Int J Clin Exp Med 2018;11(8):7601-7607
www.ijcem.com /ISSN:1940-5901/IJCEM0053074

Review Article

The interleukin 1 beta -511 C/T gene polymorphism and susceptibility to sepsis: a meta-analysis

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Received November 1, 2016; Accepted July 2, 2017; Epub August 15, 2018; Published August 30, 2018

Abstract: Numerous articles have evaluated the relationship between -511 C/T polymorphism in the Interleukin-1β (IL-1β) gene and sepsis risk. However, the specific relationship is still controversial for small sample size. We performed a meta-analysis to assess the correlation. A comprehensive search was conducted to identify all published articles on the association between IL-1β gene -511 C/T polymorphism and sepsis risk from different databases. Pooled odds ratios (ORs) with 95% confidence intervals (CI) were calculated and the heterogeneity and publication bias were assessed. A total of 5 case-control studies were finally identified. The results suggested that IL-1β -511 C/T polymorphism may not be associated with sepsis risk (for TT vs. CC: OR=0.75, 95% CI=0.42-1.33; for CT vs. CC: OR=0.72, 95% CI=0.46-1.11; for the dominant model: OR=0.70, 95% CI=0.49-1.01; and for the recessive model: OR=0.89, 95% CI=0.53-1.50). In a subgroup analysis by nationality, the results also showed no association between IL-1β gene -511 C/T polymorphism and sepsis risk. In conclusion, the -511 C/T polymorphism in the IL-1β gene might not be related to the risk of sepsis.

Keywords: Sepsis, IL-1β gene, genetic variant, meta-analysis

Introduction

Sepsis is a potentially life-threatening infection complication that causes millions of deaths globally each year [1]. In addition to the damage caused by pathogenic microorganisms, altered expression of cytokines that play key roles in the regulation of host immune response are also involved in the pathogenesis and etiotogy of sepsis [2]. Previous studies have reported that variations in the genes encoding cytokines are involved in the modulation of inflammatory responses and are responsible for the varied susceptibility to sepsis [3], such as the tumor necrosis factor-alpha 308 A/G polymorphism [4].

The interleukin-1 (IL-1) family has three members: IL-1α, IL-1β, and IL-1 receptor antagonist [5]. IL-1β is a potent proinflammatory cytokine released by macrophages during the systemic inflammatory response [5]. IL-1 is thought to play an important role in sepsis development, and regulates the inflammatory reaction and immune response by increasing the expression of other cytokines, such as IL-6 and IL-12 [6, 7]. The genes for these cytokines are clustered within a 430-kb segment on human chromosome 2. Recently, a common polymorphic allele of the regulatory region of the IL1β gene was found to be associated with increased IL-1 production [8]. Because altered expression of cytokines that regulate host immune response are also involved in the development of sepsis, we hypothesized that IL-1β single nucleotide polymorphisms (SNPs) may affect the development of sepsis. Three SNPs were found within the IL-1β gene, -31 (rs1143627) and -511 (rs16944) in the promoter region and +3954 (rs1143634) in exon 5 [9]. Of these SNPs, the -511 C/T polymorphism was previously proved to be associated with chronic gastritis, gastric ulcers, polycystic ovary syndrome, and Crohn's disease [10-12].

Although changes in other cytokine genes have been shown to affect sepsis, there have been different conclusions about the association

Table 1. Scale for quality assessment

Criteria	Score
Source of cases	
Selected from population disease registry or multiple center sites	2
Selected from hospital	1
Not described	0
Source of controls	
Population-based	3
Blood donors or volunteers	2
Hospital-based	1
Not described	0
Ascertainment of sepsis	
Standard method confirmation	2
Not described	0
Genotyping examination	
Genotyping done under blinded conditions	1
Unblinded or not mentioned	0
Hardy-Weinberg equilibrium in controls	
Hardy-Weinberg equilibrium	3
Hardy-Weinberg disequilibrium	0
Association assessment	
Assessed association between genotypes and sepsis with appropriate statistics and examining	1
Confounders and effect modifiers	0
Inappropriate statistics used	

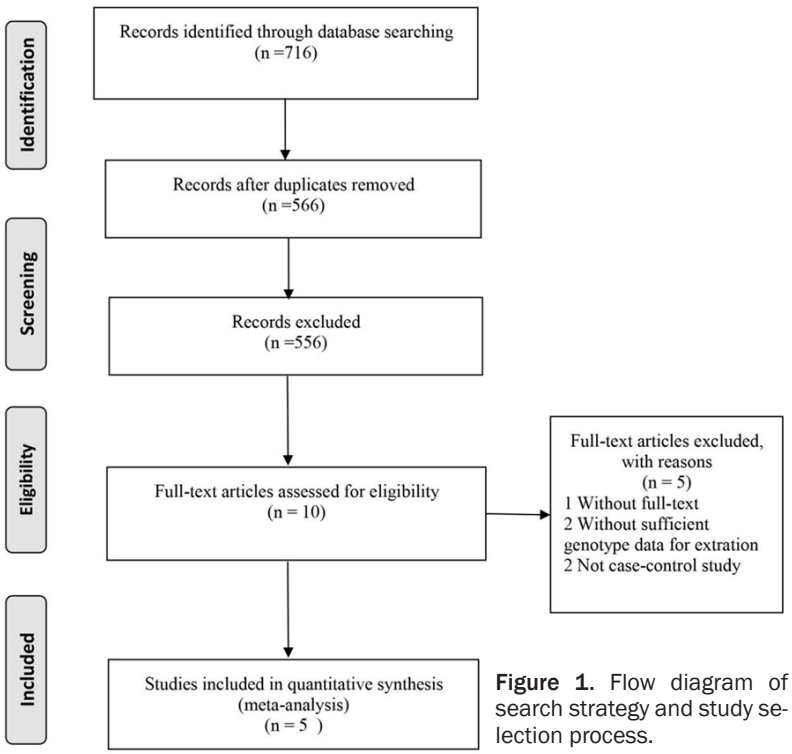

Figure 1. Flow diagram of search strategy and study selection process.

between the IL-1β -511 C/T polymorphism and sepsis risk. However, many of these studies have suffered from a relatively small sample size, limiting the robustness of the results. To better elucidate the potential relationship between the IL-1β -511 C/T polymorphism and the risk of sepsis, we performed this meta-analysis by collecting and analyzing previous published data.

Materials and methods

Identification and eligibility of relevant studies

We conducted a literature search of PubMed, Chinese BioMedical Literature (CBM), Wanfang, China Na-

Table 2. Characteristics of the included studies for meta-analysis

Study included	Year	Area	Race	Cases/Controls	Genotypes for cases			Genotypes for controls			HWE test	Quality scores
					CC	CT	TT	CC	CT	TT		
Gu	2010	China	Asian	167/140	57	83	27	34	61	45	0.15	8
Davis	2010	America	Mixed	28/53	17	6	5	19	29	5	0.20	11
Shimada	2011	Japan	Asian	123/101	33	60	30	35	46	20	0.49	8
Wan	2012	China	Asian	21/60	11	6	4	12	30	18	0.94	8
Johnson(a)	2012	America	Caucasian	245/263	103	114	28	101	120	42	053	8
Johnson(b)	2012	America	African	93/88	28	36	29	26	43	19	0.88	8

HWE = Hardy-Weinberg equilibrium.

Table 3. Summary odds ratios and 95% confidence intervals concerning the association between IL-1β -511 C/T polymorphism and sepsis risk

Variables	TT vs. CC			CT vs. CC			Dominant model			Recessive model		
	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2
Total	0.75 (0.42-1.33)	0.01	66.3%	0.72 (0.46-1.11)	0.02	61.8%	0.70 (0.49-1.01)	0.06	53.5%	0.89 (0.53-1.50)	0.01	67.4%
Asian	0.55 (0.17-1.25)	0.00	81.7%	0.73 (0.33-1.25)	0.03	72.9%	0.61 (0.30-1.25)	0.03	71.9%	0.67 (0.29-1.55)	0.02	73.3%
The others	0.87 (0.57-1.33)	0.27	24.0%	0.65 (0.34-1.25)	0.06	64.1%	0.81 (0.60-1.09)	0.20	38.2%	1.18 (0.57-2.44)	0.07	63.4%

I^2: Inconsistency index; CI: confidence interval; OR: odds ratio.

tional Knowledge Infrastructure (CNKI) and Embase databases (including publications from 1990 to 2016) using the following keywords and subject terms: "interleukin-1" or "IL-1", "polymorphism" or "allele", and "sepsis". For articles with overlapping data, we selected the study with the largest number of subjects. In addition, a manual review of references from primary or review articles was performed to identify additional relevant studies.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) evaluation of the IL-1β -511 C/T polymorphism and sepsis risk, (ii) case-control studies, (iii) sufficient published data to calculate an odds ratio (OR) with 95% confidence interval (CI), and (iv) the genotype frequencies of healthy controls were in Hardy-Weinberg equilibrium (HWE). Major exclusion criteria were: (i) articles that were only abstracts or reviews lacking primary data, (ii) animal studies, and (iii) studies that used the same dataset.

Data extraction

Three investigators independently extracted the data and reached a consensus on the inclusion of the extracted data. The following data were extracted from each study: author(s), publication date, country where the study was performed, ethnicity, sample size of cases and controls, allelic frequencies of the IL-1β -511 C/T polymorphism, and the Hardy-Weinberg equilibrium (HWE) of the control groups.

Quality score assessment

The quality of the included studies was evaluated independently by 2 investigators according to a set of predetermined criteria (**Table 1**), modified from previous studies. Any disagreements were resolved by discussion by the 2 authors to reach consensus [13]. Scores ranged from 0 (lowest) to 10 (highest), and studies with scores ≥ 6 were classified as high-quality studies and studies with scores < 6 were classified as low-quality studies.

Statistical methods

The chi-square goodness-of-fit test was used to evaluate the Hardy-Weinberg equilibrium of the controls of each study. The strength of association between the polymorphism and cancer risk was measured by the odds ratios (ORs) with 95% confidence intervals (CIs) calculated separately for the codominant genetic model (TT vs. CC; CT vs. CC), dominant model (TT+CT vs. CC), and the recessive model (TT vs. CT+CC) [14]. We quantified the effect of heterogeneity by the I^2 test. The I^2 can range between 0 and 100% and represents the proportion of inter-study

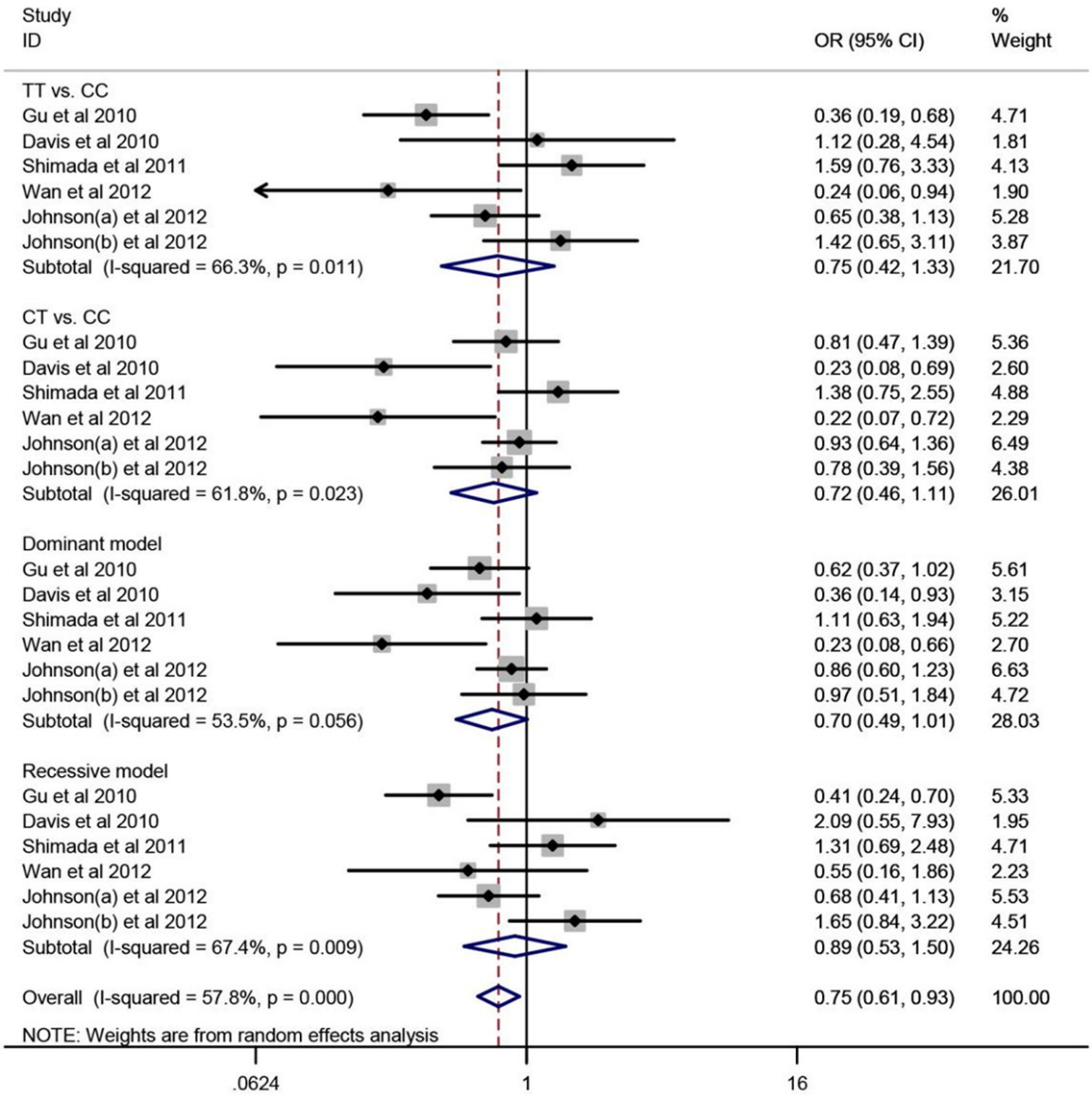

Figure 2. Forest plots showing the association of the IL-1β -511 C/T polymorphism with risk of sepsis.

variability that can be attributed to heterogeneity rather than random chance. A value of I^2 > 50% indicated heterogeneity across studies, so then requiring use of the random effects model for meta-analysis. Otherwise, the fixed effects model was used. In addition, sensitivity analyses were performed by the removal of a single study and analysis of the remaining data. The Begg's funnel plot and Egger's test methods were used to evaluate the publication bias. All statistical tests were performed with the software STATA version 12.0 (Stata Corporation, College Station, TX, USA). A *P* value < 0.05 was considered statistically significant.

Results

Study characteristics

The search strategy retrieved 447 potentially relevant studies. Based on the inclusion criteria, 5 case-control studies with full-text were selected for inclusion in this meta-analysis and 442 studies were excluded [15-19]. The flow chart of study selection is summarized in **Figure 1**. The 5 case-control studies selected included a total of 677 cases and 705 healthy controls. The HWE test was performed on the genotype distribution of the controls and all of them were in HWE (P > 0.05). The description of these 5

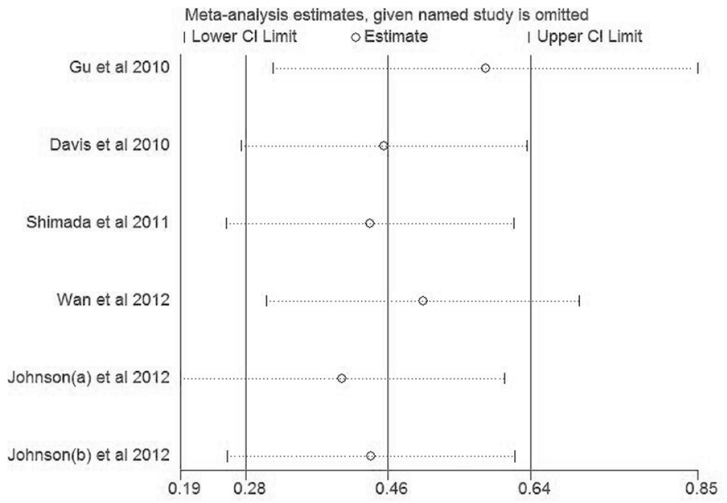

Figure 3. One-way sensitivity analysis of the pooled odds ratios and 95% confidence interval for ALDH2 Glu504Lys polymorphism, omitting each dataset in the meta-analysis.

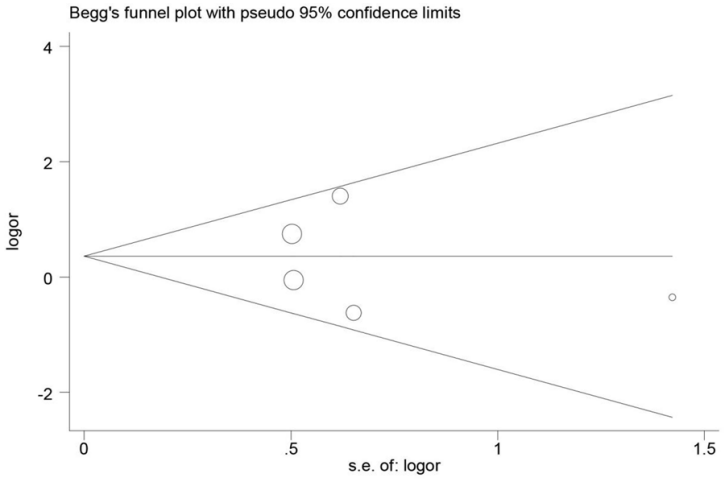

Figure 4. Begg's funnel plot test of publication bias.

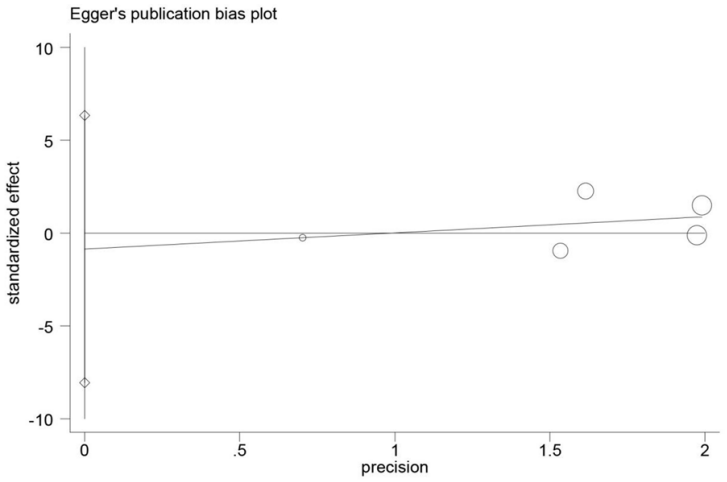

Figure 5. Egger's funnel plot test of publication bias.

studies and the numbers of cases and controls with different genotypes reported in each study are presented in **Table 2**. There were 3 studies of Asians and 2 studies of subjects of other ethnicity. The results of the quality score assessment showed that the score ranged from 8 to 11, which indicated that the methodological quality of the included studies was high.

Quantitative data synthesis

Table 3 lists the main results of the meta-analysis. When all 5 studies were pooled into the meta-analysis, there was no evidence of a significant association between the IL-1β -511 C/T polymorphism and sepsis (for TT vs. CC: OR=0.75, 95% CI=0.42-1.33; for CT vs. CC: OR=0.72, 95% CI=0.46-1.11; for the dominant model: OR=0.70, 95% CI= 0.49-1.01; and for the recessive model: OR=0.89, 95% CI=0.53-1.50) (**Figure 2**). In the subgroup analysis separated by ethnicity, statistically significant association was similarly not observed (**Table 3**).

Sensitivity analysis was performed to assess the influence of each individual study on the pooled OR by separate removal of a single study. After the removal of each data set individually from the meta-analysis, the pooled ORs remained unchanged (**Figure 3**). Thus, no single study qualitatively influenced the pooled ORs, suggesting stable results of this meta-analysis.

Evaluation of publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of the included studies for the IL-1β -511 C/T polymorphism. The shape of the funnel plot did not reveal any evidence of obvious asymmetry

(**Figure 4**). Next, the Egger's test was used to provide statistical evidence of funnel plot symmetry (**Figure 5**). The results did not indicate any publication bias for the IL-1β -511 C/T polymorphism.

Discussion

Sepsis is the systemic inappropriate inflammatory response or inappropriate defense mechanisms of the host organism to the invasion of microorganisms [20]. Previous studies have showed that inappropriate host inflammation response or inappropriate defense mechanisms contribute to the development of sepsis [21]. Among host factors, IL-1 is thought to play an important role in sepsis development. However, there were conflicting reports of the association between the IL-1β -511 C/T polymorphism and sepsis risk. To clarify this potential association, we performed this meta-analysis.

The present meta-analysis of the data from 5 studies including 677 cases and 705 controls provides the most comprehensive analysis of the relationship between the IL-1β -511 C/T polymorphism and sepsis. The results of our meta-analyses did not find an association of the IL-1β -511 C/T polymorphism with sepsis in the overall population. Subgroup analysis by ethnicity also found no association between this polymorphism and sepsis susceptibility for Asians or Caucasians. However, the potential function of this polymorphism may be affected by gene-gene and gene-environment interactions. Further large and well-designed studies are needed to test this hypothesis.

Several limitations of this meta-analysis should be addressed. Firstly, the total pooled sample size is still relatively small, and may not provide sufficient power to estimate the association between the IL-1β -511 C/T polymorphism and sepsis. Secondly, subgroup analyses to examine effects of age, gender, and other factors could not be performed due to a lack of sufficient relevant data. Thirdly, the meta-analysis approach is retrospective research that is subject to methodological limitations.

In summary, the results of our meta-analysis found no evidence for the association of the IL-1β -511 C/T polymorphism with sepsis risk. Larger datasets should be considered in future studies to further evaluate the effect of gene-environment interactions.

Disclosure of conflict of interest

None.

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