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Investigation of the IL-1β +3954 C>T polymorphism and the risk of sepsis

A case-control study

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Abstract

Studies have obtained conflicting findings regarding the association between the interleukin-1β (IL-1β) +3954 C>T polymorphism and the risk of sepsis. To evaluate the association between the IL-1β +3954 C>T polymorphism and sepsis risk in Chinese individuals, we conducted a study of 254 sepsis patients and 322 controls. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used for genotyping. We found that the IL-1β +3954 C>T polymorphism was associated with a reduced risk of sepsis. Subgroup analyses revealed that this significant association was more evident among nonsmokers, nondrinkers, individuals with body mass index <25, and individuals aged ≥60 years. The IL-1β +3954 C>T polymorphism was also associated with the 28-day mortality rate and severity of sepsis. In summary, the IL-1β +3954 C>T polymorphism confers a reduced risk of sepsis in Han Chinese. This polymorphism may serve as a marker that predicts patients' susceptibility to sepsis.

Abbreviations: BMI = body mass index, CI = confidence interval, HWE = Hardy-Weinberg equilibrium, IL-1 = interleukin-1, IL-1β = interleukin-1β, OR = odd ratio, SNP = single nucleotide polymorphism.

Keywords: +3954 C>T polymorphism, case-control study, IL-1β, sepsis

1. Introduction

Sepsis is a life-threatening disease with a high mortality rate caused by a dysregulated host response to bacterial infections.[1] Sepsis is the primary cause of death in hospitalized patients worldwide, and is associated with high mortality and morbidity.[2,3] The Third International Consensus Definitions defines 2 types of sepsis: sepsis and septic shock.[1] Sepsis is a polygenic and multifactorial disease that involves both genetic and environmental factors.[4,5] However, only some individuals exposed to environmental factors develop this disorder, suggesting that other factors (e.g., genetic characteristics) may be involved in the pathology of sepsis.[6] Identifying gene loci will help develop treatment strategies targeted to specific individuals.

Cytokines are regulators of inflammation, some of which are associated with susceptibility to sepsis and the severity of sepsis.[7,8] Interleukin-1 (IL-1) is an important cytokine related to sepsis risk. The IL-1 family contains 2 proinflammatory cytokines (interleukin-1β (IL-1β) and IL-1α) and an IL-1 receptor antagonist (IL-1Ra or IL-1RN).[9] IL-1 signaling strengthens the plasma inflammatory response to sepsis.[10] IL-1β, a potent proinflammatory cytokine, is pivotal for the host responses to injury and infection,[11] IL-1β is secreted mainly by tissue macrophages and blood monocytes. Notably, plasma IL-1β levels are elevated early and remain high in neonatal sepsis.[10] Ayazi et al indicated that IL-1β might be an ideal diagnostic marker for infections in patients with sepsis.[12]

The *IL-1β* gene is located on chromosome 2 in the human genome; it has 7 exons and 6 introns. A single nucleotide polymorphism (SNP) with a T substitution for C at position +3954, which is in the 5th intron of the *IL-1β* gene, is known as IL-1β +3954 C/T (rs1143634). The IL-1β +3954 C>T polymorphism is a synonymous variant (NM_000576.2: c.315C>T; NP_000567.1:p.Phe105=). Several recent studies have investigated the association between the risk of sepsis and this polymorphism.[13–18] However, these studies have yielded conflicting findings. Some did not find an association between the IL-1β +3954 C>T polymorphism and sepsis susceptibility in Caucasian populations.[13–16] However, Johnson et al found that this SNP was related to a decreased risk of sepsis in an American population.[17] In addition, a study of a Chinese population showed that this polymorphism did not modify the risk of septic shock.[18] Therefore, this study assessed the relationship between IL-1β +3954 C>T polymorphism and sepsis risk in a population from Eastern China.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration.

Informed consent was obtained from all individual participants included in the study.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Patients and methods

2.1. Patients

In total, 254 patients with sepsis and 322 control patients were enrolled from the Huai'an No. 1 People's Hospital. All patients with sepsis were diagnosed in accordance with the Third International Consensus Definitions.[19] Patients with sepsis were categorized into those with sepsis and those with septic shock.[19] Detailed findings regarding patients with sepsis were described in a previous report by our group.[20] This study was reviewed and approved by the Ethics Committee of our hospital; it also met the standards of the Declaration of Helsinki. The IRB number YX-P-2016-047-01. All participants provided informed consent.

2.2. Blood sampling and genotyping

Venous blood was collected from all participants. The TIANamp Blood DNA kit was used to extract genomic DNA from leukocytes (Tiangen Biotech, Beijing, China). The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was used for genotyping, with the following primers: 5′-GTTGTCATCAGACTTTGACC-3′ and 5′-TTCAGTTCA-TATGGACCAGA-3′. Ten percent of samples from patients with sepsis were randomly chosen for repeated genotyping, and the validation rate was 100%.[21]

2.3. Statistical analysis

Differences in allele and genotype frequencies were determined using the chi-square test. Categorical variables, such as sex and the use of alcohol/cigarettes, were assessed with the chi-square test.[22] Continuous variables, such as age and body mass index (BMI), were evaluated with Student's *t* test. Genotype distributions of control patients were assessed based on Hardy-Weinberg equilibrium (HWE). Logistic regression analysis was used to evaluate crude and adjusted 95% confidence intervals (CIs) and odds ratios (ORs). SPSS Statistics, ver. 20.0 was used for all statistical analyses (IBM, Armonk, NY). A two-sided *P*-value $<.05$ was considered to indicate statistical significance.

3. Results

3.1. Participant characteristics

Demographic and clinical characteristics for patients with sepsis and control patients are listed in Table 1. In this case-control study, we enrolled 254 patients with sepsis and 322 control patients. The 254 patients with sepsis included 139 men and 115 women, while the 322 control patients included 166 men and 156 women. We found no significant differences in age or sex between the sepsis and control groups ($P>.05$). However, a significantly greater proportion of patients with sepsis smoked cigarettes or drank alcohol, compared with the control group ($P<.05$).

Table 1

Patient demographics and risk factors in sepsis.

Characteristics	Case (N = 254)	Control (N = 322)	*P*
Age (SD, range)	64.7 (35–94)	63.3 (34–88)	.078
Sex			.449
Male	139 (54.7%)	166 (51.6%)	
Female	115 (45.3%)	156 (48.4%)	
Smoking			**.026**
Yes	82 (32.3%)	77 (23.9%)	
No	172 (66.7%)	245 (76.1%)	
Alcohol			**.031**
Yes	76 (29.9%)	71 (20.0%)	
No	178 (70.1%)	251 (78.0%)	
BMI	23.09 ± 3.06	22.90 ± 2.93	.451
APACHE II score	21.50 ± 5.03		
Sepsis status (n, %)			
Sepsis	157 (61.8%)		
Septic shock	97 (38.2%)		
Pathogens (n, %)			
Gram-positive	46 (18.1%)		
Gram-negative	129 (50.8%)		
Mixed Gram-negative and -positive	58 (22.8%)		
Fungus	21 (8.3%)		
Source of infection, n (%)			
Respiratory tract infection	175 (69.0%)		
Abdominal infection	43 (17.0%)		
Urinary tract infection	12 (4.7%)		
Catheter-associated infection	10 (3.9%)		
Others	14 (5.4%)		
Mortality, 28 d, n (%)	62 (24.4%)		

Bold values are statistically significant ($P<.05$). BMI = body mass index.

3.2. Relationship between IL-1β +3954 C>T polymorphism and sepsis risk

Genotyping was successful in 254 patients with sepsis and 321 control patients. Table 2 shows the allele and genotype

Table 2

Genotype frequencies of IL-1β +3954 C>T polymorphism in cases and controls.

Models	Genotype	Case (n, %)	Control (n, %)	OR (95% CI)	*P	OR (95% CI)	†P
Co-dominant	CC	156 (61.4%)	166 (51.7%)	1.00 (reference)	–	–	–
Heterozygote	CT	87 (34.3%)	129 (40.2%)	0.71 (0.50–1.01)	.058	0.72 (0.50–1.02)	.067
Homozygote	TT	11 (4.3%)	26 (8.1%)	**0.45 (0.21–0.94)**	**.033**	**0.45 (0.21–0.95)**	**.036**
Dominant	CC	156 (61.4%)	166 (51.7%)	1.00 (reference)	–	–	–
	TT + CT	98 (38.6%)	155 (48.3%)	**0.67 (0.48–0.93)**	**.018**	**0.67 (0.48–0.94)**	**.022**
Recessive	CT + CC	243 (95.7%)	295 (91.9%)	1.00 (reference)	–	–	–
	TT	11 (4.3%)	26 (8.1%)	0.51 (0.25–1.06)	.070	0.51 (0.25–1.07)	.074
Allele	C	399 (78.5%)	461 (71.8%)	1.00 (reference)	–	–	–
	T	109 (21.5%)	181 (28.2%)	**0.70 (0.53–0.91)**	**.009**		

Bold values are statistically significant ($P<.05$). CI = confidence interval; OR = odds ratio.

* χ^2 test for genotype distributions between sepsis and controls.

† Adjustment for sex and age.

Table 3

Stratified analyses between IL-1β +3954 C>T polymorphism and the risk of sepsis.

Variable	(Case/control) CC	CT	TT	CT vs CC OR (95% CI); *P*	TT vs CC OR (95% CI); *P*	TT vs CC+CT OR (95% CI); *P*	TT+CT vs CC OR (95% CI); *P*
Sex							
Male	82/82	51/70	6/13	0.73 (0.45–1.17); 0.189	0.46 (0.17–1.27); 0.128	0.53 (0.20–1.43); .201	0.69 (0.44–1.08); 0.105
Female	74/84	36/59	5/13	0.69 (0.41–1.16); 0.165	0.44 (0.15–1.28); 0.123	0.50 (0.17–1.45); 0.193	0.65 (0.39–1.06); 0.083
Smoking							
Yes	52/41	26/28	4/8	0.73 (0.37–1.44); .364	0.39 (0.11–1.40); .150	0.44 (0.13–1.53); .199	0.67 (0.31–1.48); .325
No	104/125	61/101	7/18	0.72 (0.48–1.09); .117	0.46 (0.19–1.15); .098	0.53 (0.22–1.30); .166	**0.64 (0.41–0.99); .044**
Alcohol							
Yes	40/36	33/28	3/7	1.06 (0.54–2.08); 0.864	0.39 (0.09–1.61); 0.178	0.38 (0.09–1.51); 0.274	0.93 (0.48–1.77); 0.815
No	116/130	54/101	8/19	**0.60 (0.40–0.91); 0.015**	0.47 (0.20–1.12); 0.083	0.57 (0.25–1.34); 0.193	**0.58 (0.39–0.86); 0.007**
Age (yr)							
<60	37/67	23/42	5/10	0.99 (0.52–1.90); .980	0.91 (0.29–2.85); .865	0.91 (0.30–2.78); .866	0.98 (0.53–1.80); .935
≥60	119/99	64/87	6/16	**0.61 (0.40–0.92); .020**	**0.31 (0.12–0.82); .018**	**0.38 (0.16–0.99); .048**	**0.56 (0.37–0.84); .005**
BMI							
<25	119/121	67/104	6/21	**0.65 (0.44–0.97); .034**	**0.29 (0.11–0.74); .010**	**0.34 (0.14–0.87); .024**	**0.56 (0.40–0.87); .007**
≥25	37/45	20/25	5/5	0.97 (0.47–2.02); .942	1.22 (0.33–4.52); .770	1.23 (0.34–4.45); .755	1.01 (0.51–2.01); .964

Bold values are statistically significant ($P<.05$). BMI = body mass index.

frequencies for this polymorphism. The genotype frequency of the +3954 C>T polymorphism in the IL-1β gene in the control group was consistent with the predictions of HWE ($P=.89$). When the CC genotype was used as a reference, TT+CT or TT genotype carriers showed lower risk of sepsis (TT vs CC: $P=.033$, odd ratio (OR) = 0.45, 95% confidence interval (CI) = 0.21–0.94; TT+CT vs CC: $P=.018$, OR = 0.67, 95% CI = 0.48–0.93). Regardless of adjustment for sex and age, the relationships remained statistically significant in the homozygote and dominant models. In addition, when the C allele was used as a reference, the T allele was associated with a reduced risk of sepsis (T vs C: $P=.009$, OR = 0.70, 95% CI = 0.53–0.91).

Subsequent subgroup analyses assessed age, sex, BMI, alcohol consumption, and cigarette consumption (Table 3). The risk of sepsis was significantly reduced in nonsmokers, nondrinkers, individuals with BMI < 25, and individuals aged ≥60 years. No statistically significant findings were obtained in stratified analysis by sex.

3.3. Association between IL-1β +3954 C>T polymorphism and sepsis severity and 28-day mortality

Finally, associations of this polymorphism with sepsis severity and 28-day mortality were investigated (Table 4). The results showed that the IL-1β +3954 C>T polymorphism was associated with the 28-day mortality rate and severity of sepsis.

4. Discussion

In this case-control study, the IL-1β +3954 C>T polymorphism reduced the risk of sepsis in Chinese individuals. Subgroup analyses revealed that the reduction of risk was greater among nonsmokers, nondrinkers, individuals with BMI < 25, and individuals aged ≥60 years. In addition, we observed that this SNP was linked to sepsis severity and 28-day mortality.

Cytokines regulate the host immune response and alter the expression of other cytokines, which are associated with the development of sepsis.[23] Excessive IL-1 production has been directly linked to death among patients and animals with sepsis or septic shock.[24] Previous studies showed that defective IL-1β production was a pivotal feature of sepsis that could be used to evaluate immunological status.[25,26] Fahy et al showed that the IL-1β level was significantly higher in patients with septic shock, compared with control patients[27]; this indicated that the IL-1β level is significantly associated with the development of sepsis, consistent with our findings.

Cytokine genes involved in inflammatory cascades are vital candidate genes that may determine the extent of an individual's

Table 4

The associations between IL-1β +3954 C>T polymorphism and clinical characteristics of sepsis.

Characteristics	Genotype distributions CC	CT OR (95% CI); *P*	TT OR (95% CI); *P*	CT+TT OR (95% CI); *P*
Sepsis status				
Sepsis/septic shock	102/54	52/35	3/8	55/43
OR (95% CI); *P*-value	1.0 (reference)	0.79 (0.46–1.35); .384	**0.20 (0.51–0.78); .011**	0.68 (0.40–1.14); .139
Death				
Live/dead	123/33	65/22	4/7	69/29
OR (95% CI); *P*-value	1.0 (reference)	0.79 (0.43–1.47); .460	**0.15 (0.04–0.56); .001**	0.64 (0.36–1.14); .128

Bold values are statistically significant ($P<.05$). CI = confidence interval; OR = odds ratio.

response to sepsis.[28] Recently, several studies have investigated the link between the risk of sepsis and the IL-1β +3954 C>T polymorphism. Fang et al investigated the association of this polymorphism with severe sepsis risk in a German population[13]; they did not observe a significant association.[13] Ruiz et al also found that this SNP was unrelated to sepsis susceptibility in a different Caucasian population.[14] Notably, this polymorphism did not modify the risk of sepsis in low-birth-weight infants from Hungary.[15] Moreover, Balding et al determined that the IL-1β +3954 C>T polymorphism was not associated with poor outcomes in Irish patients with meningococcal disease.[16] Furthermore, Zhang et al indicated that this polymorphism was not related to septic shock risk among Chinese patients.[18] Conversely, Johnson et al observed that this SNP was associated with a decreased risk of candidemia in an American population.[17]

Although the studies mentioned above were similar in some respects, some of the results may have been spurious due to small sample sizes. Zheng et al conducted a meta-analysis to address this issue, and found that the IL-1β +3954 C>T polymorphism reduced the risk of sepsis.[29] Stratified analysis suggested that the protective effect of this SNP against sepsis risk remained significant in Caucasians, but not in Asians.[29] Therefore, we designed the current case-control study to investigate the relationship between this polymorphism and sepsis risk in a Han Chinese population. We found that the TT or TT+CT genotype, or the T allele, was associated with a reduced risk of sepsis, which was consistent with the findings of our previous study.[20] In that previous study, we found that that IL-8 −251 A/T polymorphism was associated with a reduced risk of sepsis.[20] However, it remains unclear whether these 2 SNPs have synergistic effects on the risk of sepsis; therefore, further research is necessary.

The present study is the first to reveal an association between the IL-1β +3954 C>T polymorphism and sepsis susceptibility in a Han Chinese study population. Unexpectedly, our findings were considerably different from those of other studies. There are several potential reasons for these discrepancies. First, the exposure factors for patients with sepsis differed among studies. Second, ethnic differences among the study populations may have influenced the results. Third, the clinical heterogeneity of sepsis was diverse and the causes of sepsis were inconsistent among the prior studies. Fourth, the studies had different sample sizes. Furthermore, we found that this SNP was associated with a reduced risk of sepsis in nonsmokers, nondrinkers, individuals with BMI < 25, and individuals aged ≥ 60 years; thus, interactions between these factors and this polymorphism may have contributed to the reduced risk of sepsis. Notably, a marginal association was observed in the dominant model, but not in other genetic models. The statistically significant effects observed for nonsmokers versus smokers may have been due to the number of individuals within each of these groups, and the results should thus be interpreted with caution. Furthermore, this study revealed that the IL-1β +3954 C>T polymorphism was associated with the severity and 28-day mortality rate of sepsis. We observed a higher death rate in genotype TT carriers, which seemed to contradict the protective role of the TT genotype in the context of sepsis. However, this apparent conflict can be explained by other factors. There were only 11 TT genotype individuals in total, including patients with sepsis and those with septic shock (Table 2). Notably, 8 patients had septic shock among all TT carriers, and 7 of 8 patients with septic shock died (Table 4). Therefore, the higher mortality rate among the TT genotype individuals can be attributed to septic shock, rather than the TT genotype itself.

This study had several limitations. First, the sample size was relatively small. Second, gene-gene and gene-environment interactions were not explored. Third, the underlying mechanisms by which this SNP reduced the risk of sepsis were not fully elucidated, and require further investigation. Finally, the roles of other SNPs in IL-1β and other genes were not determined, and should be the focus of future studies.

In conclusion, the IL-1β +3954 C>T polymorphism was associated with a reduced risk of sepsis in a Han Chinese population. Studies in other Chinese populations are urgently needed to address the relationship between this locus and sepsis susceptibility.

Author contributions

Conceptualization: Peng Fu, Xiangcheng Zhang.
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