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The relationship between expression level and gene polymorphism of inflammatory factors and sepsis risk

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The biomarkers associated with sepsis have not yet been completely elucidated. The objective of the current article is to investigate whether inflammatory factors act as risk factors for sepsis. The study included 320 adult patients with sepsis, which were enrolled as experimental group. In addition, 560 healthy individuals from the same period were selected as the control group. Cytokine expressions were measured using flow cytometry with fluorescence, and gene polymorphisms were analyzed through the PCR-RFLP technique. Significantly higher expression levels of IL-1, IL-6, IL-10, and TNF-α, were detected ($p < 0.05$). This study also identified specific polymorphisms IL-1B -511 C/T, IL-10 -1082 G/A, IL-6 -174 G/C, and TNF-α -308 G/A, that were significantly associated with an increased risk of sepsis ($p < 0.05$). The expression levels of IL-1, IL-6, IL-10, and TNF-α are associated with an increased risk of sepsis. Additionally, the polymorphisms IL-1B -511 C/T, IL-6 -174 G/C, IL-10 -1082 G/A, IFN-γ + 874 A/T, and TNF-α -308 G/A are also linked to sepsis risk in the Chinese population.

Keywords Sepsis, Inflammatory factors, Gene expression, Gene polymorphism

As our understanding of sepsis continues to deepen, its definition has evolved. Sepsis is defined as multiple organ failure in a patient due to immune regulatory dysfunction caused by an infection[1]. Despite this shift in definition, what remains unchanged is its high and steadily increasing incidence[2,3]. According to the latest Morbidity and mortality report on sepsis published by the Lancet, there were 48.9 million new cases and 11 million deaths now[4]. Sepsis now kills more people than the combination of prostate cancer, breast cancer and AIDS[5]. The new definition of sepsis emphasizes that organ dysfunction is at the core of the condition; however, the exact mechanism remains unclear[6]. Research has suggested that multiple organ dysfunction syndrome (MODS) is associated with inflammatory cytokines[7]. Clinical practice has also shown that infection-induced inflammation and immune damage are central to the progression of sepsis. Both long-term immunosuppression and a heightened inflammatory response significantly increase the risk of death in sepsis patients[8]. The immune disorder mechanism of sepsis is accompanied by the production and consumption of a large number of pro-inflammatory and anti-inflammatory factors. When bacteria or microbes invade a host, the body activates the immune system through the corresponding signaling pathways, At this time, activated immune cells such as mononuclear/macrophages, dendritic (DC) cells, and neutrophils generate a large number of pro-inflammatory mediators including IL-1, IL-2, IL-6, IL-10, IL-12, IL-17, IL-18, IFN-γ and TNF-α[9], which jointly cause strong systemic inflammatory response (SIRS) in the host. SIRS can eliminate pathogenic microorganisms invading the human body, which is beneficial to the body, but a large number of pro-inflammatory mediators produce excessive protective immune response, resulting in a large number of apoptosis and necrosis of immune cells, and a large number of neutrophil extracellular traps, which aggravate the complexity of inflammatory response[10] and lead to organ and tissue damage, causes fever, high lactic acid metabolism, refractory shock, organ failure and even death[11]. Sepsis can induce apoptosis of immune cells, and these immune cells (including B cells, follicular dendritic cells (follicular DC), lymphocytes and syndactylated dendritic cells, etc.) are significantly consumed in various organs[12], thus releasing a variety of anti-inflammatory cytokines, such as IL-10, IL-1ra and IL-4, etc. Jointly resist the inflammatory response, thereby effectively reducing inflammatory symptoms and protecting the health of patients. If the infection persists, a large number of anti-inflammatory factors are secreted, resulting

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in strong compensatory anti-inflammatory response (CARS), suppression of immune function, and even more serious immune disorders, often resulting in death[13]. In the early stage of sepsis, with the enhancement of pro-inflammatory response, the release of endogenous anti-inflammatory mediators increases and enters the anti-inflammatory response period, which plays an immunosuppressive role. Under normal circumstances, the pro-inflammatory/anti-inflammatory response can maintain a balance and keep the internal environment stable. If the infection continues to worsen, the body will show an imbalance of SIRS/CARS response. When the inflammatory response is mainly manifested as pro-inflammatory response or SIRS, the host may suffer apoptosis or even shock, while when the anti-inflammatory response or CARS is mainly manifested, the immune response system will be controlled. As a result, the body appears intractable infection[14]. However, no matter what kind of symptoms, inflammation will get out of control, and eventually lead to multiple organ failure and even death[15]. In the early stages of sepsis, an excessive inflammatory response not only damages tissue cells but also disrupts immune regulation, resulting in immunosuppression and a complete imbalance of the body's inflammatory and immune mechanisms. This further exacerbates immune suppression and causes inflammation-related tissue and organ damage. As sepsis progresses, it can lead to cytokine storms, reduced organ perfusion, and immune paralysis[16]. Therefore, the level of inflammatory markers can serve as an indicator of the severity of sepsis and bloodstream infections. In fact, measuring inflammatory factors has proven to be more efficient than blood cultures in detecting sepsis.

There are limited reports on the relationship between gene expression, gene polymorphisms of inflammatory factors, and sepsis. Previous studies have primarily focused on a few well-known genes in relation to sepsis. Moreover, some genetic loci have been studied only in specific ethnic groups or populations, with little to no research conducted in eastern China. He et al. conducted a large sample size study (885 septic patients and 1101 healthy controls) reported that IL-27 rs17855750 loci showed no significant differences in the genotype/allele frequencies[17]. Mustarim et al. studied the Indonesia population and found that IL-1β rs1143643 polymorphism was associated with the incidence of neonatal sepsis[18]. The number of studies investigating the association between IL-10 gene polymorphisms and sepsis risk is relatively large. However, their results are contradictory. Zhang et al. published a meta-analysis about IL-10 gene polymorphisms and sepsis risk and they concluded that the polymorphism of IL-10 gene is closely associated with race, and two polymorphic loci (rs1800871 and rs1800896) are risk factors in Asian population[19]. All the above evidence shows that it is very meaningful to detect gene polymorphism in relevant populations in different countries and regions, especially in large samples.

It is well established that the outcomes of genetic polymorphism studies are significantly influenced by factors such as country, region, ethnicity, population, and environment. Therefore, we believe it is essential to conduct a comprehensive study on the role of all relevant inflammatory factors and thoroughly analyze their impact on sepsis patients.

Materials and methods

Patients' recruitment

The present experiment enrolled 320 adult patients with sepsis from the Department of Critical Care Medicine at Zhejiang People's Hospital between March 2018 and March 2023. The inclusion criteria for sepsis are very strict, and all of the following aspects must be met. (1) Sepsis patients must be between the ages of 18 and 75, and (2) meeting the diagnostic criteria of the 2012 International Guidelines for the Management of Severe Sepsis and Septic Shock. The exclusion criteria for sepsis patients: (1) age under 18 or over 75 years, (2) pregnancy, organ transplantation, liver cirrhosis, hematological diseases, chronic organ dysfunction, cancer, or use of immunosuppressive agents, and (3) a terminal condition. Additionally, 560 healthy individuals were enrolled as the control group, which were from the outpatient physical examination of our hospital. All of them were Han Chinese in the local area and were not related to each other. The age and gender matched the patients in the case group, and none of them had recent infection history, history of genetic disease, history of autoimmune disease or other disease history. In order to improve the accuracy of the research results as much as possible, we conducted strict screening of the research objects. The control group and the experimental group were matched on factors including age, sex, BMI, diabetes history, hypertension history, alcohol consumption and smoking history. All subjects participated in the present study obtained informed consent. We fully communicated with all patients and healthy people and obtained informed consent. This experiment was authorized by the Ethics Committee of our hospital (Ethics register number: 2024-284).

Clinical data collection and participant grouping

The general information was prospectively recorded. Patients were followed for 28 days after the diagnosis of sepsis. All patients received diagnosis and treatment, which included fluid resuscitation, antibiotic and vasoactive drug administration, lung-protective ventilation, glucocorticoid therapy, and appropriate surgical interventions as needed. Keep a detailed record of the name, age, gender, date of admission and transfer out of ICU of sepsis patients. Time of onset and conscious state, respiratory rate, body temperature, mean arterial blood pressure, heart rate, laboratory tests (whole blood cell analysis, liver and kidney function+electrolyte, blood coagulation, procalcitonin, C-reactive protein, sputum culture, blood culture), Glasgow Coma score (GCS) were recorded. The 24-hour urine output of the patients and whether they were treated with pressor drugs such as epinephrine, norepinephrine, dopamine, dobutamine after admission and whether they were mechanically ventilated with a ventilator were recorded. The name, age, sex and date of physical examination of the healthy control group were recorded. Acute physiological and Chronic Health Score (APACHE II) has been widely used in the clinical treatment of critical illness at present, and can be used to judge the severity of the disease, classify the disease, and compare the control groups, which is convenient and fast in clinic. Experimental group: This study collected various physiological indicators of patients at the time of enrollment, and used the "APACHE II scoring System" software in ICU of our hospital to calculate the APACHE II scoring scores of 320 patients with sepsis, and

divided them into the following groups according to the scores: (1) Mild group: patients with sepsis APACHE II ≤ 15 points ($n=95$); (2)Moderate group: sepsis patients 15 points < APACHE II ≤25 points ($n=111$); (3) Severe group: sepsis patients APACHE II >25 points ($n=114$). Control group: healthy subjects in the physical examination department of the Zhejiang People's Hospital during the same period ($n=560$). In order to improve the accuracy of the research results as much as possible, we conducted strict screening of the research objects. The control group and the experimental group were matched on factors including age, sex, BMI, diabetes history, hypertension history, alcohol consumption and smoking history.

Cytokine assay

A cytokine detection kit (provided by Chengdu Rui Kemi Medical Technology Co., LTD.) was used to capture specific antibodies of known size and fluorescence intensity, which bind to corresponding cytokine soluble proteins in serum and cerebrospinal fluid samples. This method forms a microbead array using flow cytometry. The detection reagent was a PE (fluorescent)-labeled antibody mixture, where the fluorescence intensity is proportional to the amount of cytokine captured on the microspheres. After incubating the capture microsphere (APC), detection antibody (PE), and the sample together, a double-antibody sandwich complex is formed. The fluorescence intensity of the microsphere and the bound antibody is then analyzed to determine the cytokine concentration in the serum and cerebrospinal fluid.

Gene polymorphism analyses

Approximately 3 mL of venous blood was collected in the morning and preserved in EDTA anticoagulant tubes for DNA extraction, using a kit from Thermo Fisher (USA). PCR-RFLP was performed according to established protocols from previous studies. Gene polymorphism analysis was conducted using the ABI3730XL system and GeneMapper 4.1 software, with sequencing performed for further verification.

Statistical analysis

The distribution of the general demographic and clinical features between sepsis and healthy controls was estimated by One-way ANOVA test and Chi-square test (χ^2) (or Fisher's exact test if required) for continuous and categorical variables, respectively. And Fisher's exact test or Bonferroni correction was also applied when appropriate. We applied binary logistic regression models to estimate ORs and 95% CIs to explore the association of various genotypes of different genetic models and sepsis risk. Furthermore, we applied a goodness-of-fit χ^2 test to detect whether the control population met the HWE balance. $P<0.05$ was deemed as statistically significant.

Results

Clinical indicators

Table 1 provides detailed data and clinical indicators for all participants. No significant associations were found for age, gender, BMI, history of diabetes, hypertension, alcohol consumption, or smoking ($p>0.05$).

Parameters	control group($n=560$)	sepsis group($n=320$)	*p*
Gender Male	327(58.4)	193(60.3)	>0.05
Female	233(41.6)	127 (39.7)	
Age(X ± S)	59.12 ± 9.67	60.84 ± 9.96	>0.05
BMI (kg/m^2, X ± S)	22.96 ± 2.34	22.27 ± 2.94	>0.05
DM history (%)	168(30.0)	102(31.9)	>0.05
Hypertension history (%)	160(28.6)	97(30.3)	>0.05
Drinking history(%)	218(38.9)	115(35.9)	>0.05
Smoking history (%)	196(35.0)	105(32.8)	>0.05
Temperature (℃, X ± S)	/	37.93 ± 1.25	/
Heart rate (time/min, X ± S)	/	85.52 ± 9.72	/
Systolic pressure (mmHg, X ± S)	/	133.58 ± 23.60	/
Diastolic pressure (mmHg, X ± S)	/	86.40 ± 8.74	/
Infection site			/
Abdominal infection	/	112(35.0)	
Pulmonary infection	/	80(25.0)	
Limb infection	/	45(14.1)	
Soft tissue infection	/	25(7.8)	
Catheter-related infection	/	24(7.5)	
Head and face infection	/	28(8.7)	
Intracranial infection	/	17(5.3)	

Table 1. Comparison of general data between sepsis group and control group.

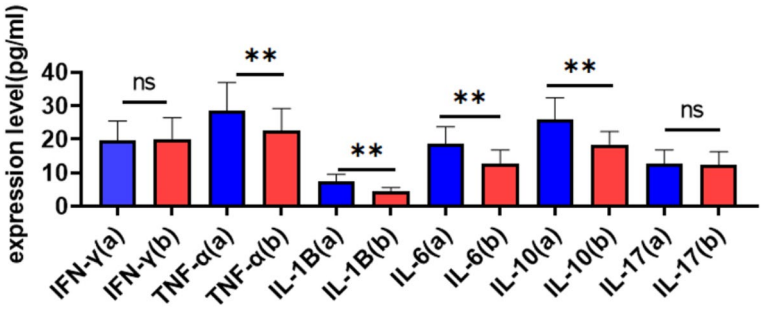

Fig. 1. The expression level of inflammatory factors between experimental group and control group.

IL-1B loci	Control group (*N* = 560)		Sepsis group (*N* = 320)		OR(95%CI) [a]	*P*[a]
	n	Percentage (%)	*n*	Percentage (%)		
-511 C/T						
CC	137	24.3	40	10.0	1.00[REF]	
TC	142	25.4	88	27.5	**2.12(1.37–3.30)**	**< 0.001**
TT	281	50.3	192	62.5	**2.34(1.57–3.48)**	**< 0.001**
C	416	37.0	168	23.6	1.00[REF]	
T	704	63.0	472	76.4	**1.66(1.34–2.06)**	**< 0.001**
+ 3954 C/T						
CC	292	52.1	164	51.2	1.00[REF]	
TC	224	40.0	128	40.0	1.02(0.76–1.36)	0.907
TT	44	7.9	28	8.8	1.13(0.68–1.89)	0.632
C	808	72.1	456	71.3	1.00[REF]	
T	312	27.9	184	28.7	1.04(0.84–1.30)	0.689

Table 2. IL-1B genotype and allele frequency for patients with sepsis. *OR* odds ratio, *CI* confidential index. [a]Adjusted for sex and age by logistic regression model.

Cytokines expression level

In analyzing serum cytokines expression level form 320 adult patients with sepsis and 560 healthy subjects, we found significant increased serum IL-1, IL-6, IL-10, and TNF-α compared with the healthy controls ($p < 0.05$). However, negative associations were detected for IL-17 or IFN-γ ($p > 0.05$). The detailed expression level can be found in Fig. 1.

Gene polymorphism analyses

The study revealed that specific polymorphisms IL-1B -511 C/T, IL-10 -1082 G/A, IL-6 -174 G/C, TNF-α -308 G/A, and IFN-γ + 874 A/T, were significantly associated with sepsis risk ($p < 0.05$). Other loci within these genes showed no significant associations ($p > 0.05$). Detailed information is provided in Tables 2, 3, 4, 5, 6 and 7.

Discussion

Sepsis is common among ICU patients, and if not effectively managed in a timely manner, it can progress to multiple organ dysfunction syndrome (MODS), potentially endangering the patient's life. Therefore, understanding the mechanisms underlying sepsis is of great importance. Current research indicates that the key pathogenesis of sepsis lies in the disruption of the inflammatory balance[20,21].

Cytokines, which are peptides or glycoproteins produced by different cell types, including immune cells, are synthesized through transcriptional and translational regulation following injury or inflammatory stimuli. These cytokines play a critical role in regulating the inflammatory response at sites of infection or injury, promoting tissue healing and clearing infections. However, excessive inflammation can lead to systemic inflammatory response syndrome (SIRS), exacerbating tissue damage and causing hemodynamic, metabolic, and homeostatic imbalances. Conversely, an excessive release of endogenous anti-inflammatory mediators triggers compensatory anti-inflammatory response syndrome (CARS)[22]. The imbalance between SIRS and CARS results in the failure to regulate the inflammatory response, leading to the overexpression of pro-inflammatory factors. These cytokines, which normally serve protective functions, shift to destructive roles, causing damage not only to local tissues but also to distant organs. This cascade of events ultimately leads to MODS, and in severe cases, to multi-organ failure (MOF) or death.

The inflammatory factors play a crucial role in the pathogenesis of sepsis. Huang et al. found that serum levels of inflammatory mediators were significantly elevated in patients with sepsis[23]. Among these, IL-6 is one

IL-6 loci	control group (*N* = 560)		sepsis group (*N* = 320)		OR(95%CI) [a]	*P*[a]
	n	Percentage (%)	*n*	Percentage (%)		
-174 G/C						
GG	198	35.4	68	21.3	1.00[REF]	
GC	228	40.7	164	51.2	2.09(1.19–2.95)	**< 0.001**
CC	134	23.9	88	27.5	2.91(1.31–2.81)	**< 0.001**
G	624	55.7	300	46.9	1.00[REF]	
C	496	44.3	340	53.1	1.43(1.17–1.73)	**< 0.001**
-1363 G/T						
GG	302	53.9	178	55.6	1.00[REF]	
GT	224	40.0	120	37.5	1.91(0.60–1.37)	0.647
TT	34	6.1	22	6.9	1.10(0.49–2.45)	0.820
G	604	73.9	476	74.4	1.00[REF]	
T	292	26.1	164	25.6	1.98(0.71–1.34)	0.884

Table 3. IL-6 genotype and allele frequency for patients with sepsis. *OR* odds ratio, *CI* confidential index
[a]Adjusted for sex and age by logistic regression model.

IL-10 loci	Control group (*N* = 560)		Sepsis group (*N* = 320)		OR(95%CI) [a]	*P*[a]
	n	Percentage (%)	*n*	Percentage (%)		
-592 C/A						
CC	156	27.9	76	23.8	1.00[REF]	
CA	224	40.0	152	47.5	1.39(0.86–2.37)	0.180
AA	180	32.1	92	28.7	0.91(0.53–1.56)	0.738
C	536	47.9	304	47.5	1.00[REF]	
A	584	52.1	336	52.5	1.01(0.77–1.34)	0.919
-1082 G/A						
GG	204	36.4	80	25.0	1.00[REF]	
GA	228	40.7	154	48.1	1.72(1.24–2.39)	**0.001**
AA	128	22.9	86	26.9	1.71(1.18–2.50)	**0.005**
G	636	56.8	314	49.1	1.00[REF]	
A	484	43.2	326	50.9	1.36(1.12–2.66)	**0.002**
-819 T/C						
TT	324	57.8	200	62.5	1.00REF	
TC	220	39.3	108	33.8	1.80(0.45–1.42)	0.530
CC	16	2.9	12	3.7	1.22(0.26–5.66)	0.881
T	868	77.5	508	79.4	1.00REF	
C	252	22.5	132	20.6	1.90(0.56–1.44)	0.735

Table 4. IL-10 genotype and allele frequency for patients with sepsis. *OR* odds ratio, *CI* confidential index.
[a]Adjusted for sex and age by logistic regression model.

of the earliest inflammatory mediators, making it valuable for early diagnosis and assessment of sepsis. Studies show that IL-6 levels are positively correlated with sepsis severity and can serve as a biomarker to evaluate both disease severity and prognosis[24]. Research has shown that the release of TNF-α damages vascular endothelial cells, promotes vasodilation, increases vascular permeability, and contributes to symptoms such as hypotension and tissue edema[25,26]. IL-1β is another important inflammatory mediator in sepsis pathogenesis. IL-1β triggers systemic inflammatory responses, leading to typical symptoms like fever and leukocytosis. In addition, inflammation-induced microcirculatory disturbance is a critical aspect of sepsis pathogenesis. Plasma levels of IFN-γ and IL-4 in sepsis patients were found to be significantly higher within 24 h of diagnosis compared to non-septic controls. Both groups exhibited increased activity of TH1 and TH2 cells, indicating that both the pro-inflammatory and immune responses are activated in the early stages of sepsis. IFN-γ, in particular, is heavily involved in mediating the pro-inflammatory response during sepsis[27]. Research into the dynamic changes in cytokine levels, such as IL-10 and IL-6, in patients with traumatic sepsis found that IL-10 levels gradually increased following diagnosis, peaking within 24 h, before declining and reaching a low point by day seven[28]. In addition, gene polymorphism is closely related to gene expression. Since inflammatory factors have an important impact on sepsis pathogenesis, any mutations in the genes of these inflammatory factors

IL-17 loci	Control group (*N* = 560)		Sepsis group (*N* = 320)		OR(95%CI) [a]	*P*[a]
	n	Percentage (%)	*n*	Percentage (%)		
rs2275913						
GG	290	51.8	160	50.0	1.00[REF]	
GA	224	40.0	132	41.3	1.07(0.71–1.61)	0.752
AA	46	8.2	28	8.7	1.10(1.54–2.26)	0.789
G	804	71.8	452	70.6	1.00[REF]	
A	316	28.2	188	29.4	1.06(0.78–1.43)	0.714
rs763780						
TT	302	53.9	178	55.6	1.00[REF]	
TC	224	40.0	120	37.5	1.91(0.60–1.37)	0.647
CC	34	6.1	22	6.9	1.10(0.49–2.45)	0.820
T	828	73.9	476	74.4	1.00[REF]	
C	292	26.1	164	25.6	1.98(0.71–1.34)	0.884

Table 5. IL-17 genotype and allele frequency for patients with sepsis. *OR* odds ratio, *CI* confidential index. [a]Adjusted for sex and age by logistic regression model.

IFN-γ loci	Control group (*N* = 560)		Sepsis group (*N* = 320)		OR(95%CI) [a]	*P*[a]
	n	Percentage (%)	*n*	Percentage (%)		
+ 874 A/T						
AA	302	53.9	158	49.4	1.00[REF]	
AT	224	40.0	120	37.5	1.02(0.68–1.55)	0.911
TT	34	6.1	42	13.1	**2.36(1.18–4.73)**	**0.014**
A	828	73.9	436	68.1	1.00[REF]	
T	292	26.1	204	31.9	1.33(0.98–1.79)	0.066
+ 2108 A/G						
AA	286	51.1	160	50.0	1.00[REF]	
AG	224	40.0	132	41.3	1.05(0.70–1.59)	0.803
GG	50	8.9	28	8.7	1.00(0.49–2.03)	0.998
A	796	71.1	452	70.6	1.00[REF]	
G	324	28.9	188	29.4	1.02(0.76–1.38)	0.888

Table 6. IFN-γ genotype and allele frequency for patients with sepsis. *OR* odds ratio, *CI* confidential index. [a]Adjusted for sex and age by logistic regression model.

affecting the production of inflammatory factors may be of candidate risk factors for the development of sepsis. In addition, the production of these inflammatory factors can also influence each other. IL-10 is one of the most important anti-inflammatory factors in the inflammatory cascade and can reduce the production of other important pro-inflammatory factors, including TNF-α, IFN-γ, IL-2, IL-6, IL-8 and IL-12[29]. Regarding the IL-1B -511 C/T polymorphism, our results are consistent with previous studies, but differ from findings in the Japanese population[30,31]. Similarly, for the IL-1B + 3954 C/T polymorphism, our results align with earlier reports but not with those observed in Caucasian populations[32]. It was reported that IL-10–592 C/A polymorphism was associated with sepsis susceptibility in Caucasian population[33]. Ferdosian et al. published a meta-analysis in 2020 and they found that IL-6 -174 G/C polymorphism were associated with sepsis susceptibility in Caucasians and Africans population but not in Asian population[34]. The above polymorphisms were not consistent with our results and we think the different results are due to racial differences. However, not all races show different polymorphic results. Varljen et al. demonstrated that TNF-α -308 A allele was a risk factor for sepsis occurrence[35], which is consistent with ours. At other polymorphic sites, our findings were also consistent with previous literatures. Interestingly, this study is the first to reveal an association between the IFN-γ + 874 A/T polymorphism and sepsis susceptibility. Our data show that the TT genotype significantly increases the risk of sepsis in the Chinese population. We think that this phenomenon may be due to the difference in the expression of the translated protein due to different genotypes. That is, the IFN-γ + 874AA genotype is associated with lower production of IFN-γ, while the TT genotype is associated with higher production of IFN-γ, which has been confirmed by most of the previous published literatures[36–50]. Although some loci have been previously studied in Chinese populations, we believe it is essential to re-examine these findings. It is well known that genetic polymorphisms are influenced by various factors, including country, region, ethnicity, climate, and environment.

TNF-α loci	Control group (*N* = 560)		Sepsis group (*N* = 320)		OR(95%CI) [a]	*P*[a]
	n	Percentage (%)	*n*	Percentage (%)		
-308 G/A						
GG	202	36.1	76	23.8	1.00[REF]	
GA	228	40.7	158	49.4	1.84(1.05–2.95)	**0.011**
AA	130	23.2	86	26.8	1.76(1.03–3.01)	**0.038**
G	632	56.4	310	48.4	1.00[REF]	
A	488	43.6	330	51.6	1.65(1.25–2.17)	**< 0.001**
-863 C/A						
CC	304	54.3	180	56.3	1.00[REF]	
CA	224	40.0	120	37.5	1.90(0.51–1.61)	0.847
AA	32	5.7	20	6.2	1.06(0.33–3.42)	0.832
C	832	74.3	480	75.0	1.00[REF]	
A	288	25.7	160	25.0	1.96(0.62–1.51)	0.959

Table 7. TNF-α genotype and allele frequency for patients with sepsis. *OR* odds ratio, *CI* confidential index. [a]Adjusted for sex and age by logistic regression model.

China, in particular, is a multi-ethnic country with 56 ethnic groups, spanning a vast territory of over 5,000 km from north to south and east to west. These geographic and environmental differences contribute to considerable variation. All of these factors can influence gene polymorphism outcomes, as has been confirmed by previous studies[36–54]. To our knowledge, this is the first study to systematically and comprehensively investigate the relationship between inflammatory factors and sepsis. The strengths of this study are clear. Previous research on the association between inflammatory factors and sepsis risk has typically focused on a limited number of genes and loci, often with relatively small sample sizes. In contrast, this study is the first to detect gene expression and polymorphisms for nearly all key inflammatory factors and their significant loci. Notably, we identified for the first time that the IFN-γ + 874 A/T polymorphism is associated with increased sepsis risk. Furthermore, with a total sample size of 880 cases, the reliability of our findings is greatly enhanced. However, there are some limitations to our research. First, the precise mechanisms by which inflammatory factors contribute to the onset and progression of sepsis remain unclear. In particular, how inflammatory factors influence the disease through key upstream and downstream genes and signaling pathways has yet to be fully elucidated. Second, given the large number of inflammatory factors and the complexity of sepsis pathogenesis, further research is needed to explore additional inflammatory factors and provide a more comprehensive understanding of the mechanisms driving sepsis.

In summary, the expression levels of IL-1, IL-6, IL-10, and TNF-α are associated with an increased risk of sepsis. Additionally, the polymorphisms IL-1B -511 C/T, IL-6 -174 G/C, IL-10 -1082 G/A, IFN-γ + 874 A/T, and TNF-α -308 G/A are also linked to sepsis risk in the Chinese population. These inflammatory factors and their gene polymorphisms can be used as biomarkers for predicting sepsis risk and they can serve as targets for personalized treatments of sepsis.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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Author contributions
Chulei Zhang designed experiments; the preliminary preparation work and data collection was carried out by Shubao Wang; Tianyu Liang wrote the manuscript; Shubao Wang worked for revision; all authors read and approved the manuscript; all authors read and approved the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
This study was conducted in accordance with the declaration of Helsinki. The studies involving human participants were reviewed and approved by the Ethics Committee of Zhejiang provincial people's hospital (Ethics register number: 2024 – 284). Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Patient consent for publication
Not applicable.

Additional information
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