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Review

Fas and FasL promoter polymorphisms and susceptibility to HBV infection: A systematic review and meta-analysis

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ABSTRACT

Apoptosis is a universal cellular defense mechanism against senescent, damaged, genetically mutated, or virally-infected cells. It also is critical for the maintenance of liver health. Fas and FasL system act as a major death pathway that triggers apoptosis cascade in the liver. In this systematic review and meta-analysis, we aimed to investigate the relationship between four major polymorphisms of Fas and FasL genes with susceptibility to or clearance of HBV infection.

All the eligible studies were extracted from PubMed and Scopus with no date and language restriction. ORs with 95% CIs were used to evaluate the strength of the association based on the following genetic models: (1) the allelic, (2) the homozygote, (3) the dominant, and (4) the recessive models.

Totally 7 related articles were included in this meta-analysis; 5 studies of 7 related articles investigated FasL -844C/T (rs763110) polymorphism, 4 studies investigated FasL IVS2nt-124, 6 studies investigated Fas -670 A/G (rs1800682), and 4 studies investigated Fas -1377 A/G (rs2234767) polymorphism. This meta-analysis showed that there is no statistically significant association between the risk or clearance of HBV infection and four studied Fas and FasL polymorphisms in their allelic comparison or genetic models.

Fas -670, Fas -1377, FasL -124, and FasL -844 polymorphisms did not show any significant association with the clearance or risk of HBV infection. Therefore, it seems that susceptibility to HBV infection or clearance of it is not affected by Fas and FasL genetic polymorphisms. But, to reach a definitive conclusion, further studies with a larger sample size of different ethnicity are still needed.

1. Introduction

Hepatitis B virus (HBV) infection is one of the major public health problem worldwide (Chisari et al., 2010; Deny and Zoulim, 2010; Liang, 2009). HBV infection is a major risk factor for liver problems such as liver cirrhosis and hepatocellular carcinoma (HCC) (Chisari et al., 2010; Deny and Zoulim, 2010; Liang, 2009). HBV infection as a major public health problem causes different clinical complications ranging from acute hepatitis to chronic hepatitis, liver cirrhosis, and HCC (Chisari et al., 2010; Deny and Zoulim, 2010; Liang, 2009). It could be diagnosed based on clinical, biochemical, histological, and serological findings (Chisari et al., 2010; Deny and Zoulim, 2010; Liang, 2009).

Activated cytotoxic T lymphocytes (CTLs) and natural killer cells (NK cells) are responsible for immunoclearance and destruction of HBV infected cells; so, the impairment of immune response mediated by CTLs and NK cells might lead to persistence of HBV infection and progression of the disease (Chisari et al., 2010; Deny and Zoulim, 2010;

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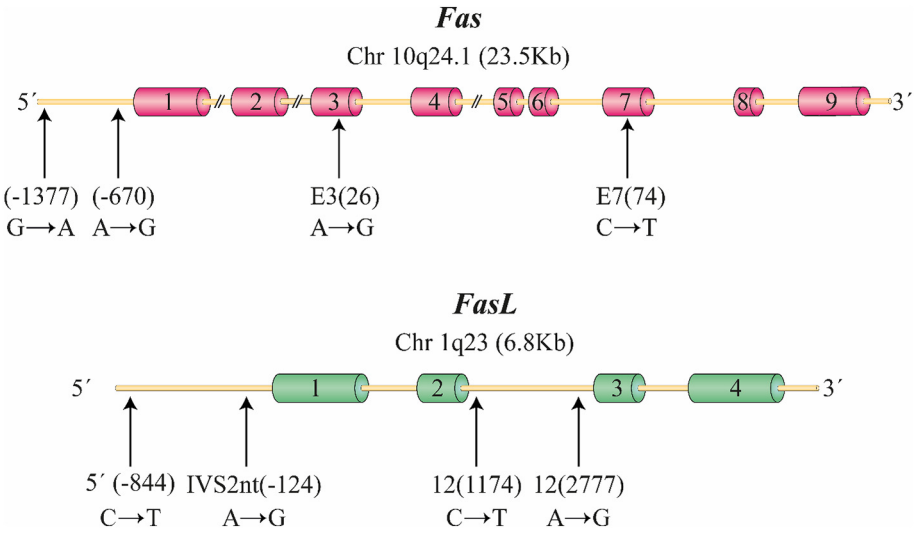

Fig. 1. The structure of the Fas and FasL genes. The Fas gene (also known as TNFSF6, CD95 or APO-1), has been mapped on human chromosome 10q24.1 or 10q23 and spans 23.5 kb of the chromosome. It has nine exons and eight introns and polymorphisms identified in the Fas promoter region are A-to-G transition at position -670 (Fas -670 A/G, rs1800682) and G-to-A transition at position -1377 (FAS-1377 G/A, rs2234767). The FasL gene (also known as CD178 or TNFSF6 or CD95L), has been mapped on human chromosome 1q23 and spans 6.8 kb of the chromosome. It has four exons and polymorphism identified in the Fas promoter region is C-to-T transition at position -844 (FasL -844C/T, rs763110).

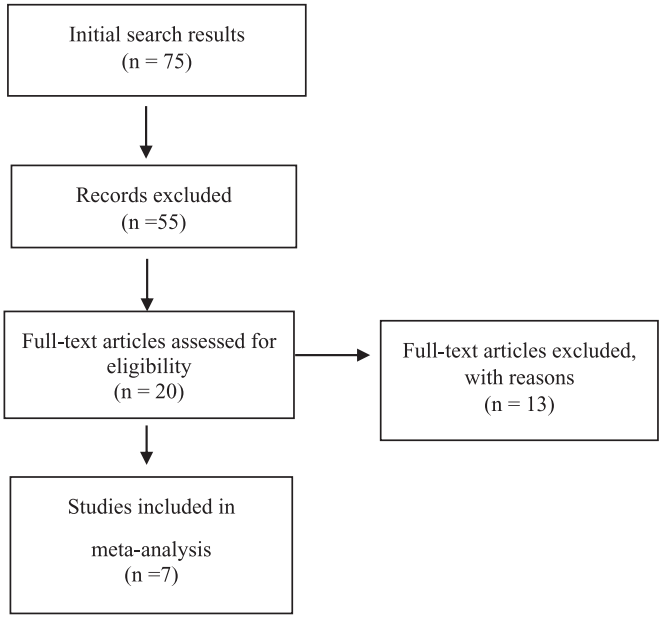

Fig. 2. The selection process of the publications.

Liang, 2009). Apoptosis through the Fas and Fas-ligand (FasL) pathway which is mainly mediated by virus-specific CTLs and NK cells is a cellular defense mechanism against viral infection (Barber, 2001; Mohammadi et al., 2019; Mohammadi et al., 2017) which finally lead to the limitation and elimination of HBV-infected cells or damage to the liver cells (Guicciardi and Gores, 2005; Schwabe and Luedde, 2018).

The Fas (CD95 or APO-1) and FasL (CD178) which are respectively mapped on the human chromosome 10q24.1 and 1q23 are essential for the induction of apoptosis in susceptible cells (Lee and Ferguson, 2003) (Fig. 1). Their ligation and interaction are involved in the induction of apoptosis in Fas-bearing cells which is important for the maintenance of immune homeostasis and regulating the balance between cell death or survival (Lee and Ferguson, 2003). The activation of the Fas/FasL pathway in CTLs and NK cells is also essential for the removal of autoreactive B cells, endothelial cells, regulation of myeloid suppressor cells, and activation of macrophages against infections (Janin et al., 2002; Nagata, 1994; Nagata and Golstein, 1995; Sinha et al., 2011). Accumulating evidence have shown the involvement of Fas/FasL system in the regulation of apoptosis in the hepatocytes and pathogenesis of the liver diseases including liver injury, liver cirrhosis, and HCC (Bortolami et al., 2008; Galle et al., 1995; Higaki et al., 1996; Lee et al., 2001). It has been proposed that the level of the Fas and FasL gene expression will be up-regulated to reach a peak following the development of hepatitis from chronic hepatitis to liver cirrhosis (Bortolami et al., 2008; Galle et al., 1995).

Single nucleotide polymorphisms (SNPs) play an important role in determining the susceptibility of an individual to various disease or determines the response to a therapeutic intervention (Alwi, 2005; Katara, 2014; McCarthy and Hilfiker, 2000). There are several SNPs in the promoter region of the Fas and FasL genes which alter the transcriptional activities of these genes (Huang et al., 1997; Wu et al., 2003). Thus, in this systematic review and meta-analysis, we aimed to investigate the relation between 4 major polymorphisms of the Fas and FasL genes including Fas -670 A/G (rs1800682), Fas -1377 A G / (rs2234767), FasL -844C/T (rs763110), and FasL IVS2nt-124, with susceptibility to or clearance of HBV infection.

2. Methods

2.1. Identification of eligible studies and data extraction

A comprehensive literature search was performed through PubMed and Scopus, to obtain articles which studied the association between Fas and FasL polymorphisms and HBV infection (up to May 2019). The following keywords and search terms were used to find the most related articles: Fas, FasL, HBV, and Hepatitis B virus. References of the selected articles were also checked for other potentially relevant publications which are not indexed in PubMed or Scopus. The selection process was not restricted by date or language of the publications. For the duplicated articles, the study with the larger sample size was selected to be included in this meta-analysis. Inclusion criteria for eligible studies were having the case-control study design, studying the association of the Fas and FasL polymorphisms with HBV, and having sufficient genotype data to calculate the odds ratio (OR) with 95% confidence interval (CI). Studies with uncertain data to obtain the number of null and wild genotypes and those studied family members based on linkage considerations were excluded from the meta-analysis.

The following information was extracted from the included articles in meta-analysis: the first author's name, year of publication, the ethnicity of the study population, demographics, genotyping method, the number of subjects and controls, the source of the control group.

2.2. Evaluation of publication bias

Although publication bias should be evaluated using funnel plot,

Table 1
Characteristics of included studies.

References	Country	Sample size		Diagnosis of cases	Selection of controls	Control matching method	Genotyping method	Polymorphisms	*PHWE*
		Case	Control						
Prasetyo and Agustin (2019)	Indonesia	45	100	serological and molecular assays	healthy adult negative for all bloodborne pathogens	NA	PCR-RFLP	FASLG IVS2nt-124 A/G FAS-670 G/A	0.00 0.19
Arababadi et al. (2010)	Iran	57	100	HBsAg and Anti-HBc screening tests	HBsAg−/anti-HBc+/HBV-DNA+	Sex, age, and socio-economic conditions	PCR-RFLP	FASLG-844 T/C FASLG IVS2nt-124 A/G	0.6 0.2
Zamani et al. (2013)	Turkey	100	108	HBsAg and Anti-HBc screening tests	Seronegative individuals with no HBV vaccination story	Sex and age	PCR-RFLP	FASLG-844 T/C FASLG IVS2nt-124 A/G FAS-670 G/A FAS-1377 G/A	0.9 0.6 0.3 0.5
Santana et al. (2013)	Brazil	116	235	HB patients under treatment at hepatology clinic	Seronegative individuals	NA	PCR-RFLP	FASLG-844 T/C FASLG IVS2nt-124 A/G FAS-670 G/A FAS-1377 G/A	0.3 0.7 0.9 0.09
Mohammadi et al. (2015)	Iran	125	100	Clinical presentations, serological markers, and liver biopsies	No history of hepatitis B, C, D, HIV, autoimmunity and alcohol consumption	Age	PCR-RFLP	FASLG-844 T/C FAS-670 G/A FAS-1377 G/A	0.8 0.8 0.6
Arababadi et al. (2011)	Iran	57	100	HBsAg and Anti-HBc screening tests	HBsAg−/anti-HBc+/HBV-DNA+	Sex, age, and socio-economic conditions	PCR-RFLP	FAS-670 G/A	0.5
Jung et al. (2007)	Korea	666	429	HBsAg and Anti-HBc screening tests	spontaneous recovered	Sex and age	TaqMan	FASLG-844 T/C FAS-670 G/A FAS-1377 G/A	0.5 0.4 0.3

NA: Not available.

Table 2
Distribution of FAS and FASL polymorphisms allele frequency.

	FASL								FAS							
	-844				-124				-670				-1377			
	Case		Control		Case		Control		Case		Control		Case		Control	
	C	T	C	T	A	G	A	G	A	G	A	G	G	A	G	A
Prasetyo and Agustin (2019)					77	13	180	20	32	58	111	89				
Arababadi et al. (2010)	72	42	121	79	94	20	160	40								
Zamani et al. (2013)	94	102	118	98	154	36	170	46	134	64	124	64	185	15	170	46
Santana et al. (2013)	149	83	310	160	215	17	431	39	127	105	218	105	148	24	414	56
Mohammadi et al. (2015)	137	113	101	99					149	101	105	101	213	37	169	31
Arababadi et al. (2011)									69	45	124	45				
Jung et al. (2007)	918	320	615	231					697	597	456	597	763	541	492	36

because of the limited number of studies in this field of research we used Egger's linear regression test to determine funnel plot asymmetry by a natural logarithm scale of ORs (Egger et al., 1997). The significance of the intercept was determined by the *t*-test, and $P < .05$ was considered representative of statistically significant publication bias.

2.3. Statistical analysis

Hardy-Weinberg equilibrium (HWE) was evaluated among control individuals using asymptotic Pearson's $\chi 2$ test for each polymorphism of each study to compare the observed genotype frequencies with the expected ones. Polymorphisms which were studied at least in three studies were included in the meta-analysis. The strength of association between Fas/FasL polymorphisms and susceptibility to HBV as the point estimates of risk was assessed based on calculated ORs with 95% CIs. To this end, four different genetic model for each polymorphism were evaluated, including: (1) allelic contrast model; (2) co-dominant model (heterozygous versus common homozygous carriers and rare homozygous versus common homozygous carriers); (3) dominant model (rare allele carriers versus common homozygous carriers); (4) recessive model (rare homozygous carriers versus common allele carriers). Heterogeneity was assessed based on Chi-square test-based Q-statistic (*p*-value < .05 was considered statistically significant, indicating heterogeneity across studies (Cochran, 1954). I^2 index statistics (Higgins and Thompson, 2002) was calculated to show the effect of heterogeneity, that ranges from 0% to 100% and measure the degree of inconsistency between studies which can be attributed to heterogeneity rather than chance (Higgins et al., 2003). Meta-analysis was performed using comprehensive meta-analysis (CMA) computer program version 2 and random-effects model (DerSimonian and Laird, 1986) for pooling data, which assesses both within-study sampling error and between-study variation and assumes that different studies have substantial diversity.

3. Results

3.1. Studies included in the meta-analysis

Following exploring the title and abstracts of the initial searched articles, 20 articles were selected for full texts reviewing, of which 13 were excluded due to the irrelevant concept and the 7 remained articles which met the inclusion criteria were included in our systematic review and meta-analysis. The reference lists of the included studies were searched to prevent missing any relevant article, but we did not find any additional article by screening the reference lists. The selection process of the articles is presented in Fig. 2 based on the PRISMA flowchart.

The included articles consisted of 5 studies on FasL -844C/T (rs763110) polymorphism with 1064 cases and 927 controls (Arababadi et al., 2010; Jung et al., 2007; Mohammadi et al., 2015; Santana et al., 2013; Zamani et al., 2013), 4 studies on FasL IVS2nt-124 with 318 cases and 543 controls (Arababadi et al., 2010; Prasetyo and Agustin, 2019; Santana et al., 2013; Zamani et al., 2013), 5 studies on Fas -670 A/G (rs1800682) with 1109 cases and 1072 controls (Arababadi et al., 2011; Jung et al., 2007; Prasetyo and Agustin, 2019; Santana et al., 2013; Zamani et al., 2013), and 4 studies on Fas -1377 A/G (rs2234767) with 1007 cases and 827 controls (Jung et al., 2007; Mohammadi et al., 2015; Santana et al., 2013; Zamani et al., 2013). Population and demographic data are summarized in Table 1. Allele frequencies of Fas/FasL studied polymorphisms are summarized in Table 2.

In the included studies all the HBsAg–/anti-HBc + samples were selected as the patient group and screened for HBV-DNA by polymerase chain reaction (PCR).

HWE test which was performed to demonstrate the genetic distribution of the Fas/FasL polymorphisms in the control group showed the consistent distribution of polymorphisms with HWE (Table 1).

3.2. Quantitative data synthesis

Forrest plots of the meta-analysis of the relation between Fas and FasL polymorphisms and HBV are presented in Figs. 3 and 4.

3.3. A meta-analysis of the relationship between the Fas polymorphisms and HBV

ORs obtained by a meta-analysis of the association between Fas polymorphisms, for allelic comparison and recessive, dominant, and homozygote contrast genetic models are summarized in Table 3.

Based on the presented ORs, Fas -1377 (rs2234767) G allele has no statistically significant increasing or even decreasing the effect on HBV infection, in all the studied subjects (OR = 0.9, 95% CI = 0.78–1.06, $p = .2$). Similar results obtained by a meta-analysis of the relation between HBV and Fas -1377 polymorphism in recessive, dominant and homozygote contrast genetic models showed no statistically significant relation (Table 3).

Meta-analysis showed the association between HBV infection and Fas -670 (rs1800682) G allele was not statistically significant (OR = 0.93, 95% CI = 0.70–1.234, $p = .6$). All other genetic models of Fas -670 polymorphism showed no relation with HBV, their association was not statistically significant (Table 3).

3.4. A meta-analysis of the relationship between the FasL polymorphisms and HBV

The association between FasL INV2nt -124 (Rs5030772) G allele and HBV was not statistically significant, (OR = 0.94, 95%

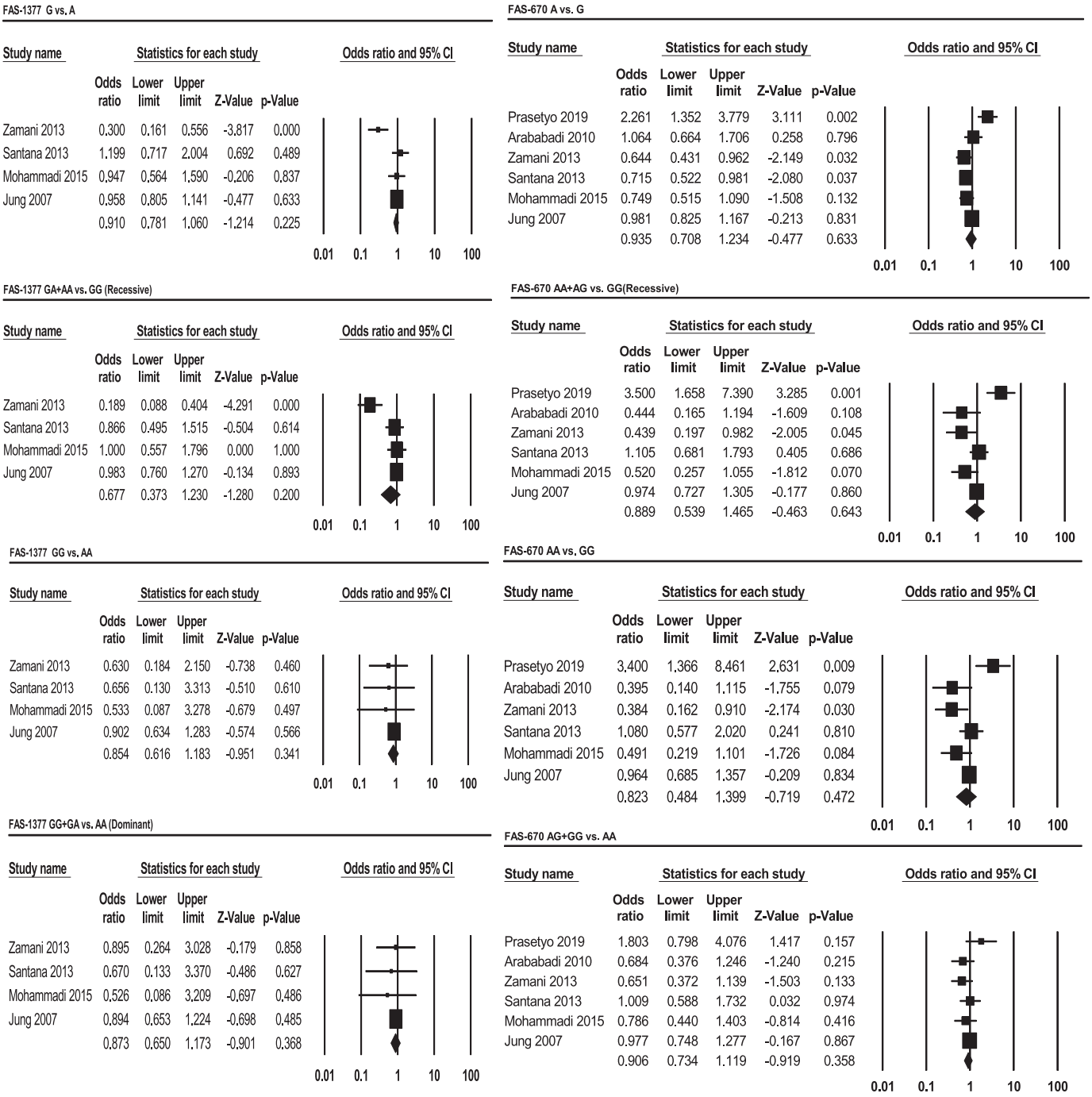

Fig. 3. ORs and 95% CIs of individual studies and meta-analysis data for allele associations between FAS polymorphisms and HBV in all study subjects.

CI = 0.7–1.261, p = .68). The meta-analysis also showed no statistically significant relation between HBV and FasL INV2nt -124 (Rs5030772) in any of the studied genetic models (Table 3).

The relation between FasL -844 (rs763110) T allele and HBV was not also statistically significant (OR = 0.97, 95% CI = 0.85–1.12, p = 3.5). The FasL -844 polymorphism did not have any statistically significant association with HBV infection in any of the studied genetic models (Table 3).

3.5. Heterogeneity and publication bias

Distribution of genotypes of the FasL and Fas polymorphisms in normal controls was consistent with HWE test and except the study of Prasetyo et al. (Prasetyo and Agustin, 2019) which showed statistically significant deviation from HWE (P < .05) in genotype distribution of FasL IVS2nt-124 controls (Table 1).

The assessment of the P-value of Cochrane Q statistics test showed significant between-study heterogeneity following meta-analysis of Fas -1377 and Fas -670 polymorphisms using the allelic comparison and recessive model. No statistically significant heterogeneity was found by the meta-analysis of FasL -844 and FasL -124 polymorphisms (Table 3).

Publication bias was only found to be significant for FasL-124 using a recessive model and Fas -1377 using a homozygote contrast model, according to Eggers regression intercept test p values presented in Table 3.

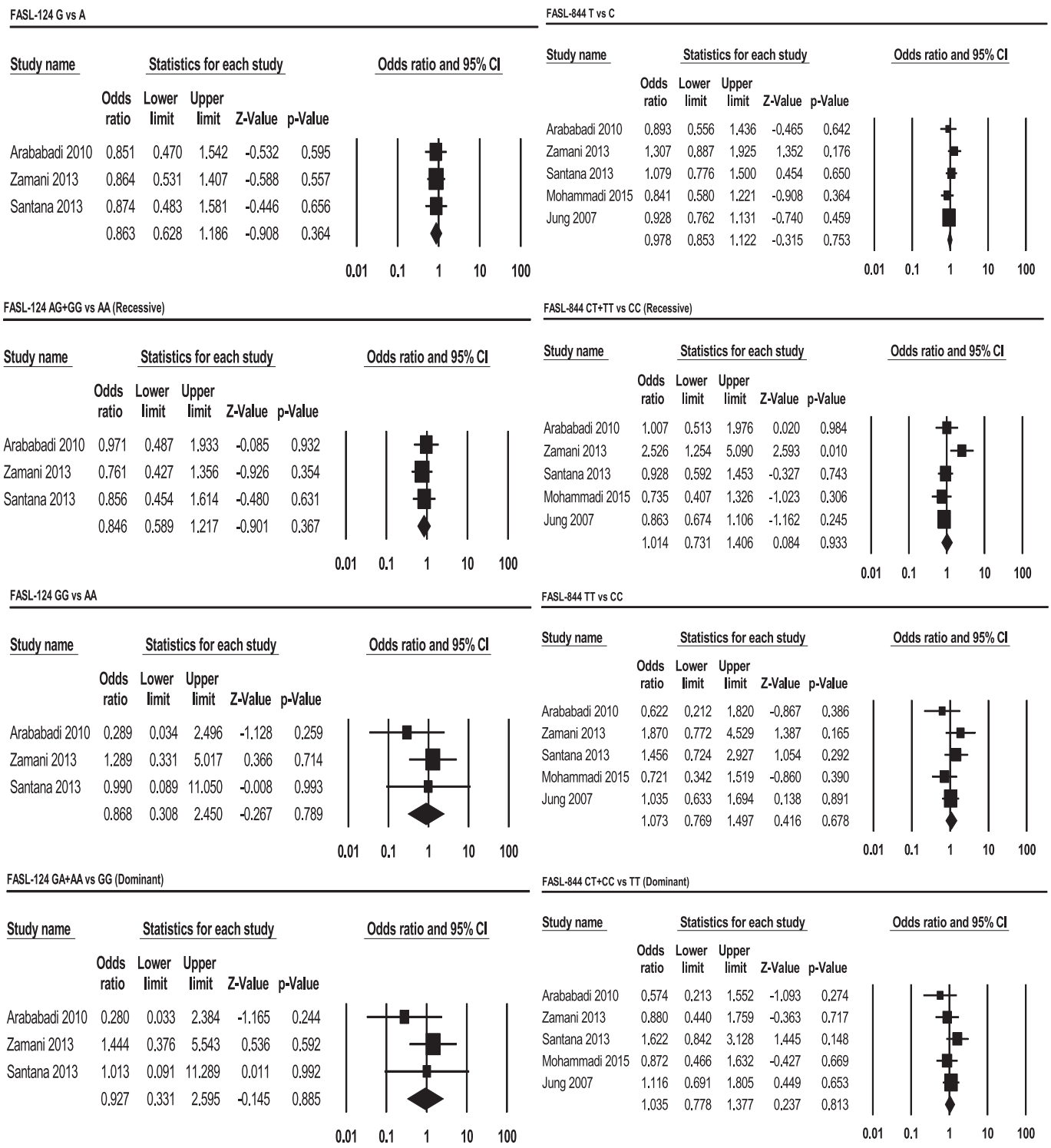

Fig. 4. ORs and 95% CIs of individual studies and meta-analysis data for allele associations between FASL polymorphisms and HBV in all study subjects.

4. Discussion

The present study addressed the genetic association between the four major candidate polymorphisms of Fas (-670 and -1377) and FasL (-844 and -124) genes with susceptibility to or clearance of HBV infection. Our study was the first that gathered all the case-control studies performed on the effect of Fas and FasL polymorphisms expression on HBV infection; the effect on other diseases has been meta-analyzed previously. The main purpose of genetic association studies such as SNPs analysis is the detection of SNPs which exhibits influence on the disease susceptibility and development or determines the response to a therapeutic intervention (Alwi, 2005; Katara, 2014; McCarthy and Hilfiker, 2000; Schwender et al., 2011). Generally, this goal is achieved by investigating and identifying the common, biologically relevant SNPs, in particular, those of the SNPs individually which could lead to the impact on the risk of disease. Moreover, to borrow strength and to identify those genes or pathways that are mostly associated with the disease, it could be helpful to consider sets of SNPs that belonging to the same gene or pathway (Schwender et al., 2011). This categorized information adds to the growing body of evidence on the identification of

Table 3
Main results of pooled ORs in the meta-analysis.

Polymorphisms	Comparison	OR (95%CI)	P-value	Heterogeneity			Egger's regression intercept
				Q- value	P-value	I-squared	
FASLG-844 T/C	C vs. T	0.97(0.85–1.12)	0.75	3.52	0.47	0.00	0.65
	CC vs. TT	1.07(0.76–1.49)	0.67	4.35	0.36	8.14	0.90
	CC/CT vs. TT	1.03(0.77–1.37)	0.81	3.74	0.44	0.00	0.35
	CT/TT vs. CC	1.04(0.73–1.4)	0.93	8.81	0.06	54.6	0.36
FASLG IVS2nt-124 G/A	G vs. A	0.94(0.7–1.26)	0.68	1.8	0.6	0.00	0.17
	GG vs. AA	0.86(0.3–2.45)	0.78	1.33	0.5	0.00	0.31
	GA + AA vs. GG	1.19(0.5–2.7)	0.67	2.25	0.52	0.00	0.26
	GG + GA vs. AA	0.9(0.64–1.27)	0.57	1.33	0.72	0.00	0.00
FAS-670 G/A	A vs. G	0.93(0.7–1.23)	0.63	19.28	0.002	74	0.86
	AA vs. GG	0.98(0.4–2.2)	0.97	1.49	0.68	0.00	0.66
	AA + AG vs. GG	0.88(0.53–1.46)	0.64	20.69	0.00	75.83	0.7
	AG + GG vs. AA	0.90(0.73–1.11)	0.35	5.6	0.34	10.74	0.91
FAS-1377 A/G	G vs. A	0.9(0.78–1.06)	0.22	13.8	0.003	78	0.55
	GG vs. AA	0.85(0.61–1.18)	0.34	0.69	0.87	0.00	0.02
	GG + GA vs. AA	0.87(0.65–1.73)	0.36	0.42	0.93	0.00	0.19
	GA + AA vs. GG	0.67(0.37–1.23)	0.2	16.5	0.00	81.3	0.33

host genetic susceptibility factors for chronicity or clearance of HBV infection. Therefore, clarifying the role of SNPs in the pathogenesis of HBV infection could be helpful in clinical and therapeutic research.

Based on previous studies, Fas and FasL are expressed on some infected hepatocytes following hepatitis viral infection and might be involved in mediating the apoptosis signals from the infected hepatocytes; so, the difference in expression of Fas and FasL might affect the pathogenesis of the liver diseases (Bortolami et al., 2008; Higaki et al., 1996; Lee et al., 2001). We found that the distribution of different genotypes and genetic models of each Fas and FasL polymorphisms (Fas -670, Fas -1377, FasL -124, and FasL -844) were not significantly different between HBV infected patients and healthy controls. In this study, no significant effect was found between Fas -670 polymorphism and HBV disease which was similar with previous meta-analyses data that showed no marked effect of Fas -670 polymorphism on overall cancer risk and susceptibility to Alzheimer's disease (Xu et al., 2014; Zhu et al., 2015). Although the significant association has been shown between Fas -670 with susceptibility to systemic lupus erythematosus (SLE), autoimmune rheumatic (AR), and intervertebral disc degeneration diseases by previous meta-analyses (Huang et al., 2018; Lee et al., 2012; Lee and Song, 2016), this relation was statistically significant only in the dominant model of this polymorphism.

Similar to Fas -670, expression of other polymorphisms including Fas -1377, FasL -124, and FasL -844 showed no statistically significant relation with susceptibility to HBV infection in this meta-analysis; however, previous studies proposed the homozygotes of Fas -1377A and FasL -844C as risk factors of cancer susceptibility that carriers were more prone to majority of malignancies than non-carriers, such as breast and lung cancers (Geng et al., 2014; Wu et al., 2013; Xu et al., 2014; Zeng et al., 2014). The significant relation between Fas -1377 and FasL -844 expressions and SLE, RA, and osteoarthritis has been reported in allele frequencies and genetic models of polymorphisms (Huang et al., 2018; Lee et al., 2012; Lee and Song, 2016). FasL -124 did not show any significant association with HBV infection, similar to its relation with musculoskeletal degenerative diseases.

The included studies in the current meta-analysis were composed of patients with various genetic patterns and different ethnic groups, which might affect the results obtained by each study. The studies on patients from Rafsanjan (Kerman, the southwest of Iran) showed no significant differences between HBV patients and healthy controls in distribution of polymorphisms (-844 and -IVS2nt-124) which are known to influence FasL expression levels. Authors also found no significant difference between HBV and healthy control groups by evaluating the Fas -670 allele frequency and genotypes. Based on their study, the types of hepatitis infection and genetic differences in populations studied might be the reasons for the various results obtained (Arababadi et al., 2010; Arababadi et al., 2011).

Similar results were obtained by our study that performed in Tehran-Iran (Mohammadi et al., 2015), which showed no difference between HBV infected patients and healthy controls regarding the FasL -844C/T polymorphism. We also did not find any statistically significant difference for distribution of Fas (-670 and -1377) polymorphisms between HBV infected patients and healthy control groups. But, we found that liver cirrhotic patients compared to the chronic carrier, chronic hepatitis, liver cirrhosis, naturally recovered and healthy control groups had higher frequency of FasL -844 CC genotypes and C allele. Over-expression of the FasL gene in chronically infected liver tissue may make hepatocytes more susceptible to apoptosis and consequently liver destruction. We also showed that FasL -844 T allele was associated with HBV clearance and protection of infected patients against liver cirrhosis.

Different results were reported in the studies on Fas -670 on Turkish and Indonesian patients (Prasetyo and Agustin, 2019; Zamani et al., 2013). They showed a statistically significant difference for Fas -670 polymorphism on allele frequency and homozygote genotype between HBV patients and controls. By evaluating Fas -1377 on Turkish patients, they also showed a significantly greater frequency of a mutant allele in HBV patients compared with controls. However other genetic models of this polymorphisms were not significantly different between groups. By evaluating the FasL polymorphisms no significant relation was found between FasL polymorphisms (-844 and -124) between groups on allelic or genotypic frequencies (Zamani et al., 2013). A similar study on Brazilian and Korean patients showed no significant difference between HBV patients and healthy controls while comparing the frequency of combined genotypes and allele frequency of the Fas and FasL polymorphisms (Jung et al., 2007; Santana et al., 2013).

Based on the HWE test, all the included studies were in HWE which shows controls could well represent the general population. There was also no significant heterogeneity that affects the study results. In summary, this meta-analysis study for the first time showed that there is no statistically significant association between the risk of HBV infection and Fas -670, Fas -1377, FasL -124, and FasL -844 polymorphisms in their allelic comparison or genetic models. In conclusion, the results of the present study suggest that susceptibility to HBV infection is not affected by the Fas and FasL genetic polymorphisms. But, to reach a definitive conclusion, further studies with a larger sample size of patients from different ethnicity are still needed.

Declaration of Competing Interest

None.

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