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Tumor Necrosis Factor-α -308G/A Genetic Polymorphism and the Susceptibility of Posttraumatic Sepsis

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Summary of background data: The association between tumor necrosis factor α (TNFα) -308G/A polymorphism and susceptibility to posttraumatic sepsis has been studied extensively. But the results have not remained very clear.

Purpose: We carried out this meta-analysis to explore the influence of TNF on susceptibility to posttraumatic sepsis.

Methods: Relevant studies were identified from PubMed, Web of Science, Embase, and China National Knowledge Internet without language limitation, following the inclusion and exclusion criteria. Statistical analyses were implemented with the STATA 12.0 statistical software.

Results: Seven case-control studies were included in the meta-analyses on the association of TNFα -308 G/A genetic polymorphism and risk of posttraumatic sepsis. TNFα -308 G/A genetic polymorphism was significantly associated with susceptibility to posttraumatic sepsis in the dominant model [odds ratio (OR), 2.17; 95% confidence interval (95% CI), 1.19–3.95; $P = 0.011$] and allelic model (OR, 1.72; 95% CI, 1.23–2.39; $P = 0.001$), but not in the heterozygous model (OR, 1.38; 95% CI, 0.58–3.39; $P = 0.489$). There was no significant publication bias for these 3 models. However, marked heterogeneity existed in the dominant model ($I^2 = 68.9\%$, $P = 0.004$) and the heterozygous model ($I^2 = 68.9\%$, $P = 0.022$).

Conclusions: TNF -308 G/A genetic polymorphism may have an influence on susceptibility to posttraumatic sepsis. Further studies with large sample sizes and well-designed studies are needed to confirm these results.

Key words: Tumor necrosis factor – Genetic polymorphism – Trauma – Sepsis

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Trauma is reported to be one of the leading causes of death and disabilities.[1] Recently, the early mortality of trauma patients has been reduced by the development of prehospital and hospital managements. Severe traumatic injury can lead to immune dysfunction that may result in increased susceptibility to sepsis after traumatic injury. Despite the advanced antibiotics and critical care taken, patients after traumatic injury were at high risk of sepsis. Posttraumatic sepsis–associated mortality was also very high. Thus, researchers made an effort to identify sepsis early after traumatic injury and improve the outcome.

Cytokines and chemokines play important roles in host immune regulation. Genetic polymorphisms in the genes encoding these chemokines and cytokines play an important role in inflammatory activation and susceptibility to sepsis. Proinflammatory cytokine tumor necrosis factor (TNF) plays a pivotal role in the regulation of immune response, with multiple functions. In the setting of posttrauma infection, TNFα causes further inflammation, and even tissue damage and organ dysfunction.[2] The encoding gene of TNFα is located on chromosome 6p21.3, and there are several single-nucleotide polymorphisms that exist in the region of TNFα promoter, among which the -308G/A genetic polymorphism was of special interest for its role in influencing TNFα promoter activity and production.[3] TNFα -308G/A polymorphism was demonstrated to be obviously related to the susceptibility and outcome of sepsis using meta-analysis.[4–6] To date, the relationship between TNFα -308G/A polymorphism and susceptibility to posttraumatic sepsis has been studied extensively. But the results do not remain very clear. Therefore, we performed this meta-analysis to clarify whether this polymorphism is related to the risk of posttraumatic sepsis.

Methods

Literature search strategy

We searched the literature in Embase, Web of Science, PubMed, and China National Knowledge Internet (CNKI), according to these key words: "TNF" or "tumor necrosis factor," "polymorphism" or "variation" or "SNP" or "single nucleotide polymorphism," "sepsis" or "infection" or "septic shock," and "trauma."

Inclusion and exclusion criteria

We used the following criteria to screen studies in the present study: (1) original case-control studies; (2) sepsis occurred after trauma; (3) reported the association between TNFα -308 genetic polymorphism and the susceptibility to sepsis after trauma. If more than 1 article used the same series of patients, the most complete and latest study would be included.

Data extraction

Two authors independently selected all searched publications and extracted the following information from all eligible studies: published year, the first author, country, the Injury Severity Score (ISS), numbers of controls and cases, and gene distributions in each group. When any discrepancies occurred, there was a discussion to reach an agreement.

Statistical analysis

Our meta-analysis was conducted following the PRISMA statement, and the Newcastle-Ottawa Scale (NOS) criteria were used to evaluate the quality of each study. If NOS $\geq$5, the study was considered to be high quality. We used pooled odds ratios (ORs) to access the association of TNFα -308 polymorphism with the susceptibility to sepsis after trauma. The χ^2-based Q test was performed to measure heterogeneity, and the fixed effects model was conducted when $I^2 < 50\%$ and $P > 0.05$. The funnel plot and Egger test were used to investigate the publication bias. All analyses in this study were conducted by STATA 12.0 software (Stata Corporation, College Station, Texas). $P < 0.05$ was considered as statistical significance.

Results

All relevant publications were searched from Embase, Web of Science, PubMed, and CNKI and then preliminarily screened. There were 210 articles, of which 51 duplicated studies and 136 irrelevant citations were excluded (Fig. 1). Then 23 articles remained, of which 1 original article lacking a sepsis group, 1 without gene distribution, 3 reference articles, 7 reviews, and 1 comment were excluded. The same case series were used in 4 articles,[7–10] so the most complete and latest study was included.[10] Finally, this meta-analysis included 7 case-control publications, all of which were written in English.[10–16] As shown in Table 1, the detailed data, including published year, the first author, country, ISS, numbers of cases and controls, the Hardy-Weinberg Equilibri-

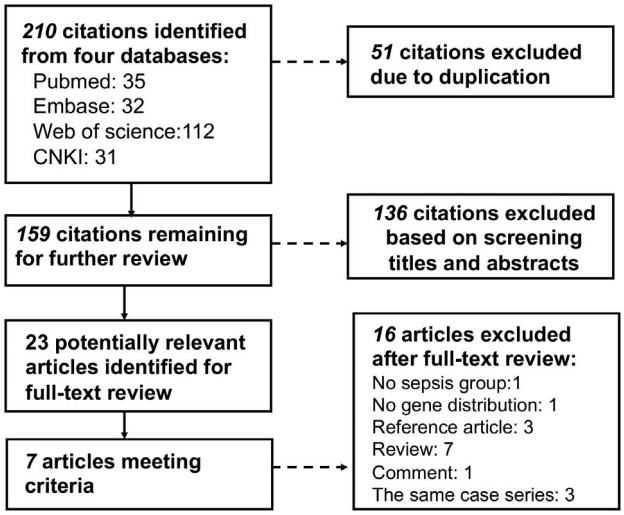

Fig. 1 Flow diagram of the search strategy and study selection.

um of the control group, and gene distributions for each study were presented.

Seven articles studied the relationship of TNFα -308 genetic polymorphism and susceptibility to posttraumatic sepsis; they included 345 trauma patients with sepsis and 677 without sepsis. Two of these studies were conducted in Asia,[10,11] 3 in America,[13,14,16] and 2 in Europe.[12,15] Significant heterogeneities existed in the dominant model (AA+AG versus GG: $I^2 = 68.9\%$, $P = 0.004$; Fig. 2A) and the heterozygous model (AG versus GG: $I^2 = 68.9\%$, $P = 0.022$; Fig. 4A), but not in the allelic model (A versus G: $I^2 = 56.8\%$, $P = 0.074$; Fig. 3A). This heterogeneity may come from ethnicity, type and degree of trauma, type of control, and so on. Therefore, subgroup analysis and metaregression should be performed to find the sources of this heterogeneity. But we did not perform these analyses, for only 7 studies were enrolled in this meta-analysis.

The results of meta-analysis showed a significant relationship between TNF -308 genetic polymorphism and susceptibility to posttraumatic sepsis in the dominant model [odds ratio (OR), 2.17; 95% confidence interval [95% CI], 1.19–3.95; $P = 0.011$; Fig. 2A) and in the allelic model (OR, 1.72; 95% CI, 1.23–2.39; $P = 0.001$; Fig. 3A), but not in the heterozygous model (OR, 1.38; 95% CI, 0.58–3.39; $P = 0.489$; Fig. 4A). In this study we did not perform the analysis for the recessive model (AA versus AG+GG), and homozygous model (AA versus GG), because only 4 studies described the gene distribution of AA, GG, and AG, and the frequency of AA is very rare.

In order to determine publication bias, Beggar test and funnel plot were performed. The results suggested that there was no significant publication bias in the dominant model ($z = -0.45$, $P = 0.652$; Fig. 2B), the allelic model ($z = 0.34$, $P = 0.734$; Fig. 3B), and the heterozygous model ($z = 0.34$, $P = 0.734$; Fig. 4B).

Discussion

Previous studies have reported the relationship between TNFα -308G/A polymorphism and susceptibility to posttraumatic sepsis, with inconsistent results. In 2002 O'Keefe *et al*[16] showed that the genotype frequency of GA in sepsis (29.8%) was higher than nonsepsis (19.0%). However, in 2015 Gupta *et al*[11] showed that the genotype frequencies of GA were 4% and 19.1% in sepsis and nonsepsis. Therefore, we performed this meta-analysis to determine the relationship of TNFα -308G/A polymorphism to the risk for posttraumat-

Table 1 Characteristics of studies and TNFα -308 gene distributions in the meta-analysis

Source, year	Country	Number of cases/controls	ISS	TNFα genotype						TNFα allele				HWE (*P* value)
				Case			Control			Case		Control		
				AA	AG	GG	AA	AG	GG	A	G	A	G	
Gupta *et al*,[11] 2015	India	25/89	21.2 ± 6.8/18 ± 8.8	2	1	22	3	17	69	5	45	23	155	>0.05
Duan *et al*,[10] 2011	China	131/174	NA	6	39	86	3	33	138	51	211	39	309	>0.05
Menges *et al*,[12] 2008	Germany	71/83	18 (7–63)/17 (5–56)	33[a]		38	9		74	—	—	—	—	>0.05
McDaniel *et al*,[13] 2007	America	31/37	NM	9[a]		22	8		29	—	—	—	—	>0.05
Barber *et al*,[14] 2004	America	36/123	NM	16[a]		20	23		100	—	—	—	—	>0.05
Majetschak *et al*,[15] 2002	Netherlands	14/56	NA	0	4	10	0	20	36	4	24	20	92	>0.05
O'Keefe *et al*,[16] 2002	America	37/115	NA	1	15	21	0	19	96	17	63	19	211	>0.05

HWE, Hardy-Weinberg Equilibrium; NA, not available; NM, not mentioned.

[a]AA+AG.

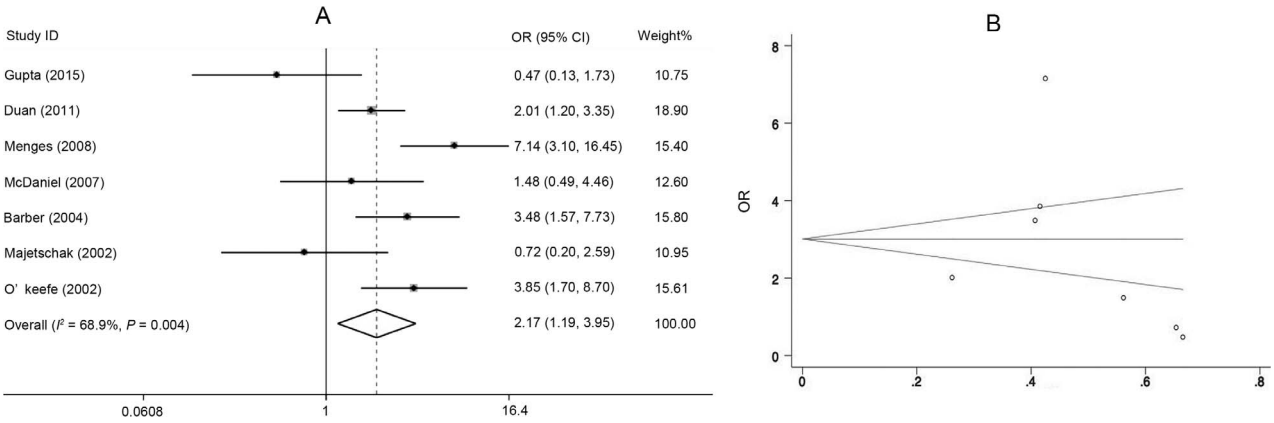

Fig. 2 (A) TNFα -308G/A polymorphism was significantly associated with susceptibility to posttraumatic sepsis for the dominant model (AA+AG versus GG); (B) there was no obvious publication bias test for this model by Egger test.

ic sepsis. The results showed that TNFα -308G/A polymorphism was significantly related to susceptibility to posttraumatic sepsis for the dominant and allelic models. These results were in accordance with the results of the meta-analysis on the relationship between TNFα -308G/A polymorphism and the risk of sepsis.

With the development of clinical care, the outcome of trauma patients became better, with a shift from mortality to sepsis and multiple organ dysfunction.[17,18] After traumatic injury, the immune system responds rapidly, with both myeloid and lymphoid cells activated, leading persistent inflammation,[2] and then a process to immunosuppression, which results in infection. TNFα -308G/A polymorphism can influence TNFα promoter activity and production, which play important roles in immune regulation. In our study, the results suggested that patients with AA/AG genotypes or A allele were more susceptible to sepsis. TNFα-308 genetic polymorphism may have a significant effect on the risk of posttraumatic sepsis.

It is necessary to perform this meta-analysis on the relationship between TNFα -308 variations and the susceptibility of posttraumatic sepsis because a single study is not powerful enough to demonstrate this relationship. However, there were some limitations to our study. First, only 7 studies were enrolled in this study. Second, there were significant heterogeneities in our meta-analysis, but neither metaregression nor subgroup analysis was conducted for the small study number. Third, this meta-analysis only included published articles; thus, publication bias may exist. Therefore, large sample, preferable studies were needed to demonstrate the results.

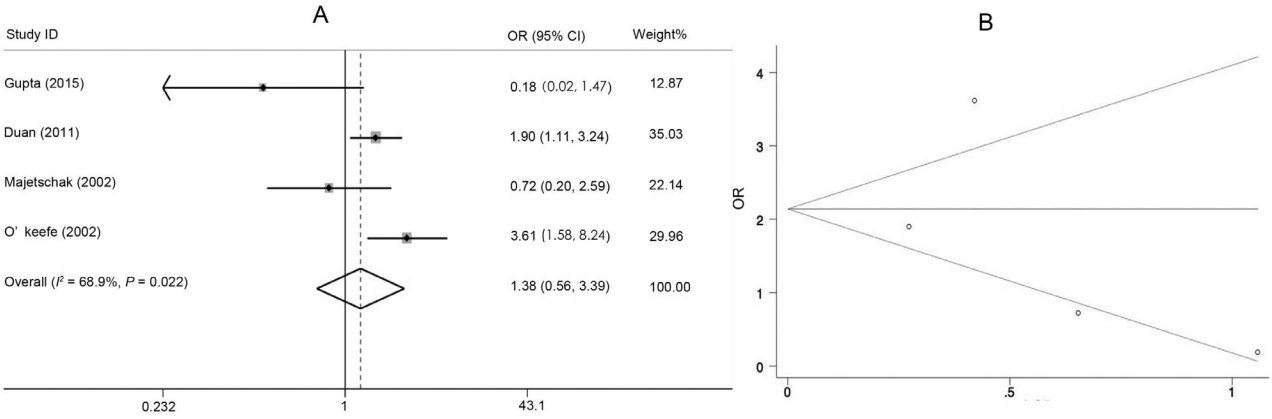

Fig. 3 (A) TNFα -308G/A polymorphism was not associated with the risk for posttraumatic sepsis for the heterozygous model (AG versus GG); (B) there was no obvious publication bias test for this model by Egger test.

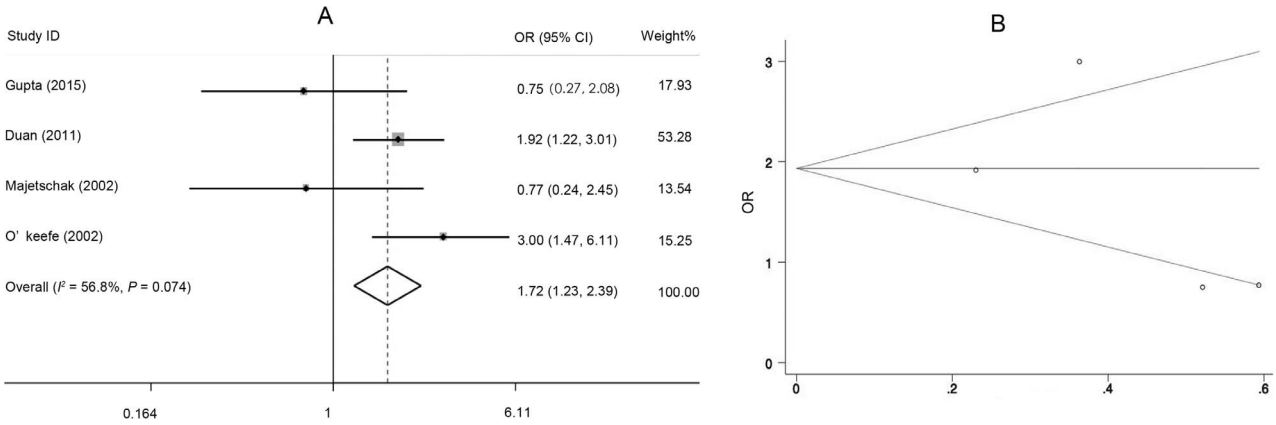

Fig. 4 (A) TNFα -308G/A polymorphism was significantly associated with the risk for posttraumatic sepsis for the allelic model (A versus G); (B) there was no obvious publication bias test for this model by Egger test.

Conclusions

In conclusion, the overall data suggested the association of TNFα-308 variations and risk of posttraumatic sepsis; the variant A allele and AA+AG genotypes of TNFα-308 polymorphism may have an influence on the susceptibility of sepsis after trauma. Studies with large samples, as well as more specified designs, are needed to demonstrate the results of this study more clearly and definitively.

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