

Genetic Association of IFITM3 rs12252 Variant with Severe COVID-19 Outcomes in Syrian Patients

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Abstract

Introduction: Following the COVID-19 pandemic, increasing attention has been directed toward host genetic factors that influence disease severity. The interferon-induced transmembrane protein 3 (IFITM3) plays a key role in restricting viral entry, and its rs12252 polymorphism has been linked to impaired antiviral defense and adverse clinical outcomes. Investigating rs12252 in the Syrian population may help clarify genetic determinants of COVID-19 progression.

Methodology: A cohort study was conducted in Syria, including 82 COVID-19 patients, who were clinically classified into two groups: severe (n = 41) and moderate (n = 41). Genomic DNA was extracted from peripheral blood samples, and genotyping of the *IFITM3* rs12252 polymorphism was performed using *MscI* restriction enzyme digestion. Genotype distributions were analyzed to evaluate potential associations with disease severity.

Results: The frequency of the *IFITM3* rs12252 C allele was higher in patients with severe COVID-19 (37.8%) compared to patients with moderate disease (29.3%). A statistically significant association was observed between the TC genotype (compared with TT and CC genotypes) and ICU admission (OR = 6.94; 95% CI: 1.48–32.54; *p* = 0.0033). After adjusting for age, the association remained significant (OR = 4.83; 95% CI: 0.93–25.09; *p* = 0.037).

Conclusions: These findings suggest that the *IFITM3* rs12252 C allele is associated with severe COVID-19 outcomes in the Syrian cohort. Screening for this variant may assist in early risk stratification and support personalized management strategies, particularly in resource-limited settings.

Key words: COVID-19; IFITM3; polymorphism.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has imposed an unprecedented burden on global health systems, economies, and societies. By October 2025, the World Health Organization (WHO) had reported approximately 779 million confirmed cases [1] and 7.1 million deaths globally [2]. A defining feature of SARS-CoV-2 infection is its broad clinical spectrum, ranging from asymptomatic infection to critical illness and death. This marked heterogeneity reflects a complex interplay of age, sex, pre-existing comorbidities, ethnicity, socioeconomic determinants, and host genetic background [3]. Among these factors, advanced age is the strongest determinant of severe disease, while cardiovascular disease, diabetes mellitus, chronic respiratory and renal disorders, cancer, and obesity substantially increase the risk of complications and mortality [4,5].

Understanding the genetic determinants underlying inter-individual variation in COVID-19 severity has become a major focus of recent biomedical research. Previous candidate gene studies have identified

multiple loci that modulate susceptibility to SARS-CoV-2 infection and disease severity, implicating genes involved in innate immune signaling, interferon pathways, viral entry, and inflammatory regulation. These findings underscore the potential utility of host genetic profiling for personalized risk stratification [6,7].

Within the innate immune system, interferon-induced transmembrane protein 3 (*IFITM3*), encoded at the *IFITM* locus on chromosome 11p15.5 [8], has emerged as a critical host restriction factor against viral infections. *IFITM3* is an interferon-stimulated gene whose protein localizes predominantly to late endosomes and lysosomes, where it inhibits an early stage of viral entry by preventing virus–host membrane fusion. Specifically, IFITM3 impedes viral fusion at the hemifusion stage by preventing fusion pore formation, thereby blocking the release of viral genomes into the cytosol and subsequent viral replication [9]. Mechanistically, insertion of the S-palmitoylated amphipathic helix of IFITM3 into the cytoplasmic leaflet of the host membrane is thought to stabilize intermediate fusion states, consistent with the ability of

amphipathic helices to modulate membrane curvature, lipid order, and stiffness [10,11]. Beyond directly restricting viral entry, IFITM3 can also limit viral replication and reduce the infectivity of newly produced virions, thereby amplifying its antiviral effect [9].

The antiviral efficacy of IFITM3 is finely tuned by its precise subcellular localization, membrane-modifying properties, oligomerization, and post-translational modifications, which collectively establish a biophysical barrier at sites of viral fusion. Through these mechanisms, IFITM3 provides broad-spectrum protection against numerous enveloped viruses, including influenza A, West Nile, chikungunya, Ebola, Marburg, Zika, and coronaviruses [10,12].

Genetic variation in *IFITM3*, most notably the rs12252 single-nucleotide polymorphism (SNP), has been associated with altered antiviral activity and adverse clinical outcomes in several viral infections [12]. The magnitude and direction of this association appear to be population-dependent. The *C* allele has been linked to severe influenza infection [13] and, in some cohorts, to increased severity or mortality from COVID-19, whereas other populations have shown weaker or no significant associations [14-23].

Proposed functional consequences of rs12252 include alternative splicing leading to N-terminal truncation [24,25], resulting in loss of the 20-YEML-23 sorting motif, which is essential for correct endosomal trafficking and effective antiviral activity. This alteration has been suggested to redistribute IFITM3 from endosomal compartments to the cell periphery [26], reduce its antiviral potency, and alter subcellular localization [27]. However, mechanistic evidence remains partly inconsistent [28].

Based on these observations, the present study investigated the association between the IFITM3 rs12252 polymorphism and COVID-19 severity in a Syrian Arab cohort to clarify its potential impact on clinical outcomes.

Methodology

Study population

Patients were recruited from Al Mouwasat University Hospital and Damascus Hospital between October 2021 and August 2022. All participants were diagnosed with COVID-19 based on a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) or antigen test.

Patients were classified according to WHO criteria into moderate- and severe-illness groups. Moderate illness was defined as clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) in the absence of

severe pneumonia, with an oxygen saturation (SpO_2) $\geq 90\%$ on room air. Severe illness was defined by clinical signs of pneumonia (fever, cough, dyspnea) plus at least one of the following: respiratory rate > 30 breaths/minute, severe respiratory distress, or $\text{SpO}_2 < 90\%$ on room air [29].

This cohort study was approved by the Scientific Research Bioethics Committee at the Faculty of Pharmacy, Damascus University (ID number: PH-200825-H32). Written informed consent was obtained from all participants or, when appropriate, from their patient companions before enrollment.

DNA Extraction and Genotyping of rs12252

Genomic DNA was extracted from peripheral blood leukocytes using the FlexiGene DNA extraction kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. The rs12252 SNP was analyzed using the Polymerase Chain Reaction – Restriction Fragment Length Polymorphism (PCR-RFLP) method.

The target DNA fragment containing the polymorphic site was amplified by PCR using a pair of primers: forward primer (CTATAGGGAGAACTGCTCTGGGCT) and reverse primer (ACTGTTGAGAAACCGAACTACTGG), with an amplicon size of 624 base pairs (bp) [30]. PCR amplification was optimized through preliminary experiments to determine the optimal annealing temperature, following this protocol: initial denaturation for 5 minutes at 95°C , 35 cycles of (1 minute at 95°C , 30 sec at 61.4°C , 1 minute at 72°C), and final extension 5 minutes at 72°C .

PCR products were analyzed by electrophoresis on 1% agarose gel, followed by digestion with *MscI* restriction enzyme (New England Biolabs, Ipswich, MA, USA), which recognizes the *T* allele (wild type). Digested fragments were visualized on 2.5 % agarose gel electrophoresis (*TT* genotype as 490 and 134 bp, *TC* genotype 624, 490, and 134, *CC* genotype as one fragment 624 bp).

Statistical analysis

All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) program version 26.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Because distributions were non-normal, continuous variables were summarized as median [interquartile range] (IQR). Categorical variables were expressed as numbers (*n*) and percentages (%). Group comparisons were

conducted using Fisher's exact test or the Chi-square test for categorical variables, and the Mann–Whitney U test for continuous variables. A $p < 0.05$ was considered statistically significant.

Genetic association analysis of rs12252 was performed using SNPStats software (Institut Català d'Oncologia, Barcelona, Spain; available at <https://www.snpsstats.net>). Logistic regression models were applied to estimate odds ratios (ORs) with 95% confidence intervals (CIs).

Results

The study cohort comprised 82 adult patients, including 41 individuals with severe SARS-CoV-2 infection. Among these, 20 patients (20/41, 48.8%) required admission to the intensive care unit (ICU). Demographic and phenotypic characteristics are summarized in Table 1.

Age, Gender, and Smoking

Age was significantly associated with disease severity. The overall median age was 45 years (IQR: 30.75–63.25 years). Patients with severe disease had a significantly higher median age (median: 61 years) compared to those with moderate disease (median: 31 years, $p < 0.001$).

Sex distribution did not differ significantly between groups: 21 males (21/41, 51.2%) in the severe group versus 15 males (15/41, 36.6%) in the moderate group.

Smoking status also showed no significant association with disease severity, with (10/41, 24.4%) smokers in the severe group and (5/41, 12.2%) in the moderate group.

Comorbidities

Regarding comorbidities, hypertension, cardiovascular disease, and diabetes were significantly more prevalent among patients with severe COVID-19.

Table 1. Demographic and phenotypic characteristics for COVID-19 patients.

Characteristic	Total (N = 82)	Moderate Disease (n = 41)	Severe Disease (n = 41)	<i>p</i>
Age, median [IQR]	45 [30.75-63.25]	31 [27-40]	61 [52-73]	< 0.001
Male sex	36 (43.9)	15 (36.6)	21 (51.2)	0.266
Smoking	15 (18.3)	5 (12.2)	10 (24.4)	0.253
Comorbidities				
Hypertension	31 (37.8)	6 (14.6)	25 (61)	< 0.001
Coronary disease	12 (14.6)	1 (2.4)	11 (26.8)	0.003
Diabetes	17 (20.7)	3 (7.3)	14 (34.1)	0.005
Lung disease	2 (2.5)	1 (2.4)	1 (2.4)	1.00
Kidney disease	4 (4.9)	1 (2.4)	3 (7.3)	0.616
Symptoms				
Fever	69 (84.1)	34 (82.9)	35 (85.4)	1.00
Fatigue	77 (93.9)	38 (92.7)	39 (95.1)	1.00
Muscle or joint pain	49 (59.8)	30 (73.2)	19 (46.3)	0.024
Loss of taste or smell	28 (34.1)	21 (51.2)	7 (17.1)	0.002
Cough	49 (59.8)	21 (51.2)	28 (68.3)	0.176
Loss of appetite	49 (59.8)	24 (58.5)	25 (61.0)	1.00
Vomiting	15 (18.3)	8 (19.5)	7 (17.1)	1.00
Diarrhea	22 (26.8)	12 (29.3)	10 (24.4)	0.804
Pharyngitis	25 (30.5)	15 (36.6)	10 (24.4)	0.337
Dyspnea	51 (62.2)	14 (34.1)	37 (90.2)	< 0.001
Vital signs, median [IQR]				
Respiratory rate	20 [18-22]	18 [18-20]	22 [20-28]	< 0.001
SpO ₂	94 [83-97]	97 [96-98]	83 [80-89]	< 0.001
Heart rate	100 [96-110]	100 [100-100]	106 [90-118]	0.657
Body temperature	39 [38-39]	39 [38.5-39]	39 [38-39]	0.743
Outcomes				
ICU admission	20 (24.4)	0 (0)	20 (48.8)	< 0.001
Death	11 (13.4)	1 (2.4)	10 (24.4)	0.007
Ventilation (oxygen supply)				
Nasal canula	15 (18.3)	0 (0)	15 (36.6)	< 0.001
Oxygen mask	15 (18.3)	0 (0)	15 (36.6)	
BiPAP	2 (2.4)	0 (0)	2 (4.9)	
Mechanical ventilation	6 (7.3)	0 (0)	6 (14.6)	
Genotyping				
TT	28 (34.1)	18 (43.9)	10 (24.4)	0.061
TC	53 (64.6)	22 (53.7)	31 (75.6)	
CC	1 (1.2)	1 (2.4)	0 (0)	
T allele	109 (66.5)	58 (70.7)	51 (62.2)	0.32
C allele	55 (33.5)	24 (29.3)	31 (37.8)	

COVID-19: coronavirus disease 2019; ICU: intensive care unit; IQR: interquartile range; SpO₂: oxygen saturation; BiPAP: Bilevel Positive Airway Pressure. Qualitative data were described using numbers and percentages and compared using the Chi-square or Fisher's Exact test, while non-normally distributed quantitative data were expressed as median [IQR] and compared using the Mann-Whitney test.

Specifically, hypertension was observed in (25/41, 61%) of patients with severe disease compared to (6/41, 14.6%) of those with moderate disease ($p < 0.001$). Cardiovascular disease occurred in (11/41, 26.8%) of severe cases versus (1/41, 2.4%) of moderate cases ($p = 0.003$).

Diabetes was present in (14/41, 34.1%) of patients with severe disease compared to (3/41, 7.3%) of patients with moderate disease ($p = 0.005$). Pulmonary and renal diseases showed no significant differences between groups ($p = 1.00$ and $p = 0.616$, respectively).

Symptoms

Several clinical manifestations were associated with disease severity. Dyspnea was significantly more frequent in the severe group ($p < 0.001$), whereas muscle or joint pain and anosmia/ageusia were more common in moderate cases, showing inverse associations with severity ($p = 0.024$ and $p = 0.002$, respectively). Other symptoms, including fever, fatigue, cough, gastrointestinal disturbances (vomiting and diarrhea), pharyngitis, and loss of appetite, were reported across both groups without significant differences.

Vital signs

Respiratory rate and blood oxygen saturation (SpO₂) were significantly associated with disease severity. Patients with severe disease had higher respiratory rates (22 vs 18 breaths/minute; $p < 0.001$) and lower oxygen saturation (83% vs 97%; $p < 0.001$). No significant differences were observed in heart rate or body temperature ($p = 0.657$ and $p = 0.743$, respectively).

Outcomes

Among severe cases, 20 patients required ICU admission. Nine deaths occurred among ICU-admitted patients, compared to two deaths among non-ICU patients, indicating a significantly higher mortality rate

among ICU-admitted individuals ($p < 0.001$).

Hypertension was significantly associated with ICU admission ($p = 0.032$), but not with mortality. Age was strongly associated with both ICU admission and mortality ($p < 0.001$ for both).

Oxygen supply

Respiratory support was required for (38/41, 92.7%) patients with severe disease, with 15 receiving oxygen via face mask, 15 via nasal cannula, two treated with BiPAP, and six requiring invasive mechanical ventilation.

Association of IFITM3 rs12252 and COVID-19 severity

To investigate the association between COVID-19 severity and a selected single-nucleotide polymorphism (SNP), genotyping was performed on all 82 patients. The genotype distribution was as follows: (28/82, 34.1%) *TT* homozygotes, (53/82, 64.6%) *TC* heterozygotes, and (1/82, 1.2%) *CC* homozygotes.

The overall mutant allele frequency was (55/164, 33.5%), with a higher frequency in the severe group (31/82, 37.8%) compared to the moderate group (24/82, 29.3%), although this difference was not statistically significant. *TT* was more frequent among moderate cases, while *TC* predominated in severe cases, showing a trend toward significance ($p = 0.061$).

Logistic regression analysis was performed under codominant, dominant, recessive, and over-dominant genetic models using SNPStats software (Table 2). The over-dominant model revealed a statistically significant association, with the *TC* genotype more frequent in the severe group (75.6%) compared to the moderate group (53.7%) ($p = 0.036$; OR = 2.68; 95% CI: 1.05–6.86).

After adjusting for age, the association between genotype and disease severity was re-evaluated. The previously significant association in the over-dominant model was attenuated (OR = 1.81; 95% CI: 0.52–6.27; $p = 0.35$), and none of the tested models showed statistically significant associations post-adjustment.

Table 2. Association between genotype and severity.

Model	Genotype	Moderate disease (n = 41)	Severe disease (n = 41)	OR (95% CI) ^a	p^a	OR (95% CI) ^b	p^b
Codominant	TT	18 (43.9)	10 (24.4)	1.00		1.00	
	TC	22 (53.7)	31 (75.6)	2.54 (0.98-6.54)	0.073	1.75 (0.50-6.08)	0.55
	CC	1 (2.4)	0 (0)	0.00 (0.00-NA)		0.00 (0.00-NA)	
Dominant	TT	18 (43.9)	10 (24.4)	1.00		1.00	
	TC-CC	23 (56.1)	31 (75.6)	2.43 (0.95-6.23)	0.061	1.69 (0.48-5.88)	0.41
Recessive	TT-TC	40 (97.6)	41 (100)	1.00		1.00	
	CC	1 (2.4)	0 (0)	0.00 (0.00-NA)	0.24	0.00 (0.00-NA)	0.52
Overdominant	TT-CC	19 (46.3)	10 (24.4)	1.00		1.00	
	TC	22 (53.7)	31 (75.6)	2.68 (1.05-6.86)	0.036	1.81 (0.52-6.27)	0.35

Logistic regression analysis was performed under codominant, dominant, recessive, and overdominant genetic models. ICU: intensive care unit; OR: odds ratio; CI: Confidence Interval; NA: not applicable. ^a p and odds ratios comparing ICU-admitted and non-ICU-admitted patients were calculated by logistic regression.

^b p and odds ratios comparing ICU-admitted and non-ICU-admitted patients were calculated by logistic regression and adjusted for age.

Association of IFITM3 rs12252 and ICU admission

Eighteen of the 20 patients admitted to the ICU carried the *TC* genotype, whereas only two carried the *TT* genotype, demonstrating a strong association between the *TC* genotype and ICU admission ($p = 0.015$). Logistic regression confirmed this association (Table 3), with the over-dominant model showing the strongest effect (OR = 6.94; 95% CI: 1.48–32.54; $p = 0.0033$). Notably, the association remained significant after adjusting for age (OR = 4.83; 95% CI: 0.93–25.09; $p = 0.037$).

Association of IFITM3 rs12252 and COVID-19 mortality

Regarding mortality, nine of the patients who died carried the *TC* genotype, and two carried the *TT* genotype. However, statistical analysis revealed no significant association between genotype and mortality ($p = 0.411$).

Discussion

SARS-CoV-2 continues to pose a global public health challenge, characterized by substantial inter-individual variability in clinical outcomes. In Syria, the scarcity of medical resources and economic constraints have limited comprehensive case documentation; nevertheless, thousands of confirmed infections and COVID-19-related deaths have been officially reported to the World Health Organization.

Within this context, host genetic predisposition has emerged as a key factor influencing disease severity. Among the genetic variants investigated, the rs12252 (T > C) SNP in the *IFITM3* gene has been linked to increased susceptibility to severe SARS-CoV-2 infection across multiple populations. Notably, this association had not previously been examined in the Syrian population, which is characterized by distinct genetic and environmental backgrounds.

This study aimed to evaluate the impact of the *IFITM3* rs12252 SNP on COVID-19 severity in Syrian

patients. Our findings indicated that the *TC* genotype of rs12252 was initially associated with increased disease severity. However, this association lost statistical significance after adjusting for age, underscoring the major confounding effect of age. Interestingly, the *TC* genotype remained significantly associated with ICU admission even after age adjustment, suggesting a potential contribution to critical outcomes independent of aging.

Age consistently emerged as a dominant factor in COVID-19 progression, with older individuals exhibiting more severe symptoms and higher rates of ICU admission. Age-related dysregulation of immune function, including immunosenescence and chronic low-grade inflammation, is believed to play a major role in the increased vulnerability of older adults to severe COVID-19 outcomes [31,32]. Our results align with these observations, demonstrating a clear correlation between advancing age and both disease severity and the need for critical care.

In contrast to several previous studies, our results showed no significant association between disease severity and either sex or smoking status, despite earlier reports suggesting a significant relationship between male sex, smoking, and increased COVID-19 severity [33–35].

In addition, hypertension was significantly associated with increased disease severity and ICU admission in our cohort, although no significant association with mortality was observed. This finding is consistent with results reported in a Syrian cohort [4], as well as studies from China identifying hypertension as the most prevalent comorbidity associated with adverse COVID-19 outcomes [36,37].

Beyond these clinical factors, the antiviral activity of *IFITM3* is primarily mediated by its ability to inhibit virus–host membrane fusion during the initial stage of infection. *IFITM3* is widely expressed across human tissues and is upregulated in response to both type I and type II interferons [38]. Previous studies have linked the

Table 3. Association between genotype and ICU admission.

Model	Genotype	Non-ICU admitted (n = 62)	ICU admitted (n = 20)	OR (95% CI) ^a	<i>p</i> ^a	OR (95% CI) ^b	<i>p</i> ^b
Codominant	TT	26 (41.9)	2 (10)	1.00		1.00	
	TC	35 (56.5)	18 (90)	6.69 (1.42–31.39)	0.012	4.76 (0.92–24.78)	0.11
	CC	1 (1.6)	0 (0)	0.00 (0.00–NA)		0.00 (0.00–NA)	
Dominant	TT	26 (41.9)	2 (10)	1.00		1.00	
	TC-CC	36 (58.1)	18 (90)	6.50 (1.39–30.49)	0.0048	4.70 (0.90–24.49)	0.042
Recessive	TT-TC	61 (98.4)	20 (100)	1.00		1.00	
	CC	1 (1.6)	0 (0)	0.00 (0.00–NA)	0.45	0.00 (0.00–NA)	0.71
Overdominant	TT-CC	27 (43.5)	2 (10)	1.00		1.00	
	TC	35 (56.5)	18 (90)	6.94 (1.48–32.54)	0.0033	4.83 (0.93–25.09)	0.037

Logistic regression analysis was performed under codominant, dominant, recessive, and overdominant genetic models. ICU: intensive care unit; OR: odds ratio; CI: Confidence Interval; NA: not applicable. ^a *p* and odds ratios comparing ICU-admitted and non-ICU-admitted patients were calculated by logistic regression.

^b *p* and odds ratios comparing ICU-admitted and non-ICU-admitted patients were calculated by logistic regression and adjusted for age.

rs12252 variant to increased severity of influenza virus infection [39,40], suggesting a potential role for this variant in modulating COVID-19 severity. Functionally, the rs12252 polymorphism is thought to impair IFITM3 antiviral activity by altering its intracellular trafficking. Disruption of the N-terminal region, which contains a critical sorting signal, may impair efficient targeting of IFITM3 to endosomal compartments where viral fusion occurs. As a result, IFITM3 becomes mislocalized toward the plasma membrane, thereby reducing its capacity to restrict virus–host membrane fusion and ultimately weakening its antiviral effect [41,42].

In this context, the *IFITM3* rs12252 polymorphism has been widely studied for its potential role in modulating susceptibility to and severity of SARS-CoV-2 infection. A meta-analysis including cohorts from Germany, Spain, China, and Saudi Arabia reported a significant association between this variant and increased susceptibility to infection; however, no consistent link with disease severity was observed [43]. In contrast, another meta-analysis identified the rs12252 *CC* genotype as a strong predictor of severe COVID-19 and mortality in Chinese patients, while the *C* allele was associated with elevated mortality risk in Caucasian populations [44]. Supporting these findings, Zhang *et al.* reported that homozygosity for the *C* allele of rs12252 in the *IFITM3* gene is associated with more severe disease in an age-dependent manner [15], and Spanish data indicated a higher frequency of *C* allele carriers among patients compared to controls [17]. Conversely, studies in German [20] and Moroccan [18] populations found no significant associations, highlighting considerable variability across ethnic and geographic groups.

Further regional studies have yielded mixed results; for example, in Egypt, Hamdi *et al.* reported a significant association between the *C* allele and infection susceptibility, although this effect disappeared after adjusting for age, suggesting that age-related factors may confound the relationship between rs12252 and disease progression [19].

Consistent with our findings that the *TC* genotype was strongly associated with ICU admission (OR = 6.94), Rashid *et al.* similarly observed that Kurdish patients carrying the *C* allele had a significantly increased risk of ICU admission (OR = 3.17) [22]. These convergent findings support the hypothesis that this genetic variant may contribute to adverse clinical outcomes, although its overall impact on disease severity remains inconclusive. A Romanian study also suggested a trend toward increased disease severity

among *TC* carriers (OR = 2.14), though statistical significance was not reached [21]. Likewise, our findings indicated a tendency toward an association between the *TC* genotype and increased disease severity. In Bangladesh, the *TT* genotype was more prevalent among patients with moderate disease, whereas the *CC* genotype was overrepresented among critically ill patients, further supporting a potential role of the *CC* genotype in severe COVID-19 [23].

Our Syrian cohort provides additional insight into this ongoing debate. We observed a higher prevalence of the *TC* genotype among patients with severe and critical illness, as well as among those who died. Specifically, nine deaths occurred in *TC* carriers compared to only two among *TT* carriers, suggesting a possible association between the presence of the *C* allele and increased mortality. Supporting this observation, a study from Saudi Arabia demonstrated that the *C* allele was associated with a markedly increased risk of COVID-19 mortality, independent of established clinical risk factors such as age, gender, and major comorbidities [14]. Furthermore, *TC* genotype carriers exhibited a significantly higher mortality risk among younger individuals infected with SARS-CoV-2, indicating the possibility of distinct pathogenic mechanisms in this subgroup. Our findings are consistent with these observations and are further supported by Iranian data reporting a higher frequency of the mutant *C* allele among deceased patients and an association between the *CC* genotype and elevated mortality risk [16]. However, the rarity of the *CC* genotype in our cohort limited statistical confirmation of this association.

Importantly, while the *C* allele was significantly associated with ICU admission independent of age, its relationship with overall disease severity lost statistical significance after age adjustment, underscoring age as a major confounding factor. Collectively, these findings suggest that the *TC* genotype may represent a potential genetic marker for increased risk of severe disease requiring intensive care in the Syrian population.

Taken together, our results are consistent with several international studies and meta-analyses reporting an enrichment of the *C* allele among patients with severe COVID-19 [45–49], while also highlighting the substantial heterogeneity observed across populations. Differences in sample size, age distribution, healthcare access, circulating viral strains, and ethnic variation in rs12252 allele frequency may contribute to these discrepancies.

Beyond its relevance to COVID-19, IFITM3 plays a critical role in host defense against emerging viral

pathogens and therefore represents an important target for future public health strategies aimed at mitigating the emergence and spread of novel infectious diseases [50]. Nevertheless, this study has several limitations, most notably the relatively small sample size, largely attributable to financial constraints and challenges related to patient recruitment and sample collection during the study period. Future studies involving larger and more representative cohorts, as well as additional host genetic markers, are warranted to clarify the role of IFITM3 polymorphisms in COVID-19 outcomes.

Conclusions

Our findings demonstrate that the *IFITM3* rs12252 C allele is more frequently observed in patients with severe COVID-19, whereas the TT genotype predominates among those with moderate disease. The TC genotype was significantly associated with ICU admission, and collectively, these results highlight the critical role of host genetic factors in determining COVID-19 disease severity. Further validation in larger, multicenter cohorts is warranted to confirm these associations.

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Conflict of interest

No conflict of interest is declared.

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