Provisional chapter

Cytokine Gene Polymorphism and Sepsis

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Additional information is available at the end of the chapter

Abstract

Trauma is a significant problem across the globe with mortality more than 50%. Despite the advancement of pre-hospital care to trauma patients, early resuscitation in the emergency department, surgical interventions and intensive care monitoring mortality rate has not improved yet. The higher rate of mortality in trauma patients is usually associated with development of complications such as sepsis, septic shock, and MOF which may occur due to hysterical immune inflammatory responses. Trauma patients who developed these complications in the ICU have comparatively higher chances of mortality. Cytokines are very important for host immune response against infections and play vital roles in the regulation of innate and adaptive immunity. The slanted expression of cytokines due to trauma may be involved in development of sepsis and related complications. The recently published work from various studies suggested that slanted expression of cytokines correlates with the variations in the promoter and structural regions of cytokine genes, which may be responsible for inter-individual differences in susceptibility to sepsis. Therefore, understanding the variations in cytokine genes and associated outcomes due to trauma would possibly contribute to the event of latest genetically changed diagnostic and therapeutic interventions that will improve the outcome in post-traumatic sepsis patients.

Keywords: trauma, cytokine, multiple organ failure, septic shock and inflammation

1. Introduction

Trauma remains a significant public health issue and is the fourth leading cause of death in persons younger than 40 years [1, 2]. Worldwide, about 16,000 people die every day as a result

of an injury (5.8 million deaths per year), and the projections for 2020 show that 8.4 million deaths per year are expected [3].Consequently, injury will be the second most common cause of disability adjusted years of life lost within the next 13 years (second only to cardiovascular disease). Undoubtedly, the major burden of injury is increasingly occurring in the developing world as it industrializes, adopts motorized transportation, and remains the major center for armed conflict [4, 5]. Despite advancement in primary care to trauma patients, early resuscitation in the emergency department, surgical interventions, and intensive care monitoring, mortality rate has not improved yet. The higher rate of mortality to trauma patients is usually associated with development of various complications such as sepsis, septic shock, and the development of the multiple organ dysfunction syndrome (MODS) [6, 7]. The outcome of trauma patients is not determined only by trauma but also by the impacts of immune-inflammatory insult. The inflammatory response is crucial for the host defense against infections, but hysterical immune inflammatory responses are generated due to imbalance in the production of inflammatory and anti-inflammatory cytokines which may lead to various complications and consequently unfavorable outcomes [8, 9]. According to the biphasic model of trauma etiology, dysregulations in the production of both inflammatory and anti-inflammatory cytokines primarily lead to the sepsis-associated mortalities and outcomes [10, 11]. Posttraumatic sepsis which may cause hysterical immune inflammatory responses is one of the leading sources of MODS in the ICU. Although there have been many advances in the development of broad and narrow spectrum of antibiotics and thoughtful care, sepsis remains a serious and deadly problem with high mortality rates across the globe. Therefore, prognostic biomarkers to identify high-risk trauma patients in the early stages are immediately needed for early detection and preventive care of sepsis. The management of severely injured and multiple trauma patients who developed sepsis, septic shock, and MODS due to inflammatory insults is challenging for the physician in the ICU. Trauma leads to imbalance in production of pro-inflammatory and anti-inflammatory cytokines which may subsequently lead to the SIRS, sepsis, septic shock, and MODS which are shown in **Figure 1**.

1.1. SIRS

Systemic inflammatory response syndrome (SIRS) is a term that was developed in an attempt to describe the clinical manifestations that result from the systemic response to injury. The criteria of SIRS are considered as having at least two of the following four clinical parameters abnormal:

1. Temperature < 36°C or > 38° C
2. Heart rate > 90 beats/min
3. Respiratory rate > 20 breaths/min or $Paco_2$ < 32 mm Hg
4. WBC count >12,000 cells/μL or < 4000 cells/μL, or > 10% immature forms

1.2. Sepsis

Sepsis is a common, deadly, and often underappreciated disease process in emergency departments. In the intensive care unit, if patients have SIRS along with documented cultures reports

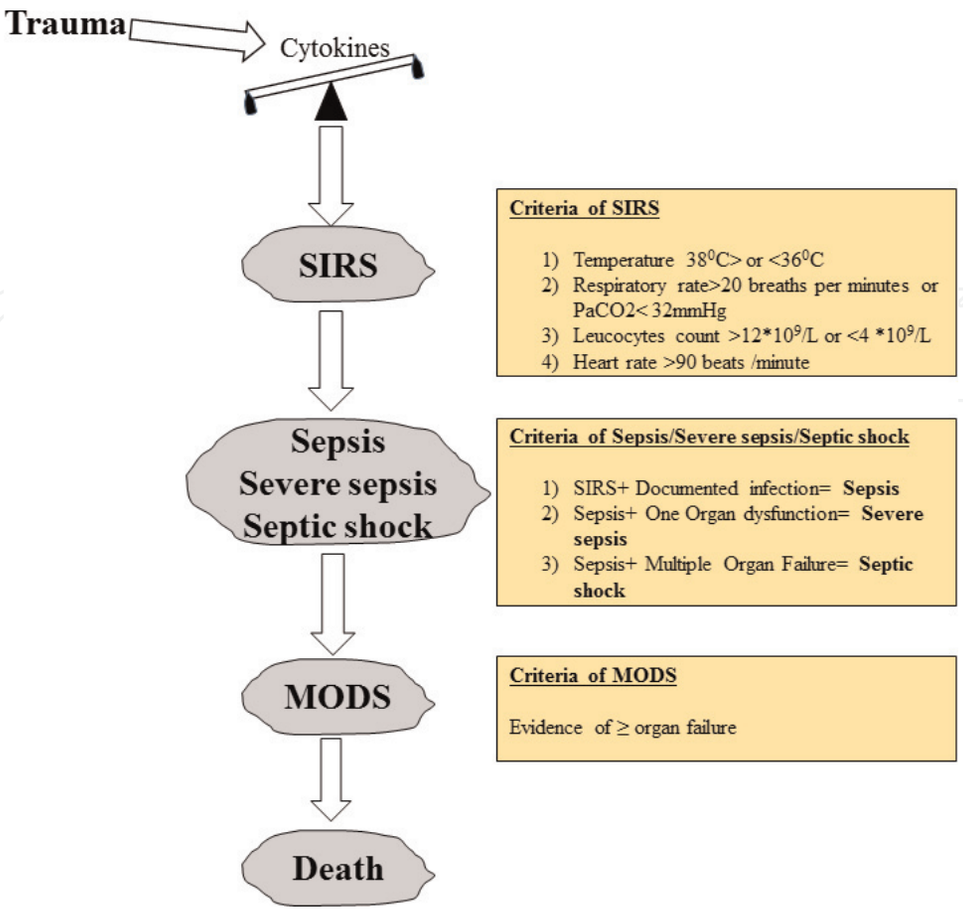

Figure 1. This figure shows that trauma leads to the imbalanced cytokine production which may subsequently lead to the sepsis, severe sepsis, septic shock, MODS, and at last death. This figure also shows the criteria which are used to define the SIRS sepsis, severe sepsis, septic shock, and MODS.

positive is called sepsis. Sepsis results in physiologic alterations that occur at the capillary endothelial level.

1.3. Severe sepsis

Sepsis accompanied by signs of failure of at least one organ. Cardiovascular failure is typically manifested with hypotension, respiratory failure by hypoxemia, renal failure by oliguria, and hematologic failure by coagulopathy.

1.4. Septic shock

Severe sepsis with organ hypoperfusion and hypotension that are poorly responsive to initial fluid resuscitation.

2. Multiple organ failure (MOF)

Multiple organ failure is a clinical syndrome in which the functionality of several organs fails subsequently or simultaneously (i.e., liver, lungs, kidneys, heart). Multiple organ failure after

trauma has a multifactorial etiology, which can be divided in endogenous and exogenous factors [12]. The endogenous factors, such as genetic predisposition, form the basis of the patient's susceptibility for the development of organ failure. Recent studies have shown that genetic variations (e.g., TNF-α polymorphisms) are strongly associated with the development of organ failure [13].The exogenous factors, such as injury itself (the "first hit" or "trauma load") and the resuscitation or surgical intervention (the "second hit" or "intervention load"), play a crucial role in the development of organ failure. Organ damage and subsequent organ failure are the result of dysfunctional immune system [11, 14].

3. Role of cytokines in development of sepsis-related complications

Cytokines are low molecular weight polypeptides, and pharmacologically active molecules possess autocrine, paracrine, and juxtracrine effects [15]. These molecules are classified into several classes (i.e., interleukins, interferons, colony-stimulating factors, tumor necrosis factors,

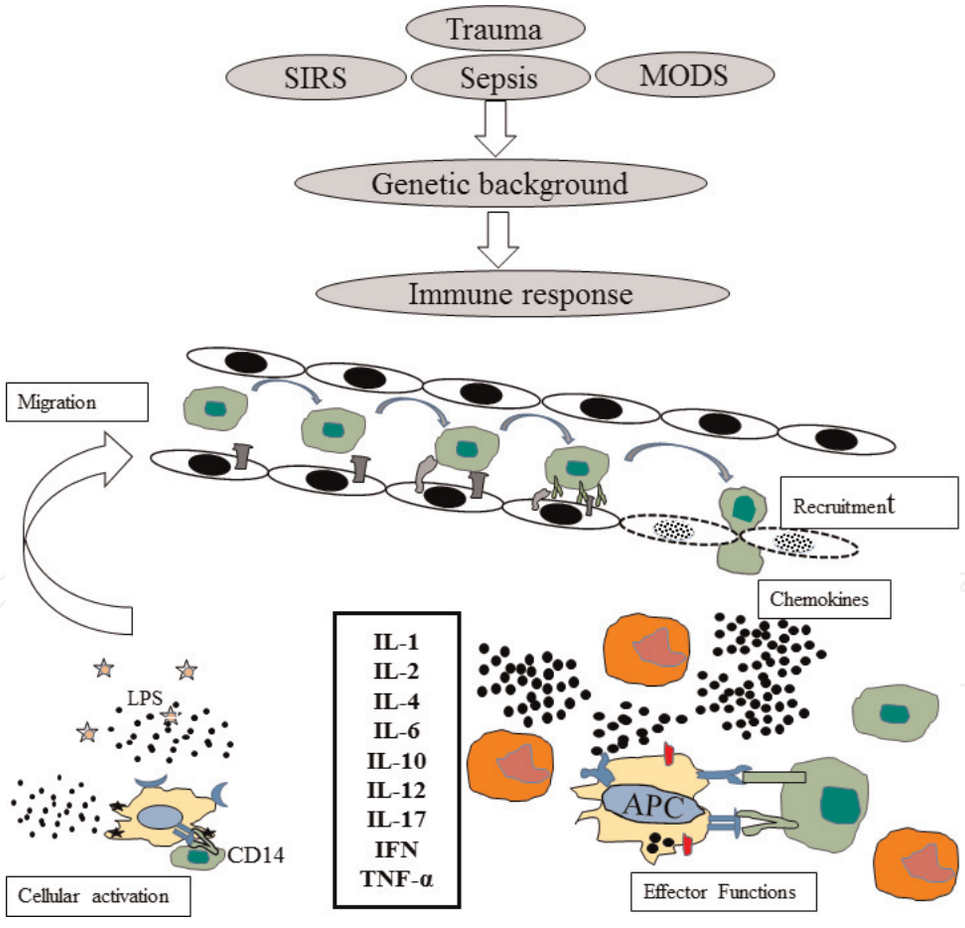

Figure 2. The outcome of trauma patients depends on induced inflammatory response due to trauma such as migration of leukocytes, cellular activation, and effecter functions, which may subsequently depend on genetic background of individuals.

transforming growth factors, and chemokines), which are relevant to mediate the humoral and cellular immunity to protect the host against pathogens [16]. Cytokines are produced by a wide variety of lymphoid and nonlymphoid cells in the body, playing an important role in many physiological responses against infections and injury. In addition, cytokines exert important pleiotropic actions as cardinal effectors of injury [17]. They play vital roles in the regulation of host immune response, and distorted expression of cytokines is proven to be involved in development of complications such as sepsis, septic shock, and MODS. Many studies suggested that the genetic background of individuals determines the impacts of immune inflammatory response after trauma which may lead to differential cellular activations of immune cells, leukocyte migrations, and effector functions (**Figure 2**). Previous research suggests that the variations in the genes encoding cytokines are also involved in the inflammatory responses and also responsible for inter-individual differences in susceptibility to sepsis and in its severity [13, 18, 19]. Therefore, understanding the variations in cytokine genes and associated differences in response to trauma might contribute to the development of new genetically modified diagnostic and therapeutic interventions that may improve outcome in posttraumatic sepsis patients.

4. Role of cytokine gene polymorphism in sepsis

Cytokine gene polymorphism, therefore, is advocated as the underlying reason to distinguish individual specific immune responses. The cytokine gene polymorphism studies may be considered as powerful biomarkers for the identification of trauma patients who have higher risk to develop sepsis complications in the ICU [20, 21]. Therefore, understanding the associations between genetic polymorphisms and sepsis or MODS may lead to the better understanding of sepsis. Nowadays the significance of genetic variations [particularly single-nucleotide polymorphisms (SNPs)] as key determinants of inter-individual variations in both inflammatory responses and clinical outcome in trauma patients is advocated [13, 22]. Single-nucleotide polymorphisms are the key factors to regulate the expressional variation of human genes and found to be associated with the disease susceptibility and progression. To understand the importance of cytokine gene polymorphism (CGP) while predicting the occurrence of sepsis, the SNPs in the promoter, coding, and noncoding regions of 13 cytokine genes with 22 loci are commonly used. Single-nucleotide polymorphisms of 13 cytokine genes including interleukin IL-1-α (T/C-889), IL-1-β (-511 C/T, T/C + 3962), IL-1 RA (T/C mspal 1100), IL-4 RA (G/A + 1902), IL-4(T/G-1098, T/C-590, T/C-33), IL-6 (G/C-174, G/A nt560), IL-10 (G/C-1082, C/T-819, C/A-592), IL-12 (C/A-1188), γIFN (+874 A/T), TGF-β1(C/T codon 10, G/C codon 25), TNF α (G/A -308, G/A-238), and IL-2(T/G-330 G/T + 166), to investigate the susceptibility towards sepsis in trauma patients, are commonly used. All the cytokine genes and their polymorphic loci which are commonly used to investigate the genetic basis of susceptibility towards disease are shown in **Table 1.** Various studies also showed the associations of these SNPs in the development of sepsis and outcomes. The polymorphic loci in the promoter region of TNF-α-308 and TNF-α-238 have been reported by various studies and showed susceptibility and resistance between

populations [23, 24]. These two polymorphisms are well recognized and associated with susceptibility for tuberculosis, heart disease, and Graves' disease [25–27]. The interleukin 6 is an important cytokine and plays a very important role in the activation of T17 cells. The polymorphisms in the promoter region of IL-6 (−174 G/C) and structural region (+560) are well characterized in various diseases. However, the polymorphism in the promoter regions (−174G/C) showed significant association with celiac disease, bowel syndrome, cancer, and autoimmunity [28–31]. Interestingly, the polymorphism in the promoter region of IL-6 (−174 G/C) influenced the immunopathogenesis of sepsis and associated with outcomes in European population of trauma [32, 33]. We have also reported the association of IL-6 (−174 G/C) polymorphism and susceptibility of sepsis in the Indian trauma patients [34]. IL-10 is an important anti-inflammatory cytokine and plays a very crucial role in the inflammation, autoimmunity, and tolerance. Many studies suggested that elevated level of IL-10 activates the transcription factor Fox P3 which may subsequently lead to the production T regulatory cells. Polymorphism in the promoter regions of IL-10 gene −1082(G/A), −819(C/T), and − 592 (C/A) is well established and showed significant association with various infectious diseases, autoimmunity, cancer D, and diabetic retinopathy [35–37]. These IL-10 promoters, −1082(G/A), −819(C/T), and − 592(C/A) polymorphisms, are associated with resistance to sepsis in the Caucasian population [38, 39]. Interleukin (IL-1) gene complex consists of IL-1α, IL-1β, IL-1R, and IL-RA genes with five potent polymorphic loci in the structural and promoter regions [40]. These polymorphic loci are associated with susceptibility for sepsis in trauma patients of the Chinese population [41, 42] and also associated with other diseases, such as cancer and autoimmunity [43, 44]. In our study, we have reported the changes in alleles and genotype frequency at the promoter region of IL-1β (−511) gene. We have also reported the significant association of this polymorphism with susceptibility for sepsis in Indian trauma patients. The recently published work by Gupta et al., 2016, showed that polymorphisms in the structural and promoter regions of TNF-α, IL-β, IL-6, and IL-10 are significantly associated with susceptibility to sepsis and outcomes in trauma patients [34] **(Figure 3)**.

S.No	Allelic specificity(based on SNP nomenclature commonly used in literature	Corresponding Genotype/Haplotype	Size of the allele-specific amplicon (bp)	Size of the amplication control (bp) CRPgene-90bp/β-globin gene-440bp	Name of the cytokine
1	T at pos. -889	T	220bp	440bp	IL-1α
2	Cat pos.-889	C	220bp	440bp	IL-1α
3	C at pos.-511	C	215bp	440bp	IL-1β
4	T at pos. -511	T	215bp	440bp	IL-1β
5	T at pos.+3962	T	340bp	440bp	IL-1β
6	C at pos.+3962	C	340bp	440bp	IL-1β
7	C at pos.pstl 1970	C	290bp	440bp	IL-1R
8	T at pos.pstl 1970	T	290bp	440bp	IL-1R
9	T at pos.mspa1111100	T	300bp	440bp	IL-1RA
10	C at pos.mspa111100	C	300bp	440bp	IL-1RA
11	G at pos.+1902	G	140bp	440bp	IL-4R
12	A at pos.+1902	A	140bp	440bp	IL-4R
13	C at pos.-1188	C	800bp	440bp	IL-12
14	A at pos-1188bp	A	800bp	440bp	IL-12
15	A at pos.+874	A	180bp	440bp	IFN-Y
16	T at pos.+874	T	180bp	440bp	IFN-Y
17	C at codon 10;G at codon 25	CG	80bp	440bp	TGF-β
18	C at codon 10;C at codon 25	CC	80bp	440bp	TGF-β
19	T at codon 10;G at codon 25	TG	80bp	440bp	TGF-β
20	T at codon 10;C at codon 25	TC	80bp	440bp	TGF-β

21	C at codon 10	CG or CC	195bp	440bp	TGF-β
22	C at codon 10	TG or TC	195bp	440bp	TGF-β
23	G at pos.-308;G at pos.-238	GG	110bp	440bp	TNF-α
24	G at pos.-308;G at pos.-238	AG	110bp	440bp	TNF-α
25	G at pos.-308;G at pos.-238	GA	110bp	440bp	TNF-α
26	A at pos.-308;A at pos.-238	AA	110bp	440bp	TNF-α
27	T at pos.-330bp;G at pos.-238	TG	560bp	440bp	IL-2
28	G at pos.-330bp;G at pos.-238	GG	560bp	440bp	IL-2
29	G at pos.-330bp;G at pos.-238	GT	560bp	440bp	IL-2
30	T at pos.-330bp;T at pos.-238	TT	560bp	440bp	IL-2
31	T at pos.-10-98;T at pos-590	TT	560bp	90bp	IL-4
32	T at pos.-10-98;C at pos-590	TC	560bp	90bp	IL-4
33	G at pos.-10-98;T at pos-590	GT	560bp	90bp	IL-4
34	G at pos.-10-98;C at pos-590	GC	560bp	90bp	IL-4
35	T at pos.-590;T at pos-33	TT	560bp	90bp	IL-4
36	T at pos.-590;TCat pos-33	TC	610bp	90bp	IL-4
37	C at pos.-590;T at pos-33	CT	610bp	90bp	IL-4
38	C at pos.-590;C at pos-33	CC	610bp	90bp	IL-4
39	G at pos-174;G at pos+565	GG	610bp	90bp	IL-6
40	C at pos-174;G at pos+565	CG	430bp	90bp	IL-6
41	G at pos-174;A at pos+565	GA	430bp	90bp	IL-6
42	C at pos-174;A at pos+565	CA	430bp	90bp	IL-6
43	G at pos-1082;C at pos-819	GC*=GCC or GCA	430bp	90bp	IL-10
44	G at pos-1082;C at pos-592	G*C=GCC or GAC	305bp	90bp	IL-10
45	A at pos-1082;C at pos-819	AC*=ACC or ACA	305bp	90bp	IL-10
46	A at pos-1082;T at pos-819	AT*=ATC or ATA	305bp	90bp	IL-10
47	A at pos-1082;C at pos-592	A*C=ACC o ATC	305bp	90bp	IL-10
48	A at pos-1082;A at pos-592	A*A=ACA or ATA	530bp	90bp	IL-10

Table 1. Twenty-two single-nucleotide polymorphism in 13 cytokine genes including structural and coding regions.

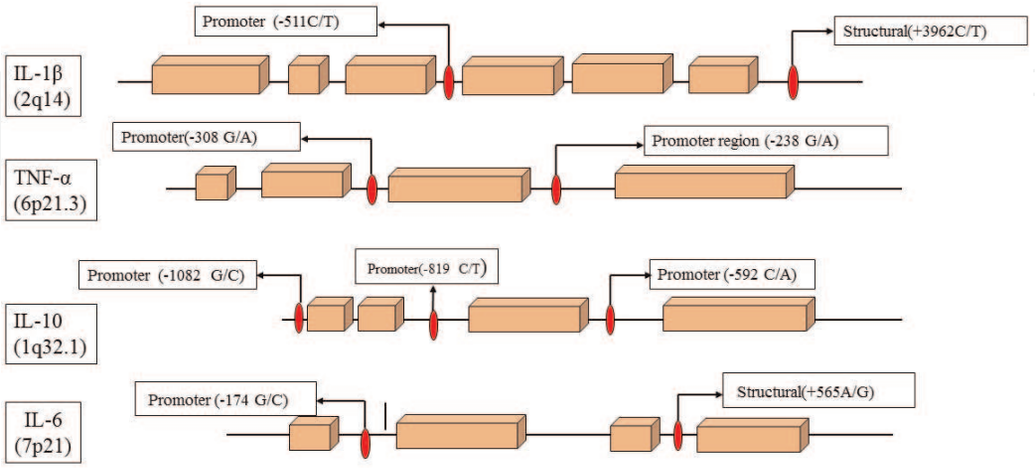

Figure 3. This figure shows the cytokine genes and its polymorphic loci present in the structural and promoter regions which are significantly involved in susceptibility for sepsis, septic shock, and death.

5. Conclusion

The purpose of this chapter is to bring together currently available information of cytokine gene polymorphisms in pro-inflammatory and anti-inflammatory cytokine genes in the development of various complications such as sepsis, septic shock, and MODS in trauma patients. Specific emphasis is placed on the polymorphism of those cytokines which potentially contributed to the development of these complications and correlates with unfavorable outcomes.

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Conflict of interest

The authors have no conflicts of interest.

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References

[1] Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. Nature Reviews. Immunology. Oct. 2008;**8**(10):776-787

[2] Moore K. Trauma mortality: Understanding mortality distribution to improve outcomes. Journal of Emergency Nursing. Jul. 2014;**40**(4):405-406

[3] Mikkelsen R, Møller Hansen O, Brink O. Non-survivors after admission to trauma Centre. Danish Medical Journal. Oct. 2014;**61**(10):A4928

[4] Spence RT, Scott JW, Haider A, Navsaria PH, Nicol AJ. Comparative assessment of in-hospital trauma mortality at a South African trauma center and matched patients treated in the United States. Surgery. 2017;**162**(3):620-627

[5] Luu MH, Cramer CL, Cabezas MN, Soshnik-Schierling L, Barnhardt WF, Young JS. The evolution of trauma care: Relative mortality analysis at a level 1 trauma center over two decades. The American Surgeon. Aug. 2017;**83**(8):e274-e276

[6] Nguyen HB et al. Severe sepsis and septic shock: Review of the literature and emergency department management guidelines. Annals of Emergency Medicine. Jul. 2006;**48**(1):54.e1

[7] Bone RC, Grodzin CJ, Balk RA. Sepsis: A new hypothesis for pathogenesis of the disease process. Chest. Jul. 1997;**112**(1):235-243

[8] Gupta DL, Bhoi S, Mohan T, Galwnkar S, Rao DN. Coexistence of Th1/Th2 and Th17/Treg imbalances in patients with post traumatic sepsis. Cytokine. 2016;**88**:214-221

[9] Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet. Jul. 2018; **392**(10141):75-87

[10] Chakraborty S, Karasu E, Huber-Lang M. Complement after trauma: Suturing innate and adaptive immunity. Frontiers in Immunology. 2018;**9**:2050

[11] Hietbrink F, Koenderman L, Rijkers G, Leenen L. Trauma: The role of the innate immune system. World Journal of Emergency Surgery: WJES. May 2006;**1**:15

[12] Ramírez M. Multiple organ dysfunction syndrome. Current Problems in Pediatric and Adolescent Health Care. Dec. 2013;**43**(10):273-277

[13] Majetschak M et al. Relation of a TNF gene polymorphism to severe sepsis in trauma patients. Annals of Surgery. Aug. 1999;**230**(2):207

[14] Cohen J. The immunopathogenesis of sepsis. Nature. Dec. 2002;**420**(6917):885-891

[15] Lanas A, Sekar MC, Hirschowitz BI. Objective evidence of aspirin use in both ulcer and nonulcer upper and lower gastrointestinal bleeding. Gastroenterology. Sep. 1992;**103**(3): 862-869

[16] Yao YM, Luan Y. Precision evaluation of immune status and its significance in sepsis after burns or trauma. Zhonghua Shao Shang Za Zhi. Nov. 2018;**34**(11):786-789

[17] Chang HR, Bistrian B. The role of cytokines in the catabolic consequences of infection and injury. JPEN Journal of Parenteral and Enteral Nutrition. Jun. 1998;**22**(3):156-166

[18] Zhao Y et al. The -144C/A polymorphism in the promoter of HSP90beta is associated with multiple organ dysfunction scores. PLoS One. Mar. 2013;**8**(3):e58646

[19] Fowler EV. TNF and IL10 SNPs act together to predict disease behaviour in Crohn's disease. Journal of Medical Genetics. Jun. 2005;**42**(6):523-528

[20] Stanilova SA, Miteva LD, Stanilov NS, Stefanov CS, Karakolev ZT. Interleukin-12b polymorphisms in association with susceptibility to severe sepsis. Laboratoriums Medizin. Jan. 2010;**41**(1):47-50

[21] Bauer I et al. Influence of gender on stimulated cytokine response in patients with severe sepsis. Anaesthesist. May 2006;**55**(5):515-527

[22] Bidwell J et al. Cytokine gene polymorphism in human disease: On-line databases. Genes and Immunity. Sep. 1999;**1**(1):3-19

[23] Gordon AC et al. TNF and TNFR polymorphisms in severe sepsis and septic shock: A prospective multicentre study. Genes and Immunity. Dec. 2004;**5**(8):631-640

[24] Azevedo ZM et al. Tumor necrosis factor (TNF) and lymphotoxin-alpha (LTA) single nucleotide polymorphisms: Importance in ARDS in septic pediatric critically ill patients. Human Immunology. Jun. 2012;**73**(6):661-667

[25] Ceylan E, Karkucak M, Coban H, Karadag M, Yakut T. Evaluation of TNF-alpha gene (G308A) and MBL2 gene codon 54 polymorphisms in Turkish patients with tuberculosis. Journal of Infection and Public Health. Dec. 2017;**10**(6):774-777

[26] Huangfu F, Zhao X, Wang X, Tang L, Jiang J. There is no association between TNF-α gene polymorphisms and the risk of coronary artery heart disease: A meta-analysis. The Journal of Cardiovascular Surgery. Oct. 2017;**58**(5):770-778

[27] Tu Y, Fan G, Zeng T, Cai X, Kong W. Association of TNF-α promoter polymorphism and Graves' disease: An updated systematic review and meta-analysis. Bioscience Reports. 2018;**38**(2):27

[28] Akbulut UE, Çebi AH, Sağ E, İkbal M, Çakır M. Interleukin-6 and interleukin-17 gene polymorphism association with celiac disease in children. The Turkish Journal of Gastroenterology. Nov. 2017;**28**(6):471-475

[29] Bashashati M, Moradi M, Sarosiek I. Interleukin-6 in irritable bowel syndrome: A systematic review and meta-analysis of IL-6 (-G174C) and circulating IL-6 levels. Cytokine. 2017; **99**:132-138

[30] Zhai K, Yang Y, Gao Z-G, Ding J. Interleukin-6-174G>C gene promoter polymorphism and prognosis in patients with cancer. Oncotarget. Jul. 2017;**8**(27):44490-44497

[31] Hu S et al. Association between IL-6-174G/C polymorphism and risk of multiple sclerosis: A meta-analysis. Genetic Testing and Molecular Biomarkers. Feb. 2014;**18**(2):127-130

[32] Jeremić V et al. Clinical relevance of IL-6 gene polymorphism in severely injured patients. Bosnian Journal of Basic Medical Sciences. 2014;**14**(2):110-117

[33] Sapan HB et al. Pattern of cytokine (IL-6 and IL-10) level as inflammation and anti-inflammation mediator of multiple organ dysfunction syndrome (MODS) in polytrauma. International Journal of Burns and Trauma. 2016;**6**(2):37-43

[34] Gupta DL, Nagar PK, Kamal VK, Bhoi S, Rao DN. Clinical relevance of single nucleotide polymorphisms within the 13 cytokine genes in north Indian trauma hemorrhagic shock patients. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. Nov. 2015;**23**:96

[35] Wu H, Guo J, He Y, Yin H, Shu J. Relationship between IL-10 gene -819C/T polymorphism and the risk of inflammatory bowel disease: A meta-analysis. African Health Sciences. Sep. 2016;**16**(3):866-872

[36] Sharma N, Toor D. Interleukin-10: Role in increasing susceptibility and pathogenesis of rheumatic fever/rheumatic heart disease. Cytokine. 2017;**90**:169-176

[37] Wattanathum A, Manocha S, Groshaus H, Russell JA, Walley KR. Interleukin-10 haplotype associated with increased mortality in critically ill patients with sepsis from pneumonia but not in patients with extrapulmonary sepsis. Chest. Sep. 2005;**128**(3):1690-1698

[38] Jeremić V, Alempijević T, Mijatović S, Arsenijević V, Ladjevic N, Krstić S. Clinical relevance of IL-10 gene polymorphism in patients with major trauma. Medicinski glasnik (Zenica). Aug. 2014;**11**(2):326-332

[39] Liese AM, Siddiqi MQ, Siegel JH, Deitch EA, Spolarics Z. Attenuated monocyte IL-10 production in glucose-6-phosphate dehydrogenase-deficient trauma patients. Shock. Jul. 2002;**18**(1):18-23

[40] Garlanda C, Dinarello CA, Mantovani A. The interleukin-1 family: Back to the future. Immunity. Dec. 2013;**39**(6):1003-1018

[41] Zhang A-Q et al. Associations between interleukin-1 gene polymorphisms and sepsis risk: A meta-analysis. BMC Medical Genetics. Jan. 2014;**15**:8

[42] Wen A-Q et al. Clinical relevance of IL-1β promoter polymorphisms (−1470, −511, and −31) IN patients with major trauma. Shock. Jun. 2010;**33**(6):576-582

[43] Raza Y et al. Combination of interleukin 1 polymorphism and *Helicobacter pylori* infection: An increased risk of gastric cancer in Pakistani population. Pathology Oncology Research. Oct. 2017;**23**(4):873-880

[44] Fontanella M et al. Interleukin-1 cluster gene polymorphisms and aneurysmal subarachnoid hemorrhage. Neurosurgery. Jun. 2010;**66**(6):1058-1063

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