Association of OAS1 gene polymorphism with the severity of COVID-19 infection

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Abstract. The ongoing coronavirus disease 2019 (COVID-19) pandemic has underscored the critical need to investigate host genetic factors that may influence disease susceptibility and severity. Among these, the 2'-5'-oligoadenylate synthase 1 (OAS1) single nucleotide polymorphism (SNP) rs10774671 has been implicated in the antiviral response against coronaviruses and clinical outcomes. The aim of the present retrospective study was to investigate the association between the OAS1 gene polymorphism and the severity of COVID-19. A total of 200 subjects were enrolled, including 75 healthy controls and 125 patients with COVID-19. The OAS1 SNP rs10774671 was assessed using PCR-RFLP analysis. The findings revealed an upward trend in the prevalence of the A allele among individuals, who developed a severe course of COVID-19. Specifically, 17.8% of the patients with severe infection carried the GG genotype, 52.8% had the GA genotype and 30.4% carried the AA genotype (P=0.0001). Notably, the AA genotype was exclusively detected in patients with severe COVID-19 infection (P<0.0001). Moreover, the frequency of the A allele was markedly higher than that of the G allele in patients with severe COVID-19 infection (P=0.0001). Multivariate analysis revealed that individuals with the rs10774671 AA genotype had a 6.8-fold greater likelihood of progressing to a more severe course of COVID-19 (odds ratio, 6.86; 95% CI, 2.83-16.63; P<0.0001). Thus, the OAS1 SNP rs10774671 holds promise as a potential genetic marker that could be valuable in predicting the progression and outcome of COVID-19 infection.

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Introduction

The infectious coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, has emerged as a menacing global public health crisis, posing a significant threat to the well-being and safety of the population worldwide (1,2). Globally, >762 million verified COVID-19 infections have been reported, with 6.8 million recorded deaths. Of note, only in the first week of the pandemic, there were ~354,900 thousand new cases and >1,500 related deaths. The highest affected regions were Europe and the Americas (275 and 192 million), with >13 million vaccine doses that have been administered until April, 2023 (3).

In Egypt, there have been 516,023 confirmed cases of COVID-19 with 24,830 related deaths in the period between January 3, 2020 until December, 2023, with the administration of 102,190,000 doses of vaccines, as per the WHO (4,5). Nevertheless, according to the available data, the severity of the COVID-19 pandemic in Egypt was comparatively milder compared to its neighboring countries in North Africa and other nations. The number of cases indicates that Egypt did not encounter significant surges in the pandemic, such as those observed in North Africa (3,6). Worldwide, individuals are affected by COVID-19 heterogeneously. The majority of SARS-Co-V2-infected individuals experience mild-to-moderate illness and recover without the need for hospitalization. Nonetheless, other individuals develop a severe course of disease and require hospital admission (7,8).

In addition to fever, cough and chest pain, COVID-19 can cause respiratory distress syndrome in extreme cases. It has been reported that severe symptoms are more common in individuals with comorbid conditions, an older age and the male sex (7). Apart from causing severe respiratory disorders, COVID-19 can cause damage to other organs, particularly the heart, brain, liver, kidneys and skin, which eventually may lead to death (1).

In patients with COVID-19, the early immune escape and enormous viral replication leads to the overexpression of inflammatory genes and the activation of pro-inflammatory responses. It has been reported that COVID-19 substantially activates the immune cells, triggers IFN and a number of IFN-stimulated genes (ISGs) with potent immunopathogenic effects (9). ISGs and IFN production play a crucial role in viral clearance as a host defense mechanism (10,11).

Anyone may be at risk of SARS-Co-V2 infection, which may lead to severe illness at any age and eventually, mortality. Previous studies have shown that the age of the patient has a significant impact on the severity and predicted outcomes of COVID-19 (8). Adults >65 years of age are at a 23-fold higher risk of mortality than those <65 years of age, and they account for 80% of hospital admissions (12,13).

Vaccination strategies have had a significant impact on the successful containment of the SARS-CoV-2 pandemic. These strategies encompass a range of approaches, including mRNA-based vaccines (14,15), vector-based vaccines (16,17) and implementing immunoinformatic approaches focusing on B-T cell epitopes for developing peptide vaccines (18). Protein subunit vaccines, exemplified by the development of Novavax, utilize purified spike protein or its subunits to stimulate the immune system (19). The development of SARS-CoV-2 vaccines has demonstrated notable efficacy in limiting COVID-19 infection and suppressing the severity of illness. However, it should be noted that in the USA, individuals who remained unvaccinated faced significantly higher risks of mortality due to COVID-19. Specifically, the risk of mortality was 25-fold higher for patients aged 50-64 years, 60-fold higher for patients aged 65-74 years, and 140-fold higher for patients aged 75-84 years (20). Furthermore, the disparities in socioeconomic status, race and culture have a significant impact on the COVID-19 pandemic. Recently, it has been found that racial and ethnic variations can cause severe outcomes in patients with COVID-19, which lead to higher rates of hospitalization, admission to intensive care units and mortality rates (21-23). It has been established that the prevalence and presence of single nucleotide polymorphism (SNPs) differ among populations, which may affect the expression of certain genes that are strongly related to coronavirus infection. These diverse SNPs underscore the significant role of host genetic factors in influencing COVID-19 susceptibility and disease outcomes.

2'-5'-Oligoadenylate synthase (OAS) genes are essential components of innate immunity that are involved in immune responses and the COVID-19 cytokine storm. A highly transcriptional profile of OAS1 genes has been reported in patients with COVID-19 (24,25). OAS1 is a crucial immune regulator which induces RNaseL and plays a vital role in antiviral activity (26-28). The functional activity of the OAS1 protein has been demonstrated to be affected by variations in SNPs in the gene, which has an impact on the capacity of an individual to generate a successful immune response to viral infections. The OAS1 SNP (rs10774671) is known as splice quantitative trait locus (sQTL) as it influences alternative splicing and produces different OAS isoforms p46 and p48. The presence of the A allele (AA at acceptor site) ablates the splice site, resulting in low OAS1 enzyme activity (p48 and p52), while the G allele at this site preserves splicing and leads to high OAS1 enzyme activity (p46) (29,30). Additionally, it has been observed that individuals possessing the G allele exhibit an elevated OAS1 activity (p46) compared with those with only the A allele (31,32). These results suggest that the OAS1 genetic variation at rs10774671 affects the susceptibility of the host to viral infection, thus influencing the disease progression and outcomes (33,34). The variant (rs10774671-A) is present in the majority of individuals of Europeans ancestry, while the G allele is dominant in the African populations (rs10774671-G) (35). Recently, it was documented that the OAS1 rs10774671-G allele provides protection against severe COVID-19 infection in Moroccans (36).

Recently, previous studies have explored the association between the OAS1 SNPs with the susceptibility of an individual to SARS-CoV-2 infection, the severity of the disease and clinical outcomes. These studies have explored and highlighted the significant influence of OAS1 (rs10774671) gene variations in determining individual susceptibility to SARS-CoV-2 infection across different populations (30,31,36-38).

In a previous study, the authors developed a mathematical model to analyze the transmission of COVID-19 during the first wave in Egypt, with a focus on the impact of detection and control measures (39). Additionally, the authors investigated COVID-19 infection in the Egyptian population and discovered an association between age, case severity and the neutrophil-lymphocyte ratio (NLR), highlighting the importance of including C-reactive protein (CRP) and a CT chest scan for a more accurate diagnosis. These findings underscore the increased risk of symptomatic COVID-19 in older individuals in Egypt and suggest the potential utility of an integrated panel including CT chest scan, CRP and NLR for assessing disease severity (40). The present study investigated whether the OAS SNP (rs10774671) is related to the susceptibility to COVID-19 infection and whether it influences its severity by comparing hospitalized vs. non-hospitalized Egyptian patients. The results present different clinical COVID-19 outcomes related to the functional OAS1 SNP rs10774671, which may aid in identifying susceptible populations, predicting clinical outcomes and improving the effectiveness of individualized coronavirus treatment.

To the best of our knowledge, the present study is the first to investigate the association between the OAS1 gene polymorphism rs10774671 and the severity of COVID-19 infection in the Egyptian population.

Patients and methods

Ethical statement, patients and methods. The present study was initiated following the ethical approval of the Research Ethics Committee for Experimental and Clinical Studies at the School of Pharmacy, Newgiza University (Giza, Egypt;

no. CP-0008). Prior to enrollment in the study, all patients provided written informed consent for research purposes upon admission. The STROBE guidelines were followed when writing the manuscript (41). All methods employed in research involving human subjects adhered to ethical guidelines established by our national and institutional research committees, in accordance with the Declaration of Helsinki 1964 and its subsequent revisions.

Study plan and population. The present study represents a tricentric, retrospective evaluation of the OAS1 gene signature in Egyptian patients. Data for the evaluated patients were obtained from computerized medical records of Egyptian patients treated at three healthcare institutions connected with the General Organization for Teaching Hospitals and Institutes (GOTHI). The data were retrieved for the period spanning from November 1, 2021 to January 1, 2022. Three hospitals that are all located in Cairo were included in the study; Ahmed Maher Teaching Hospital, El-Gomhoria Teaching Hospital and Mataria Teaching Hospitals. The accurate diagnosis of COVID-19 was established according to the positive results from the reverse transcription-polymerase chain reaction (RT-PCR) laboratory test. Individuals who either lacked RT-PCR results or had negative results were omitted from the study. The patients with COVID-19 were categorized according to disease severity into three groups as mild, moderate, or severe based on clinical symptoms and lung CT findings. Mild cases were characterized by mild symptoms and no pneumonia on a lung CT scan. Moderate cases involved fever, cough and pneumonia on a lung CT scan, with oxygen saturation level (SpO_2) of ≥90% on room air at rest. Severe cases were defined by respiratory distress, including a respiratory rate >30 breaths per minute, an SpO_2 <90% at rest, and/or a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) of ≤300 mmHg lung infiltrates covering >50% of the lung area.

Data collection and operational definitions. Laboratory data encompassed a range of tests and measurements that included the results of a complete blood count (CBC) with differential count, CRP levels, liver function tests, renal function tests and D-dimer levels. By collecting this comprehensive set of data, the authors aimed to gain a comprehensive knowledge of the clinical and laboratory records of the patients. This would enable the analysis and investigation of the association between the OAS gene polymorphism and the degree of the severity of COVID-19 infection in Egyptian individuals.

Sample collection and DNA extraction. Whole blood samples were collected from 200 subjects into EDTA tubes. The subjects included 75 healthy controls and 125 patients with COVID-19. To extract genomic DNA, the DNA mini-kit (Qiagen GmbH) was used according to the manufacturer's instructions. Briefly, 200 μl whole blood were digested using 20 μl proteinase K (included with the kit), and lysis buffer was then added followed by incubation for 10 min at 56˚C. This was followed by the addition of ethanol, and the samples were then transferred to silica membrane-based spin columns (included with the kit). Following several washing steps, DNA was eluted and measured using the NanoDrop Spectrophotometer (Thermo Fisher Scientific, Inc.) and finally the DNA was stored at -20˚C until further use.

Detection of OAS rs10774671 G/A polymorphism. PCR was utilized to amplify the OAS1 rs10774671 using the below-mentioned primers according to the study by El Awady *et al* (32). The 203 bp PCR fragment covers the AG splice acceptor site area at OAS exon 7. For the PCR reaction, 1X PCR buffer (Promega Corporation), 2.5 mM MgCl2 (Promega Corporation), 200 mM dNTPs (Promega Corporation), 500 nM of each primer, 500 ng of DNA and 1U DNA polymerase (Promega Corporation) were used in a total volume of 25 μl. The PCR amplification was performed using a standard thermal cycler (PTC-200, MJ Research, Inc.). The thermal cycling protocol comprised of 5 min of denaturation at 94˚C, 30 sec of annealing at 58˚C, and 1 min of extension at 72˚C, followed by a final extension phase of 10 min at 72˚C. The forward OAS1 primer sequence was 5'-tgcaatgcaggaagactcc-3', and the reverse primer sequence was 5'-tgcaggtccagtcctcttct-3'.

Subsequently, the restriction fragment length polymorphism (RFLP) test developed by El Awady *et al* (32) was applied to detect the A/G allelic nucleotides at OAS1 rs10774671 Briefly, the 203-bp long PCR fragments of all the subjects were digested with the restriction endonuclease *Alu*I (Thermo Fisher Scientific, Inc.), which is capable of identifying the AG^CT splice site of the OAS1 rs10774671 sequence. The reaction was a total volume of 20 μl and contained 8 μl of the PCR product, 1X buffer and 5 U of *Alu*I. The restriction digestion was performed for 4 h. Following this, 10 μl of the digested products were visualized through a 2% agarose gel that had been stained with ethidium bromide and examined under a UV light source.

Statistical analysis. Categorical data are presented as frequency (percentages), whilst numerical variables are presented as the mean (SD) or median (IQR). The Chi-squared test was applied to evaluate the nominal clinical characteristics between the three groups. The Chi-squared test was also utilized to identify whether there was a statistically significant difference in the genotype frequencies between the three groups. Alternatively, Fisher's exact test was used, if the expected count of any cell was <5. The Bonferroni method was applied to adjust for multiple statistical tests, and a corrected P-value of 0.025 (based on the number of Chi-squared tests), was considered to indicate a statistically significant difference. Additionally, the distribution of different genotypes was tested for accordance with the Hardy-Weinberg equilibrium (HWE) using the online available HWE calculator (https://www.had2know.org/academics/hardy-weinberg-equilibrium-calculator-2-alleles.html), which either uses the Chi-squared or Fisher's exact test to evaluate whether the observed genotype frequencies in a population are consistent with the expected frequencies. Finally, logistic regression analysis was carried out to evaluate the determinants of severe disease. A multivariable model was established to test for independent predictors. The relative risk confidence was determined by the 95% confidence interval (CI) and odds ratio (OR) and P-values <0.05 were considered to indicate statistically significant

Table I. Demographic and clinical characteristics, and laboratory records in the patients with COVID-19 in the present study.

Characteristic	Mild group (n=33)	Moderate group (n=36)	Severe group (n=56)
Age, median (IQR)	63 (53-72)	61 (46-67)	60 (54-73)
Sex, male/female	11/22	15/21	24/32
Diabetes mellitus	3	9	15
WBCs (thousands/cmm), median (IQR)	8.4 (4.8-13.4)	9.3 (6.9-11.1)	7.5 (6.2-10.7)
Lymphocytes (x10^9/l), median (IQR)	2.45 (0.75-5.85)	1.55 (0.8-2.4)	1.3 (0.9-1.97)
Haemoglobin, mean (SD)	11.7±1.9	11.7± 3	12.04±2.3
Platelets (thousands/cmm), mean (SD)	262.4±108	249.2±110	242.9±109
AST, median (IQR)	39.5 (29-54)	34 (25-44)	35 (21-60)
ALT, median (IQR)	21 (15-32)	27 (16-41)	22 (17-40)
D-dimer (mg/l)	0.4 (0.26-0.8)	0.45 (0.3-0.8)	0.94 (0.58-3.05)
CRP (mg/l)	12 (6-39)	13 (8-48)	63.5 (21.3-122)

WBCs, white blood cells; AST, aspartate transaminase; ALT, alanine aminotransferase; CRP, C-reactive protein.

differences. The statistical software program STATA 15.1 was used for the statistical analyses.

Results

Clinical records of Egyptian individuals infected with COVID-19. The present study comprised 200 subjects (75 healthy controls and 125 patients with COVID-19). The patients were grouped into three categories as follows: Mild, moderate and severe. Firstly, the mild group included 33 patients (11 males and 22 females), ranging in age from 53 to 72 years, with a median age of 63 years. Secondly, the moderate group consisted of 36 patients (15 males and 21 females), varying in age from 46 to 67 years, with a median age of 61 years. Finally, the severe group included 56 patients (24 males and 32 females), with ages between 54 to 73 years, with a median age of 60 years. The control group comprised 75 individuals (35 males and 40 females), with a median age of 49 years, with ages spanning from 39 to 67 years. The different clinical parameters of all the patients with COVID-19 are presented in Table I.

Frequency of OAS1 SNP rs10774671 genotypes in the controls and patients with COVID-19. The GG genotype was identified by the occurrence of the intact 203 bp PCR fragment, whereas the AA genotype was confirmed by the breakdown of the 203 bp with *Alu*I to two separate fragments of 150 and 53 bp. However, the presence of three distinct fragments of 203, 150 and 53 bp indicated the presence of the heterozygote AG genotype. The different OAS genotypes are presented in Fig. 1. The frequencies of various OAS genotype alleles in both the healthy subjects and patients with COVID-19 are summarized in Table II.

Within the control cohort, the OAS genotype distribution was 52% GG, 40% GA and 8% AA. In the patients with COVID-19, the genotypes were 39% GG, 47% GA and 14% AA. In general, the G allele was more prevalent in both cohorts: In the controls and patients with COVID-19 (72 and 63%, respectively) than the A allele (28 and 37%, respectively). The frequency of the GG genotype was slightly lower in the patients with COVID-19 than in the controls (39 vs. 52%), although the difference was not statistically significant (P=0.078; Table SI).

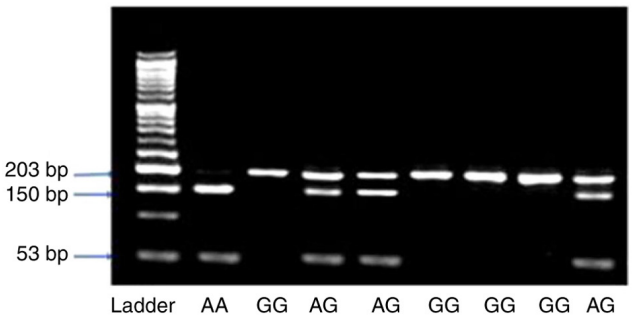

Figure 1. Restriction fragment length polymorphism for SNP rs10774671. Digestion with *Alu*I enzyme revealed three different genotypes. Homozygous AA (AGCT) was digested into two fragments at 53 and 150 bp. Homozygous GG (GGCT) is not recognized by *Alu*I and is retained at 203 bp. Heterozygous AG appears as three bands, at 53, 150 and 203 bp.

In order to identify a potential association of the genetic variants with disease severity, the Chi-squared test was used to determine the presence of statistically significant differences in the genotype frequencies between the different patient groups. The prevalence of different OAS genotypes and alleles in the patients with mild, moderate and severe COVID-19 infection is presented in Table II. The findings demonstrated that the distribution of the OAS GG genotype was 49% in the mild, 30.6% in the moderate, and 20.4% in the severe group, while the AA genotype was only found in the severe group (100%), as shown in Fig. 2.

Compliance of the OAS1 rs10774671 polymorphism in the studied groups with HWE. To exclude potential genotyping errors or disrupting factors, the formula developed by Hardy and Weinberg was used to examine whether the frequency of each genotype obtained corresponded to the expected values, with P<0.05 indicating a deviation from HWE. However, the genotype frequencies in the control, mild, moderate and severe groups agreed with the HWE (P>0.05), as depicted in Table III,

Table II. Frequency of OAS1 rs10774671 genotypes and alleles in patients with mild, moderate and severe COVID-19.

rs10774671 genotype	Control group (n=75) (%)	Patient group (n=125) (%)	Study cohort (n=125)			P-value
			Mild (n=33) (%)	Moderate (n=36) (%)	Severe (n=56) (%)	
GG	39 (52)	49 (39.2)	24 (72.7)	15 (41.67)	10 (17.86)	**<0.0001**[a] **0.0006**[b]
GA	30 (40)	59 (47.2)	9 (27.3)	21 (58.33)	29 (51.79)	0.0285[a] 0.2752[b]
AA	6 (8)	17 (13.6)	0 (0)	0 (0)	17 (30.36)	**0.0013**[#]
G	108 (72)	157 (62.8)	57 (86.43)	51 (70.8)	49 (43.7)	**<0.0001**[a,b] **<0.0001**[a,b]
A	42 (28)	93 (37.2)	9 (13.6)	21 (29.2)	63 (56.3)	

Values in bold font indicate statistically significant differences (P<0.025). Data were analysed using the Chi-squared test followed by the Bonferroni correction. [a]Mild group vs. severe group; [b]moderate group vs. severe group. OAS1, 2'-5'-oligoadenylate synthase 1.

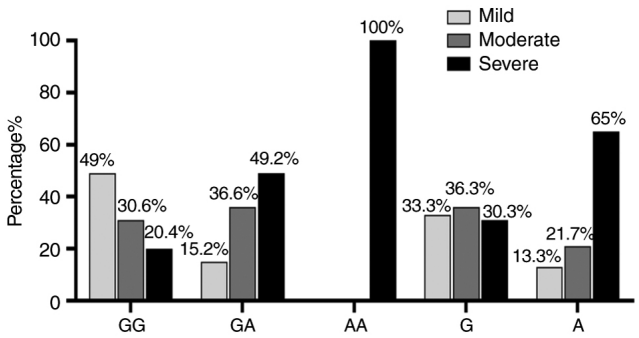

Figure 2. The distribution of OAS1 rs10774671 genotypes and alleles in patients with mild, moderate and severe COVID-19. A total of 125 patients with COVID-19 were subjected to (PCR-RFLP) analysis to detect OAS1 SNP rs10774671. The percentage of OAS1 genotypes (GG, GA and AA) and alleles (G and A) were compared in the mild group (n=33; light grey bar), moderate group (n=36; dark grey bar) and severe group (n=56; black bar). OAS1, 2'-5'-oligoadenylate synthase 1.

Table III. Hardy Weinberg equilibrium for OAS1 (rs10774671).

Groups	Observed genotype			Expected genotype			P-value
	GG	GA	AA	GG	GA	AA	
Control	39	29	7	38.2	30.7	6.2	0.63
Mild	24	9	0	24.6	7.8	0.6	0.36
Moderate	21	18	0	23.1	13.8	2.1	0.06
Severe	10	30	12	12	26	14	0.26

OAS1, 2'-5'-oligoadenylate synthase 1.

assuming the genotype frequencies remained constant across generations due to absence of disturbing factors including mutation, non-random mating and selection.

Multivariate analysis of the factors predicting the severe outcomes of patients with COVID-19. The significance of different clinical variables in determining the degree of severity of infection with COVID-19 was examined using stepwise logistic regression modelling. Firstly, the univariate analysis was performed to determine whether any of the clinical parameters were linked to the severe outcomes of COVID-19. Logistic regression analysis was then used to assess predictors of severe COVID-19 infection against mild-moderate cases. The univariate analysis demonstrated that OAS genotypes, as well as higher D-dimer and CRP levels, were substantially associated with a higher risk of developing severe illness. The OAS genotype AA was found to be an independent factor associated with a 6.8-fold increased risk of developing severe COVID-19 infection in multivariate regression analysis (OR, 6.86; 95% CI, 2.83-16.63; P=0.0001). In addition, elevated D-dimer and CRP levels were found to be significantly associated with an increased risk of developing severe illness, as indicated by the ORs (Table IV).

Discussion

The COVID-19 outbreak has caused widespread concern and has placed challenges to global health care systems. The severity of COVID-19 infection differs greatly among infected individuals, ranging from asymptomatic to severe clinical manifestations and fatality. Individuals with particular SNPs in various genes have been found to be more vulnerable to COVID-19 infection. Multiple SNPs in certain genes have been reported to influence the severity of COVID-19 infection, such as angiotensin-converting enzyme 2 (42), transmembrane protease serine 2 (43) and Interferon-induced transmembrane protein 3 gene (44). Moreover, emerging evidence suggests that the OAS1 SNP rs10774671 is a genetic factor that influences the inter-individual variation in COVID-19 outcomes. This SNP affects the crucial OAS1 enzyme activity, which is involved in the natural response of the immune system to infections caused by viruses. To this end, the present study investigated the potential implications of the OAS1 SNP (rs10774671) in Egyptian individuals infected with COVID-19.

Table IV. Ordinal logistic regression analysis to determine the predictors of the three degrees of severity.

	Univariat regression		Multivariate regression	
Parameter	OR (95% CI)	P-value	OR (95% CI)	P-value
Age, years	1.02 (0.99-1.1)	0.2		
Sex, female	0.68 (0.29-1.61)	0.4		
Diabetes mellitus	1.38 (0.55-3.46)	0.5		
Hypertension	0.83 (0.35-1.95)	0.66		
Genotype, AA vs. AG vs. GG	6.33 (3.1-13.1)	**<0.0001**	6.86 (2.83-16.63)	**<0.0001**
WBCs	1.003 (0.93-1.08)	0.9		
Platelets	0.99 (0.99-1.003)	0.9		
D-dimer >0.5	4.69 (1.9-11.7)	**0.001**	4.1 (1.29-12.89)	**0.02**
CRP >75	4.39 (1.64-11.73)	**0.003**	2.25 (0.68-7.42)	0.05

Values in bold font indicate statistically significant differences (P<0.05). WBCs, white blood cells; CRP, C-reactive protein.

The present study identified the GG genotype in 52% of the controls and 39.2% of patients with COVID-19. Moreover, the genotype frequencies were consistent with HWE (P>0.05), indicating that the genotype frequencies remained constant across generations excluding potential genotyping errors or population stratification. Generally, in both the controls and patients with COVID-19, the G allele was more prevalent than the A allele. Furthermore, the prevalence of the A allele is increasing from mild (13.2%), moderate (21.6%) to severe (65%) COVID-19 patients. These findings support the notion that the A allele leads to the production of the OAS1 p42 isoform, which exhibits a reduced antiviral activity (29,33). This isoform has been shown to be associated with West Nile virus infection (45), respiratory infection (46) and failure to control hepatitis C virus inflammation and liver fibrosis (27). Moreover, type 1 diabetes (47), multiple sclerosis (48) and tuberculosis (49) have been shown to be associated with OAS1 SNP rs10774671. However, little is known regarding the impact of OAS1 exon 7 SNP rs10774671 on the severity of COVID-19 infection. Therefore, the present study categorized the 125 patients with COVID-19 into the mild and moderate (n=69) and severe (n=56) groups to explore the influence of OAS1 rs10774671 different genotypes and alleles on the disease severity and outcomes. The comparison of the OAS genotype distribution in the mild/moderate group to that of the severe group underlined a strong association between the severity of the disease and genotypes with the A allele (P<0.0001). Notably, the G Allele was more common in the mild/moderate (69.6%) group than the A allele (33.8%) (P=0.001). These findings highlighted that the G allele at OAS1 SNP (rs10774671) confers an enhanced antiviral response, which could lead to a more robust immune reaction against COVID-19, resulting in a more rapid viral clearance and milder disease outcomes. It has also been documented that the GG genotype is associated with a higher enzymatic activity compared with other genotypes, which enhance the degradation of viral RNA and improve the ability of the host to control viral infections. Recently, studies have shown the significance of OAS1 rs10774671 on COVID-19 susceptibility and the degree of disease severity (31,50). The G allele has been reported to provide protection against severe COVID-19 infection, whereas the A allele did not exhibit any anti-COVID-19 activity (31). However, it is essential to emphasize that COVID-19 is a complex disease characterized by a variety of genetic and environmental variables, and the precise significance of the OAS1 SNP in COVID-19 outcomes warrants additional research.

On the other hand, it has been revealed that the protection conferred by the rs10774671 G allele against COVID-19 hospitalization in individuals of African ancestry is similar to that of those of European ancestry, despite the rs10774671 G allele frequency being lower in individuals of European ancestry (32% vs. 58%) than in those of African ancestry (30). Herein, to evaluate the role of rs10774671 in influencing the severity of COVID-19 infection, multivariate analysis was performed. The results revealed that the OAS rs10774671 genotype AA was an independent factor associated with a 6.8-fold greater probability of developing a severe course of COVID-19 infection (OR, 6.86; 95% CI, 2.83-16.63; P=0.0001). These results emphasize that COVID patients having the AA genotype are not able to control the disease at an early phase of infection, which may lead to an exaggerated immune response, leading to severe inflammatory reactions. This hyperactive immune response, often referred to as the 'cytokine storm', induces extensive tissue damage, particularly in the lungs, leading to severe outcomes (51,52). The findings of the present study corroborate the results of prior investigations (50,53,54). In addition, studies on other viral infections support the current data and have demonstrated that specific OAS1 genotypes are associated with an increased ability to control and clear viruses (49,55,56). However, the biological mechanisms underlying the association between rs10774671 and COVID-19 outcomes remain unclear. Furthermore, the different results in various populations necessitate additional research with larger, well-defined cohorts and functional validation to clarify the role of this SNP in COVID-19 outcomes.

The presents study has certain limitations which should be mentioned. A larger sample size from different centers would increase the statistical power of the study and improve the reliability of the findings. Several potential confounding factors need to be considered when interpreting the association

between the AA genotype of the OAS1 rs10774671 polymorphism and severe COVID-19 outcomes, such as race, comorbidities, age, sex and socioeconomic factors. Different functional studies are necessary to confirm the biological mechanisms and provide direct evidence of how different OAS1 variants affect viral replication and immune responses. Finally, longitudinal studies tracking patients over a period of time are required to provide insight into how the OAS1 polymorphism influences the progression and long-term outcomes of patients with COVID-19.

In conclusion, the findings of the present study demonstrate a significant association between the AA genotype of the OAS1 rs10774671 polymorphism and the degree of severity of COVID-19 infection in Egyptian patients. Notably, an upward trend was observed in the prevalence of the A allele among patients with severe COVID-19 infection, with the AA genotype being detected exclusively in this group. The results highlight the clinical relevance of the OAS1 polymorphism as a potential genetic marker for identifying high-risk individuals. The study cohort was limited to only 200 patients due to the availability of clinical data for patients involved in the study and for the controls. However, the rs10774671 genetic variation in OAS gene may influence susceptibility to COVID-19 infection, antiviral response and subsequent disease progression. Additional studies focusing on the functional consequences of rs10774671 and its potential impact on the COVID-19 pathogenesis are required.

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Availability of data and materials

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

Authors' contributions

NGBED conceived the study, designed the experiments, and wrote the manuscript with input from all authors. RIM, EG, HE and RES conducted DNA extraction, PCR, RFLP analysis and contributed to statistical analysis, and the drafting of the manuscript. NMH and MMA contributed to sample preparation, statistical analysis and designed the figures. MES, AAY, MSM, ASS, and MMA were in charge of sample collection and the clinical data sheets. NGBED and HE confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee for Experimental and Clinical Studies at School of Pharmacy, Newgiza University (Giza, Egypt; no.CP-0008). Each subject signed an informed consent form before participating in the study. All the study procedures and protocols met the ethical standards of the Declaration of Helsinki 1964 (2008 revision).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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