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Original Article

Interferon-induced transmembrane protein-3 genetic variant rs12252 is associated with COVID-19 mortality

Jahad Alghamdi [a,*], Manal Alaamery [b,c,d], Tlili Barhoumi [e], Mamoon Rashid [f], Hala Alajmi [a], Nasser Aljasser [a], Yaseen Alhendi [a], Hind Alkhalaf [a], Hanadi Alqahtani [a], Omer Algablan [a], Abdulraham I. Alshaya [g], Nabiha Tashkandi [h], Salam Massadeh [b,c,d], Bader Almuzzaini [i], Salleh N. Ehaideb [j], Mohammad Bosaeed [k,l], Kamal Ayoub [m], Saber Yezli [n], Anas Khan [n,o], Ahmed Alaskar [p], Abderrezak Bouchama [j,*]

[a] Saudi Biobank, King Abdullah International Medical Research Center, King Saud Bin Abdulaziz University for Health Sciences, Ministry of National Guard – Health Affairs, Riyadh, Saudi Arabia
[b] Developmental Medicine Department, King Abdullah International Medical Research Center, King Saud Bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Ministry of National Guard- Health Affairs, Riyadh, Saudi Arabia
[c] KACST-BWH Centre of Excellence for Biomedicine, Joint Centers of Excellence Program, King Abdulaziz City for Science and Technology (KACST), Riyadh, Saudi Arabia
[d] King Abdulaziz City for Science and Technology (KACST), Saudi Human Genome Project (SHGP), Satellite Lab at King Abdulaziz Medical City (KAMC), Ministry of National Guard Health Affairs (MNG-HA), Riyadh, Saudi Arabia
[e] Core Facility and Research Platforms, King Abdullah International Medical Research Center, King Saud Bin Abdulaziz University for Health Sciences, Ministry of National Guard – Health Affairs, Riyadh, Saudi Arabia
[f] Department of Bioinformatics, King Abdullah International Medical Research Center, King Saud Bin Abdulaziz University for Health Sciences, Ministry of National Guard – Health Affairs, Riyadh, Saudi Arabia
[g] College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Ministry of National Guard – Health Affairs, Riyadh, Saudi Arabia
[h] Nursing Services, Ministry of the National Guard - Health Affairs, King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[i] Medical Genomics Research Department, King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, Ministry of National Guard – Health Affairs, Riyadh, Saudi Arabia
[j] Experimental Medicine Department, King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, Ministry of National Guard – Health Affairs, Riyadh, Saudi Arabia
[k] Department of Medicine, Ministry of the National Guard - Health Affairs, Riyadh, Saudi Arabia
[l] College of Medicine, King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia
[m] King Abdulaziz Cardiac Center, Ministry of the National Guard - Health Affairs, King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[n] The Global Centre for Mass Gatherings Medicine, Ministry of Health, Riyadh, Saudi Arabia
[o] College of Medicine, King Saud University, Riyadh, Saudi Arabia
[p] Oncology Department, Ministry of the National Guard - Health Affairs, King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

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ABSTRACT

Interferon-induced membrane proteins (IFITM) 3 gene variants are known risk factor for severe viral diseases. We examined whether *IFITM3* variant may underlie the heterogeneous clinical outcomes of SARS-CoV-2 infection-induced COVID-19 in large Arab population. We genotyped 880 Saudi patients; 93.8% were PCR-confirmed SARS-CoV-2 infection, encompassing most COVID-19 phenotypes. Mortality at 90 days was 9.1%. IFITM3-SNP, rs12252-G allele was associated with hospital admission (OR = 1.65 [95% CI; 1.01–2.70], $P = 0.04$]) and mortality (OR = 2.2 [95% CI; 1.16–4.20], $P = 0.01$). Patients less than 60 years old had a lower survival probability if they harbor this allele (log-rank test $P = 0.002$). Plasma levels of IFNγ were significantly lower in a subset of patients with AG/GG genotypes than patients with AA genotype ($P = 0.00016$). Early identification of these individuals at higher risk of death may inform precision public health response.

* Corresponding author.
E-mail addresses: alghamdija@ngha.med.sa (J. Alghamdi), bouchamaab@ngha.med.sa (A. Bouchama).

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List of abbreviations

ACE	Angiotensin Converting Enzyme
IFITM3	Interferon-Induced Transmembrane Protein 3
IFN	Interferon
INFγ	Interferon Gamma
IQR	Inter-Quartile Range
IRB	Institutional Review Board
IRF7	Interferon Regulatory Factor 7
KAIMRC	King Abdullah International Medical Research Center
MAF	Minor Allele Frequency
MOH	Ministry Of Health
OR	Odds Ratio
PCR	Polymerase Chain Reaction
qPCR	Quantitative Polymerase Chain Reaction
RNA	Ribonucleic Acid
SARS-CoV-2	Severe Acute Respiratory Syndrome–Coronavirus
SD	Standard Deviation
SNP	Single Nucleotide Polymorphism
TLR3	Toll-Like Receptor 3
TMPRSS2	Transmembrane Serine Protease 2
TNF-α	Tumor Necrosis Factor-α

1. Introduction

Coronavirus disease 2019 (COVID-19) is a viral respiratory illness due to a novel pathogen Severe Acute Respiratory Syndrome–Coronavirus 2 (SARS-CoV-2), that emerged in China and spread worldwide [1,2]. To date, SARS-CoV-2 infected more than 115 million people, resulting in death reaching 2.5 million, in addition to the societal and economic burden [3]. Epidemiological data revealed that the majority of COVID-19 infections were asymptomatic or displayed a mild illness, while a sizable number (up to 20%) develop either severe hypoxemic pneumonia or critical illness culminating in death [2,4,5]. The large variability in clinical expression and outcomes of COVID-19 was associated with host factors such as old age, gender, comorbidities, ethnicity, and lower economic status [2,4,6]. Emerging studies suggest that host-genetic factors may also contribute to the difference in COVID-19 phenotypes [7–15].

Studies investigating the role of host genetic factors in COVID-19 pathogenesis are rapidly growing, revealing several gene susceptibility variants, although with different levels of evidence [7,8,10–15]. Two approaches have been used, including candidate gene [7,8,10,11] or genome-wide association [13,15]. Selected gene candidates included *ACE-2*, *TMPRSS2*, *IFITM3,* Toll-like receptor 3 (*TLR3*), and interferon regulatory factor 7 (*IRF7*) based on their role in SARS-CoV-2 tropism to the human cells, including binding, entry, and replication as well as host-immune response to the virus [7–12]. Several variants of *ACE2* and *TMPRSS2* genes were identified, but none was associated with COVID-19 severity [7,8,10]. In contrast, the variant G allele rs12252 of *IFITM3* gene was recognized as a risk factor for COVID-19 hospital (but not ICU) admission in the Caucasian population, and for severity in Chinese patients [11,12]. However, both studies included small cohorts that do not reflect the extreme clinical heterogeneity of COVID-19, which ranges from no symptoms to death [11,12].

More recently, a large cohort of 659 patients, including life-threatening COVID-19 pneumonia, showed that a small number of patients (3.5%) had variants in *TL3* and *IRF7* genes associated with the severity of COVID-19 [9]. This strengthened the current understanding of the central role of type I and III interferon (IFN) response in the human defense against SARS-CoV-2 infection. Likewise, genome-wide-association studies identified three gene variants (*DPP9*, *IFNAR2*, and *OAS1* to *3*) associated with host immunity, and ABO blood group, lending further evidence that host immune genetic factors interaction with SARS-CoV-2 may underlie the different clinical outcomes of COVID-19 [13–15].

Therefore, we postulated that the difference in clinical manifestations in COVID-19 might be due to gene variants that govern the host defense mechanisms against the virus [16]. The family of interferon-induced membrane proteins (IFITM 1 to 5) is a critical barrier to the virus entry into the cells. It can block the fusion pore formation between the virus and host membranes, preventing the virus from crossing the cellular membrane. Among the IFITM members, variants of the IFITM3 gene, particularly the G allele rs12252 single nucleotide polymorphism (SNP) has been consistently associated with severe viral diseases, including more recently COVID-19 [11,12,17–20]. Accordingly, we tested the hypothesis that the G allele rs12252 variant might contribute to the severity of COVID-19 in a large cohort of uniquely homogenous ethnic Arab Saudi population infected with SARS-CoV-2 and encompassing all COVID-19 phenotypes. This is with the perspective that a better understanding of the host genetic factors at play in COVID-19 may be crucial to inform preventive and therapeutic interventions.

2. Methods

2.1. Study design

This is an observational prospective cohort study approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (KAIMRC) with IRB 20/182, as well as the Central IRB of Ministry of Health (MOH) with a log number (20-#630). All the patients enrolled in the study signed written informed consent.

2.2. Study participants

We recruited adult patients over 18 years old from a tertiary hospital and several health authorities assigned quarantine locations in Riyadh, Saudi Arabia, between March 2020 and September 2020. We selected only Saudi patients diagnosed as COVID-19 either with positive polymerase chain reaction (PCR) test or being in close contact with a confirmed positive COVID-19 patient and showed COVID-19 related symptoms, even though testing negative by PCR. Patients recruited from the hospital included those admitted because of COVID-19 or found positive for COVID-19 during hospitalization for an underlying medical condition. Patients recruited from the quarantine sites were either asymptomatic or exhibited mild illness and were opted to stay in quarantine due to the unavailability of a suitable isolation area in their home. Blood samples were obtained after signing informed consent and a case report form that collected demographic and clinical information. Electronic Medical health records of all admitted patients were accessed to retrieve clinical, laboratory variables and outcomes.

2.3. DNA extraction and genotyping assay

We selected the variant rs12252 in IFITM3 based on previous evidence of its association with other viral respiratory infections, including coronavirus [11,12,17–20]. Likewise, we ensured that its global minimum allele frequency (MAF) was above 5% in the Saudi population. Genomic DNA was extracted from the peripheral blood using the Puregene Blood Kit (QIAGEN, Germany) following the manufacturer's protocol, the detailed method of the genotyping experiment is provided in the supplementary methods.

2.4. Enzyme-linked immunosorbent assays (ELISA) measurements

Plasma samples were prepared to measure the levels of INFγ and TNF-α using ELISA assay kits from Solarbio life sciences (TNF-α SEKH-0047 and INFγ SEKH-0046). All reagents and standards were prepared according to the manufacturer's instructions. Detailed method of the ELISA experiment is provided in the supplementary methods.

2.5. Clinical data collection

Electronic Medical records of the patients admitted to the hospital

were screened by three independents reviewers to retrieve information about patients' disease course, including patients' demographic, pre-existing comorbidities, signs and symptoms, laboratory results, treatment, complications, and outcome. These complications included acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), shock state, and the need for invasive mechanical ventilation. Time to event was calculated for any cause mortality from the first positive PCR test or diagnostic in PCR negative patients until an event (i.e. hospitalization, Intensive Care Unit (ICU) admission, or death). For patients recruited from quarantine sites, we relied on the patients self-reporting medical history and disease severity, and we followed-up with the patients until complete recovery. Overall, patients were categorized into one of the four groups based on the disease severity; asymptomatic, which include patients without any COVID-19-related symptoms; mild consisted of patients with mild signs and symptoms who did not require hospital admission; severe and critical, comprised patients who were admitted to the hospital ward and ICU, respectively.

2.6. Statistical analysis

We summarized categorical variables as number (%) and continuous variables (numerical variables) as mean and standard deviation (SD) or median and inter-quartile range (IQR). The normality assumptions were assessed for all numerical variables using the Shapiro–Wilk test and graphical representation (i.e., histograms and Q-Q plots). Normally distributed continuous variables were compared using a two-sample independent *t*-test, otherwise with the Mann-Whitney *U* test. We compared categorical variables using the Chi-square or Fisher exact test. Allelic frequency of the selected variant was carried out in PLINK to calculate the minor MAF and Hardy-Weinberg Equilibrium [21]. Univariate and multivariate logistic regression were used to assess the association between the selected genetics variant and phenotypes after adjusting for age. Survival distributions of the patients' group were compared using a nonparametric log-rank test. We assessed model fit using the Hosmer-Lemeshow goodness-of-fit test. The odds ratios (OR) were reported for the associations. Log-rank test was also used to compare survival distribution of patients during hospital stay among disease severities and between different genotypes. We considered a *P* value of <0.05 statistically significant and used R version 4.0.2 for all statistical analyses.

3. Results

3.1. Patients

A total of 952 Saudi patients were enrolled from a tertiary care hospital and two quarantine sites; 72 subjects were excluded because of missing clinical information or low sample quality (Fig. S1). Of the remaining 880 patients included in the study, 466 (53%) were monitored as outpatients, and 414 (47%) were treated as inpatients. The main cause of hospital admission was due to COVID-19 in 328 (79.2%) patients, and the remainder 86 (20.8%) were unrelated. However, this latter group was diagnosed with COVID-19 during their hospital stay. Overall, 825 (93.8%) of the patients had a laboratory-confirmed SARS-CoV-2 infection.

3.2. Baseline characteristics of the study population

Table 1 displays the demographic and baseline clinical characteristics of the study population. Older patients were highly represented in critical and severe groups than mild or asymptomatic groups. The prevalence of major coexisting illnesses and chronic medications such as antihypertensive and antidiabetic therapies were significantly higher in the severe and critical groups. The most-reported signs and symptoms of COVID-19 were fever (61%), dry cough (45%), and shortness of breath (39%) (Table S1).

3.3. Complications, therapy, and outcome of COVID-19

3.3.1. Complications

Multiple organs failure, including ARDS, AKI, and shock state, were the most common causes for admission to ICU (Table 2). The majority (90.4%) required ventilatory support, particularly endotracheal intubation and mechanical ventilation. Most of the patients were screened

Table 1
Demographic and baseline clinical characteristics of the study population.

Characteristics	Asymptomatic ($n = 55$)	Mild ($n = 449$)	Severe ($n = 210$)	Critical ($n = 166$)	*P* value*
Age, mean ± SD	37.2 ± 14.8	29.9 ± 10.5	54.1 ± 16.2	64.3 ± 14.7	<0.0001
Distribution - n (%)					<0.0001
<60	51 (92.7)	440 (98.0)	124 (59.0)	49 (29.5)	–
60–69	2 (3.6)	7 (1.6)	45 (21.4)	49 (29.5)	–
70–79	2 (3.6)	2 (0.4)	34 (16.2)	44 (26.5)	–
≥80 yr	0 (0)	0 (0)	7 (3.3)	24 (14.5)	–
Sex – n (%)					0.0002
Male	25 (45.5)	288 (64.1)	104 (49.5)	108 (65.1)	–
Female	30 (54.5)	161 (35.9)	106 (50.5)	58 (34.9)	–
BMI - kg/m^2 (SD)					<0.0001
<18	1 (2.2)	17 (4.9)	4 (1.9)	3 (1.9)	–
18–25	19 (42.2)	129 (37.0)	34 (16.3)	32 (19.9)	–
25–30	9 (20.0)	99 (28.4)	60 (28.8)	59 (36.6)	–
>30	16 (35.6)	104 (29.8)	110 (52.9)	67 (41.6)	–
Pregnancy	11 (20.0)	2 (0.4)	7 (3.3)	0 (0)	<0.0001
Previous coexisting disease – n (%)					
Diabetes	8 (14.5)	23 (5.1)	101 (48.1)	84 (50.6)	<0.0001
Hypertension	11 (20)	26 (6)	110 (52)	95 (57)	<0.0001
Cardiovascular disease	0 (0)	6 (1.3)	34 (16.2)	31 (18.7)	<0.0001
Chronic lung disease	4 (7.3)	35 (7.8)	24 (11.4)	17 (10.2)	0.42
Chronic liver disease	2 (3.6)	3 (0.7)	14 (6.7)	3 (1.8)	0.00007
Chronic kidney disease	4 (7.3)	5 (1.1)	38 (18.1)	21 (12.7)	<0.0001
Malignancy	0 (0)	1 (0)	9 (4)	8 (5)	0.0001
Thyroid dysfunction	0 (0)	6 (1)	25 (12)	10 (6)	<0.0001
Hyperlipidemia	4 (7.3)	3 (0.7)	51 (24.3)	49 (29.5)	<0.0001
Chronic medication – n (%)					<0.0001
Antihypertensive	8 (14.5)	13 (2.9)	94 (44.8)	112 (67.5)	<0.0001
Antidiabetic	3 (5.5)	15 (3.3)	37 (17.6)	29 (17.5)	<0.0001
Insulin	3 (5.5)	8 (1.8)	46 (21.9)	112 (67.5)	<0.0001
Lipid lowering medication	3 (5.5)	7 (1.6)	97 (46.2)	93 (56.0)	<0.0001
SARS-CoV-2 test result (PCR) – n (%)					0.70
Positive	51 (92.7)	422 (94.0)	194 (92.4)	158 (95.2)	–
Negative	4 (7.3)	27 (6.0)	16 (7.6)	8 (4.8)	–

* *P* is for Chi-square test or ANOVA.

on admission for community-acquired viral respiratory infection (Table S2). One patient in each group of severe and critical tested positive for seasonal coronavirus and rhinovirus, respectively. As expected, the frequency of nosocomial infection was significantly higher in critical as compared with severe patients.

3.3.2. Therapy

The patients received various medications, including antiviral, antibiotic, anticoagulants, and antithrombotic dictated by their condition during the course of hospitalization (Table S3). The patients admitted to ICU were more likely to receive dexamethasone and other steroids than severe patients.

3.3.3. Outcome

Eighty (9.1%) of the 880 patients did not survive COVID-19 at 90 days (Table 2). Non-survivors were significantly older, with multiple previous comorbidities and chronic medications (Table S4). Likewise, higher mortality was observed among overweight and obese patients (12.3% and 11.1%, respectively). The cause of death was predominantly due to ARDS (55%), followed by cardiopulmonary arrest (50%) and multiple organs failure (32.5%; Table S5).

3.4. Genetics testing

The allelic frequency of rs12252 (*IFITM3*) and its association with hospital admission as a proxy for disease severity and mortality is provided in Table 3. The additive model that is adjusted for age and gender showed that the G allele of rs12252 is significantly associated with hospital admission with an odds ratio of 1.65 [95% CI; 1.01–2.70, $P = 0.04$] and mortality with an odds ratio of 2.2 [95% CI; 1.16–4.20, $P = 0.01$. The IFITM3 genotypes showed that non-survivors with AG genotype tend to be younger and healthier, with few comorbidities and progress to severe forms earlier than the groups of patients with AA genotype, although none was statistically significant (Table S6).

Kaplan-Meier survival analysis revealed that survival probability is significantly lower in patients carrying the IFITM3-SNP, rs12252 genotype AG/GG ($P = 0.01$, log-rank test) (Fig. 1A). Stratifying the analysis by age groups revealed that patients younger than 60 years old and G allele has significantly lower survival probability (Fig. 1B), but not in the older age groups. Fig. 1B

Table 2
Complications, therapy, and outcome of patients with severe and critical COVID-19.

Characteristics	Severe ($n = 211$)	Critical (n = 166)	*P* value[d]
Complications – n (%)			
ARDS[a]	10 (4.8)	145 (87.3)	<0.00001
AKI[b]	11 (5.2)	101 (60.8)	<0.00001
Shock state[c]	7 (3.3)	76 (45.8)	<0.00001
Cerebrovascular events	4 (1.9)	6 (3.6)	<0.00001
Concomitant viral infections – n (%)[e]	1 (1.8)[f]	1 (1.7)[g]	0.99
Hospital-acquired infection	9 (4.3)	97 (58.4)	<0.00001
Therapy – n (%)			
Dexamethasone	67 (31.9)	133 (80.1)	<0.00001
Anticoagulant	198 (94.3)	165 (99.4)	0.008
Ventilatory support	79 (37.6)	150 (90.4)	<0.00001
Oxygen only	75 (35.7)	41 (24.7)	0.025
Invasive mechanical ventilation	4 (1.9)	109 (65.7)	<0.00001
Case fatality at day 90– n (%)	6 (2.9)	74 (44.6)	<0.00001

[a] ARDS-Acute Respiratory Distress Syndrome defined as PaO2/FiO2 < 200 mmHg and radiological evidence of lung injury.
[b] AKI-Acute Kidney Injury defined as Serum Creatinine >30% compared to baseline within 72 h.
[c] Shock state defined as blood pressure < 90 mmHg and requirement of vasopressor.
[d] *P* value is for Chi-square test or ANOVA.
[e] 111(52.6), and 120 (72.2%) were tested for viral and bacterial respiratory infection (list of virus and bacteria is shown in supplemental table S2).
[f] Coronavirus 229E was detected.
[g] Human Rhinovirus was detected.

3.5. Association of IFITM3 with plasma levels of IFNγ and TNFα

To assess whether the IFITM3-SNP, rs12252 affects the host immune response, we measured the production of IFNγ and TNFα in-vivo in the three genotypes GG, A/G, and A/A matched for age, gender, and COVID-19 severity in 20 patients. The analysis revealed that patients with GG or AG genotype displayed significantly lower plasma levels of IFNγ as compared to the AA genotype (0.65, 0.66, and 1.12 pg/ml, respectively; $P = 0.004$ and 0.0001 for GG vs. AA, and AG vs. AA, respectively; Fig. 2). No statistical differences in IFNγ levels between AG and GG genotypes were demonstrated, suggesting that a dominance pattern of the association. Plasma levels of TNFα were not associated with the IFITM3-SNP, rs12252 genotype.

4. Discussion

Our study shows that the IFITM3-SNP, rs12252, is associated with COVID-19 severity and mortality following SARS-CoV-2 infection in Saudi individuals less than 60 years old. To the best of our knowledge, this is the first genetic study that reveals a gene variant that may increase the odds of death in young individuals infected with SARS-CoV-2. Recent reports of small cohorts of Caucasian and Chinese individuals documented an association between IFITM3-SNP, rs12252, and risk of

Table 3
Association of rs12252 (IFITM3) with COVID-19 disease severity.

Disease severity	Genotype/Allele frequency	Yes	No	Odd ratio (95% CI)	P value
Hospitalization	AA	330 (82)	372 (81)	Ref	
	AG	73 (18)	82 (18)	1.0 (0.70–1.42)	0.98
	GG	1 (0.2)	3 (1)	0.37 (0.03–3.63)	0.39
	A	733 (91)	826 (90)	0.96 (0.69–1.32)	0.8
	G	75 (9)	88 (10)		
	AA+AG vs GG			0.37 (0.04–3.63)	0.4
	AA Vs AG + GG			0.92 (0.7–1.39)	0.98
	Additive model[a]			**1.65 (1.01–2.70)**	**0.04**
Mortality	AA	56 (73)	646 (82)	Ref	
	AG	21 (27)	134 (17)	1.3 (0.76–2.22)	0.34
	GG	0 (0)	4 (1)	0.91 (0.05–17.19)	0.95
	A	133 (9)	1426 (91)	1.56 (0.97–2.59)	0.06
	G	21 (13)	142 (87)		
	AA + AG Vs GG (Recessive)			1.12 (0.06–20.9)	0.9
	AA Vs AG + GG (Dominance)			**1.76 (1.03–2.99)**	**0.04**
	Additive model[a]			**2.20 (1.16–4.20)**	**0.01**

Bold indicates statistically significant *P*-value. Abbreviation: OR, odds ratio, CI, Confidence Interval.
[a] Based on a logistic model that assumes an additive model with adjustment for gender, age.

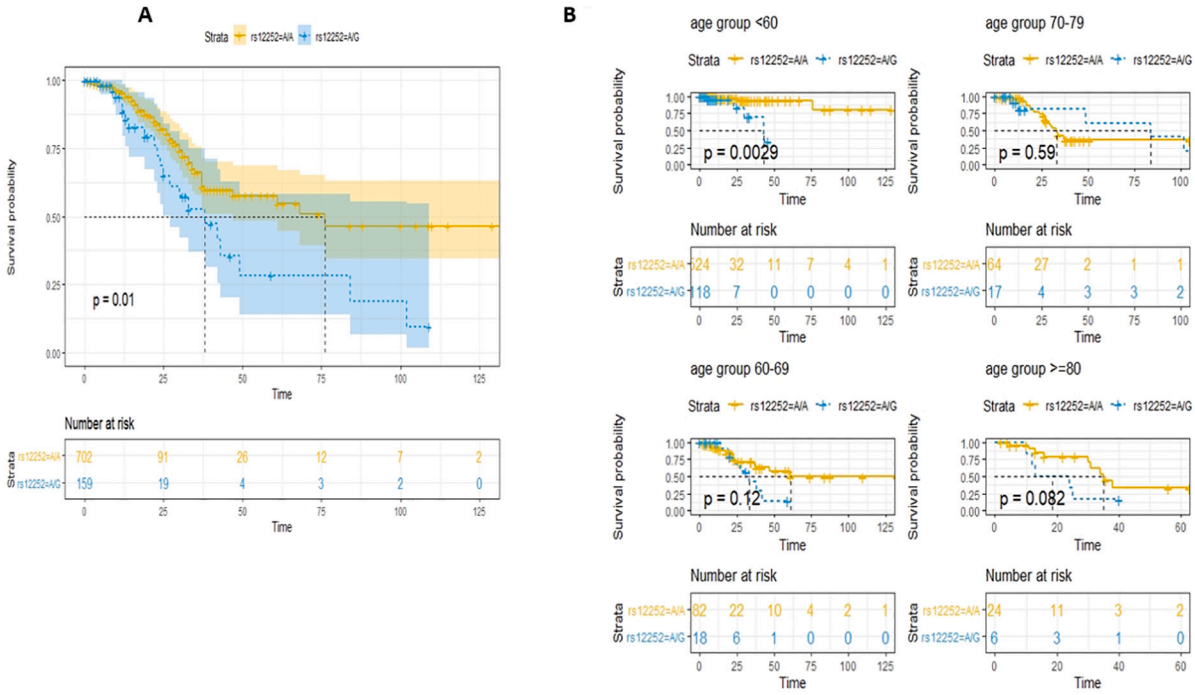

Fig. 1. Survival analysis for COVID-19 mortality according to rs12252 genotypes using diagnosis day as time-to-event. A) In the overall population. B) Stratified by age groups.

hospitalization and severity of COVID-19, respectively [11,12]. Taken together, the findings suggest a prominent role of IFITM3 in the pathogenesis of COVID-19.

IFITM3 gene encodes an interferon-induced membrane protein with broad antiviral activity against many viruses, including influenza A H1N1 virus, Ebola and Marburg virus, West Nile virus, dengue virus, and SARS-CoV [17–20,22,23]. The protective mechanisms are not fully elucidated, but findings from *IFITM3* Knockout (KO) cells suggest that IFITM3 proteins prevent the viral genomes from entering the cytosol and starting the replication [16]. This was postulated to be through lessening the virus-endosome fusion and accelerating the shuttle of endosomal viral cargo to lysosomes for destruction [24]. On the other hand, a variant, *IFITM3*-SNP, rs12252 with GG genotype was associated with severity and outcome of several viral illnesses, including influenza A H1N1/09 and H7N9, Hantan virus infection and acute human immunodeficiency (HIV) infection [22,23,25,26].

In the present study, we show that allele G presence nearly doubles the odds of dying from COVID-19 during SARS-CoV-2 infection. The predictive value of G allele was independent of robust clinical risk factors, such as old age, gender, BMI, or even major underlying comorbidities. Notably, the IFITM3-SNP, rs12252 with A/G genotype enhances significantly the odds of dying for younger population infected with SARS-CoV-2, hence raising a novel hypothesis on the pathogenic mechanisms that may lead to death in this category of the population.

The study also revealed that the frequency of the minor rs12252-G allele was 9%, in Saudis, which is closer to the frequency in the European population (4%), but much lower than East Asia (53%) and global population (24%) as reported in the 1000 genome project [27]. The low frequency of the G–allele in the Saudi population explains why the homozygote genotype was hardly represented in our cohort. Further, the association of rs12252-G allele with clinical expression and outcome of many viral illnesses differed between ethnic groups ranging from none in the European to severity and lethality in the East Asian population [11,18,23,28]. Here, we showed that in a relatively large and homogenous cohort of ethnic Arabs, the *IFITM3*, rs12252 with A/G genotype is significantly associated with mortality in COVID-19. The explanation for this discrepancy in outcome between ethnic groups remains unclear but warrants further research as the findings may inform a precision public health response such as social distancing and vaccination.

The mechanisms that underlie the pathogenicity of the *IFITM3*, rs12252 with minor G allele association with morbidity and mortality are not fully elucidated. The polymorphism was postulated to result in low IFITM3 protein expression [29], a weakened antiviral activity due to the encoded 21-amino acid truncation [30], or alteration of cellular localization of the protein between the membrane and endosome [30,31]. Nevertheless, in KO mouse model lacking IFITM3 challenged with a low dose of influenza virus or diminished viral pathogenicity demonstrated that it results in higher, lung, heart, spleen, and systemic viral replication than the wild-type control [32,33]. As a consequence, the KO mice developed fulminant pneumonia, arrhythmias, and myocardial damage that rapidly progressed to death. Lung pathology disclosed edema, hemorrhage, and inflammation, while the heart exhibited myocarditis and enhanced fibrotic response. IL-6 concentration was increased in both lung and heart tissues, thus suggesting that lack of IFMT3 resulted in viral and inflammatory-induced organ injury and damage [33].

Lung and heart are common targets of SARS-CoV-2 induced COVID-19, as documented in our cohort. We did not observe any significant difference in the incidence or severity of ARDS, need for mechanical ventilation, hemodynamic instability, or troponin levels between the patients with *IFITM3* rs12252-A/A and rs12252-A/G genotypes. However, the patients with the *IFITM3* rs12252-A/G genotype were younger, with few comorbidities, had a shorter time from disease onset to admission to ICU, and higher mortality, although these did not reach statistical significance. Likewise, we observed lower circulating IFNγ and higher TNFα in a subset of patients with G allele IFITM3 relative to A/A genotype, indicating a dysregulated innate immune response of the host carrying the IFITM3 variant. However, this evidence remains indirect, and accordingly, further studies are needed to unravel the precise pathogenic mechanisms at play in individuals with G allele IFITM3 variant.

Our study has some important limitations; first, we prioritized

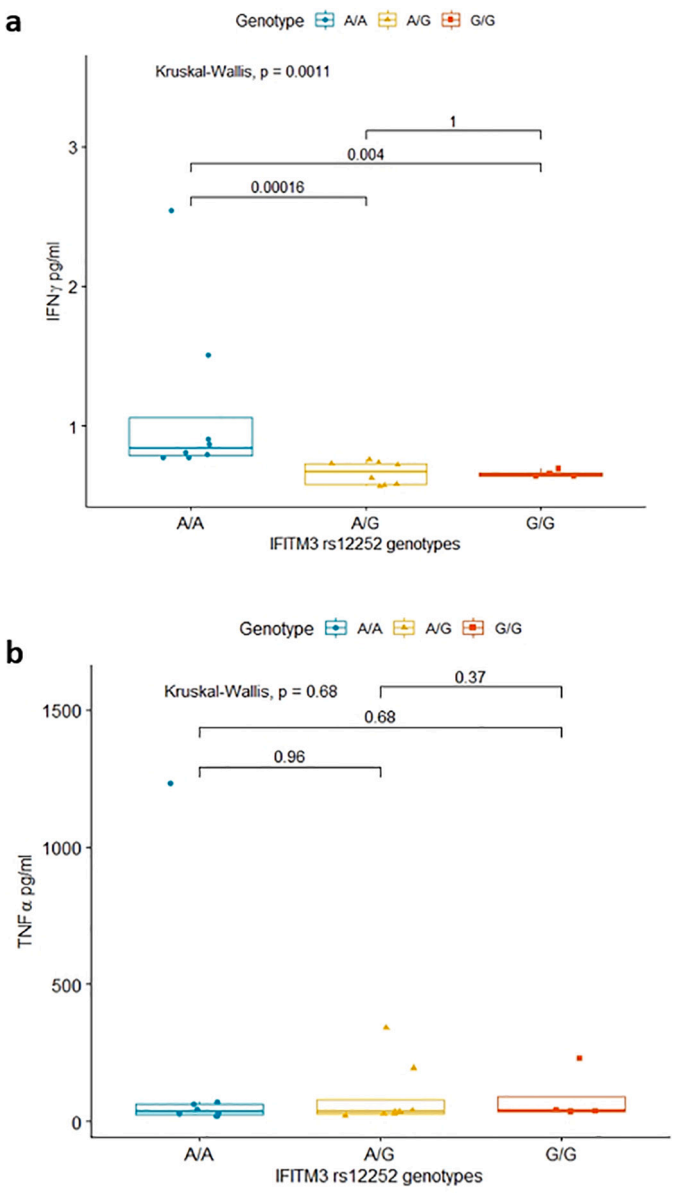

Fig. 2. Plasma levels of IFNγ (A) and TNFα (B) in age and gender-matched patients according to IFITM3 rs12252 genotypes.

genotyping rs12252 based on its previous role in respiratory viral infections and the a priori probability that it might underlie the clinical outcomes of COVID-19. Another studied variant, rs34481144, has also been reported to be associated with viral respiratory diseases [29], and the frequency of the combined haplotype involving the two variants has been shown to be in line with standardized mortality ratios [34]. Nevertheless, both variants were reported to be located within the same linkage disequilibrium (LD) block, with strong LD with a mutual variant (rs642194) [35]. Second, we missed recording some early signs and symptoms of admitted patients due to the difficulty to directly communicate with the patients, particularly those admitted immediately with severe forms of the disease, and thus relied solely on the documented information in their electronic health records. Nonetheless, this study benefits from a relatively large sample size of a homogenous population from the same ethnic background, with a very explicit patient phenotyping encompassing a wide range of COVID-19 manifestations. Moreover, we have measured the plasma levels of two biomarkers, although in small subsets that might serve as endophenotypes. If the findings are confirmed on a larger scale, this would further strengthen the observed association at the phenotype level.

In conclusion, this study in the Saudi population showed that the G allele of rs12252 within *IFITM3* is significantly associated with the need for hospital admission and mortality in COVID-19 patients, particularly in younger population. Early identification of subjects carrying the G allele may help target preventive and therapeutic measures toward these individuals at higher risk of death.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (KAIMRC) with IRB 20/182, as well as the Central IRB of Ministry of Health (MOH) with a log number (20-#630). All the patients enrolled in the study signed written informed consent.

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CRediT authorship contribution statement

Jahad Alghamdi: Conceptualization, Methodology, Formal analysis, Supervision, Funding acquisition, Writing - original draft, Writing - review & editing. **Manal Alaamery:** Resources, Writing - review & editing. **Tlili Barhoumi:** Methodology, Investigation, Writing - review & editing. **Mamoon Rashid:** Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Hala Alajmi:** Investigation, Writing - review & editing. **Nasser Aljasser:** Investigation, Writing - review & editing. **Yaseen Alhendi:** Investigation, Writing - review & editing. **Hend Alkhalaf:** Project administration, Writing - review & editing. **Hanadi Alqahtani:** Project administration, Writing - review & editing. **Omer Algablan:** Project administration, Writing - review & editing. **Abdulraham I. Alshaya:** Resources, Writing - review & editing. **Nabiha Tashkandi:** Resources, Writing - review & editing. **Salam Massadeh:** Resources, Writing - review & editing. **Bader Almuzzaini:** Methodology, Writing - review & editing. **Salleh N. Ehaideb:** Conceptualization, Writing - original draft, Writing - review & editing. **Mohammad Bosaeed:** Resources, Writing - review & editing. **Kamal Ayoub:** Resources, Writing - review & editing. **Saber Yezli:** Resources, Writing - review & editing. **Anas Khan:** Resources, Writing - review & editing. **Ahmed Alaskar:** Resources, Supervision, Writing - review & editing. **Abderrezak Bouchama:** Conceptualization, Methodology, Supervision, Funding acquisition, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygeno.2021.04.002.

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