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Altered expression of Toll-like Receptors across the Spectrum of COVID-19: A Disease Severity-dependent Perspective

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ABSTRACT

OBJECTIVE: Identifying the factors related to the severity of COVID-19 has been one of the biggest challenges since the outbreak of this disease. Disrupted innate immune responses are a significant factor in the severity of COVID-19.

METHODOLOGY: In this case–control study, we explored the expression of Toll-like receptors (*TLR3, TLR4, TLR7, and TLR9*) and retinoic acid–inducible gene I (*RIG-I*) in peripheral blood mononuclear cells (PBMCs) of patients with COVID-19. of included 30 patients with varying disease severity (15 mild/moderate and 15 severe cases) and 15 healthy individuals. We recruited patients from Afzalipour Hospital, Kerman, Iran, between February and April 2021, and measured gene expression levels using real-time PCR.

RESULTS: TLR gene expression levels, as well as RIG-I expression, were higher in COVID-19 patients than in the control group, and this increase was significant for some genes. Additionally, comparing these genes in severe patients with those in mild patients revealed lower expression of *TLR3* (p-value = 0.038) and higher expression of *TLR4* (p-value = 0.026).

CONCLUSION: These data indicate that dysregulation of the *TLR* signaling pathway, particularly *TLR3* and *TLR4*, may be associated with COVID-19 severity.

KEYWORDS: SARS-CoV-2, Inflammation, Retinoic acid-inducible gene I (*RIG-I*), Toll-like receptors (*TLRs*), COVID-19 severity

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging disease of global proportions in recent human history that occurred in 2019[1,2]. Despite the passage of over five years after the emergence of COVID-19 and control of the COVID-19 pandemic, significant knowledge gaps still exist regarding the etiology of the disease and the immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[3-5]. In many cases, patients show no noticeable symptoms or recover following a self-limiting antiviral response characterized by the production of neutralizing antibodies and cell-mediated immunity. 13.9% of patients with moderate COVID-19 infection suffer from acute respiratory distress syndrome, lymphopenia, and extensive chest X-ray abnormalities, and 6.1% of people manifest severe disease, with respiratory and multi-organ failure and need admission to intensive care units (ICU)[6,7]. Based on available evidence and clinical observations, the development of severe disease is frequently linked with a hyperinflammation state (also known as cytokine storm), a state characterized by dysregulated and excessive production of cytokines, immunomodulatory dysfunction accompanied by systemic inflammation affecting several organs.

Although the mechanism underlying exaggerated inflammation in COVID-19 remains well understood, accumulating evidence suggests that aberrant function of Pattern recognition receptors (PRRs) plays an important role in orchestrating host immunity and influencing disease severity and complications[8]. Among virus-sensing PRRs, key sensors, including TLRs, NLRs, and RIG-I-like receptors, play important roles in sensing key viral molecular signatures. These receptors detect multiple moieties present on viral pathogens. Upon detection of these ligands, they orchestrate a series of complex signalling events. This cascade of events is crucial for triggering the innate immune system, the first line of defence against viral intrusion. Moreover, these receptors cross-modulate the effector components of adaptive immunity, refining the immune response to make it more efficient and focused against the viral threat. Besides these roles, activation of these PRRs significantly influences the production of cytokines (signaling molecules that help immune cells communicate). It therefore shapes the overall immune response during a viral infection (9). *TLR3*, *TLR4*, *TLR7*, *TLR8,* and *TLR9* genes play an important role in the antiviral response, including defense against SARS-CoV-2 infection[10]. Among them, *TLR3,* together with *RIG-I,* detects viral double-stranded RNA, while *TLR4* recognizes the viral spike (S) protein. Endosomal *TLR7* and *TLR8* sense single-stranded RNA, and *TLR9* contributes to the detection of viral RNA. Collectively, these receptors initiate early immune signaling pathways, shaping the host's initial antiviral response[11,12]. Upon viral sensing, *TLR*-mediated signaling pathways are rapidly activated, leading to the modulation of transcriptional programs governed by IRFs and NF-κB. This signaling network enhances the expression of inflammatory mediators and drives robust innate immune activation, which may exacerbate inflammatory damage in SARS-CoV-2 infection. Also, *TLRs* induce type I interferon responses through the alternative IRF3 pathway[8,10,11]. Type I interferons are secreted by virus-infected cells, and through the JAK-STAT signaling pathway, they induce interferon-stimulated genes (*ISGs*) and play an important role in the cellular antiviral response[12-14]. Immune system defects, especially defects in the interferon signalling pathway, and excessive inflammation caused by excessive activation of the TLR-NF-κB signalling pathway have been identified as one of the important factors affecting the severity of the disease of COVID-19. Both *TLR- NF-κB and TLR-IRF3 pathways play a role in viral defense, and in healthy individuals* with normal immune systems, the two pathways occur in a relative balance and lead to the elimination of infection. But in individuals with immune system deficiencies, the imbalance between the two pathways causes an increase in the *TLR- NF-κB* pathway response and a relative decrease in

the antiviral response of the *TLR-IRF3* pathway, failing to remove virus-infected cells, leading to ongoing production of abnormal cytokines, and death [11,12].
As a consequence, *TLRs* assume a dual function during viral infections. Various studies have shown that increasing or decreasing TLR expression plays a significant role in COVID-19 severity of COVID-19. Accordingly, this research aimed to investigate whether differential expression of *TLR3, TLR4, TLR7, TLR9*, and *RIG-I* in peripheral blood mononuclear cells is associated with COVID-19 disease severity, thereby providing insights into the role of innate immune dysregulation in SARS-CoV-2 infection.

METHODOLOGY

Study participants and sampling method

This case–control study included 30 patients with COVID-19 consecutively recruited from Afzalipour Hospital, Kerman, Iran, between February and April 2021. We invited all eligible patients who met the inclusion criteria during the study period to participate. We obtained samples from the PBMCs of COVID-19 patients. Based on the severity of the disease the samples was separated 15 samples with mild/ moderate COVID-19 infection (with positive results of real-time PCR test with or without clinical symptoms, without evidence of pneumonia or mild pneumonia, no need for hospitalization), 15 samples with severe COVID-19 infection (with positive results of real-time PCR test, with oxygen saturation < 94%, respiratory rate > 30, needing intensive care unit) and 15 samples as control samples (without history of COVID-19). We confirmed the control samples were negative by real-time PCR. Inclusion criteria included patients aged ≥18 years with a laboratory-confirmed COVID-19 diagnosis by PCR; exclusion criteria included immunodeficiency, cancer, HIV infection, tuberculosis, or other specific viral diseases. We matched the participant groups by age and sex. We also recorded the demographic characteristics of each patient.

RNA extraction, cDNA synthesis, and quantitative real-time PCR

We extracted RNA from PBMC samples using a TRIzol total RNA extraction kit (Yekta Tajehiz, Iran) according to the manufacturer's instructions. Extracted RNA was converted into cDNA via a cDNA synthesis kit from Parstous. Then, we used quantitative real-time PCR to measure the relative mRNA levels of target genes using gene-specific primers (Table 1) and SYBR Green Master Mix (AMPLICON) on an ABI StepOnePlus real-time PCR system (Applied Biosystems; Thermo Fisher Scientific, Inc.), of normalized target gene expression using GAPDH as a housekeeping gene. Results were expressed as relative gene expression using the $2\text{-}\Delta\Delta^{Ct}$ method.

Table I: The primer sequences used for quantifying *TLRs* mRNA expression using real-time PCR are listed below

Gene	Forward primer (5′ → 3′)	Reverse primer (5′ → 3′)	Annealing temperature (℃)	Reference
TLR3	CAAACACAAGCATTCGGAATCTG	AAGGAATCGTTACCAACCACATT	58	(15)
TLR4	AGTTGATCTACCAAGCCTTGAGT	GCTGGTTGTCCCAAAATCACTTT	58	(16)
TLR7	TCAAGAAAGTTGATGCTATTGGG	CTAGCCCCAAGGAGTTTGGAA	59	(17)
TLR9	AATCCCTCATATCCCTGTCCC	GTTGCCGTCCATGAATAGGAAG	58	(18)
RIG-I	CGTAAGAGTGATAGAGGAATGCC	GGCTTGGGATGTGGTCTACTC	59	(17)
GAPDH	CCCACTCCTCCACCTTTGAC	CATACCAGGAAATGAGCTTGACA	60	(19)

Statistical analysis

SPSS (version 22) was used to determine the frequency, percentage, mean, and standard deviation. Chi-square tests, t-tests, and one-way ANOVA were employed for data analysis. Additionally, GraphPad Prism 9 software was used to create the graphs and tables.

Ethical considerations

The study protocol was approved by the Ethics Committee of Kerman University of Medical Sciences (Approval No.: IR.KMU.AH.REC.1401.202). The study followed the ethical principles of the Declaration of Helsinki. We obtained written informed consent from all participants before their inclusion in the study.

RESULTS

Demographic characteristics

As mentioned above, the present study assessed 30 COVID-19 patients, including mild/moderate and severe cases, and 15 healthy individuals. In total, 22 (48.8%) were male, including 7 (46.6%), 6 (40%), and 9 (60%) in the mild/moderate, severe, and healthy groups, respectively. The mean age of participants was 48.73 ± 10.98, 47.40 ± 6.02, 53.40 ± 15.51, and 45.40 ± 11.41 in the mild/moderate, severe, healthy, and control groups, respectively (**Table II**). We compared demographic features across the mild/moderate, severe, and control groups and found no statistically significant differences (gender, p=0.536; age, p=0.159).

Table II: Demographic characteristics of participants

Variables	Mild/moderate (n=15)	Severe (n=15)	Control (n=15)	For the X^2 test	P
Age (years, mean±SD)	47.40 ± 6.02	53.40. ± 15.51	45.40 ± 11.41	1.917	0.159
Male, n (%)	7 (46.6)	6 (40)	9 (60)	1.245	0.536

mRNA expression of TLRs

Overall analysis of *TLR* and *RIG-I* gene expression revealed a general upregulation in PBMCs of COVID-19 patients compared with control subjects. However, this increase was statistically significant only for specific genes (**Figure 1**).

The results showed a significant increase in the mRNA expression of *TLR4* (fold change = 3.030±1.07, p <0.0001) and *TLR9* (fold change = 2.2±0.88, p = 0.0015) in the severe group compared to the control group. In contrast, the upregulation of *TLR7* (fold change = 2.00±2.393, p = 0.5726), *TLR3* (fold change = 1.500±1.726, p = 0.5259) and *RIG-I* (fold change = 1.040±1.378, p >0.9999) was not statistically significant in the severe group compared to the control group.

In the mild/moderate group, TLR3 mRNA expression increased significantly (fold change = 2.500±1.602, p <0.0001) compared with the control group. Still, there was no significant upregulation of *TLR9* (fold change = 1.300±0.63268, p = 0.5609), *TLR7* (fold change = 1.090±1.024, p >0.9999), *TLR4* (fold change = 0.901±0.911, p >0.9999), and *RIG-1*(fold change = 1.449±1.698, p = 0.8925) in the mild/ moderate group compared to the control group.

Additionally, the severe group showed significant upregulation of TLR4 expression (p = 0.026) and significant downregulation of TLR3 expression (p = 0.038) compared with the mild/moderate group.

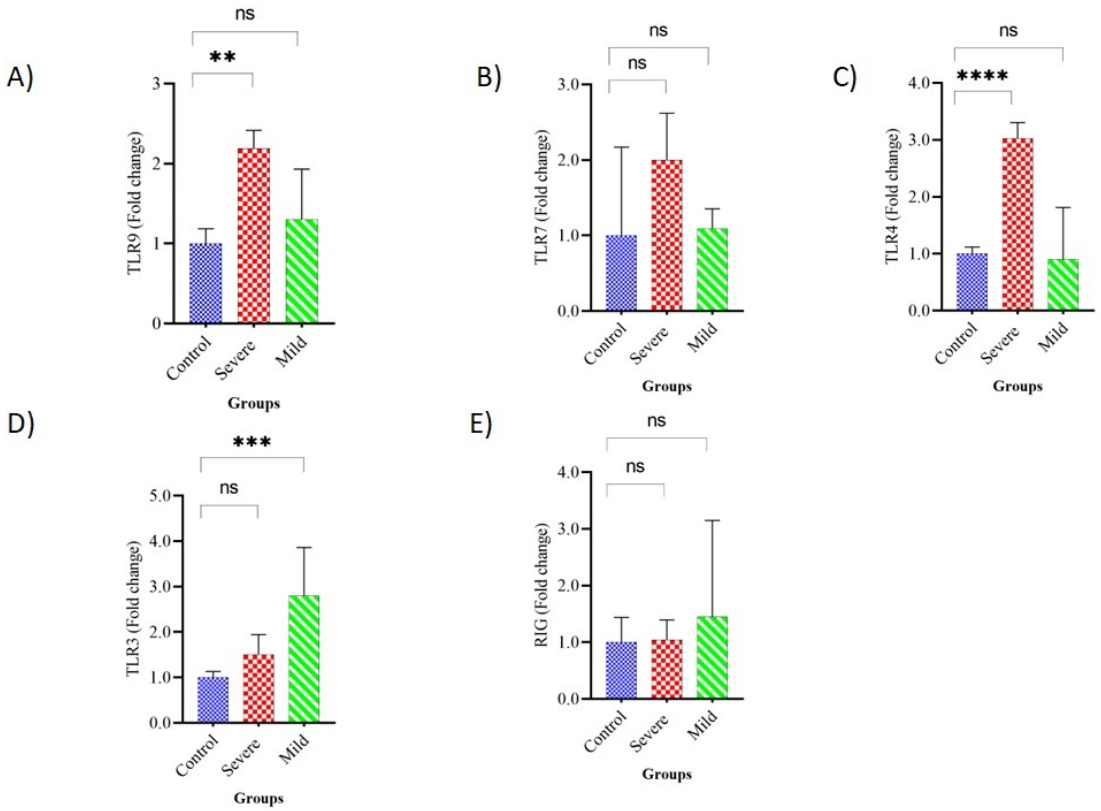

Figure 1: mRNA expression levels of *TLRs* in COVID-19 patients compared to the healthy individuals; A: *TLR9*, B: *TLR7*, C: *TLR4*, D: *TLR3*, E: *RIG-1*

DISCUSSION

Since the emergence of COVID-19, researchers have made considerable progress in defining the clinical features of the disease, its transmission dynamics, and diagnostic approaches. Yet our understanding of how the human immune system responds to SARS-CoV-2 remains surprisingly incomplete. Several lines of evidence have highlighted the crucial role of interferons and certain immune cell populations in disease progression, but many mechanistic details remain unknown[20]. After the acute pandemic phase, the virus continues to circulate, and new variants keep emerging; therefore, investigating these mechanisms remains crucial to develop better tools to manage long-term post-COVID and prepare for future coronavirus threats. They can also deepen our fundamental understanding of innate and antiviral immunity. *TLRs* are key pattern-recognition receptors in the innate immune system and among the first sensors to detect SARS-CoV-2.

Interestingly, these receptors appear to have dual, contradictory roles: they help mount an antiviral response and promote viral clearance, but they can also drive harmful hyperinflammation that contributes to severe outcomes. Therefore, a clearer picture of how SARS-CoV-2 engages *TLR*-dependent signaling pathways is essential for rationally designing both preventive and therapeutic interventions. As indicated above, the literature on *TLR* expression during COVID-19 is inconsistent. Some groups have reported upregulated *TLR* levels in severe cases, whereas others have documented the opposite pattern[21-24]. Given these conflicting findings, the present study aimed to evaluate the gene expression of several key antiviral PRRs, specifically *TLR3, TLR4, TLR7, TLR9*, and *RIG-I,* in patients with confirmed SARS-CoV-2 infection with different severity states and in healthy controls.

In this study, we observed higher expression of TLR3, TLR4, TLR7, TLR9, and RIG-I in COVID-19 patients than in uninfected individuals. However, the increase was not uniform across all receptors. This selective pattern suggests that SARS-CoV-2 likely triggers a specific subset of innate sensing pathways rather than global activation. These results agree with several earlier reports. For example, Hosseinabadi and colleagues found significantly higher levels of *TLR3, TLR7, TLR8*, and *TLR9* expression in people with mild, moderate, and severe COVID-19 compared to healthy controls[21]. Similarly, Menezes et al. reported increased transcript levels of *TLR3, TLR7, TLR9*, and *RIG-I* in patients with varying degrees of disease severity[20]. When we classified the COVID-19 patients of our study according to clinical severity, a clearer picture emerged. Interestingly, individuals with severe disease showed markedly higher *TLR4* expression and significantly lower TLR3 expression than those with mild or moderate illness. Downregulation of *TLR3* in severe COVID-19 suggests a weakened antiviral interferon response, which may impair viral clearance and contribute to disease progression.

In contrast, upregulation of *TLR4* may enhance pro-inflammatory signaling and promote cytokine-mediated tissue injury, thereby exacerbating disease severity. Altogether, this pattern suggests a shift from effective antiviral defence to excessive inflammation in severe cases. These findings highlight *TLR3* and *TLR4* as potential therapeutic targets. Enhancing *TLR3*-mediated antiviral responses or inhibiting *TLR4*-driven inflammatory pathways may be promising strategies to restore immune balance in severe COVID-19; however, further clinical validation is required.

To our knowledge, this reciprocal pattern of gene expression, decreased *TLR3* and increased *TLR4* in the most severe cases, may represent an immunologic signature linked to worse clinical trajectories. Menezes and co-workers[20] previously described the same directional change (lower TLR3, higher TLR4 in severe versus non-severe disease). Furthermore, Shon et al. have shown enhancement of *TLR4* expression in patients with severe COVID-19[24]. As mentioned previously, *TLR3* has been identified as a critical element of the immune system's

response to RNA viruses[23]. It seems that the *TLR3* gene plays a significant part in the immune system's response to COVID-19 infection, and the decrease in expression of the *TLR3* gene causes a drop in the generation of type 1 interferons. As a result, the virus cannot be cleared, and it can spread. Zhang and colleagues found that mutations in the *TLR3* gene can lead to severe, inherited immune deficiencies in COVID-19 patients, emphasizing the gene's essential role in antiviral protection[25].

Additionally, Menezes et al. proposed that differences in TLR3 expression between the mild and severe groups may be linked to the severe group's higher neutrophil count, as peripheral blood evidence suggests that *TLR3* expression is augmented in T-cells. The decreased *TLR3* expression in the COVID-19 severe group may indicate a diminished fraction of lymphocytes in their peripheral blood samples[20]. However, the lower expression of *TLR3* in severe COVID-19 than in the mild group is not only due to the elevated neutrophil count; more research is required to ascertain the origin of the variation in *TLR3* expression. Researchers have identified a significant association between pathological inflammation and *TLR4* signalling, especially in COVID-19. *TLR4* can recognize lipopolysaccharide from Gram-negative bacteria26; however, in silico investigations suggest it may also play a role in the immune response to SARS-CoV-2 infection[27].

Furthermore, Aboudounya et al. hypothesized that the coronavirus spike glycoprotein binds to TLR4 and activates signalling, which then increases surface expression of ACE2. As a result, increased *ACE2* allows the virus to enter cells more frequently, worsening the illness (28). Menezes et al. suggested that this finding, i.e., increased *TLR4* gene expression in severe COVID-19 patients, may indicate a compensatory response by leukocytes in conditions of decreased *TLR3* gene expression.

From there, *TLR3* and *TLR4* act synergistically against viral challenge and use the same intracellular signaling pathways, so it seems reasonable that the reduction of *TLR3* expression leads to a compensatory increase in *TLR4* expression[20]. Furthermore, Aboudounya's study showed that during COVID-19, decreased pulmonary surfactant secretion led to increased TLR4 expression in airway cells. HMGB1 (High mobility group box 1 protein) released by lysed cells can also activate *TLR4* and cause further inflammation and fibrosis. Furthermore, SARS-CoV-2 may activate *TLR4*, enhancing the PI3K/Akt signalling pathway in infected cells, which suppresses apoptosis and prolongs viral replication. Aberrant inflammatory signaling may also involve extra-pulmonary *TLR4*-expressing tissues, potentially contributing to multi-organ damage in COVID-19 (28). In our study, we found no significant differences in *TLR7, TLR9*, or *RIG-I* expression between mild and severe cases, despite previous reports such as Fallerini indicating reduced *TLR7* expression in patients with severe disease[22].

Also, Solanich found a lack of *TLR7* function in several men with severe COVID-19 disease[29]. Investigations have shown that in men with severe COVID-19, defects in X-chromosomal copies of TLR7 have been detected; decreased TLR7 expression has resulted in diminished production of IFN1/2, reduced antiviral response, and deterioration of patients' condition. Furthermore, previous studies indicate that because the TLR7 gene of located on the X chromosome, its expression is higher in women than in males[22,29]; however, we did not observe this in our investigation, which may be related to the small sample size. This study has several limitations. First, the relatively small sample size may have limited the statistical power. Second, this single-centre study at Afzalipour Hospital, Kerman, Iran, may limit the generalizability of the findings. Third, the study evaluated only mRNA expression; it did not assess protein expression or perform functional immune assays. Therefore, larger multi-centre studies incorporating protein expression analyses and functional immunological assays are needed to validate and extend these findings. Overall, the findings show that immune system deficiencies, particularly impairments in the TLR signalling pathway, can affect the severity of COVID-19. As a result, *TLR* immune modulators, such as agonists and

antagonists, may one day be used as adjuvants in vaccines or medications to treat hyperinflammatory reactions following SARS-CoV-2 infection.

CONCLUSION

This study shows that dysregulation of TLR signaling pathways, particularly altered expression of *TLR3* and *TLR4,* is associated with COVID-19 disease severity. Downregulation of *TLR3* may be linked of impaired antiviral interferon responses, while upregulation of TLR4 may exacerbate inflammatory signalling; these regulatory patterns may contribute to severe clinical outcomes. Altogether, these results indicate that manipulation of *TLR*-mediated pathways can serve as a potential therapeutic approach for controlling excessive inflammation while preserving effective antiviral immunity in COVID-19 patients.

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AUTHOR CONTRIBUTION

Karimi N: Performed concepts, design and definition of intellectual content, did literature searches and clinical studies, performed experimental studies, analyzed the data, performed manuscript preparation and manuscript editing
Lajmiri H: Performed literature searches and clinical studies
Mousavi E: Developed concepts, performed experimental studies, performed a manuscript review
Maskouni EJ: Performed literature searches and clinical studies, performed manuscript preparation and manuscript editing
Meymandi B: Analyzed the data, performed manuscript preparation and manuscript editing
Farrokhnia M: Performed a manuscript review
Ebrahimi S: Performed concept development, performed the design and definition of intellectual content, analyzed the data, performed manuscript preparation and manuscript editing, performed a manuscript review

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