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Original paper

Association between interleukin 6 polymorphisms (rs1800796, rs1800795, rs2069837, rs17147230, and rs1800797) and hepatocellular carcinoma susceptibility: a meta-analysis

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Abstract

Aim of the study: We reported the association between interleukin 6 polymorphisms (rs1800796, rs1800795, rs2069837, rs17147230, and rs1800797) and hepatocellular carcinoma (HCC) susceptibility in a meta-analysis.

Material and methods: The studies were retrieved by searching the search terms in Scopus, PubMed, Web of Science, and Cochrane Library databases until June 2020. The analyses were done by RevMan 5.3 software using odds ratios (ORs) and 95% confidence intervals (CIs) and the analysis of publication bias and sensitivity analyses were performed by CMA 2.0 software.

Results: Searching through the databases, 316 records were retrieved and finally 13 studies were analyzed in the present meta-analysis. For the rs1800797 polymorphism, there was an elevated risk of AA genotype (OR = 2.68, $p = 0.03$) in HCC patients compared to healthy controls. Also, there was an elevated risk of AA (OR = 3.06, $p = 0.04$) and GA (OR = 2.61, $p = 0.005$) genotypes in HCC patients compared to liver cirrhosis patients. For rs2069837 polymorphism, there was an elevated risk of GG genotype (OR = 2.25, $p = 0.01$) in HCC patients compared to healthy controls. For rs17147230, T allele (OR = 1.31, $p = 0.03$) and TT genotype (OR = 1.83, $p = 0.02$) had elevated risks in HCC patients compared to healthy controls.

Conclusions: The present meta-analysis confirmed that there was an elevated risk of the AA and GA genotypes of rs1800797 polymorphism and the GG genotype of rs2069837, and the T allele and TT genotype of rs17147230 in HCC.

Key words: polymorphism, interleukin 6, hepatocellular carcinoma, hepatitis, cirrhosis.

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of death from liver cancer worldwide, especially in patients with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections [1, 2] and is more common in developing countries, with a higher prevalence than in developed countries [3]. The incidence of HCC varies widely around the world, but HCC is 3 to 4 times more common in men than women [4]. Different cytokines play an important role in regulating the immune response and defending against viruses. One study has shown that cytokine production in various diseases is related to polymorphisms affecting the cytokine gene [5]. Inflammatory cytokines may have a positive or negative effect on the growth and development of HCC [6]. Interleukin 6 (IL-6) is a multifunctional cytokine that has recently been identified as one of the most important

compounds in the cancer-related cytokine complex that ultimately leads to systemic immune stimulation along with the suppression of the immune system caused by cancer, which ultimately protects cancer cells [7]. A recent meta-analysis reported elevated serum levels of IL-6 in HCC patients compared to patients with chronic hepatitis (CH) or liver cirrhosis (LC) and healthy controls, which may indicate a significant association of this cytokine with an increased risk of HCC [8]. Studies have shown that polymorphisms in the IL-6 promoter region are included in the pathogenesis of various diseases [9, 10]. The potential association of *IL-6* polymorphism with HCC risk has been investigated in many studies. However, the results are highly controversial and not conclusive [11-14]. A meta-analysis with eight studies without subgroup analysis in 2014 that assessed the association of rs1800795 and rs1800796 polymorphisms of *IL-6* with the risk of HCC [15] suggested that the G allele of *IL-6* rs1800795 polymorphism could have an elevated HCC risk; however, the rs1800796 polymorphism was not associated with HCC risk. Based on our knowledge, there was no meta-analysis about other polymorphisms of *IL-6* (rs2069837, rs17147230, and rs1800797) in the literature. The aim of the present meta-analysis was to evaluate the association between *IL-6* polymorphisms (rs1800796, rs1800795, rs2069837, rs17147230, and rs1800797) and susceptibility to HCC with more studies.

Material and methods

Search strategies

One reviewer (M.S.) retrieved the studies of the meta-analysis by the search terms ("interleukin 6" or "IL-6") and ("hepatocellular carcinoma" or "HCC" or "liver cancer") and ("polymorphism" or "variant" or "genotype" or "allele") in Scopus, PubMed, Web of Science, and Cochrane Library databases from their start date to June 2020.

Study selection and selection criteria

The studies on the association between *IL-6* polymorphisms and HCC susceptibility were selected without restrictions of language, period, gender, and age. The studies were analyzed if they: 1) were case-control reporting the patients with LC, CH, or healthy controls as the control group; 2) included *IL-6* polymorphisms of rs1800796, rs1800795, rs2069837, rs17147230, and rs1800797; 3) reported HCC diagnosis pathologically; 4) reported healthy control subjects without systematic diseases; 5) reported HCC patients with/without HBV or HCV infections. The studies were excluded if they did not have the required data regarding genotype distributions, meta-analyses, and conference papers. One reviewer (O.E.A.) checked the relevant articles based on the eligibility criteria.

Data extraction

The studies involved in the meta-analysis were checked by one reviewer (M.S.) for extracting the relevant data. Another author (O.E.A.) re-evaluated the data. Disagreements were resolved by the third reviewer (P.O.).

Statistical analyses

The heterogeneity percentage between the studies was evaluated by the Cochrane Q test and I^2 statistic. The analyses were done by Review Manager 5.3 (RevMan 5.3, The Cochrane Collaboration, Oxford, United Kingdom) with a random-effects model using odds ratios (ORs) and 95% confidence intervals (CIs) which, in the case of lack of heterogeneity ($I^2 < 50\%$, P_h or $P_{heterogeneity} > 0.1$), led to use of a fixed-effects model. The p-value (2-sided) < 0.05 was considered statistically significant. Subgroup analysis based on ethnicity was performed for rs1800796 polymorphism with sufficient/acceptable studies included in the analysis. The funnel plot analyses with both Begg's and Egger's tests (for evaluation of the publication bias across the studies) and sensitivity analyses (for confirming the stability of the results) – one removed study and cumulative analysis – were performed by Comprehensive Meta-Analysis 2.0 (CMA 2.0) software.

Results

Study selection

Searching through four databases, 316 records were retrieved (Fig. 1). After removing duplicates and irrelevant data, 19 full-text articles were evaluated for eligibility. After that, six articles were excluded with reasons (one study mixed HCC and LC patients together; three studies were meta-analyses/systematic reviews; one study reported a new polymorphism of interleukin 6; one study reported rs1800795 between HCC and CH patients). Finally, 13 studies were included in the present meta-analysis.

Study characteristics

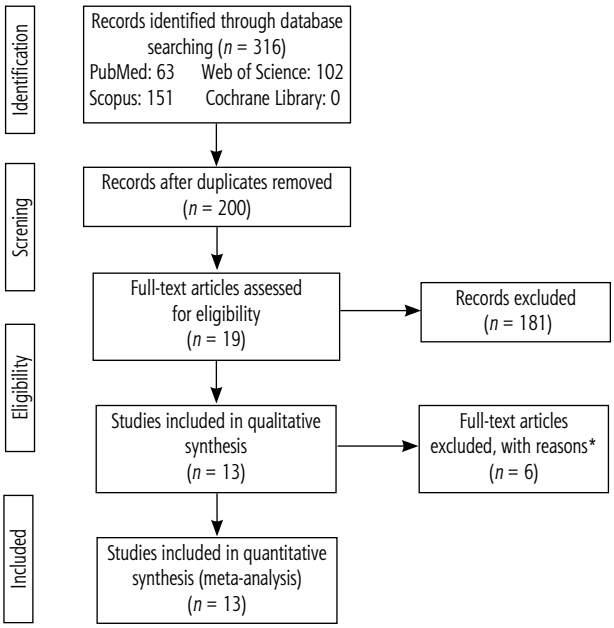
The characteristics of the 13 studies [11-14, 16-24] are shown in Table 1. The studies were published from 2003 to 2020. Six studies [11, 13, 17, 22-24] were re-

ported from China, two [18, 19] from Italy, one [20] from the USA, one [21] from Korea, one [12] from Egypt, and one [16] from Pakistan. Out of 13 studies, seven included [11, 13, 17, 21-24] Asian, five [12, 14, 16, 18, 19] Caucasian, and one mixed [20] ethnicities. Other characteristics such as the source of controls and sample size of each study are shown in Table 1.

Table 2 illustrates the prevalence of genotypes of the *IL-6* polymorphisms (rs1800796, rs1800795, rs2069837, rs17147230, and rs1800797) in the HCC group compared to LC, CH, or healthy control groups. The control groups in four studies showed a deviation from Hardy-Weinberg equilibrium (HWE) (HCC vs. LC for rs1800795 in one study [19], HCC vs. LC and HCC vs. healthy control for rs1800796 in two [12, 14] and one [14] studies, respectively, HCC vs. healthy control for rs2069837 in one study [16], and HCC vs. healthy control for rs17147230 in one study [16]).

Pooled analysis

The pooled ORs of the association between the *IL-6* polymorphisms and HCC risk have been abstracted in



*1 study mixed hepatocellular carcinoma and cirrhosis patients together. 3 studies were meta-analyses/systematic reviews. 1 study reported new polymorphism of interleukin-6. 1 study reported rs1800795 between hepatocellular carcinoma and hepatitis patients.

Fig. 1. Flowchart of the study selection

Table 1. Characteristics of the studies included in the meta-analysis (HCC vs. LC/CH/HC)

First author, publication year	Country	Ethnicity	Source of controls	Sample size (case/control)
Park, 2003 [21]	Korea	Asian	LC	221/475
			CH	221/280
Falleti, 2009 [18]	Italy	Caucasian	LC	66/153
			HC	66/236
Ognjanovic, 2009 [20]	USA	Mixed	HC	117/221
Giannitrapani, 2011 [19]	Italy	Caucasian	LC	105/95
			HC	105/98
Qiu, 2011 [13]	China	Asian	CH	381/340
			HC	381/359
Liu, 2012 [11]	China	Asian	CH	500/286
			HC	500/304
Tang, 2013 [22]	China	Asian	LC	148/265
			CH	148/292
			HC	148/153
Bei, 2014 [17]	China	Asian	HC	720/784
Saxena, 2014 [14]	India	Caucasian	HC	61/83
Tang, 2014 [23]	China	Asian	CH	505/395
Zheng, 2015 [24]	China	Asian	HC	205/209
Madkour, 2018 [12]	Egypt	Caucasian	HC	60/55
			CH	60/50
Adnan, 2020 [16]	Pakistan	Caucasian	CH	72/38

HCC – hepatocellular carcinoma, LC – liver cirrhosis, CH – chronic hepatitis, HC – healthy control

Table 2. Prevalence of genotypes of the interleukin-6 polymorphisms

First author, publication year	Polymorphism	HCC	LC	CH	HC	*P*-value of HWE for control group(s)
Park, 2003 [21]	rs1800796	117/92/12	391/261/44	175/88/17	NA	0.959/0.193
Falleti, 2009 [18]	rs1800796	0/9/57	1/17/135	NA	0/33/203	0.569/0.248
	rs1800795	1/35/30	18/63/72	NA	31/103/102	0.463/0.536
	rs1800797	2/34/30	18/62/73	NA	30/99/107	0.391/0.348
Ognjanovic, 2009 [20]	rs1800795	71/46*	NA	NA	103/118*	NA
Giannitrapani, 2011 [19]	rs1800795	63/36/6	66/21/8	NA	51/37/10	**0.004**/0.401
Qiu, 2011 [13]	rs1800796	259/110/12	NA	210/107/23	241/105/13	0.071/0.710
Liu, 2012 [11]	rs1800796	315/169/16	NA	206/74/6	193/99/12	0.829/0.875
Tang, 2013 [22]	rs1800796	90/51/7	101/46/6	194/87/11	176/78/11	0.791/0.749/0.529
Bei, 2014 [17]	rs1800796	485/213/22	NA	NA	523/232/29	0.605
Saxena, 2014 [14]	rs1800796	20/25/16	6/38/19	16/41/8	33/8/42	**0.039**/0.415/**< 0.001**
	rs1800797	28/26/5	40/18/3	NA	75/55/8	0.604/0.559/0.614
Tang, 2014 [23]	rs1800796	310/173/22	NA	267/118/10	NA	0.473
Zheng, 2015 [24]	rs2069837	92/113/21	NA	NA	111/98/11	0.068
	rs17147230	80/107/39	NA	NA	90/109/21	0.141
Madkour, 2018 [12]	rs1800796	4/11/45	NA	3/9/43	5/14/31	**0.023**/0.100
Adnan, 2020 [16]	rs2069837	14/48/10	NA	NA	24/6/8	**< 0.001**
	rs17147230	14/48/10	NA	NA	24/0/14	**< 0.001**

**Data show GC + CC genotypes. Bolded numbers are statistically significant (p < 0.05).*
HWE – Hardy-Weinberg equilibrium, NA – not available, HCC – hepatocellular carcinoma, LC – liver cirrhosis, CH – chronic hepatitis, HC – healthy control. Arrangement of genotypes: rs2069837 (AA/AG/GG), rs17147230 (AA/AT/TT), rs1800796 (CC/CG/GG), rs1800795 (GG/GC/CC), rs 1800797 (GG/GA/AA)

Table 3. The funnel plots were not shown due to the large numbers as well as the format of the journal. The results just showed the significant association between three polymorphisms and HCC risk without heterogeneity. For rs1800797 polymorphism, there was an elevated risk of AA genotype (OR = 2.68, 95% CI: 1.09, 6.59, $p = 0.03$) in HCC patients compared to healthy controls. Also, there was an elevated risk of AA (OR = 3.06, 95% CI: 1.05, 8.90, $p = 0.04$) and GA (OR = 2.61, 95% CI: 1.33, 5.13, $p = 0.005$) genotypes in HCC patients compared to LC patients. For rs2069837 polymorphism, there was an elevated risk of GG genotype (OR = 2.25, 95% CI: 1.18, 4.29, $p = 0.01$) in HCC patients compared to healthy controls. For rs17147230, T allele (OR = 1.31, 95% CI: 1.02, 1.67, $p = 0.03$) and TT genotype (OR = 1.83, 95% CI: 1.08, 3.09, $p = 0.02$) had elevated risks in HCC patients compared to healthy controls.

Subgroup analysis

The subgroup analysis based on ethnicity for evaluation of the association between rs1800796 polymorphism and HCC risk is shown in Table 4. As it illustrates, there was no significant association between rs1800796 polymorphism and HCC risk reporting HCC patients compared to healthy controls or CH patients ($p > 0.05$).

Sensitivity analysis

Both "one study excluded" and "cumulative analysis" were performed for rs1800796 polymorphism and the pooled ORs did not change qualitatively. Therefore, the analyses showed that the pooled ORs under all genetic models were stable and trustworthy. Also, we removed the studies with a deviation of HWE for their controls. Removing one study [14] for the association between rs1800796 polymorphism and the risk of HCC comparing HCC patients compared to LC patients and healthy controls, the previous pooled results did not change. Also, removing another study [12] for the association between rs1800796 polymorphism and the risk of HCC comparing HCC patients compared to CH patients, the previous pooled result did not change.

Publication bias

Figure 2 shows the funnel plots of all genetic models to evaluate the association between HCC risk and rs1800796

Table 3. Pooled results of association between the interleukin-6 polymorphisms and hepatocellular carcinoma risk

Polymorphism (*N*)	Comparison	Allele	Homozygote	Heterozygote	Recessive	Dominant
		OR (95% CI), *p*-value, I^2 (P_h)	OR (95% CI), *p*-value, I^2 (P_h)	OR (95% CI), *p*-value, I^2 (P_h)	OR (95% CI), *p*-value, I^2 (P_h)	OR (95% CI), *p*-value, I^2 (P_h)
rs1800796 (7)	HCC vs. HC	0.93 (0.83, 1.05), 0.25, 36% (0.15)	0.86 (0.69, 1.19), 0.37, 0% (0.81)	1.15 (0.89, 1.49), 0.28, 57% (0.04)	1.03 (0.90, 1.18), 0.69, 0% (0.79)	0.83 (0.63, 1.10), 0.20, 40% (0.12)
rs1800796 (4)	HCC vs. LC	1.00 (0.83, 1.20), 0.96, 47% (0.13)	0.75 (0.76, 1.24), 0.26, 39% (0.18)	0.83 (0.42, 1.64), 0.59, 72% (0.01)	0.83 (0.44, 1.58), 0.57, 72% (0.01)	0.88 (0.59, 1.32), 0.54, 0% (0.95)
rs1800796 (7)	HCC vs. CH	1.13 (0.92,1.39), 0.24, 62% (0.01)	1.09 (0.79, 1.51), 0.60, 42% (0.11)	1.18 (0.91, 1.52), 0.21, 60% (0.02)	1.16 (0.91, 1.49), 0.23, 59% (0.02)	1.08 (0.80, 1.46), 0.62, 49% (0.07)
rs1800795 (2*)	HCC vs. HC	0.83 (0.62, 1.11), 0.22, 0% (0.40)	1.88 (0.09, 40.24), 0.69, 86% (0.008)	2.44 (0.17, 35.57), 0.51, 85% (0.01)	0.92 (0.39, 2.16), 0.85, 75% (0.02)	0.93 (0.58, 1.51), 0.78, 29% (0.23)
rs1800795 (2)	HCC vs. LC	0.98 (0.71, 1.33), 0.88, 33% (0.22)	2.07 (0.21, 20.52), 0.53, 74% (0.05)	3.23 (0.62, 16.84), 0.16, 62% (0.11)	2.79 (0.51, 15.07), 0.23, 64% (0.09)	0.87 (0.52, 1.45), 0.59, 0% (0.58)
rs1800797 (2)	HCC vs. HC	1.98 (0.76, 5.15), 0.16, 88% (0.003)	**2.68 (1.09, 6.59), 0.03, 0% (0.33)**	2.18 (0.55, 8.56), 0.26, 67% (0.08)	2.09 (0.62, 7.07), 0.24, 61% (0.11)	1.08 (0.66, 1.77), 0.77, 0% (0.54)
rs1800797 (2)	HCC vs. LC	1.36 (0.95, 1.95), 0.09, 22% (0.26)	**3.06 (1.05, 8.90), 0.04, 0% (0.68)**	**2.61 (1.33, 5.13), 0.005, 3% (0.31)**	**2.31 (1.23, 4.35), 0.010, 0% (0.69)**	0.98 (0.57, 1.67), 0.93, 0% (0.39)
rs2069837 (2)	HCC vs. HC	1.06 (0.26, 4.24), 0.94, 0.94% (< 0.0001)	**2.25 (1.18, 4.29), 0.01, 0% (0.92)**	4.13 (0.44, 38.89), 0.22, 94% (< 0.0001)	1.89 (0.98, 3.65), 0.06, 54% (0.14)	1.15 (0.37, 3.58), 0.82, 69% (0.07)
rs17147230 (2)	HCC vs. HC	**1.31 (1.02, 1.67), 0.03, 0% (0.54)**	**1.83 (1.08, 3.09), 0.02, 0% (0.39)**	11.36 (0.05, 2579.79), 0.38, 93% (0.0002)	2.86 (0.53, 15.48), 0.22, 92% (0.0004)	0.77 (0.11, 5.26), 0.79, 92% (0.0004)

**In recessive model, three studies were included. Bolded numbers are statistically significant (p < 0.05). N – number of studies, OR – odds ratio, CI – confidence interval, P_h – $P_{heterogeneity}$, HCC – hepatocellular carcinoma, LC – liver cirrhosis, CH – chronic hepatitis, HC – healthy control. Arrangement of genotypes: rs2069837 (AA/AG/GG), rs17147230 (AA/AT/TT), rs1800796 (CC/CG/GG), rs1800795 (GG/GC/CC), rs1800797 (GG/GA/AA)*

Table 4. Pooled results of association between rs1800796 polymorphisms and hepatocellular carcinoma risk based on ethnicity

rs1800796 polymorphism (*N*)	Comparison	Allele	Homozygote	Heterozygote	Recessive	Dominant
		OR (95% CI), *p*-value, I^2 (P_h)	OR (95% CI), *p*-value, I^2 (P_h)	OR (95% CI), *p*-value, I^2 (P_h)	OR (95% CI), *p*-value, I^2 (P_h)	OR (95% CI), *p*-value, I^2 (P_h)
Ethnicity						
Asian (4)	HCC vs. HC	0.93 (0.82, 1.05), 0.26, 40% (0.17)	0.88 (0.61, 1.27), 0.48, 0% (0.90)	1.03 (0.89, 1.17), 0.70, 0% (0.75)	1.06 (0.89, 1.28), 0.51, 0% (0.64)	0.87 (0.60, 1.25), 0.44, 0% (0.94)
Caucasian (3)		1.02 (0.60, 1.74), 0.93, 54% (0.11)	0.82 (0.41, 1.63), 0.57, 40% (0.20)	2.51 (0.50, 12.58), 0.26, 69% (0.07)	0.98 (0.79, 1.21), 0.87, 0% (0.51)	0.86 (0.32, 2.28), 0.75, 79% (0.008)
Ethnicity						
Asian (5)	HCC vs. CH	1.16 (0.91, 1.48), 0.24, 74% (0.004)	1.12 (0.63, 1.99), 0.71, 59% (0.04)	1.27 (1.00, 1.61), 0.05, 59% (0.04)	1.23 (0.95, 1.59), 0.12, 68% (0.02)	1.09 (0.60, 1.98), 0.78, 59% (0.04)
Caucasian (2)		1.02 (0.68, 1.54), 0.91, 0% (0.52)	1.27 (0.53, 3.04), 0.59, 0% (0.46)	0.55 (0.26, 1.15), 0.11, 0% (0.52)	0.70 (0.35, 1.39), 0.31, 0% (0.83)	1.29 (0.73, 2.25), 0.38, 37% (0.21)

For all analyses, there was no statistically significant association (p > 0.05).
N – number of studies, OR – odds ratio, CI – confidence interval, P_h – $P_{heterogeneity}$, HCC – hepatocellular carcinoma, CH – chronic hepatitis, HC – healthy control. Arrangement of genotypes: rs1800796 (CC/CG/GG)

polymorphism. The *p*-values of Begg's/Egger's tests were 0.452/0.524, 0.038/0.111, 0.850/0.588, 0.188/0.044, and 0.051/0.432 for the allele, homozygote, heterozygote, recessive, and dominant models, respectively, comparing HCC patients to healthy controls. Also, The *p*-values of Begg's/Egger's tests were 0.176/0.807, 0.880/0.611, 0.652/0.475, 0.452/0.559, and 0.452/0.151 for the allele, homozygote, heterozygote, recessive, and dominant models, respectively, comparing HCC patients to CH patients. Begg's test revealed a publication bias for the homozygote model and Egger's test for the recessive model, comparing HCC patients to healthy controls.

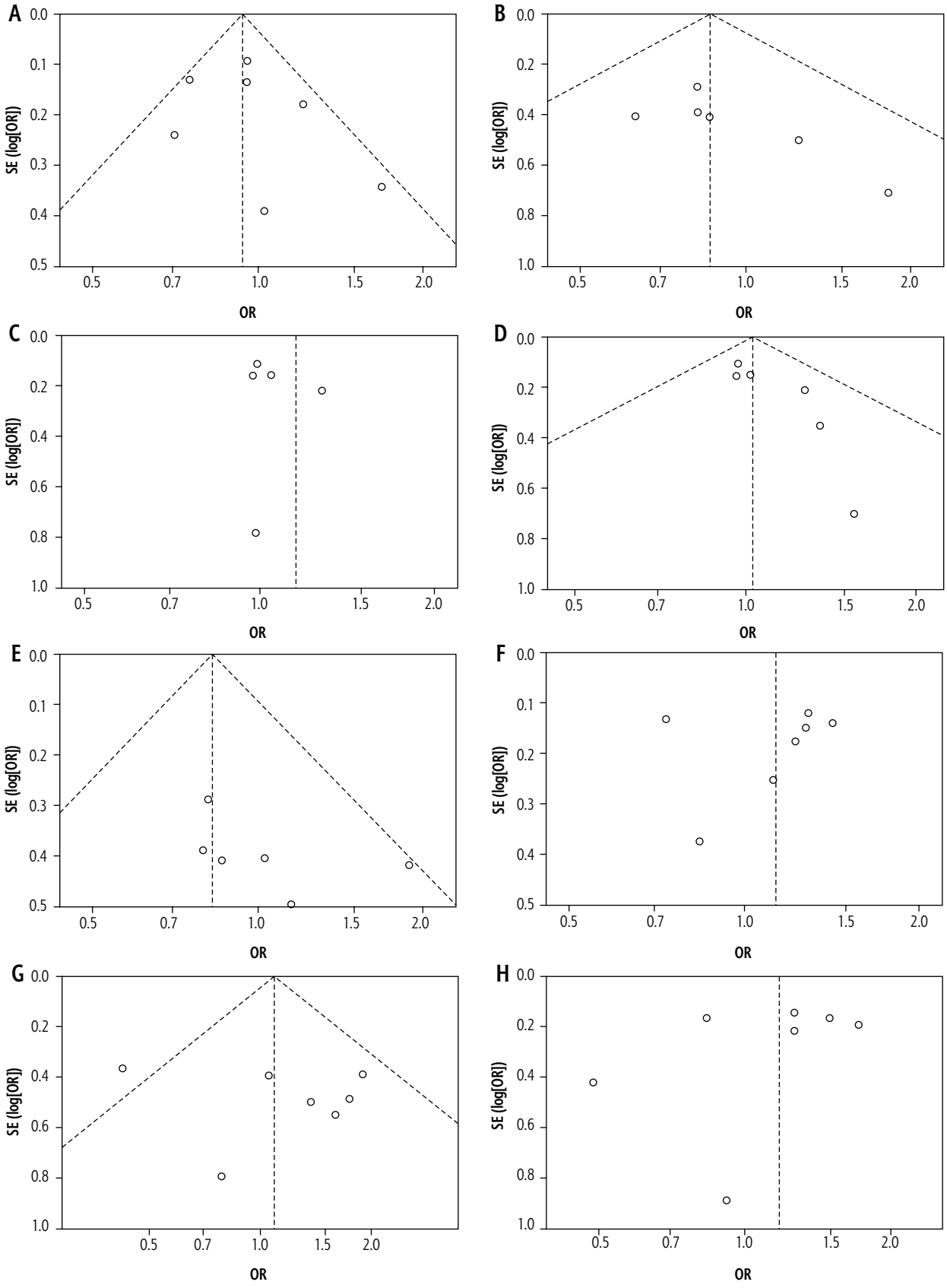


Fig. 2. Funnel plots of association of rs1800796 polymorphism and risk of hepatocellular carcinoma. **A, B, C, D,** and **E** for hepatocellular carcinoma compared to healthy control and **F, G, H, I,** and **J** for hepatocellular carcinoma compared to chronic hepatitis, showing allele, homozygote, heterozygote, recessive, and dominant models, respectively

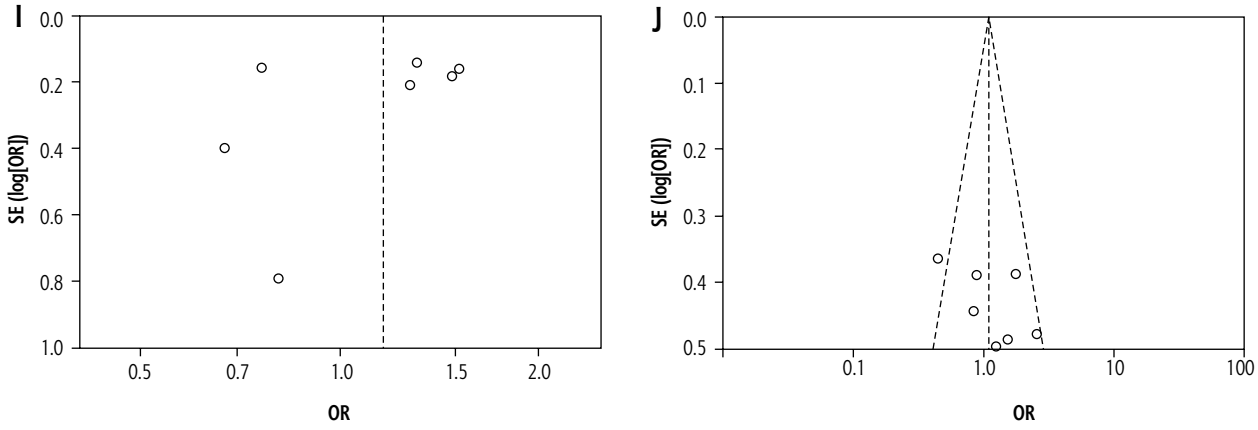


Fig. 2. Cont.

Discussion

The present meta-analysis reported that among *IL-6* polymorphisms (rs1800796, rs1800795, rs2069837, rs17147230, and rs1800797), there was an elevated risk of the AA genotype of rs1800797 in HCC patients compared to healthy controls, and an elevated risk of the AA and GA genotypes of rs1800797 polymorphism in HCC compared to LC. There was an elevated risk of the GG genotype of rs2069837 polymorphism in HCC compared to healthy controls and the T allele and TT genotype of rs17147230 had elevated risks in HCC compared to healthy controls.

Chronic inflammation is the result of inflammatory cells adsorbed to the inflamed site, which is associated with the induction of anti-apoptotic mechanisms [25]. Interleukin 6 plays a significant role in this process because of its bilateral and anti-inflammatory cytokine capacity, which in turn supports cell growth and anti-apoptotic activity associated with chronic inflammation [26]. The authors in a meta-analysis concluded that the rs1800796 polymorphism could not be a candidate for susceptibility to HCC, but rs1800795 had an association with a higher risk of HCC. Another meta-analysis assessing *IL-6* gene polymorphisms and the risk of liver diseases showed that rs1800795, rs1800796, or rs1800797 allele or *IL-6* genotypes might be associated with susceptibility to liver diseases with an ethnic-dependent base [27]. In our meta-analysis with more studies and with a subgroup analysis on ethnicity, there was no association between two *IL-6* polymorphisms (rs1800796 and rs1800795) with susceptibility to HCC, whereas rs1800797 polymorphism was associated with the risk of HCC.

The study of Giannitrapani *et al.* [28] showed the possibility of a genetic link between rs1800795 polymorphism and some specific liver diseases. This has been observed in patients with HCV-related CH, and in LC and HCC patients, but not for patients with HBV-related CH. Some studies have shown the potential role of rs1800796 polymorphism in HBV development and pathogenesis [14, 29], but the rs1800796 polymorphism may not be a determining factor in predicting the outcome of HCV infection [12]. Therefore, it can be assumed that the differences in the results of studies evaluating the association between *IL-6* polymorphisms and HCC risk may be due to the difference in the percentage of HCC patients with HBV or HCV infection. This subject can be considered in the future to obtain better results about this association.

Potential confounding factors, such as sex and ethnicity, can be important for the difference in the association between *IL-6* polymorphisms and the risk of HCC. One study reported that the protective role of female gender against the occurrence of HCC is mainly effective among carriers of high IL-6 producer phenotypes [18]. Some studies have shown that there were ethnic differences in the frequency of alleles of rs1800795 polymorphism, with lower frequencies in Caucasians than in others [30, 31]. In the present meta-analysis, ethnicity was not a confounding factor for the association of rs1800796 polymorphism and HCC risk, which may be because there were low numbers of studies included in each ethnicity.

There were several limitations for this meta-analysis: 1) a low number of studies in each analysis; 2) simultaneous presence of viral infections in HCC patients; 3) the sample size in some of the studies was small; 4) a number of studies showed deviations from HWE; 5) existence of publication bias.

Conclusions

The findings of the present meta-analysis showed that there was an elevated risk of the AA and GA genotypes of rs1800797 polymorphism and the GG geno-

type of rs2069837, and the T allele and TT genotype of rs17147230 in HCC. Future studies need to consider possible confounding factors such as viral infection, sex, and ethnicity and include a larger number of participants.

Disclosure

The authors declare no conflict of interest.

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