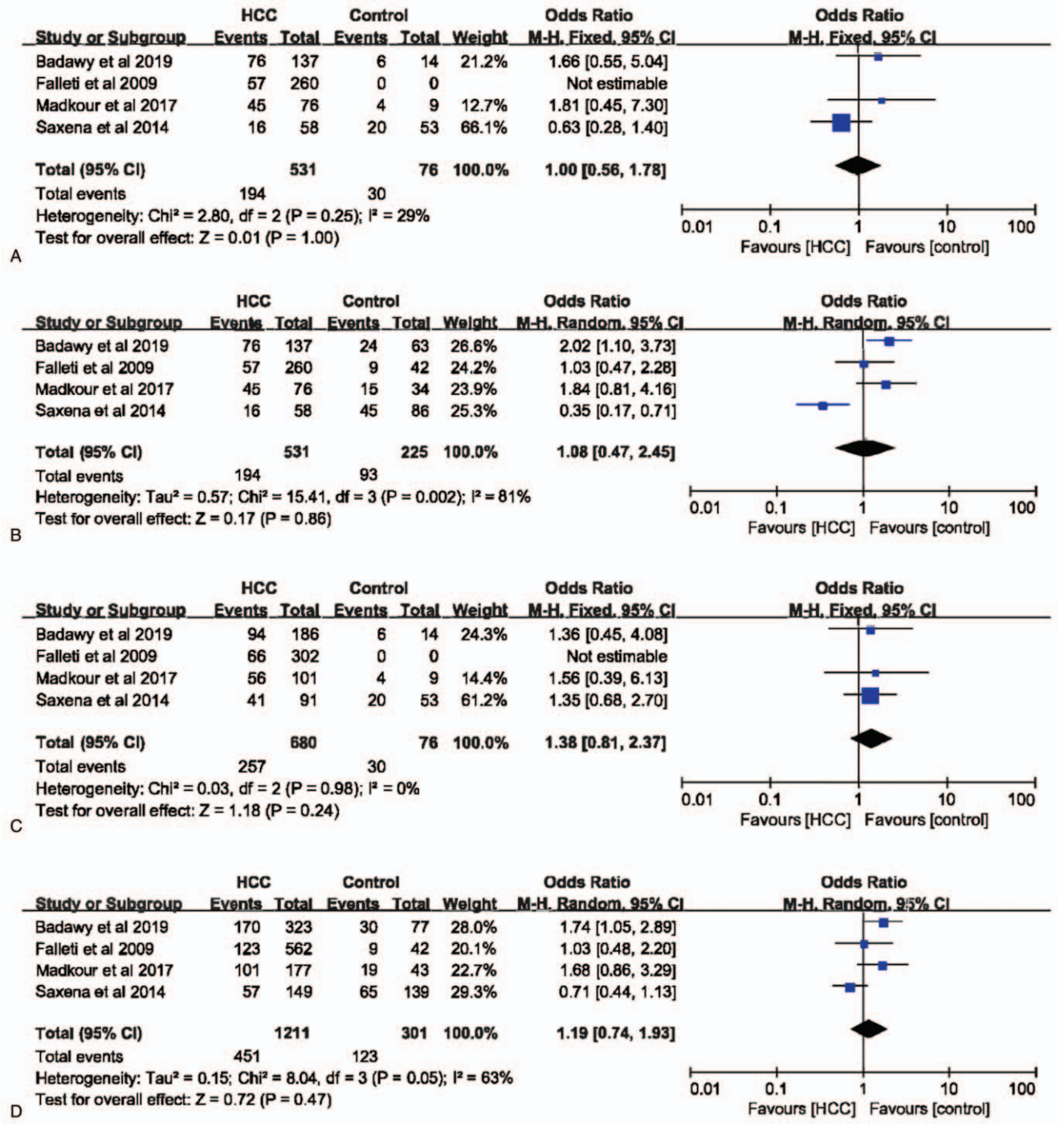

Figure 7. The association between interleukin-6 gene –572G>C polymorphism and hepatocellular carcinoma susceptibility based on normal controls. A. Codominant model; B. Dominant model; C. Recessive model; D. Allele model.

analysis based on populations. Finally, we found that in non-Italian Caucasian population, IL-6 –174G>C polymorphism was significantly related with the occurrence of HCC in both dominant and allele models without heterogeneity. When healthy individuals were set as control group. Similar findings could be observed. Taken together, these results indicated that IL-6 –174G>C polymorphism was significant related with the susceptibility of HCC, especially in non-Italian Caucasian population.

IL-6 –572G>C polymorphism has been reported to been linked to HCC development. IL-6 (–572) GC genotype shared a negative association with HCC development among HBV carriers.[17] In a study of Han population, the authors found that –572G>C polymorphism of IL-6 gene was associated with susceptibility to HBV-related HCC in a male Chinese participant cohort.[18] Consistent with previous studies,[16] we found no significant association between IL-6 –572G>C polymorphism and risk of HCC in this meta-analysis. Considering many human

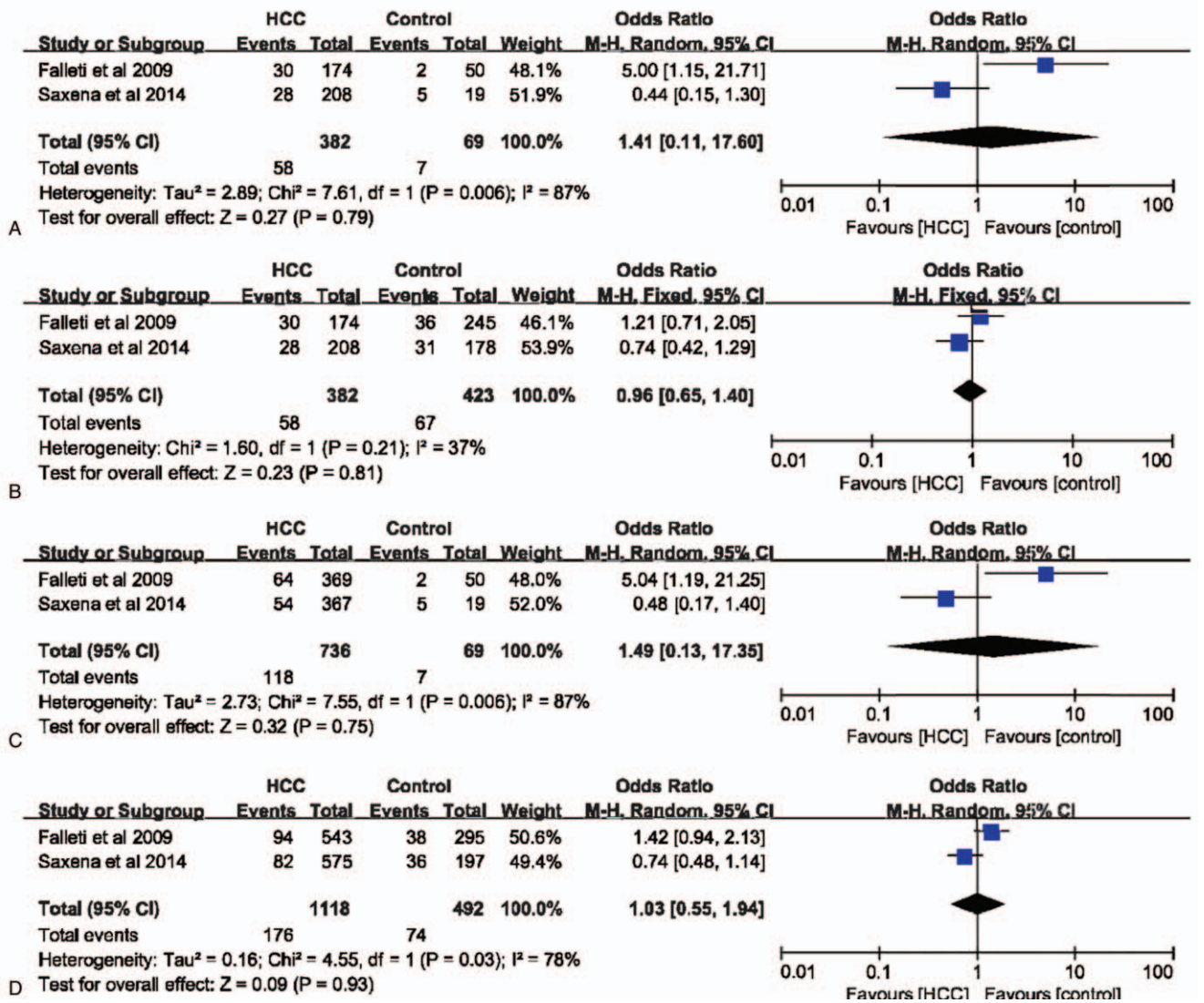

Figure 8. The association between interleukin-6 gene –597G>A polymorphism and hepatocellular carcinoma susceptibility based on overall controls. A. Codominant model; B. Dominant model; C. Recessive model; D. Allele model.

disorders have potential linkage with genetic background, especially between Caucasian and non-Caucasian populations, we performed a subgroup analysis for –572G>C polymorphism of IL-6 gene and the risk of HCC in Caucasian and non-Caucasian populations. Again, no significant correlation was found. Collectively, these results indicated that IL-6 –572G>C polymorphism did not influence on the occurrence of HCC.

This study also evaluated the potential association between –597G>A polymorphism of IL-6 gene and HCC susceptibility. No significantly positive connection was observed. Only 2 studies were included, and high heterogeneity existed when assessing the correlation between IL-6 –597G>A polymorphism and HCC susceptibility. The interpret of this result should be cautious.

Our study has several strengths. First, this is the largest study to date evaluating the associations between IL-6 gene polymorphism (–174G>C, –572G>C, and –597G>A) and the risk of HCC. Second, NOS scores of included studies indicated that the quality of literatures was relatively high and the heterogeneity was relatively low in data synthesis. Third, participants from different genetic backgrounds made it possible to analyze the relationships in different populations. However, our study also has some limits. First, for IL-6 –597G>A polymorphism, high heterogeneity existed and limited studies were included when performing the data synthesis. As a result, further study is still needed. Second, academic dissertations and conference papers were not included, so there may have been bias in provision of data.

In summary, we performed this up-to-date meta-analysis to evaluate the association between several common IL-6 gene polymorphisms and the susceptibility of HCC. Finally, we found that –174G>C polymorphism of IL-6 gene was associated with risk of HCC, especially in non-Italian Caucasian population. However, –572G>C and –597G>A polymorphisms of IL-6 gene had no impact on the incidence of HCC.

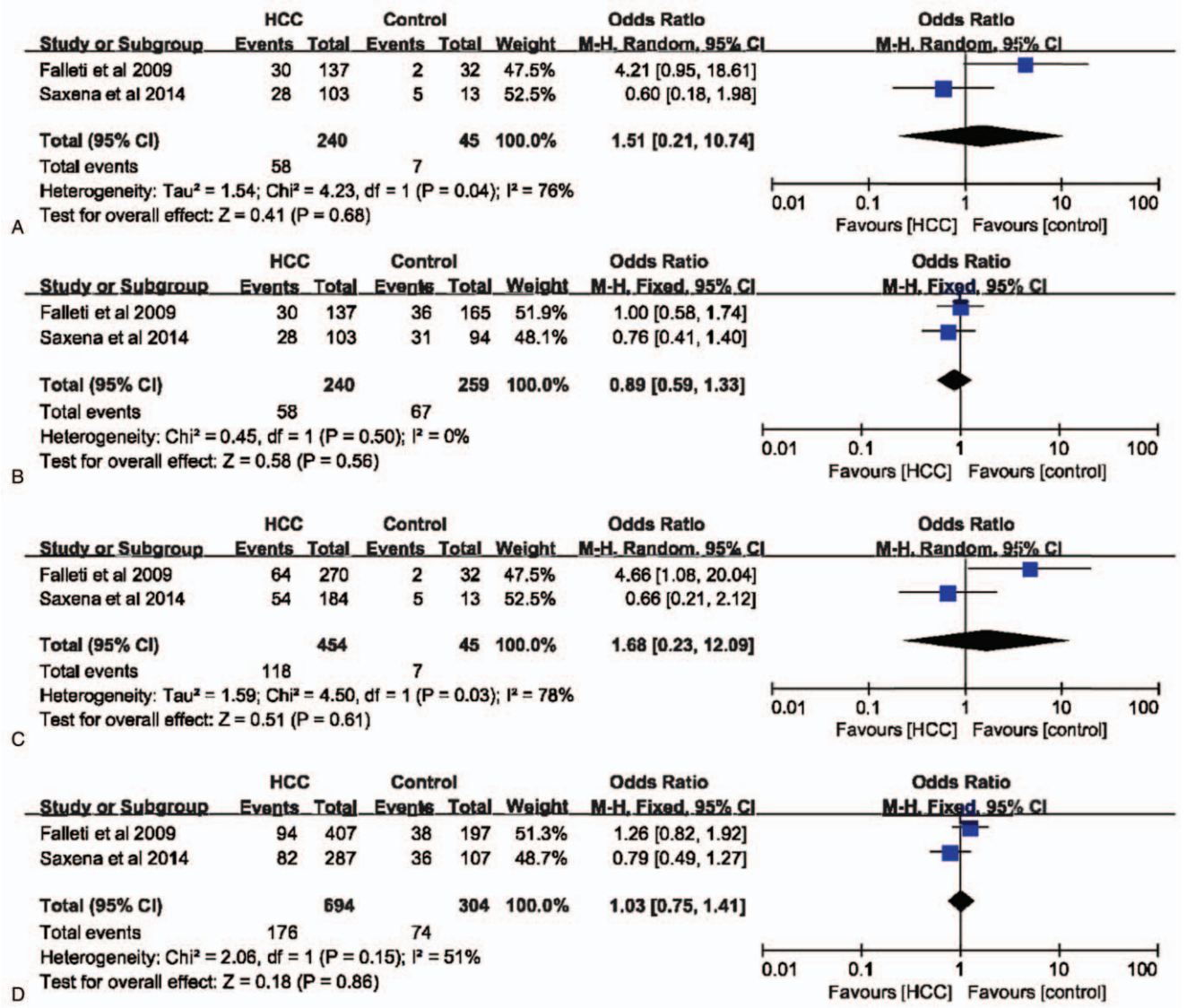

Figure 9. The association between interleukin-6 gene –597G>A polymorphism and hepatocellular carcinoma susceptibility based on normal controls. A. Codominant model; B. Dominant model; C. Recessive model; D. Allele model.

Table 2

Publication bias analysis of the included studies.

	Begg test		Egger test	
	z	Pr > |z|	t	*P*
–174 G>C				
Codominant	0.000	1.000	1.380	.399
Dominant	1.040	0.296	5.750	.110
Recessive	–0.340	1.000	0.310	.783
Allele	1.040	0.296	5.950	.106
–572 G>C				
Codominant	0.300	0.764	0.400	.706
Dominant	0.600	0.548	0.420	.693
Recessive	0.600	0.548	0.340	.748
Allele	0.300	0.764	0.550	.607

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Author contributions

Pei-Pei An, Li-Na Feng, Xiao-Xue Zhang, and Qing-Long Jin conceived the study. Pei-Pei An, Li-Na Feng, Xiao-Xue Zhang, and Qing-Long Jin designed the study and analyzed the data. Pei-Pei An and Qing-Long Jin wrote this manuscript. All authors discussed and revised the manuscript before submission.

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Data curation: Pei Pei An, Li Na Feng, Xiao Xue Zhang, Qing-Long Jin.
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Software: Pei Pei An, Li Na Feng, Xiao Xue Zhang, Qing-Long Jin.
Supervision: Qing-Long Jin.
Validation: Pei Pei An, Li Na Feng, Xiao Xue Zhang, Qing-Long Jin.
Visualization: Xiao Xue Zhang, Qing-Long Jin.
Writing – original draft: Pei Pei An, Qing-Long Jin.
Writing – review & editing: Pei Pei An, Qing-Long Jin.

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