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Original article

Interferon-induced transmembrane protein 3 (IFITM3) gene polymorphisms in COVID-19 patients in Assiut University Hospitals

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ABSTRACT

Background and aims: Interferon-induced transmembrane protein 3 (IFITM3) plays an important antiviral role in the adaptive and innate immune response, it prevents hemifusion of the viral membrane and host cellular membrane in a broad spectrum of enveloped viruses, e.g. influenza A, ebola, marburg or SARS-CoV. This study aimed to evaluate correlation of IFITM3 gene polymorphisms (rs12252) and infection susceptibility, severity and mortality rate of COVID-19 patients. **Patients and methods:** The IFITM3 SNP (rs12252) polymorphism was genotyped by (RT-PCR) in 100 SARS-CoV-2-negative controls and 100 SARS-CoV-2- positive, who admitted to Chest, Assiut University and other quarantine Hospitals respectively in Assiut city, Egypt. **Results:** The minor allele frequency (rs12252 (G)) were significantly more frequent in the patients compared to controls after age and sex matching (*p*-value = 0.011, OR (95% CI) =2.44 (1.20-4.97). This allele (G) was significantly more common among patients who ICU admitted than non-ICU admitted (*p* -value = 0.001, OR (95% CI) =3.78 (1.64-8.75)). Also, was significantly more frequent in dead patients than cured patients (*p* -value = 0.005, OR (95% CI) =3.33 (1.37-8.10**)). Conclusion:** The present study has shown significant association between G (the mutant type) allele variant of IFITM3 rs12252 and COVID-19 infection susceptibility and disease severity and mortality.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a problem for global health [1]. The COVID-19 prevalence had spread to almost every country in the world. As of March 2023, more than 6.8 million confirmed COVID-19 deaths had occurred [2]. The total death rate is around 2%, and 23% of COVID-19 patients have severe disease, necessitating intensive care and mechanical ventilation in 11% and 7%, respectively [3].

The primary symptoms of COVID-19 are fever, a dry cough, and exhaustion. Patients with more serious conditions frequently have dyspnea and/or hypoxemia, which can quickly lead to acute respiratory distress syndrome, septic shock,

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metabolic acidosis, coagulation issues, and multiple organ failure [4].

Epidemiological data revealed that the majority of COVID-19 patients were found to have mild cases which can recover quickly but the condition can also progress quickly and aggressively as seen by growing rates of hospitalization, ICU admission, and fatality [5].

There is a large amount of variation in the clinical manifestation and prognosis of COVID-19, which has been connected to host factors like advanced age, gender, comorbidities, ethnicity, and low socioeconomic level [6]. Recent studies suggest that the differences in COVID19 phenotypes may potentially be influenced by host-genetic variable [7].

Early risk factor identification would be very beneficial in order to more precisely identify the defining clinical and epidemiological characteristics, as well as to enable timely access to the intensive care unit (ICU) if necessary and to provide the right supportive care [8].

Research on how host genetic variables contribute to COVID-19 pathogenesis is expanding quickly, and these studies have identified multiple gene susceptibility variations with varying degrees of evidence [7, 9].

Based on their function in SARS-CoV-2 tropism to human cells, including binding, entrance, and replication as well as host-immune response to the virus, the following gene candidates were selected: Angiotensin-converting enzyme 2(ACE-2), Type II transmembrane serine protease (TMPRSS2), Interferon-Induced Transmembrane Protein 3 (IFITM3), Toll-like receptor 3 (TLR3), and interferon regulatory factor 7 (IRF7) [10].

Interferon Inducible Transmembrane protein 3 (IFITM3) belongs to the IFITM family, The IFITM proteins are important in antiviral protection in adaptive and innate immunity, The human IFITM loci are located on chromosome 11p15.5 and contain five genes, one of which is IFITM3 [11]. The IFITM3 protein is mostly expressed on membrane of endosomes and lysosomes of the host cell and is an IFN stimulated gene (ISG). It prevents fusion of the viral membrane to the host cellular membrane in a broad spectrum of enveloped viruses e. g. influenza A, Ebola, Marburg or SARS-CoV [11,12].

Previous studies have reported that single nucleotide polymorphisms (SNPs) in the gene IFITM3 have been linked to increased infection susceptibility and disease severity or IFITM3 SNPs may diminish the antiviral effects of IFITM3 causing a higher infection susceptibility and disease severity [13]. For example, the severity of pandemic influenza A 2009 infection and susceptibility to this virus have been linked to three transcription-related regulatory single nucleotide polymorphisms (SNPs), rs12252, rs34481144, and rs6598045 [13, 14, 15].

The mechanisms that underlie the pathogenicity of the polymorphism IFITM3 (rs12252) minor G allele, and its association with COVID-19 morbidity and mortality are not fully elucidated [8]. It was hypothesized that the polymorphism would cause reduced expression of the IFITM3 protein[11], a weakened antiviral activity due to the encoded 21-amino acid truncation or alteration of cellular localization of the protein between the membrane and endosome[16].

Accordingly, our objective of the current study was to evaluate correlation between gene polymorphisms of IFITM3 gene (rs12252) and infection susceptibility, disease severity and mortality in COVID-19 patients..

Subjects and methods

Participants in the study

This cross-sectional analytic study was conducted from January 2022 to August 2022 in Chest, Assiut University Hospitals and other quarantine Hospitals respectively in Assiut city, Egypt. One hundred of COVID-19 patients who admitted to hospitals were included in this study. They were positive for SARS-CoV-2 by (RT-PCR). A total of 32 cases needed critical care support (ICU) including high-flow oxygen, positive-pressure ventilation or vasoactive drugs, a total of 68 patients did not require intensive care (ICU) and were thus classified as non-severe following other research [10]. Follow-up was completed on October, 2022, at which time all patients either were discharged from the hospital as “cured” or had a fatal outcome of the disease. Control group included 100 healthy controls and were selected from age and sex matched with patients. They were negative for SARS-CoV-2 by RT-PCR. Patients below 18 years old, patients diagnosed with other viral infections such as HIV, HCV, HBV, or another common respiratory virus, as well as solid organ or hematological transplantation patients and patients who receive immune modulatory drugs as

corticosteroids were excluded from the study. Demographic and clinical data was collected. Whole blood samples (3 mL) were collected for DNA extraction and genotyping.The sample size was calculated using G power software version 3.1.3, using Z test for comparison difference between two proportion. Informed consent from patients was taken and Ethical Approval for this study was obtained from Institutional review board (IRB) and approved by The Ethical Committee of the Faculty of Medicine - Assiut University prior to study execution (at a date of 3/11/2021 with IRB local approval number (04-2023-200342)). in accordance with the guidelines of human subjects' materials of Declaration of Helsinki. To confirm the adjustment of the observed genotype frequencies tothe Hardy-Weinberg equilibrium we used an online programme (https://wpcalc.com/en/equilibrium-hardy-weinberg).

DNA extraction and Genotyping of IFITM3 (rs12252) assay

A total of 3 ml whole blood samples were obtained from all participants in EDTA tube for genomic DNA (gDNA) extraction. While genotyping of IFIRM3 (rs12252) by RT-PCR analysis have been done in medical research center of Faculty of Medicine - Assiut University by The 7500 Real-Time PCR Applied Biosystem,USA.Genotyping of all samples were performed according to the manufacturers'instructions.The technique was done in three main steps: Genomic DNA extraction: DNA was extracted using QIAamp DNA Mini Kit cat.no 51104 (QIAGEN, Germany) for rapid and efficient purification of high-quality genomic DNA from whole blood. Amplification of the extracted DNA: The extracted DNA was amplified using TaqMan genotyping Master Mix cat.no.4371355 (Thermo-Fisher Scientific, USA) and ready-made TaqMan SNP genotyping assay kit for IFITM3 rs12252 SNP. Allelic discrimination by real time PCR: The real-time PCR instrument software plots the results of the AD data as a scatter plot of Allele A (VIC® dye) versus Allele G (FAM™ dye). On the plot, each well of the 96-well reaction plate is represented by a separate point as shown in figure (1)

Statistical analysis

Data analysis performed using statistical package for the social science (IBM-SPSS) version 26.0 software. Categorical data presented in the form of frequencies and percentages. All numerical variables tested before evaluation to determine the normality of data by Shapiro–Wilk test and mean ± SD was used to express quantitative variables as age.Chi square ($\chi 2$) test and Fisher Exact tests used to compare proportion between groups and the association between IFITM3 genotypes, its alleles and COVID-19 infection was estimated by computing the odds ratio (OR) and 95% confidence intervals (95% CI).independent Sample T test compare mean age between died and cured patients The data were considered significant if P values were ≤ 0.05, highly significant if $P < 0.001$.

Results

Demographic data, IFITM3 (rs12252) genotype and allele frequencies among COVID-19 patients and controls

The present study was conducted on 200 Egyptian participants who were subclassed into two main groups: healthy control (n = 100), COVID-19 patients (n = 100), who divided to severe patients (ICU=32), non-severe patients (Non ICU=68). Also, COVID-19 patients divided to died (n=18) and cured patients (n=82). The observed genotype frequencies did not differ from the expected under the Hardy-Weinberg equilibrium in both, patients and controls. Demographic data, IFITM3 (rs12252) genotype and allele frequencies for each group are presented in Table 1.

The mean age of COVID 19 patients was 61.13±14.25, ranged from 22 to 97 years. Controls aged 58.06 ±16.04, ranged from 21 to 88 years. 56.0 % of COVID 19 patients were ≥ 60 years and 65.0% of them were males. 49.0% of controls were ≥ 60 years and 54.0% of them were males. According to genotyping, AA genotype (the wild type) was 88.0% among controls. On the other hand, the GG genotype (the mutant type) was 3.0% among patients only, p value = 0.042. The minor allele frequency (rs12252 G) was significantly more frequent in the patients compared to controls, P-value = (0.011), OR (95% CI) =2.44 (1.20-4.97) as shown in Table (1).

Data is expressed as Mean ± SD (range), or frequency (%), OR (95% CI): odds ratio (95% confidence interval), (a) Independent Sample T test compare mean difference between groups. (b) Chi square test compares proportion between different groups. (c) Fisher Exact test compares proportion between different groups.

The IFITM3 (rs12252) Genotype and allele frequencies among COVID-19 patients according to comorbidities, ICU admission and patient's outcome

Overall, 100 COVID-19 patients, GG genotype was significantly more frequent in patients with comorbidities 3 (4.9%) than patients with no comorbidities (0%), p-value =0.008. G allele was significantly more frequent in patients with comorbidities than No comorbidities, p-value=0.001, OR (95% CI) = 6.12 (1.77-21.1)). (Table 2). According to severity, GG genotype was significantly more frequent in patients who ICU admitted 2 (6.3%) than patients who ICU not admitted 1(1.5%), p-value =0.006. G allele was significantly more frequent in patients who ICU admitted than patients who not ICU admitted, p-value= 0.001, OR (95% CI) = 3.78 (1.64-8.75) (Table 2)

According to the mortality, GG genotype was significantly more frequent in dead patients 2(11.1%) than cured patients 1(1.2%), p-value=0.022. G allele was significantly more frequent in dead patients than cured patients, p-value = 0.005, OR (95% CI) = 3.33 (1.37-8.10). as shown in (Table 2, Figure 2, 3, 4).

Data is expressed as frequency (%), OR (95% CI): odds ratio (95% confidence interval), NA (non-applicable). (a) Chi square test compares proportion between different groups. (b) Fisher Exact test compares proportion between different groups.

Figure 1. Results of allelic discrimination plot for some samples in this study.

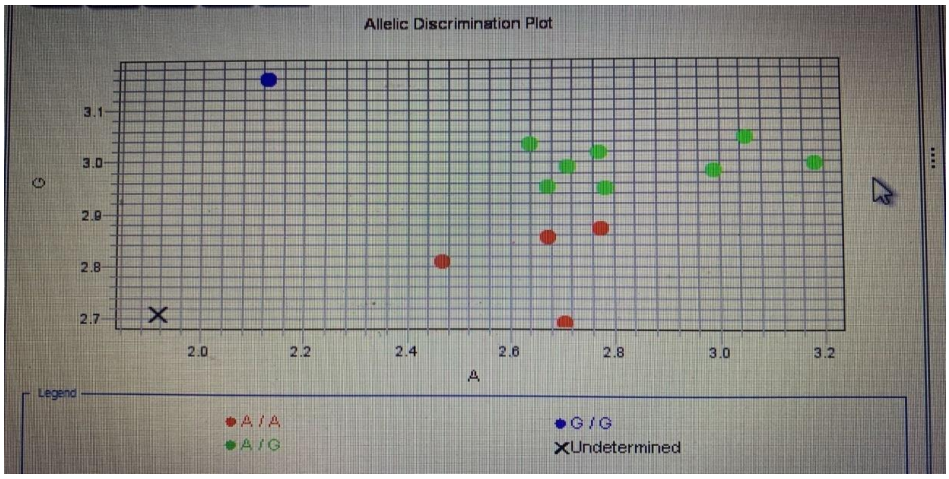


Table 1. Demographic data, IFITM3 (rs12252) genotype and allele frequencies among COVID-19 patients and controls.

Variables	Patients (N=100)	Controls (n=100)	P-value
Age (years)			
Mean ± SD (Range)	61.13±14.25 (22-97)	58.06±16.04 (21-88)	0.154[a]
▪ **<60**	44 (44.0%)	51 (51.0%)	0.322[b]
▪ **≥60**	56 (56.0%)	49 (49.0%)	
Gender			
▪ **Male**	65 (65.0%)	54 (54.0%)	0.150[b]
▪ **Female**	35 (35.0%)	46 (46.0%)	
Genotype			
▪ **AA**	76 (76.0%)	88 (88.0%)	**0.042**[b*]
▪ **AG**	21 (21.0%)	12 (12.0%)	
▪ **GG**	3 (3.0%)	0 (0.0%)	
OR (95% CI) for AG vs AA=2.02 (1.01-4.38)			
▪ **AA+AG**	97 (97.0%)	100 (100.0%)	0.246[c]
▪ **GG**	3 (3.0%)	0 (0.0%)	
▪ **AA**	76 (76.0%)	88 (88.0%)	**0.027**[b*]
▪ **AG+GG**	24 (24.0%)	12 (12.0%)	
OR (95% CI) for AG+GG vs AA=2.32 (1.11-4.94)			
Alleles			
▪ **A**	173 (86.5%)	188 (94.0%)	**0.011**[b*]
▪ **G**	27 (13.5%)	12 (6.0%)	
OR (95% CI) for Allele G vs A= 2.44 (1.20-4.97)			

Table 2. Distribution of IFITM3 (rs12252) genotype and allele frequencies among COVID-19 patients according to comorbidities, ICU admission and patient's outcome.

Genotype	Comorbidities		OR (95% CI)	χ^2	P-Value
	Yes (N=61)	**No (n=39)**			
AA	40 (65.6%)	36 (92.3%)	**Reference**	**9.54**	**0.008**[a*]
AG	18 (29.5%)	3 (7.7%)	5.4 (1.46-19.86)		
GG	3 (4.9%)	0 (0.0%)	NA		
AA+AG	58 (95.1%)	39 (100.0%)	**Reference**	1.977	0.279[b]
GG	3 (4.9%)	0 (0.0%)	NA		
AA	40 (65.6%)	36 (92.3%)	**Reference**	**9.32**	**0.003**[b*]
AG+GG	21 (34.4%)	3 (7.7%)	6.3 (1.73-22.9)		
Alleles					
A	98 (80.3%)	75 (96.2%)	**Reference**	**10.21**	**0.001**[b*]
G	24 (19.7%)	3 (3.8%)	6.12 (1.77-21.1)		
	ICU				
	Admitted (N=32)	**Not admitted (n=68)**			
AA	18 (56.3%)	58 (85.3%)	**Reference**	**10.17**	**0.006**[a*]
AG	12 (37.5%)	9 (13.2%)	4.29 (1.56-11.83)		
GG	2 (6.3%)	1 (1.5%)	6.44 (0.55-75.28)		
AA+AG	30 (93.8%)	67 (98.5%)	**Reference**	1.71	0.239[b]
GG	2 (6.3%)	1 (1.5%)	4.46 (0.39-51.18)		
AA	18 (56.3%)	58 (85.3%)	**Reference**	**10.06**	**0.002**[a*]
AG+GG	14 (43.8%)	10 (14.7%)	4.51 (1.71-11.88)		
Alleles					
A (wild)	48 (75.0%)	125 (91.9%)	**Reference**	**10.66**	**0.001**[a*]
G (mutant)	16 (25.0%)	11 (8.1%)	3.78 (1.64-8.75)		
	Outcome				
	Died (n=18)	**Cured (N=82)**			
AA	10 (55.6%)	66 (80.5%)	**Reference**	**7.61**	**0.022**[a*]
AG	6 (33.3%)	15 (18.3%	2.64 (0.83-8.39)		
GG	2 (11.1%)	1 (1.2%)	13.2 (1.1-59.3)		
AA+AG	16 (88.9%)	81 (98.8%)	**Reference**	2.14	0.083[b]
GG	2 (11.1%)	1 (1.2%)	10.12 (0.86-118-46)		
AA	10 (55.6%)	66 (80.5%)	**Reference**	**5.03**	**0.025**[a*]
AG+GG	8 (44.4%)	16 (19.5%)	**3.30 (1.12-9.7)**		

Alleles					
A (wild)	26 (72.2%)	147 (89.6%)	**Reference**	**7.66**	**0.005**[a*]
G (mutant)	10 (27.8%)	17 (10.4%)	3.33 (1.37-8.10)		

Figure 2. Distribution of IFITM3 (rs12252) genotype and allele frequencies among COVID-19 patients according to their comorbidities.

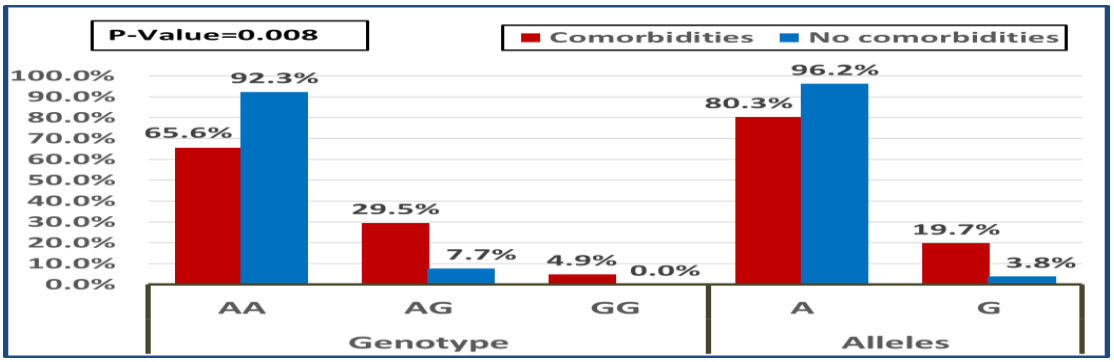


Figure 3. Distribution of IFITM3 (rs12252) genotype and allele frequencies among COVID-19 patients according to ICU admission.

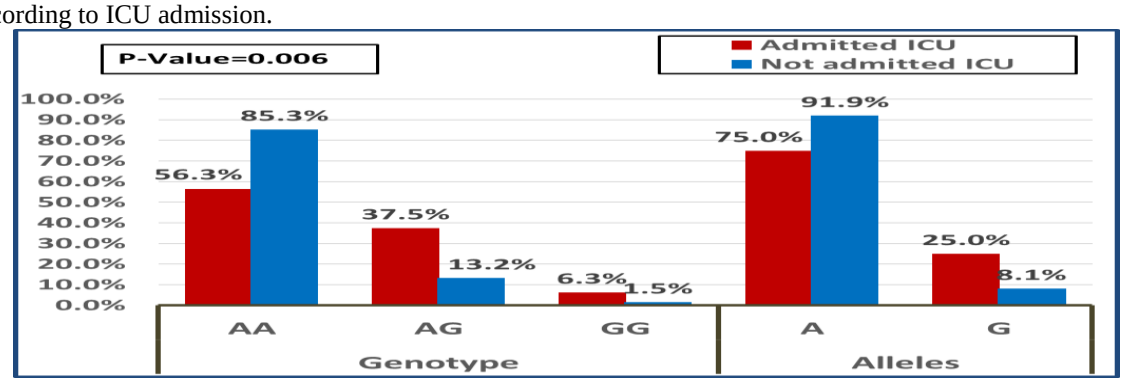
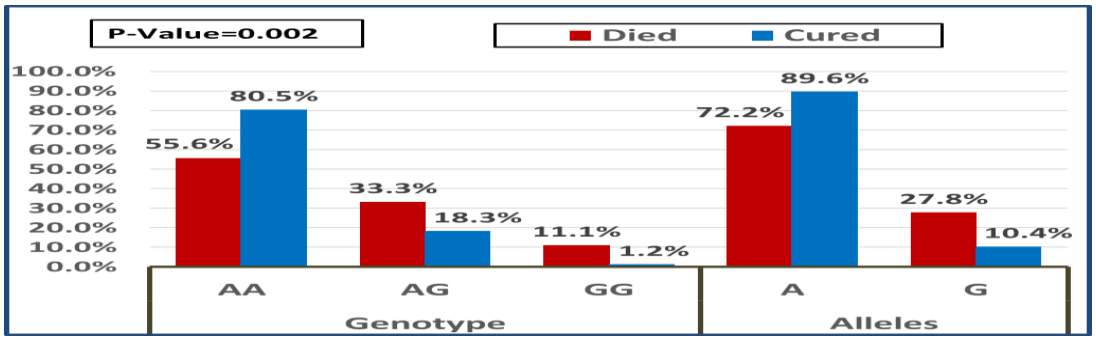


Figure 4. Distribution of IFITM3 (rs12252) genotype and allele frequencies among COVID-19 patients according to their outcome.



Discussion

The IFITM3 gene produces an interferon-induced membrane protein that exhibits broad antiviral activity against a variety of viruses, such as the SARS-CoV, dengue, West Nile, Ebola, and influenza A H1N1 viruses [17, 18, 19, 20].

On the other hand, the severity and result of multiple viral illnesses, such as influenza A H1N1/09 and H7N9, Hantan virus infection, and acute human immunodeficiency (HIV) infection, were linked to a variant, IFITM3-SNP, rs12252 with GG genotype [19, 20, 21, 22].

It is postulated that AA genotype of rs12252 SNP of the IFITM3 gene causes restriction of COVID-19 virus fusion with endosomal membrane of host cell and prevents the subsequent entry of genomic material into the cytoplasm and further progression of COVID-19 disease, whereas GG genotype acts as a risk factor for developing a severe disease due to loss of antiviral function of IFITM3 gene by SNP variant [23].

In the present study, it was observed that AA genotype (the wild type) was 76.5% among patients compared to 88.0% among controls, GG genotype (the mutant type) was 3.0% among patients compared to 0.0% among controls, p-value =0.042. The G allele carriers of IFITM3 rs12252 were found to have more than 2-fold greater risk of COVID-19 infection than the control group OR (95% CI) = 2.44 (1.20-4.97) where p-value =0.011.

A long with our finding Gomez et al. [10], found that TT genotype (the wild type) was 90% among patients compared to 94% among controls, CC genotype (the mutant type) was 1% among patients compared to 0.0% among controls. The C allele carriers of IFITM3 rs12252 were found to have more than 2-fold greater risk of COVID-19 infection than the control group OR (95% CI)= 2.14 (1.28-3.56) where p-value =0.003.

Also, our results were comparable with that reported by Cuesta-Llavona et al. [24] who found that AA genotype was 89% among patients compared to 92% among controls, GG genotype was 1% among patients compared to 0.0% among controls. The G allele carriers of IFITM3 rs12252 were found to have more than one-fold greater risk of COVID-19 infection than the control group OR (95% CI) = 1.51 (0.83-2.74) where p-value =0.18.

Only one study found no association between IFITM3 rs12252 polymorphisms and infection risk or severity in A German cohort [11]. So additional studies are needed to clarify the influence of the rs12252 GG genotype on COVID-19.

The present study revealed that the frequency of the minor (rs12252-G) allele was 13.5%, which is closer to the frequency in the Saudis population (9%) as conducted by Alghamdi et al. [25], this is significant because the minor allele frequency of IFITM3 (rs12252 G) was frequently found uncommon among European populations (1–8%), South Asian populations (10–18%), and African people (21–33%). However, much lower than East Asia (53%) as reported in the 1000 genome project [26, 27].

These previous results explain, why control group (healthy) were more protected against the disease as they carried protective (AA) genotype while, the patients were more susceptible to the disease, as they carried risk/ mutant (GG) genotype [11, 27].

Regarding to comorbidities, the present study observed that, AA genotype (the wild type) was 65.5% among patients with comorbidities compared to 92.3% among patients with no comorbidities. GG genotype (the mutant type) was 4.9% among patients with comorbidities compared to 0.0% among patients with no comorbidities, p-value =0.008.

Regarding to severity (ICU or not ICU admission), it was observed that the AA genotype was 56.3% among patients who admitted ICU compared to 85.3% among patients who not admitted ICU. GG genotype was 6.3% among patients who ICU admitted compared to 1.5% among patients who ICU not admitted, p-value =0.006. The G allele carriers of IFITM3 (rs12252) were found to have more than 3-fold greater risk of patients who ICU admitted than ICU not admitted OR (95% CI) = 3.78(1.64-8.75) where p value =0.001.

These results were similar that reported by Gomez et al. [10], who found that the TT genotype (the wild type) was 88% among patients who ICU admitted compared to 91% among patients who ICU not admitted, the CC genotype (the mutant type) was 1% among patients who ICU admitted compared to 0.5% among patients with ICU not admitted. The C allele carriers of IFITM3 rs12252 were found to have more than one-fold greater risk of patients who admitted ICU than not admitted ICU OR (95% CI)= 1.72(0.87-3.41) where p-value =0.11.

Similarly, Cuesta-Llavona et al. [24] reported that the AA genotype was 88% among patients who admitted ICU compared to 90% among patients with not ICU admitted, the GG genotype was 1% among patients who admitted ICU compared to 1% among patients with not ICU admitted. The G allele carriers of IFITM3 rs12252 were found 7% of patients who admitted ICU compared to 5% not admitted ICU.

In concordance to our study, Mulla et al. [28] showed that TT genotype (the wild type) was more prevalent among a moderate patient group while CC genotype (the mutant type) was found to be more frequent in critically ill COVID-19 patients. Moreover, a meta-analysis by Li et al. [27] and his team including 1989 patients indicated that IIFITM3 (rs12252) gene polymorphisms were associated with COVID-19 susceptibility and that the rs12252-C variant was particularly critical for severity [27].

The results of our study showed that the GG and AA genotypes of IFITM3 (rs12252) might be a risk factor for mortality and a protective factor for COVID-19 recovery respectively in Egyptians patients. It was observed that the AA genotype was 55.6% among died patients compared to 80.5% among cured patients, the GG genotype was 11.1% among died patients compared to 1.2% among cured patients, p-value =0.022.

The G allele frequency was 27.8% among died patients compared to 10.4% among cured patients, p value=0.005. Patients with the mutant G allele had 3.33 times more chance of disease mortality than those without that allele [OR (95% CI): 3.33 (1.37-8.10)].

These results were similar that reported by Ahmadi et al. [29] who found that the TT genotype was 38.7% among died patients compared to 72.7% among cured patients, the CC genotype was 35% among died patients compared to 7.5% among cured patients. The C allele frequency was 48% among died patients compared to 17% among cured patients, So, Ahmadi et al. [29] and his team showed that the CC and TT genotypes of IFITM3 rs12252 might be a risk factor for mortality and a protective factor for COVID-19 recovery in Iranian patients, respectively.

An investigation in Saudi Arabia revealed that the presence of the G allele substantially doubled the risk of COVID-19 mortality, they also showed that IFITM3 rs12252 with the T/C genotype significantly augmented the risk of mortality in younger people infected with SARS-CoV-2, raising a unique theory on the pathogenic pathways that may lead to death in this group of people [25].

Regarding the ICU patients (severe cases), who might progress to death, Cuesta-Llavona et al. [24] found no statistically significant difference between COVID-19 died patients and cured patients, as he found that the G allele frequency was 7% among died patients compared to 7% among cured patients.

In conclusion, there are alimited number of previous studies that have discussesd correlation between gene polymorphisms of IFITM3 gene (rs12252) and infection susceptibility, disease severity and mortality in COVID-19 patients separately. But this study diacussed all in the same time. Furthermore, there were differences throughout ethnic groups in the relationship between the rs12252-G allele and the clinical manifestation and prognosis of several viral diseases, ranging from none in the European to severity and lethality in the East Asian population [13, 20, 30]. Here, this study consider the second arab study after Saudi Arabia, and the first Egyption study has shown significant association between G (the mutant type) allele variant of IFITM3 rs12252 and COVID-19 infection susceptibility and disease severity and mortality.

There are some limitations on our study that should be considered. Small sample size (as it only confined to 100 patients and 100 controls of study subjects. Furthermore, there was no information about patient's prior vaccinations.

Conclusion: The present study has shown significant association between G (the mutant type) allele variant of IFITM3 rs12252 and COVID-19 infection susceptibility and disease severity and mortality.

Competing interests

Non declared.

Funding

Non declared.

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