# Association Between MMP-9 -1562 C/T Polymorphism and the Risk of Sepsis in a Chinese Population: A Case-control Study

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**Research**

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# Abstract

**Background:** Matrix metalloproteinase-9 (MMP-9) plays an important role in the development of sepsis. In order to explore the relationship between MMP-9 -1562 C/T polymorphism and sepsis risk in Chinese Han population, we conducted a case-control study with a sample size of 312 sepsis patients and 413 controls.

**Methods:** The ABI PRISM SNaPshot method (Applied Biosystems, Carlsbad, CA, USA) was performed to genotype the MMP-9 -1562 C/T polymorphism.

**Results:** Our data indicated that MMP-9 -1562 C/T polymorphism was associated with an increased risk of sepsis (CT vs. CC: $P = 0.032$, OR=1.45, 95%CI =1.03-2.05; TT + CT vs. CC: $P = 0.019$, OR =1.49, 95%CI = 1.07-2.07). Stratified analyses demonstrated that this increased risk was more evident in smokers, drinkers, females, and overweight individuals (BMI ≥ 25). In addition, cross-over analyses suggested that the combination of smoking and CT genotype of MMP-9 -1562 C/T polymorphism contributed to a higher risk for sepsis.

**Conclusion:** In conclusion, MMP-9 -1562 C/T polymorphism is associated with an increased risk of sepsis in Chinese Han population. MMP-9 -1562 C/T polymorphism may serve as a diagnostic marker for sepsis patients.


# Background

Sepsis is defined as an infection associated with organ injury distant from the site of infection [1]. In high-income countries, 31.5 million sepsis and 19.4 million cases of severe sepsis occur globally each year, with potentially 5.3 million deaths annually [1]. The most common cause of sepsis is pneumonia, which accounts for about half of all cases, followed by intraperitoneal and urinary tract infections [2–5]. Increasing studies have indicated that the influence of single-nucleotide polymorphisms of certain genes in the development of infection and sepsis [6–9]. However, genetic studies of sepsis face fundamental challenges to conduct and interpretation.

Matrix metalloproteinase-9 (MMP-9), a zinc-dependent proteinase, is predominantly released by neutrophils and macrophages, which regulates numerous signaling pathways of pivotal importance in inflammation. Meanwhile, MMP-9 remodels the extracellular matrix and regulates the activity of numerous cytokines, growth factors, chemokines and cell adhesion molecules essential to inflammation [10, 11]. In sepsis, MMP-9 is associated with increased vascular permeability, which is due to the degradation of collagen present in the basement membrane of the blood vessel, promoting the migration of inflammatory cells and regulating the inflammatory response [12]. The mechanism of MMP-9 in sepsis is still unclear. Previous studies indicated that plasma MMP-9 levels were increased in severe sepsis patients [13]. In addition, MMP-9 was negatively associated with the disease severity of sepsis [13].

The MMP-9 gene is located on chromosome 20q11.2-13.1. The − 1562 C/T polymorphism of the MMP-9 gene was reported to influence the production of MMP-9 [14]. Several studies have researched the correlation between MMP-9 -1562 C/T (rs3918242) polymorphism and sepsis risk [14–16]. However, they obtained negative findings. Thus, this study aimed to explore the association between the MMP-9 -1562 C/T polymorphism and sepsis risk in a Chinese Han population.

## Patient And Methods

# Subjects

This study enrolled 312 sepsis patients and 413 controls from the Affiliated Huai'an No.1 People's Hospital of Nanjing Medical University. All sepsis patients were diagnosed according to the Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock [17]. Sepsis was classified as sepsis and septic shock. Severe sepsis was defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. Septic shock is defined as the persistence of septic induced hypotension despite adequate fluid resuscitation [18]. Exclusion criteria were as follows: patients < 18 or > 80 years old, patients with uremia or end-stage renal disease, patients with diabetes mellitus, malignant tumors, human immunodeficiency virus, or autoimmune diseases. The controls were selected from the same hospital in the same period. Individuals with potential infection, heart disease history or receiving immunosuppressive therapy were excluded. All of the cases and controls were enrolled consecutively. Demographic and risk factor information were collected using a written questionnaire, including age, sex, smoking, alcohol, and body mass index (BMI). Smokers were defined as smoking more than 1 cigarette per day for at least 1 year. Drinkers were classified as consuming alcoholic beverages at least once a week for more than 1 year.

This study was approved by the Ethics Committee of the Affiliated Huai'an No.1 People's Hospital of Nanjing Medical University and met the standards of the *Declaration of Helsinki*. Written informed consent was obtained from all subjects.

# Blood Sampling and Genotyping

Genomic DNA of cases and controls was extracted from peripheral blood leukocytes using a TIANamp Blood DNA kit (Tiangen Biotech, Beijing, China). Extracted DNA was stored at − 80 °C. The quality and concentration of the extracted DNA were measured at 260 and 280 nm using a NanoDrop (Thermo Scientific, Waltham, MA, USA). The ABI PRISM SNaPshot method (Applied Biosystems, Carlsbad, CA, USA) was performed to genotype the MMP-9 -1562 C/T. To genotype the MMP-9 -1562 C/T polymorphism, the following primers were designed by using Primer Premier 5.0 and synthesized by Sangon Biological Company (China): 5' GCC-TGG-TGG-CAC-ATA-GTA-GGC-CC-3' (sense); 5' CTT-CCT-AGC-CAG-CCG-GCA-TC-3' (antisense). Approximately 10% of the samples were randomly re-examined by genotyping the SNP to validate the accuracy. The results were 100% concordant.

# Statistical analysis

All statistical analyses were conducted on SPSS 22.0 (SPSS Inc., Chicago, USA) with the significance level at $P < 0.05$. The variables of cases and controls were estimated using either Student's t-tests (continuous variables) or Chi-square ($\chi^2$) tests (categorical variables). Hardy-Weinberg equilibrium (HWE) among the controls was tested using a goodness-of-fit chi-square test. The differences in genotype and allele frequencies of the MMP-9 -1562 C/T polymorphism were evaluated using the $\chi^2$ test. Using logistic regression analysis, the crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to assess the relationship between the MMP-9 -1562 C/T polymorphism and the sepsis risk. Subgroup analyses were performed by sex, age, alcohol consumption, smoking and BMI. Cross-over analysis was used to investigate gene–environmental interactions (such as gene–smoking and gene–drinking). $P < 0.05$ were considered statistically significant.

# Results

## Characteristics of the study population

In this case-control study, 312 sepsis patients and 413 controls were recruited. Demographic information and clinical characteristics of all individuals are shown in Table 1. HWE analysis revealed no difference in the control group. The case and control groups were matched in age and sex. The percentage of drinkers and smokers yielded no significant differences between the patients with sepsis and the controls. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score of the sepsis patients was 20.26 ± 5.30. The sepsis patients included 201 sepsis, and 111 septic shock patients.

Table 1
Patient demographics and risk factors in sepsis

| Characteristics | Case (N = 312) | Control (N = 413) | *P* |
|---|---|---|---|
| Age (years) | 60.39 ± 10.10 | 60.81 ± 9.99 | 0.573 |
| Sex | | | 0.662 |
| Male | 163(52.2%) | 209(50.6%) | |
| Female | 149(47.8%) | 204(49.4%) | |
| Smoking | | | 0.764 |
| YES | 134(42.9%) | 182(44.1%) | |
| NO | 178(57.1%) | 231(55.9%) | |
| Alcohol | | | 0.477 |
| YES | 116(37.2%) | 143(34.6%) | |
| NO | 196(62.8%) | 270(65.4%) | |
| BMI | 23.03 ± 3.05 | 22.80 ± 2.67 | 0.289 |
| APACHE II score | 20.26 ± 5.30 | | |
| Sepsis status (n, %) | | | |
| Sepsis | 201(64.4%) | | |
| Septic shock | 111(35.6%) | | |
| Pathogens (n, %) | | | |
| Gram-positive | 60(19.2%) | | |
| Gram-negative | 161(51.6%) | | |
| Mixed Gram-negative and -positive | 61(19.6%) | | |
| Fungus | 30(9.6%) | | |
| Source of infection, n (%) | | | |
| Respiratory tract infection | 203(65.1%) | | |
| Abdominal infection | 56(17.9%) | | |
| Urinary tract infection | 18(5.8%) | | |
| Catheter-associated infection | 14(4.5%) | | |
| Others | 21(6.7%) | | |

# Relationship between MMP-9 -1562 C/T polymorphism and sepsis risk

The genotype and allele frequencies of the MMP-9 -1562 C/T polymorphism are presented in Table 2. Data showed that the CT or TT + CT genotype was associated with an increased risk of sepsis (CT vs. CC: *P* = 0.032, OR = 1.45, 95%CI = 1.03–2.05; TT + CT vs. CC: *P* = 0.019, OR = 1.49, 95%CI = 1.07–2.07). The results were remained significant after adjusting for sex and age. Similarly, the T allele carriers showed a higher risk for sepsis.

Table 2
Genotype frequencies of MMP-9 -1562 C/T polymorphism in cases and controls

| Models | Genotype | Case (n, %) | Control (n, %) | OR (95% CI) | [a] *P* value | OR (95% CI) | [b] *P* value |
|---|---|---|---|---|---|---|---|
| Co-dominant | CC | 215(68.9%) | 316(76.7%) | 1.00(reference) | - | - | - |
| Heterozygote | CT | 87(27.9%) | 88(21.4%) | **1.45(1.03–2.05)** | **0.032** | **1.41(1.02–2.03)** | **0.031** |
| Homozygote | TT | 10(3.2%) | 8(1.9%) | 1.84(0.71–4.73) | 0.201 | 1.81(0.70–4.71) | 0.197 |
| Dominant | CC | 215(68.9%) | 316(76.7%) | 1.00(reference) | - | - | - |
| | TT + CT | 97(31.1%) | 96(23.3%) | **1.49(1.07–2.07)** | **0.019** | **1.46(1.05–2.06)** | **0.017** |
| Recessive | CT + CC | 302(96.8%) | 404(98.1%) | 1.00(reference) | - | - | - |
| | TT | 10(3.2%) | 8(1.9%) | 1.67(0.65–4.29) | 0.280 | 1.65(0.63–4.27) | 0.276 |
| Allele | C | 517(82.9%) | 720(87.4%) | 1.00(reference) | - | - | - |
| | T | 107(17.1%) | 104(12.6%) | **1.43(1.07–1.92)** | **0.016** | | |

[a] $\chi^2$ test for genotype distributions between sepsis and controls. Bold values are statistically significant ($P < 0.05$). The genotyping was successful in 312 cases and 412 controls.

[b] Adjustment for sex and age.

Next, we conducted stratified analyses of age, sex, alcohol, smoking, and BMI (Table 3). An increased risk of sepsis was shown in smokers, drinkers, females, and overweight individuals (BMI ≥ 25). Nevertheless, no significant results were observed in the stratified analyses by age.

Table 3
Stratified analyses between MMP-9 -1562 C/T polymorphism and the risk of sepsis.

| Variable | (case/control) | | | CT vs. CC | TT vs. CC | TT vs. CC + CT | TT + CT vs. CC |
|---|---|---|---|---|---|---|---|
| | CC | CT | TT | OR (95% CI); *P* | OR (95% CI); *P* | OR (95% CI); *P* | OR (95% CI); *P* |
| Sex | | | | | | | |
| Male | 116/156 | 43/49 | 4/3 | 1.18(0.73–1.90);0.494 | 1.79(0.39–8.17); 0.705 | 1.72(0.38–7.79); 0.744 | 1.22(0.77–1.93); 0.407 |
| Female | 99/160 | 44/39 | 6/5 | **1.82(1.11-3.00); 0.017** | 1.94(0.58–6.52); 0.227 | 1.67(0.50–5.58); 0.400 | **1.84(1.14–2.96); 0.012** |
| Smoking | | | | | | | |
| Yes | 94/155 | 37/26 | 3/3 | **2.35(1.34–4.12); 0.003** | 1.65(0.33–8.34); 0.853 | 1.38(0.28–6.96);1.000 | **2.27(1.32–3.91); 0.003** |
| No | 121/161 | 50/62 | 7/5 | 1.09(0.71–1.68); 0.686 | 1.86(0.58–6.01); 0.291 | 1.83(0.57–5.85); 0.304 | 1.13(0.74–1.73); 0.567 |
| Alcohol | | | | | | | |
| Yes | 80/118 | 32/21 | 4/4 | **2.25(1.21–4.18); 0.009** | 1.48(0.36–6.07); 0.861 | 1.24(0.30–5.07); 1.000 | **2.12(1.19–3.81); 0.011** |
| No | 135/198 | 55/67 | 6/4 | 1.20(0.79–1.83); 0.384 | 2.20(0.61–7.94); 0.365 | 2.09(0.58–7.52); 0.405 | 1.26(0.84–1.89);0.264 |
| Age (years) | | | | | | | |
| < 60 | 98/145 | 37/39 | 5/4 | 1.40(0.84–2.36); 0.198 | 1.85(0.49–7.06); 0.571 | 1.70(0.45–6.46); 0.653 | 1.45(0.88–2.37); 0.145 |
| ≥ 60 | 117/171 | 50/49 | 5/4 | 1.49(0.94–2.36); 0.087 | 1.83(0.48–6.95); 0.581 | 1.65(0.44–6.23); 0.688 | 1.52(0.97–2.37); 0.066 |
| BMI | 157/244 | 66/78 | 7/5 | | | | |
| < 25 | 58/72 | 21/10 | 3/3 | 1.32(0.90–1.93); 0.162 | 1.81(0.60–5.50); 0.286 | 1.69(0.56–5.08);0.349 | 1.37(0.94–1.99); 0.100 |
| ≥ 25 | | | | **2.61(1.14–5.97); 0.021** | 1.24(0.24–6.38); 1.000 | 1.04(0.20–3.30);1.000 | **2.29(1.07–4.89); 0.030** |

Bold values are statistically significant ($P < 0.05$).

# Cross-over analysis

We next analyzed the joint effects of the MMP-9 -1562 C/T polymorphism and either smoking or alcohol consumption on sepsis risk (Table 4). We found that smokers carrying the CT genotype of MMP-9 -1562 C/T had a significantly increased risk of sepsis compared with non-smokers carrying CC genotype of MMP-9 -1562 C/T (OR = 2.32, 95% CI = 1.17–4.57; $P = 0.014$). However, no significant association was observed between drinking and the risk of sepsis. The data suggested significant interactions between genetic (CT genotype of MMP-9 -1562 C/T polymorphism) and environmental (smoking) factors.

Table 4
Genetic (G) and environmental (E) factors 2*4 fork analysis.

| G[a] | E[b] | Case | Control | OR (95%CI); P value | Reflecting information |
|---|---|---|---|---|---|
| **rs12700386** | | | | | |
| TT vs. CC | Smoking | | | | |
| + | + | 3 | 3 | 1.33(0.26,6.71); 1.000 | G, E combined effect |
| + | - | 7 | 5 | 1.86(0.58,6.01); 0.291 | G alone effect |
| - | + | 94 | 155 | 0.81(0.57,1.14); 0.227 | E alone effect |
| - | - | 121 | 161 | 1.00 (reference) | Common control |
| CT vs. CC | Smoking | | | | |
| + | + | 37 | 26 | **1.89(1.09,3.30); 0.023** | G, E combined effect |
| + | - | 50 | 62 | 1.09(0.71,1.68); 0.686 | G alone effect |
| - | + | 94 | 155 | 0.81(0.57,1.14); 0.227 | E alone effect |
| - | - | 121 | 161 | 1.00 (reference) | Common control |
| TT vs. CC | Drinking | | | | |
| + | + | 4 | 4 | 1.47(0.36,5.97); 0.862 | G, E combined effect |
| + | - | 6 | 4 | 2.20(0.61,7.94); 0.365 | G alone effect |
| - | + | 80 | 118 | 0.99(0.70,1.42); 1.000 | E alone effect |
| - | - | 135 | 198 | 1.00 (reference) | Common control |
| CT vs. CC | Drinking | | | | |
| + | + | 32 | 31 | 1.51(0.88,2.60); 0.131 | G, E combined effect |
| + | - | 55 | 67 | 1.20(0.79,1.83); 0.384 | G alone effect |
| - | + | 80 | 118 | 0.99(0.70,1.42); 1.000 | E alone effect |
| - | - | 135 | 198 | 1.00 (reference) | Common control |

[a]G (+): MMP-9 -1562 C/T variants (Heterozygous or homozygous); G (-): wild type

[b]E(+): smoking/non-smoking; E(-): non-smoking/non-drinking

# Discussion

In this study, MMP-9 -1562 C/T polymorphism was associated with an increased risk of sepsis. Subgroup analyses suggested that the increased risk was more evident in the smokers, drinkers, females, and overweight individuals (BMI ≥ 25). Furthermore, the combination of smoking and CT genotype of MMP-9 -1562 C/T showed a significantly higher risk for sepsis.

MMP-9 is a pro-inflammatory biomarker belonging to a family of zinc containing endoproteases, which are implicated in chronic cell remodeling, apoptosis, adhesion and migration [19]. Since MMP-9 is mainly released by neutrophils and macrophages, this molecule is involved in the immune exacerbation in sepsis. A study conducted by Lorente et al. found that surviving patients with severe sepsis had elevated levels of MMP-9 [20]. Meanwhile, Hoffmann et al. suggested that the levels MMP-9 in patients with severe sepsis were significantly higher than that in healthy individuals [21]. Interestingly, Sachwani et al. demonstrated that there was a significant and early association between MMP-9 and blood glucose levels in in patients with severe sepsis and septic shock [19].

Recently, several studies explored the association between MMP-9 -1562 C/T polymorphism and the risk of sepsis. However, they obtained negative findings. Martin et al. firstly investigated the association between MMP-9 -1562 C/T polymorphism and sepsis risk in a Spanish population [14], and no significant association was observed. However, an association of MMP-9 levels with sepsis was also shown in their study [14]. A subsequent study from Spanish also showed that MMP-9 -1562 C/T polymorphism was not a risk factor for this Spanish population [15]. In addition, Bermúdez-Mejía et al. from Colombia showed that this SNP was not related to the risk of sepsis [16]. In addition, they found that − 1562 C/T polymorphism was not associated with MMP-9 levels and sepsis mortality [16]. Although these studies found similar results to some extent, the findings of some studies may be false-positive due to limited sample sizes. Therefore, we designed this case-control study to investigate the association between MMP-9 -1562 C/T polymorphism and sepsis risk in Chinese individuals. We found that CT or TT + CT genotype or T allele was associated with an increased risk of sepsis. To our knowledge, this is the first Chinese study to uncover an association between MMP-9 -1562 C/T polymorphism and sepsis susceptibility in Chinese Han population. Our findings were significantly different from those of other studies. Some factors may be accounted for these paradoxical results. First, clinical heterogeneity may be a potential factor. Second, the varied sample sizes may contribute to it. Third, racial difference was neglectable. Fourth, exposure factors for sepsis patients were different between these studies. Furthermore, stratified analyses showed that the risk of sepsis was significantly increased in smokers, drinkers, females, and overweight individuals (BMI ≥ 25). Therefore, the interactions between the MMP-9 -1562 C/T polymorphism and these factors may contribute to an increased risk of sepsis. To further evaluate the interactions between environmental factors (smoking or drinking) and genetic factors on sepsis susceptibility, we used the cross-over analysis and found that the combination of smoking and CT genotype of MMP-9 -1562 C/T showed a significantly higher risk for sepsis.

Potential limitations in this study should be addressed. First, the sample size of this study was not large enough, which may yield false positive results. Second, this study only investigated MMP-9 -1562 C/T polymorphism, whether other genetic variants of MMP-9 gene contributed to the genetic sepsis risk should be explored. Third, due to our use of a hospital-based case-control design, selection bias was unavoidable. Last, the potential mechanisms of MMP-9 -1562 C/T polymorphism affecting the incidence of sepsis should be investigated.

In conclusion, MMP-9 -1562 C/T polymorphism is associated with an increased risk of sepsis in Chinese Han population.

# Declarations

# Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Affiliated Huai'an No.1 People's Hospital of Nanjing Medical University and met the standards of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

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None

# Author contribution

Conceptualization: Z.C.J. and W.J.; Methodology: W.J.; Software and data analysis: Z.C.J.; Writing - original draft preparation: Z.C.J.; Writing - review and editing: X.S.X.

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# Availability of data and material

The data can be available from the corresponding author on reasonable request.

# Consent for publication

Not applicable

# Competing interests

The authors declare that there are no competing interests associated with the manuscript.

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