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Genetic Insights into COVID-19 Severity: The Role of *TLR3* and *IRF7* Polymorphisms in Egyptian patients

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ABSTRACT

Objectives: This study was conducted to explore the impact of *TLR3* (rs3775296) and *IRF7* (rs373394984) gene polymorphisms on the severity of COVID-19 in Egyptian patients. **Methods:** The present study included 175 COVID-19 patients, 87 with severe COVID-19 symptoms and 88 who were asymptomatic or with mild symptoms. Blood samples were collected from all patients for DNA extraction. DNA Genotyping assay was performed for detecting specific SNPs (rs3775296) and (rs373394984) in the purified genomic DNA samples. **Results:** Although the two studied SNPs (rs3775296 and rs373394984) did not show a statistically significant difference between severe and mild COVID-19 cases, they may still have a protective effect. Our results indicate that both SNPs are associated with reduced severity, as the odds ratios are less than 1. Individuals carrying the mutant A allele have a 0.3 times lower likelihood of developing severe symptoms for rs373394984 and 0.5 times lower for rs3775296 compared to non-carriers. Furthermore, the mutant A allele of rs373394984 was predominant in cases which were associated with other co-morbidities. **Conclusion:** The studied SNPs (rs3775296 and rs373394984) may have a protective effect. This effect may suggest that these SNPs are involved in mechanisms that reduce severity of the disease. These findings highlight the potential role of genetic factors in COVID-19 severity and may contribute to a better risk assessment and targeted interventions in affected populations.

Keywords: COVID-19; SNPs; *IRF7*; *TLR3*; Egyptian; comorbidities

INTRODUCTION

Coronaviruses are a group of highly diverse, enveloped, positive-sense, and single-stranded RNA

viruses. They cause several diseases involving respiratory; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also named COVID-19¹, enteric, hepatic, and neurological systems which vary in

severity among humans and animals ².

SARS-CoV-2 virus attaches to the host cells using its spike protein, which interacts with the angiotensin converting enzyme 2 (ACE2) receptor on respiratory epithelial cells, facilitating viral entry. Following the replicating within the cells, the virus is released either in vesicles or through cell lysis. The immune response to SARS-CoV-2 infection involves both innate and adaptive immunity. Innate immunity includes macrophages and dendritic cells that detect pathogen-associated molecules (PAMPs) via pattern recognition receptors (PRRs). The adaptive immune response involves T-cells and B-cells that recognize specific antigens presented by antigen-presenting cells (APCs). Humoral immunity is a part of the adaptive immunity which involves B-cells, produce antibodies against specific antigens derived from B-cells to combat SARS-CoV-2 pathogens ³.

Interferons (IFNs) are cytokines that play an important role in both innate and adaptive antiviral immunity. They have proven to be vital in combating COVID-19 and may be a promising option for treating affected patients ^{1,4}.

Recent research has indicated that the dysregulation of IFNs is crucial in understanding the pathogenesis of COVID-19. Conversely, effective stimulation or early prophylactic administration of IFNs can limit viral infection and prevent the progression of COVID-19 ⁵. Studies have shown that severe COVID-19 cases often involve mutations in genes that regulate type I and III IFN immunity ⁶. In severe and critical COVID-19 patients, a distinct phenotype has been observed, characterized by a significantly impaired IFN-I response, which includes low levels of IFN-I and ISG production and activity. This impairment is associated with a persistent viral load in the blood and an exacerbated inflammatory response ⁷.

IFNs are essential for defense against viral infections but also drive recruitment of inflammatory cells to sites of infection, a key feature of severe COVID-19 ⁸.

IFN genes expression is regulated by a family of DNA- binding transcription factors called Interferon regulatory factors (IRFs). They are involved in several biological events like antiviral response, immune cells development and inflammation. IRF7 was originally identified as a master member of transcriptional factors that are crucial for production of IFN-I and regulation of the innate immune response. Subsequent studies have revealed that IRF7 performs multifaceted and versatile functions in multiple biological processes ⁹.

On the other hand, Toll like receptors (TLRs) are a type of cellular proteins that play an essential function in the innate immune response. TLR3 is found in various epithelial cells, fibroblasts, nerve cells and immune cells. It primarily detects viral double-stranded

RNA (dsRNA), self-RNAs from damaged cells and the replication intermediates produced during the life cycle of single-stranded RNA (ssRNA) viruses and DNA viruses ¹⁰.

The activation of TLRs has a dual impact on the progression of COVID-19. It is believed that the activation of different TLRs, such as TLR2, TLR3, TLR4, TLR7, and TLR9, induces the production of proinflammatory cytokines, which significantly contributes to the pathogenesis and severity of COVID-19. Severe COVID-19 cases involve immunopathological processes triggered by the interaction of TLRs with virus particles ¹¹.

The present study designed to explore the impact of *TLR3* and *IRF7* SNPs on the severity of COVID-19 in Egyptian patients.

Subjects and Methods

Patients and samples

The present study included: 175 COVID-19 patients confirmed with positive PCR tests, 87 with severe COVID-19 symptoms and 88 who were asymptomatic or with mild symptoms. Patients were recruited from the inpatient and outpatient departments of Helwan General Hospital and Abassya Chest Diseases Hospital Cairo, Egypt. All patients were subjected to full history (age, gender, duration of disease, presence of chronic diseases). Samples were collected with the written consent of the participants. The study was performed according to the regulations and recommendations of the declaration of Helsinki and approved by the scientific research ethics committee at faculty of pharmacy, Helwan University, (Approval number 09H2024). Blood samples were collected from all patients in 0.5 ml EDTA-containing tubes and stored at -80 °C for DNA extraction.

Genomic DNA extraction and identification of SNPs

Genomic DNA from whole blood was extracted by using Thermo Scientific GeneJET Whole Blood Genomic DNA Purification Mini Kit #K0781, #K0782 according to the manufacturer's instructions. DNA Genotyping assay was performed utilizing TaqMan® SNPS Genotyping Assay Kit and TaqMan® Genotyping Master Mix kit. SNPS genotyping assay was used for amplifying and detecting specific SNPS (rs3775296) and (rs373394984) in the purified genomic DNA samples using a real-time PCR TaqMan® 5'nuclease allelic discrimination assay technique using TaqMan probes labeled with the fluorescent dyes VIC® and FAM®, to identify three possible genotypes (CC, CA, and AA) for TLR3 (rs3775296); (AA, AG, and GG) for *IRF7* (rs373394984)

For rs3775296, probes sequence was ACTTTTAAATGTTTCTTTTCTACAG [C/A]

AGAATCATGAGACAGACTTTGCCT

For rs373394984, probes sequence was
GAACGTGCAGCTCGGGTGTCCACCA[AT]
CCTTCTGCAGCACCGTGC GGCCCTT

Real-time PCR was conducted in a total volume of 25 μ L under the conditions recommended by the manufacturer. Data analysis was performed, and the genotype of each sample was automatically determined by measuring allele-specific fluorescence using the Rotor gene Q integrated software for allele discrimination (QIAGEN).

Statistical analysis

Hardy-Weinberg equilibrium was assessed within both mild and severe groups using a goodness-of-fit χ^2 test. Genotype and allele frequencies were compared between the studied groups using a Chi Square test or Fisher's exact test when necessary. The odds ratio (OR) and confidence intervals (CI) were performed. Probability values <0.05 were considered statistically significant. All statistical analysis and graphs were generated using GraphPad Prism 6 for Windows® (GraphPad Software Inc., V-602, USA).

RESULTS

The demographic characteristics of all subjects included in this study are listed in (Table 1). The studied groups had a matched age and sex as the mean age of mild group was 47.3 years which showed non statistically significant difference from severe group (52.7 years). In addition, the genotypes and alleles distributions of studied SNPs were in Hardy-Weinberg equilibrium for (rs3775296) and (rs373394984). The severe group associated with many comorbidities as diabetes (24% of cases), hypertension (30% of cases), cardiovascular disease (10% of cases) and other comorbidities which have (14% of cases) compared to mild group which has less comorbidities as severe group as shown in (Table 1) while mild group associated with no any comorbidities (69% of cases) compared to 42% in severe patients.

The assessment of the impact of genotypes and alleles frequencies of TLR3 gene polymorphism (rs3775296) on the risk of severity on patients of COVID-19 showed that the frequencies of CC, CA and AA genotypes of gene TLR3 polymorphism and that of C and A alleles were not significantly different between severe and mild groups ($p=0.83$) and ($P=0.71$), respectively. The same results were obtained for IRF7 (rs373394984) as no significant difference between genotypes and alleles frequencies in the two studied groups ($P=0.14$) and ($P=0.62$), respectively as shown in (Table 2).

To study association of TLR3 and IRF7 single nucleotide polymorphisms with gender, severe and mild COVID-19 patients were sub-grouped according to gender (Figures 1 and Table 3), respectively. For TLR3

(rs3775296), the mutant CA genotype was more significantly predominant in females in both mild and severe COVID 19 patients at ($P<0.05$) which was not seen in IRF7 (rs373394984).

Moreover, we evaluated the association between TLR3 (rs3775296) and IRF7 (rs373394984) genotypes with COVID-19 severity based on gender (Table 4). We found that for TLR3 (rs3775296), there were no significant differences based on gender. i.e., between the males of severe and mild COVID-19 groups ($p>0.05$) nor between females of severe and mild groups ($p>0.05$). While for IRF7 (rs373394984), IRF7 rs373394984 AT was significantly different only in the males with mild COVID-19 (10%), compared to the corresponding subjects in the severe group 2% ($p<0.05$). However, this result was not noticed in the females between severe and mild groups ($p>0.05$).

Each studied group (severe and mild) was further divided into 2 subgroups, patients with other co morbidities as hypertension, cardiovascular diseases (CVD), and diabetes, etc. and patients without any comorbidities. There was no statistical difference between wild and mutant genotypes regarding different chronic diseases individually associated with two groups as shown in (Table 5).

Furthermore, by stratifying the patients with chronic disease compared to patients without any chronic disease collectively there was a significant statistical difference in genotypes regarding rs373394984 as mutant genotypes (AT) was associated with mild cases with chronic diseases (8%, $P=0.0068$) than in severe cases as illustrated in Figure 3A, B. But there is no statistical difference between mutant genotypes and wild genotypes regarding rs3775296 with chronic disease compared to patient without any chronic disease as shown in Figure 2A, B.

DISCUSSION

There is a raising perception that genes, particularly those regulating the host immune response may confer variable vulnerability and impact the outcomes of SARS-COV-2 infection¹². In a genetic study of COVID-19 patients, severe COVID-19 was linked to mutations in genes involved in the regulation of type I and III IFN immunity¹³. Genetic defects and autoantibodies that inhibit the IFN response have been significantly linked to approximately 14% of patients with severe COVID-19⁵.

TLRs are involved in the progression of COVID-19. The interaction of TLRs with virus particles leads to immunopathological processes that can be fatal in COVID-19 patients (Patra, Das, and Mukherjee 2020). Moreover, studies showed that COVID-19 patients are presented with chronic diseases like diabetes,

Table 1. Demographic characteristics of COVID-19 patients in different study groups (mild & severe).

Parameters (Mean $\pm$ SEM)	Mild group (n=88)	Severe group (n=87)	P value
Age (year)	47.3 $\pm$ 1.9 (Range 18-65)	52.7 $\pm$ 1.9 (Range 18-65)	P > 0.05
Gender	Male: 38 (43%) Female: 50 (57%)	50 (57%) 37(43%)	P > 0.05
Co-morbidities			
Diabetes	5(6%)	21(24%)	---
Hypertension	13(15%)	26(30%)	---
Cardiovascular disease	5 (6%)	9(10%)	---
Others	4 (4%)	12 (14%)	---
No co-morbidities	61 (69%)	37 (42%)	---

Numerical data were done by independent t tests. Categorical data were compared by Chi square test (X^2) P values <0.05 are considered significant.

Table 2. Distribution of TLR3 gene polymorphism (rs3775296) and IRF7 gene polymorphism (rs373394984) genotypes and allele frequencies in the studied subjects.

SNPS	Modal	Genotypes	Genotype frequencies (No, %)		P value	OR (CI 95%)
			Mild group (n=88)	Severe group (n=87)		
TLR3 (rs3775296)	Codominant	CC	(56, 64%)	(58, 67%)	-	Ref
		CA	(29, 33%)	(28, 32%)	0.83	0.9 (0.49 - 1.7)
		AA	(3, 3%)	(1, 1%)	0.33	0.3 (0.03 - 3.2)
	Dominant	CC	(56, 64%)	(58, 67%)	-	Ref
		CA+AA	(32, 36%)	(29, 33%)	0.67	0.8 (0.47 - 1.6)
	Recessive	CC+ CA	(85, 97%)	(86, 99%)	-	Ref
		AA	(3, 3%)	(1, 1%)	0.34	0.3 (0.03 - 3.2)
	allele C		(141, 80%)	(144, 83%)	-	Ref
	allele A		(35, 20%)	(30, 17%)	0.7161	0.5 (0.48 - 1.4)
IRF7 (rs373394984)	Codominant	AA	(83, 94%)	(86, 99%)	-	Ref
		AT	(5, 6%)	(1, 1%)	0.14	0.2 (0.02 - 1.7)
	allele T		(165, 97%)	(169, 99%)	-	Ref
	allele A		(5, 3%)	(1, 1%)	0.62	0.3 (0.03 - 3.16)

N: Number; Data were compared using Chi square test (X^2); p values <0.05 are considered significant.

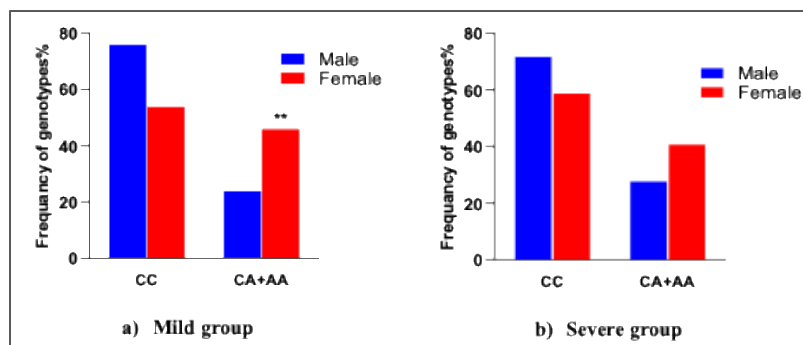


Figure 1. Distribution of TLR3 gene polymorphism (rs3775296) genotypes between genders within mild and severe groups at (P=0.0056) (P=0.0360), respectively using Chi-square test.

Table 3. Distribution of *IRF7* (rs373394984) genotypes between genders within mild and severe COVID-19 patients.

SNP	Genotype	Mild COVID-19		P value	Severe COVID-19		P value
		Male (No, %)	Female (No, %)		Male (No, %)	Female (No, %)	
<i>IRF7</i> (rs373394984)	AA	(35, 92%)	(48, 96%)	0.4	(49, 98%)	(37, 100%)	0.49
	AT	(3, 8%)	(2, 4%)		(1, 2%)	(0, 0%)	
	Total	38	50		50	37	
	OR (95% CI)	0.4 (0.15 – 1.5)			0.1 (0.1- 2. 55)		

No: Number; Data were compared using Fisher's exact test; P values <0.05 are considered significant.

Table 4. Distribution of *TLR3* (rs3775296) and *IRF7* (rs373394984) genotypes in male and female COVID-19 patients with mild and severe symptoms.

SNPs	Genotypes	Males		P -Value OR (95% CI)	Females		P -Value OR (95% CI)
		Mild (n=38)	Severe (n= 50)		Mild (n= 50)	Severe (n= 37)	
<i>TLR3</i> (rs3775296)	CC	(29, 76%)	(36, 72%)	P=0.6 OR=1.2 (0.59 – 2.3)	(27, 54%)	(22, 59%)	P=0.56 OR=0.8 (0.45 – 1.44)
	CA+ AA	(9, 24%)	(14, 28%)		(23, 46%)	(15, 41%)	
<i>IRF7</i> (rs373394984)	AA	(34, 89%)	(49, 98%)	P=0.01* OR=0.2 (0.04 – 0.73)	(48, 96%)	(37, 100%)	P=0.12 OR=0.1 (0.1 – 1.1)
	AT	(4, 11%)	(1, 2%)		(2, 4%)	(0, 0%)	

OR: odd ratio; N: Number; Data were compared using Chi square (χ^2) and fisher's exact test; p values <0.05 were considered significant.

Table 5. Distribution of TLR3 gene polymorphism (rs3775296) and IRF7 gene (rs373394984) polymorphism genotypes between the studied subjects according to associated co morbidities.

SNPS	Co-morbidities	Mild group		Severe group		P value
		Wild Genotype (CC)	Mutant Genotype (CA+AA)	Wild Genotype (CC)	Mutant Genotype (CA+AA)	
TLR3 (rs3775296)	Hypertension	20 (11%)	6 (3%)	45 (26%)	7 (4%)	0.66
	Diabetes	7 (4%)	3 (2%)	35 (20%)	7 (4%)	0.57
	CVD	10 (6%)	0	16 (9%)	2 (1%)	0.99
	No co-morbidities	37 (61%)	24 (39%)	26 (70%)	11 (30%)	0.2
IRF7 (rs373394984)	Co-morbidities	Wild Genotype (AA)	Mutant Genotype (AT)	Wild Genotype (AA)	Mutant Genotype (AT)	P value
	Hypertension	23 (13%)	1 (05%)	52 (30%)	0	0.32
	Diabetes	11 (6%)	1 (0.5%)	42 (24%)	0	0.22
	CVD	10 (65%)	0	18 (10%)	0	0.26
	No co-morbidities	57 (95%)	3 (5%)	35 (97%)	1 (3%)	0.72

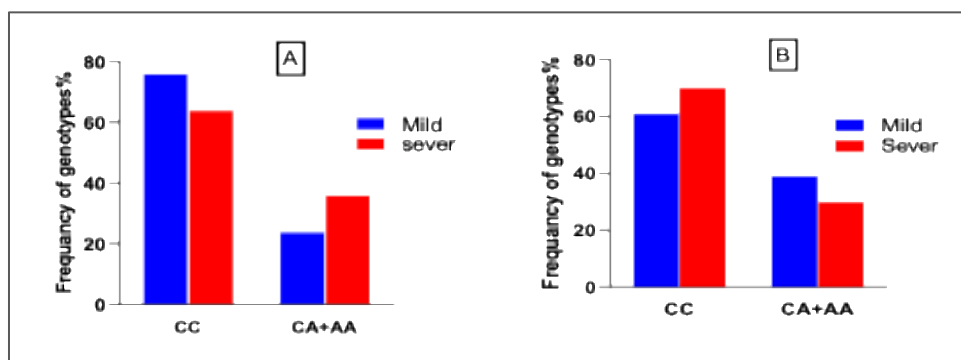


Figure 2. Distribution of *TLR3* gene polymorphism (rs3775296) genotypes frequencies in mild and severe groups A: with other chronic diseases and B: without chronic diseases using Chi-square test.

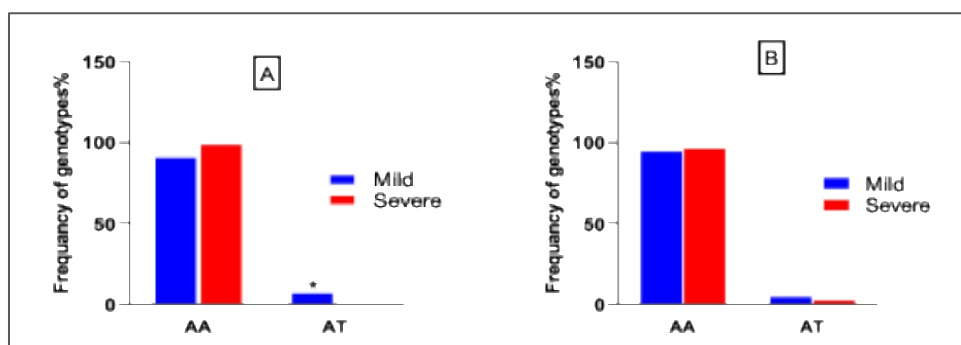


Figure 3. Distribution of *IRF7* gene polymorphism (rs373394984) genotypes frequencies in mild and severe groups A: with other chronic diseases and B: without chronic diseases using Fisher's exact test.

hypertension, and coronary heart diseases are more likely to progress to severe illnesses^{14, 15}.

This study was performed to investigate the possible association of *TLR3* and *IRF7* polymorphisms with susceptibility to severe COVID-19 infection. We aimed to inspect *TLR3* (rs3775296) and *IRF7* (rs373394984) polymorphisms in severe COVID-19-infected patients, in comparison to individuals with mild COVID-19 among Egyptian patients.

Results showed that the SNPS in *TLR3* (rs3775296) showed no significant association with COVID-19 severity in Egyptian patients which was consistent with a previous work on Iranian population¹⁶.

Additionally, our results align with other studies, such as one by Zayed *et al.*¹⁷, which found no significant association between HCV-positive patients and the control group, indicating that rs3775296 does not affect disease progression. Another study by Habib Abadi *et al.* reported that rs3775296 was significantly associated with HTLV-I infection and may be a protective factor against this viral infection¹⁸.

In a trial to explore the effect of the gender on severity of COVID-19 in *TLR3*(rs3775296) SNPS the present study did not find any significant difference between female and male in severe and mild groups. However, it showed that the mutant CA genotype was more predominant in females compared to males in mild and severe groups.

The genotype of *TLR3* (rs3775296) SNPS in COVID-19 patients with comorbidities like chronic diseases in mild and severe groups was significantly different between severe and mild COVID-19 patients. This SNPS was associated with the severity of COVID-19. While patients without chronic diseases carrying the mutant showed no significant difference between severe and mild groups.

To date, no studies have investigated the association between *IRF7*(rs373394984) SNPS and the severity of COVID-19 and this is the first study according to our knowledge.

The current study showed that there was no significant difference between severe and mild groups meaning that individual carrying the mutant AT genotype of *IRF7* (rs373394984) is not more susceptible to the severity of COVID-19.

Regarding the effect of gender on the severity of COVID-19 disease in *IRF7* (rs373394984), we found that in the male group the mutant AT in the mild group was 10%, which was significantly different from the severe group, which was 2%. However, there was no significant difference between the females in severe and mild groups. In patients with associated chronic diseases in *IRF7* (rs373394984) AA, AT genotypes were 100%, 0% in the severe group, and 92%, 8% in the mild group, respectively. There was a significant difference between severe and mild groups, which suggests that this SNPS

may be a protective factor against the severity of COVID-19. While in patients without chronic diseases there was no significant difference between severe and mild groups.

CONCLUSION

In conclusion, our study suggests that rs3775296 and rs373394984 SNPS appear to confer a protective effect, potentially through mechanisms that mitigate the clinical severity of COVID-19. These observations highlight the contribution of host genetic variation to disease outcomes and underline the relevance of these loci in modulating susceptibility and progression. Such findings may enhance the precision of risk stratification and enlighten the development of targeted therapeutic or preventive strategies in affected populations.

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Conflicts of Interest

Authors declare that they have no competing interests.

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