Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Interferon-induced transmembrane protein 3 gene polymorphisms are associated with COVID-19 susceptibility and severity: A meta-analysis

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SUMMARY

Background: Recent evidence has linked the interferon-induced transmembrane protein 3 gene (IFITM3) to coronavirus disease 2019 (COVID-19) outcomes, but the results are inconsistent. The purpose of this meta-analysis was to evaluate the association of IFITM3 gene polymorphisms with COVID-19 susceptibility and severity.

Method: A systematic search was performed with PubMed, Web of Science, Cochrane Library, and Embase from the date of inception to 20 December 2021. The results were analyzed with pooled odds ratios (ORs) and 95% confidence intervals (95% CIs). The robustness was performed using the method of sequential removal for each trial.

Results: Four studies involving 1989 subjects were included, from which 1114 patients were positive for COVID-19. For IFITM3 rs12252, the pooled OR showed that there was a significant association between the genotype frequencies and infection with COVID-19 in any of the gene models, i.e., the allelic model (OR = 1.91, 95% CI, 1.36–2.68), the dominant model (OR = 1.80, 95% CI, 1.27–2.56), the recessive model (OR = 5.67, 95% CI, 1.01–31.77), the heterozygous model (OR = 1.65, 95% CI, 1.16–2.36) and the homozygous model (OR = 5.88, 95% CI, 1.05–32.98). The results stratified by severity showed that there was a significant correlation only between the allelic (OR = 0.69, 95% CI, 0.49–0.97) and recessive (OR = 0.43, 95% CI, 0.20–0.93) models. Our results did not support the associations between the IFITM3 rs34481144 gene polymorphism and COVID-19 susceptibility or severity in any of the gene models.

Conclusions: The findings indicated that IFITM3 rs12252 gene polymorphisms were associated with COVID-19 susceptibility and that the rs12252-C variant was particularly critical for severity. Genetic factors should be considered in future vaccine development.

Introduction

Coronavirus disease 2019 (COVID-19) was prevalent in late 2019 and was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has rapidly spread worldwide with the characteristics of rapid transmission and high mortality.[1] As of January 11, 2022, confirmed cases were more than 304 million, and deaths were more than 5.4 million.[2] The COVID-19 pandemic created a global health crisis of historic proportions and forced governments around the world to impose huge restrictions within and between countries. To fight against COVID-19, home quarantine and investment in epidemic prevention materials have had serious social and economic burdens. Unfortunately, the speed of vaccine development often lags behind the rate of virus mutation, causing great disaster to mankind.

Individuals infected with COVID-19 often have different outcomes. Nearly 80% of people infected with COVID-19 were reported to have mild to moderate disease, 13.8% had severe disease, and 6.1% had critical disease.[3] Some studies also showed that up to 20% of asymptomatic carriers would experience fatal disease symptoms.[4,5] Emerging studies have tended to suggest that COVID-19 susceptibility is related to viral receptors expressed in vivo.[6-8] While environmental and socioeconomic factors were suggested to contribute to this trend, they arguably do not explain the range of the differences observed, allowing for possible genetic implications.

The interferon-induced transmembrane 3 (IFITM3) protein plays a vital role in adaptive immunity against viral infection and has been proven to enable cells to fight infection by both enveloped and nonenveloped viruses.[9-11] The IFITM3 gene induced by

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interferons is a strong candidate gene for preventing multiple influenza viruses[12]. In the state of virus invasion, IFITM3 can disrupt viral replication to improve human defenses[12,13]. The positive association of IFITM3 gene polymorphisms with influenza virus susceptibility and clinical outcomes has also been highlighted in several recent meta-analyses.[14,15] The association between IFITM3 and COVID-19 outcomes has received positive attention in the context of the pandemic. Several recent clinical studies have investigated the association of IFITM3 gene polymorphisms with COVID-19 susceptibility and severity, but with conflicting results. Therefore, we systematically summarized the available evidence to assess the association between IFITM3 gene polymorphisms and COVID-19 susceptibility.

Method

Search strategy

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16] We searched the PubMed, Embase, Cochrane Library, and Web of Science databases from inception to 20 December 2021. The following keywords were combined and adjusted based on the characteristics of the database: (interferon-induced transmembrane protein 3 or IFITM3) and (COVID-19 or SARS-CoV-2) and (polymorphism or variant or mutation or SNP). Literature retrieval was performed without restriction on publication languages or publication types.

Inclusion and exclusion criteria

Eligible studies met the following criteria: 1) reported an association between IFITM3 gene polymorphisms and COVID-19 susceptibility and 2) reported an association between IFITM3 gene polymorphisms and COVID-19 severity. There were no restrictions on the study design. The exclusion criteria were as follows: 1) duplicates, animal experiment, letter to editor, brief report, and comment; 2) the content of the article did not meet the requirements; and 3) data were unavailable.

Data extraction and quality assessment

Data extraction and quality assessment were independently conducted by two review authors (YPL and NYL) following the predesigned data extraction sheet. The following information was extracted: author, publication year, country, study type, ethnicity, age, sample size, sex, and genotyping methods. “T” and “C” were used to represent the wild-type and mutant alleles of the single-nucleotide polymorphism (SNP) rs12252, respectively (T > C); “G” and “A” were used to represent the wild-type and mutant alleles of the SNP rs34481144, respectively (*G* > A). We evaluated the quality of the selected studies according to the Newcastle–Ottawa Scale (NOS), which was designed to evaluate the quality of case–control and cohort studies.[17] A “star” system was used for allocation, and the scores ranged from 0 to 9. Less than 7 stars can be considered moderate or low quality, and seven or more stars can be considered high quality.[18] The quality of the cross-sectional studies was evaluated by the Agency for Health care Research and Quality quality assessment score, which consisted of 11 items with a total score of 11.[19] The following classification was used to interpret article quality: high quality = 8–11; moderate-quality = 4–7; low quality = 0–3. Divergent opinions were resolved after discussion with a third author.

Statistical analysis

Statistical analyses were performed using R statistical software (version 4.1.1). We calculated the pooled odds ratio (OR) and 95% confidence interval (95% CI) to evaluate the strength of the association using fixed- and random-effects models. Next, the chi-square test was applied to evaluate Hardy–Weinberg equilibrium (HWE) for the genotype frequencies, and we defined a *P* value less than 0.05 as a significant imbalance. The present meta-analysis was performed using the following five genetic models: the allelic, dominant, recessive, heterozygous, and homozygous models. In the IFITM3 rs12252 gene polymorphism, for example, the five genetic models are “C vs. T”, “TC+CC vs. TT”, “CC vs. TT+TC”, “TC vs. TT” and “CC vs. TT”. For the IFITM3 rs34481144 gene polymorphism, the genetic models were “A vs. G”, “GA+AA vs. GG”, “AA vs. GG+GA”, “GA vs. GG” and “AA vs. GG”, respectively. Heterogeneity was quantified with the use of the I^2 statistic and classified as low (< 50%, using fixed-effects models) and high (≥50%, using random-effects models) heterogeneity.[20] We used the *Z* test to conduct pooled ORs and considered a *P* value less than 0.05 to indicate statistical significance. A sensitivity analysis was performed to assess the stability of the results by sequentially omitting each study.

Results

Literature search

The literature search initially yielded 32 relevant studies from the four databases, and one record was retrieved from other sources. Sixteen records were retained after the removal of duplicates, animal experiments, and reviews. Seven studies were excluded by reviewing the titles and abstracts according to the objectives of the present meta-analysis. The full text of the remaining 9 studies was screened according to the criteria mentioned above, and 5 articles were excluded due to letter to editor, brief report, and comment. Finally, four studies met the inclusion criteria, including three case–control studies and one single-arm study. The detailed literature search process is shown in **Fig. 1**.

Study characteristics

The study characteristics are presented in **Table 1**. A total of 1989 subjects were enrolled, from which 1114 patients (56% of the total) were positive for SARS-CoV-2 (PCR test). All studies classified patients as COVID-19 positive according to the severity of the disease. Of these, 332 patients (29.80% of the total number of cases) were classified as severe because they needed intensive care units, such as high-flow oxygen, positive-pressure ventilation, or vasoactive drugs. Among them, patients in three studies were Caucasian[21-23], and patients in the fourth study were Asian[24]. The mean age ranged from 50.29 to 71.25 years. In **Tables 2** and **3**, we display the genotype frequencies according to both “COVID-19 vs. controls” and “mild vs. severe”, respectively.

Quality assessment

Two studies were assessed as high quality[21,23], while the remaining two studies were considered moderate quality[22,24]. The average score was 6.7 on the NOS and 6 on the AHRQ. In three case–control studies, the rs12252 polymorphism genotypes in the control groups were in HWE. Since there was no control group in the single-arm study, we observed the effect of Zhang et al.[24] on the pooled OR and 95% CI in the sensitivity analysis.

Meta-analysis of the association between the IFITM3 rs12252 gene polymorphism and COVID-19 susceptibility

For the association between the IFITM3 rs12252 gene polymorphism and COVID-19 susceptibility, a fixed-effects model was

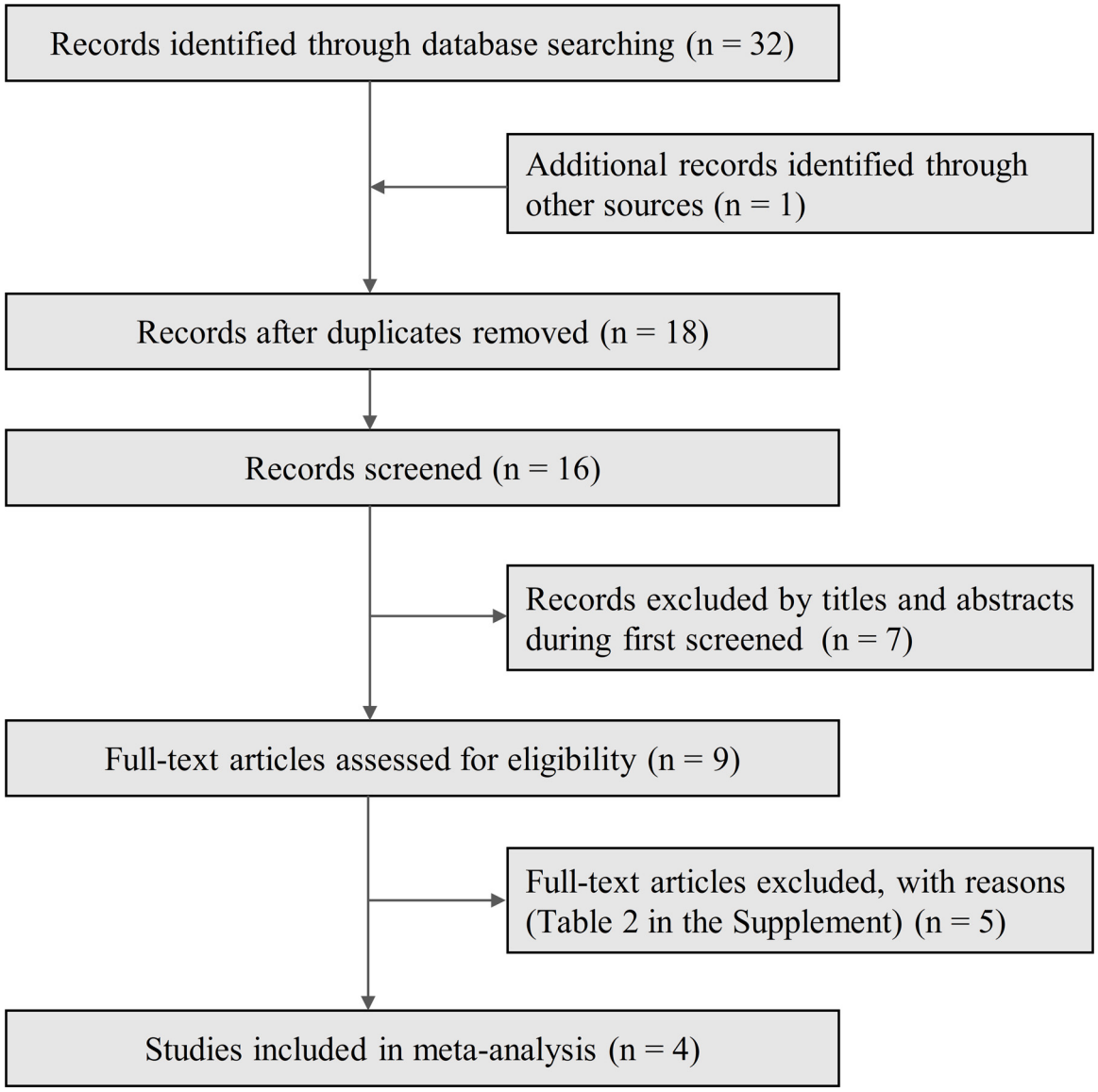

Fig. 1. Flow diagram of the literature search process for the meta-analysis.

adopted to pool the results of the OR, as the heterogeneity of all gene models was less than 50% (all I^2 = 0%). Fig. 2 illustrates the primary relationships between the genotype frequencies and COVID-19. Overall, the pooled OR in a fixed-effects model showed that there were significant associations between the genotype frequencies and infection with COVID-19 in any of the gene models, i.e., the allelic model (OR = 1.91, 95% CI ranging from 1.36 to 2.68), the dominant model (OR = 1.80, 95% CI ranging from 1.27 to 2.56), the recessive model (OR = 5.67, 95% CI ranging from 1.01 to 31.77), the heterozygous model (OR = 1.65, 95% CI ranging from 1.16 to 2.36) and the homozygous model (OR = 5.88, 95% CI ranging from 1.05 to 32.98). Forest plots for the meta-analysis of patients with COVID-19 stratified by severity (mild vs. severe) are provided in Fig. 3. Similarly, there was no significant heterogeneity (all I^2 < 50%), and the results generated using a fixed-effects model revealed similar effect estimates between the allelic and recessive models. The results are as follows: allelic model: OR = 0.69, 95% CI ranging from 0.49 to 0.97; dominant model: OR = 0.75, 95% CI ranging from 0.50 to 1.11; recessive model: OR = 0.43, 95% CI ranging from 0.20 to 0.93; heterozygous model: OR = 0.81, 95% CI ranging from 0.53 to 1.23 and homozygous model: OR = 0.56, 95% CI ranging from 0.23 to 1.39. (Table 4)

Meta-analysis of the association between IFITM3 rs34481144 gene polymorphism and COVID-19 susceptibility

For the association between the IFITM3 rs34481144 gene polymorphism and COVID-19 susceptibility, meta-analyses were performed with a fixed-effect model, as the heterogeneity assessment showed I^2 = 30% and 36% in the recessive and heterozygous models, respectively. In contrast, random-effects models were used in other gene models with high heterogeneity (I^2 > 50%). **Supplementary Fig. 1** presents a summary of the meta-analysis results for the relationships between the IFITM3 rs34481144 frequencies and infection with COVID-19 in the forest plot. Overall, the pooled OR showed that there were no significant associations between the IFITM3 rs34481144 frequencies and infection with COVID-19 in any of the gene models, i.e., the allelic model (OR = 1.14, 95% CI ranging from 0.84 to 1.54), the dominant model (OR = 1.18, 95% CI ranging from 0.80 to 1.76), the recessive model

Table 1
The study characteristics of the 4 papers finally included in the meta-analysis.

Author	Year	Country	Study type	Ethnicity	Age, y		Sample size, N		Sex, Male (%)		Genotyping methods	NOS/AHRQ
					COVID-19	Controls	COVID-19 (Mild/Severe)	Controls	COVID-19	Controls		
Cuesta-Llavona et al.	2021	Spain	Case-control study	Caucasian	66±16	67±11	484 (332/152)	182	276 (57%)	93 (51%)	PCR	8
Gómez et al.	2021	Spain	Case-control study	Caucasian	65.23±15.16	71.25±9.54	311 (230/81)	440	174(56%)	200(48%)	PCR	5
Schönfelder et al.	2021	Germany	Case-control study	Caucasian	58.97±14.50	62.79±13.34	239 (164/75)	253	141(59%)	147(58.1%)	RT-PCR	7
Zhang et al.	2020	China	Single-arm study	Asian	50.29±19.44		80 (56/24)		33(41.25%)		RT-PCR	6

COVID-19: Coronavirus disease 2019; NOS: Newcastle-Ottawa scale; AHRQ: Agency for Healthcare Research and Quality.

(OR = 1.16, 95% CI ranging from 0.82 to 1.63), the heterozygous model (OR = 1.17, 95% CI ranging from 0.89 to 1.53) and the homozygous model (OR = 1.27, 95% CI ranging from 0.69 to 2.32). **Supplementary Fig. 2** provides forest plots for the meta-analysis of patients with COVID-19 stratified by severity (mild vs. severe) in the IFITM3 rs34481144 gene polymorphism. Heterogeneity assessment showed I^2 = 74% and 81% in the dominant and heterozygous models, respectively, and random-effects models were used. In contrast, fixed-effects models were used in other gene models with low heterogeneity (I^2 = 0%). The pooled results showed that the IFITM3 rs34481144 gene polymorphism was not significantly associated with the severity of COVID-19 infection. The results are reported as follows: the allelic model: OR = 1.00, 95% CI ranging from 0.80 to 1.26; the dominant model: OR = 0.85, 95% CI ranging from 0.42 to 1.75; the recessive model: OR = 1.09, 95% CI ranging from 0.71 to 1.69; the heterozygous model: OR = 0.80, 95% CI ranging from 0.33 to 1.97 and the homozygous model: OR = 0.99, 95% CI ranging from 0.61 to 1.62. (**Table 4**)

Sensitivity analysis

The results of the sensitivity analysis were similar to the previously pooled OR in both IFITM3 rs12252 and rs34481144 gene polymorphisms after sequentially omitting each study, which indicated that the results of the present meta-analysis were stabilized. (**Supplementary Fig. 3–6**)

Discussion

To our knowledge, this is the first meta-analysis on the association of IFITM3 gene polymorphisms and susceptibility to COVID-19. Pooled effect estimates using a fixed-effect model indicated a significant association between the IFITM3 rs12252 gene polymorphism and COVID-19 infection in all genetic models. However, stratification by disease severity only showed a significant association in allelic and recessive models. Our results did not support an association between the IFITM3 rs34481144 gene polymorphism and COVID-19 susceptibility or severity in any genetic model.

There were significant associations between the IFITM3 rs12252 gene polymorphism and COVID-19 infection in all of the gene models. However, only the allelic and recessive model showed a significant correlation for the severity of the infection with COVID-19. Nikoloudis et al.[25] collected the allele frequencies of 26 populations from the 1000 Genomes Project and performed correlation analysis with the combined haplotypes of rs12252. The results showed a significant correlation between mortality and the combined haplotype frequencies of the two reference alleles. Additionally, Kim et al.[8] reported a strong relationship between the mortality of COVID-19 and the allele frequency of the rs6598045 SNP of the IFITM3 gene. Since there are few studies on the relationship between the rs6598045 gene polymorphism and COVID-19 susceptibility, this study did not consider the inclusion of the rs6598045 gene polymorphism. Interestingly, Fouladseresht et al.[26] reported that COVID-19 susceptibility was related to individual immune status, which might be closely related to the expression of IFITM3[27].

Furthermore, we found that the SNP rs12252-C variant was critical for the severity of COVID-19, as the allelic and recessive models showed positive results. The synonymous SNP rs12252, the first exon of IFITM3, has been confirmed to be related to the severity of influenza, especially the SNP rs12252-C variant[12,28]. Our findings were in accordance with the recent findings of Alghamdi et al.[6], who found that 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) were associated with the rs12252-G allele, and patients younger than 60 years with this gene had a poor survival rate. Although

Table 2
Genotype frequency of IFITM3 rs12252/rs34481144 gene polymorphism in patients with COVID-19 and the control groups.

SNP	Authors	Genotype										HWE
		COVID-19					Controls					
rs12252 Genotype		**T**	**C**	**TT**	**TC**	**CC**	**T**	**C**	**TT**	**TC**	**CC**	
	Cuesta-Llavona et al. (2021)	913	55	433	47	4	354	10	172	10	0	*P*>0.05
	Gómez et al. (2021)	584	38	276	32	3	854	26	414	26	0	*P*>0.05
	Schönfelder et al. (2021)	452	26	215	22	2	487	19	234	19	0	*P*>0.05
	Zhang et al. (2020)	67	93	15	37	28						
rs34481144 Genotype		**G**	**A**	**GG**	**GA**	**AA**	**G**	**A**	**GG**	**GA**	**AA**	
	Cuesta-Llavona et al. (2021)	597	371	181	235	68	248	116	84	80	18	*P*>0.05
	Schönfelder et al. (2021)	266	212	73	120	46	278	228	75	128	50	*P*>0.05

COVID-19: Coronavirus disease 2019; SNP: single nucleotide polymorphisms; HWE: Hardy–Weinberg equilibrium.

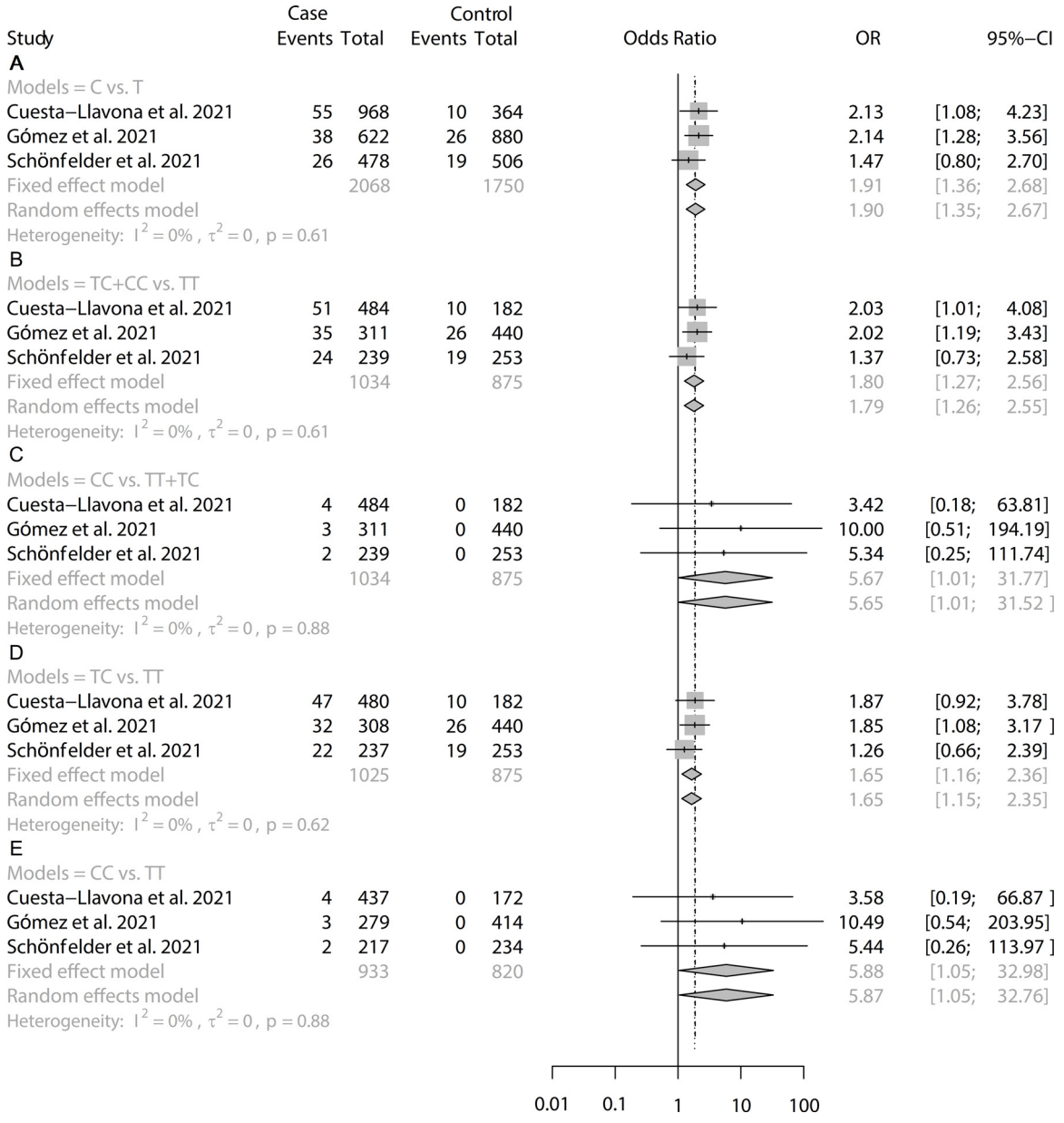

Fig. 2. Forest plot of the association between the IFITM3 rs12252 gene and control: A, C vs. T; B, TC+CC vs. TT; C: CC vs. TT+TC; D: TC vs. TT; E: CC vs. TT.

Table 3
Genotype frequency of IFITM3 rs12252/rs34481144 gene polymorphism in patients with COVID-19 stratified by severity.

SNP	Authors	Genotype											
		N	Mild					N	Severe				
rs12252 Genotype			**T**	**C**	**TT**	**TC**	**CC**		**T**	**C**	**TT**	**TC**	**CC**
	Cuesta-Llavona et al. (2021)	332	630	34	300	30	2	152	283	21	133	17	2
	Gómez et al. (2021)	230	616	24	297	22	1	81	148	14	69	10	2
	Schönfelder et al. (2021)	164	309	19	147	15	2	75	143	7	68	7	0
	Zhang et al. (2020)	56	50	62	10	30	16	24	17	31	5	7	12
rs34481144 Genotype			**G**	**A**	**GG**	**GA**	**AA**		**G**	**A**	**GG**	**GA**	**AA**
	Cuesta-Llavona et al. (2021)	332	406	258	120	166	46	152	191	113	61	69	22
	Schönfelder et al. (2021)	164	186	142	56	74	34	75	80	70	17	46	12

COVID-19: Coronavirus disease 2019; SNP: single nucleotide polymorphisms.

Table 4
Meta-analysis of the association between IFITM3 rs12252/rs34481144 gene polymorphism and COVID-19 susceptibility.

SNP	Comparison	N	Models	Pooled estimate value			Heterogeneity	
				OR (95%CI)	*Z*	*P*	I^2,%	*P*
COVID-19 vs. Controls								
rs12252 Genotype								
	C vs. T	3	Fixed	1.91(1.36–2.68)	3.75	0.0002	0	0.61
	TC+CC vs. TT		Fixed	1.80(1.27–2.56)	3.30	0.0010	0	0.61
	CC vs. TT+TC		Fixed	5.67(1.01–31.77)	1.97	0.0487	0	0.88
	TC vs. TT		Fixed	1.65(1.16–2.36)	2.77	0.0056	0	0.62
	CC vs. TT		Fixed	5.88(1.05–32.98)	2.01	0.0442	0	0.88
rs34481144 Genotype								
	A vs. G	2	Random	1.14(0.84–1.54)	0.81	0.4173	66	0.09
	GA+AA vs. GG		Random	1.18(0.80–1.76)	0.84	0.4028	57	0.13
	AA vs. GG+GA		Fixed	1.16(0.82–1.63)	0.84	0.4014	30	0.23
	GA vs. GG		Fixed	1.17(0.89–1.53)	1.13	0.258	36	0.21
	AA vs. GG		Random	1.27(0.69–2.32)	0.77	0.4422	59	0.12
Mild vs. Severe								
rs12252 Genotype								
	C vs. T	4	Fixed	0.69(0.49–0.97)	−2.15	0.0316	24	0.26
	TC+CC vs. TT		Fixed	0.75(0.50–1.11)	−1.43	0.1515	7	0.36
	CC vs. TT+TC		Fixed	0.43(0.20–0.93)	−2.15	0.0317	0	0.53
	TC vs. TT		Fixed	0.81(0.53–1.23)	−0.97	0.3297	14	0.32
	CC vs. TT		Fixed	0.56(0.23–1.39)	−1.25	0.2119	0	0.46
rs34481144 Genotype								
	A vs. G	2	Fixed	1.00(0.80–1.26)	0.00	0.9963	0	0.39
	GA+AA vs. GG		Random	0.85(0.42–1.75)	−0.43	0.6667	74	0.05
	AA vs. GG+GA		Fixed	1.09(0.71–1.69)	0.39	0.6936	0	0.43
	GA vs. GG		Random	0.80(0.33–1.97)	−0.48	0.6286	81	0.02
	AA vs. GG		Fixed	0.99(0.61–1.62)	−0.03	0.9756	0	0.69

COVID-19: Coronavirus disease 2019; SNP: single nucleotide polymorphisms; OR: odds ratio.

an association between the IFITM3 rs12252/rs34481144 gene polymorphism and susceptibility to COVID-19 was reported, it was not included in this meta-analysis because SARS-CoV-2-negative participants were included. Interestingly, a study published by Lee et al.[29] found that the CC genotype of IFITM3 rs12252 cumulatively contributed to increased mortality with influenza infection.

In contrast, our findings did not support the associations between the IFITM3 rs34481144 gene polymorphism and COVID-19 susceptibility in any of the gene models or the severity of the disease. The rs34481144 (*G*>*A*) mutant results in decreased messenger RNA production and altered IFITM3 levels in peripheral blood monocytes.[30,31] Cuesta-Llavona et al.[21] found a significantly higher frequency of rs34481144 T carriers among COVID-19-positive patients. In the work of Schönfelder et al.[23], the authors indicated that the higher frequency of rs34481144 A-allele carriers was not evident in "severe" COVID-19 patients. In a genotyping analysis of three different patient cohorts, Eisfeld et al.[32] showed that individuals carrying the rs34481144-A allele were approximately 2.6 times more likely to have a severe outcome following influenza virus infection. Although there have been limited reports on the relationship between rs34481144 and COVID-19 susceptibility, Pati et al.[7] speculated that the rs3448114 gene polymorphism might be positively associated with COVID-19 susceptibility and mortality based on existing studies. Interestingly, the distribution of rs3448114 and rs12252 followed the principle of opposite trends, and the recessive genotypes of the two polymorphisms were not inherited together.

Interferon-induced transmembrane protein 3 has activity against influenza A virus, SARS coronavirus, and many other viruses and has emerged as an important innate immune barrier against vertebrate viral infections.[33] It has been reported that IFITM3 may function as an antiviral effector molecule by increasing the "rigidity" of endosomal membranes to limit viral fusion.[34] Additionally, IFITM3 may also prevent viral entry by altering the rate of viral endosome fusion and/or accelerating the transport of endosomal cargo to lysosomes for destruction.[30] Recent studies have highlighted that IFITM3 can inhibit SARS-CoV-2 endocytosis, thereby blocking fusion with the endosomal membrane.[35] Moreover, IFITM3 gene polymorphisms may be closely associated with the selective infection of SARS-CoV-2. It has been reported that the mechanism by which the rs12252-C variant susceptibility to COVID-2019 may be related to the loss of antiviral activity caused

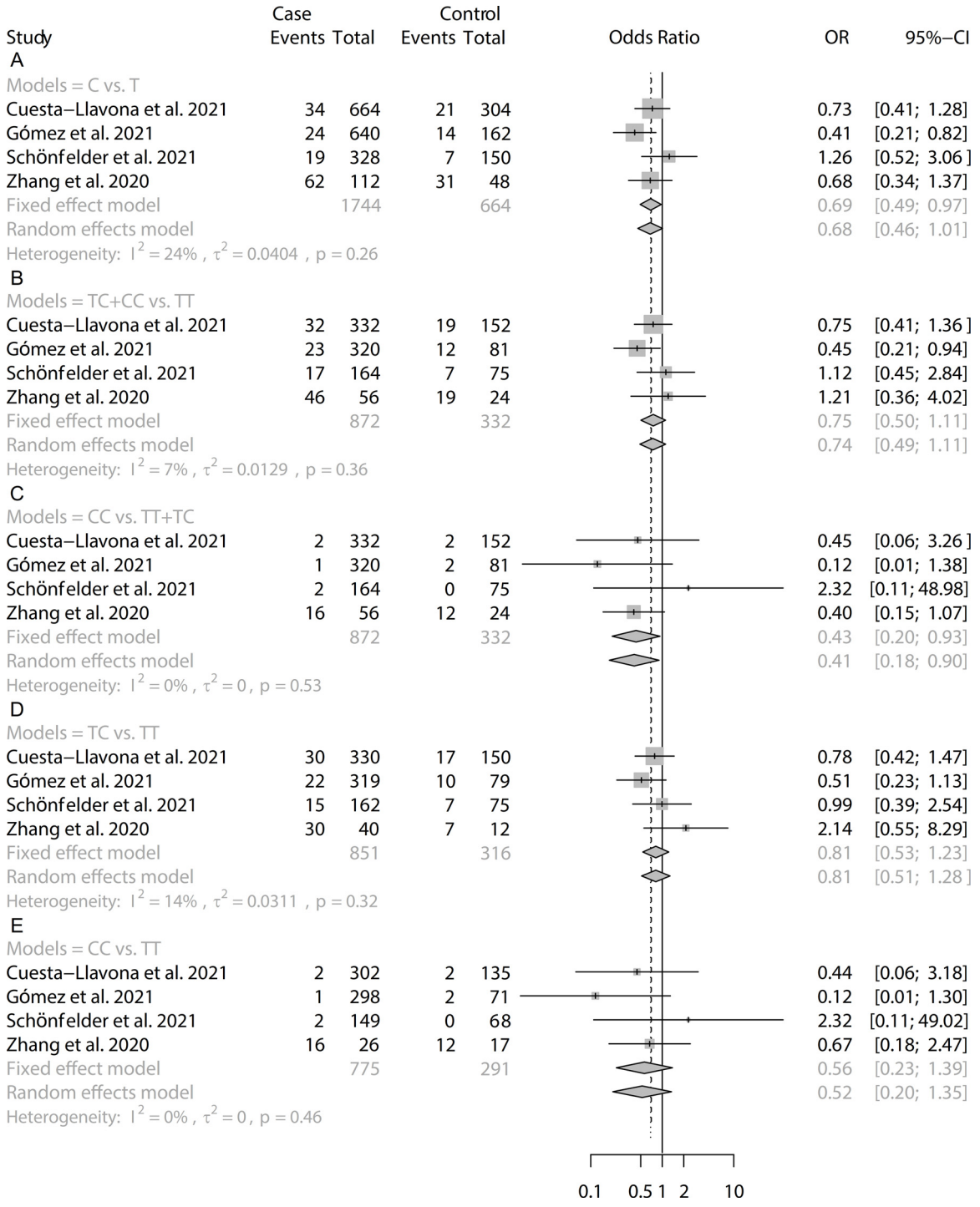

Fig. 3. Forest plot of the IFITM3 rs12252 gene between mild and severe: A, C vs. T; B, TC+CC vs. TT; C: CC vs. TT+TC; D: TC vs. TT; E: CC vs. TT.

by the truncated variant of the 21 amino acids at the N-terminal of the protein.[7] Furthermore, the rs34481144 genotype is resistant to influenza virus by upregulating IFITM3 protein expression[32], which emphasizes that genetic variation (*G*>*A*) may affect the expression of IFITM3 to further interfere with resistance to SARS-CoV-2.

It is well known that allele frequencies vary by ethnicity. Based on the results of the 1000 Genomes Project, we found that the rs12252 mutant allele frequency was 0.177 in the American patients, 0.260 in the African patients, 0.041 in the European patients, 0.147 in the South Asian patients, and 0.528 in East Asia patients. The rs34481144 mutant allele frequency was 0.233 in the Americas, 0.043 in Africa, 0.462 in Europe, 0.207 in South Asia, and 0.006 in East Asia. Interestingly, the rs12252 mutant allele frequency was significantly higher in East Asia than in other populations, while the rs34481144 mutant allele frequency was significantly lower in East Asia than in other populations.[36] Allelic differences in IFITM3 SNPs are directly related to the clinical manifestations after SARS-CoV-2 infection. Our findings suggest that in studies involving European populations, the mutant allele frequency of rs12252 was higher in the COVID-19 group than in the healthy group. However, for the rs34481144 genotype, the COVID-19 group had lower mutant allele frequencies than the healthy group.

Previous research highlights the critical role of genetics in the immune response to vaccines. Genetic factors (also known as heritability) range from 36.0% to 88.5% among the factors that induce vaccine responses.[37] Gene polymorphisms affect the vaccine immune response rate to a certain extent. Understanding the functional and mechanistic effects of these genetic polymorphisms on immune response variation may aid in new vaccine design. For example, Gelder et al.[38] conducted an association study of human leukocyte antigen (HLA) and the humoral immune response to the influenza vaccine. They compared the allele levels of vaccine-immunized normal responders with nonresponders and found that HLA gene polymorphisms affected antibody levels after influenza vaccination. Although the constructive contribution of IFITM3 gene polymorphisms to COVID-19 vaccine design has not been further explored, our aim is to remind medical decision-makers to consider IFITM3 gene polymorphisms when designing future vaccines for COVID-19.

We performed a sensitivity analysis for the IFITM3 rs12252/rs34481144 gene polymorphism in any genetic model. The pooled effect estimates did not change substantially, indicating the robustness of the results. It should be noted that we did not perform the HWE test for the study by Zhang et al.[24] because there was no control group.

There are some limitations in this study. First, IFITM proteins are a family of homologous proteins, and proteins with immune functions include IFITM1–3 and IFITM6. In the present study, we selected the most powerful candidate gene, IFITM3 rs12252/rs34481144, to prevent influenza virus infection, and the remaining related protein genes were too few to be considered. Second, only 4 available primary studies were included, which had a certain bias to the results. Third, different genes were reported to be unevenly distributed in different populations. IFITM3 rs12252 is rare in European populations and common in Asian populations.[39] In contrast with rs12252, IFITM3 rs34481144 was rare in East Asian populations and common in European populations.[40] Theoretically, it was necessary to perform subgroup analysis by population in this study, but there was only one Asian population in the rs12252-related article, and the sensitivity analysis can partially reflect the effect of race on the results. However, the two articles related to rs34481144 were both European populations, so subgroup analysis of the population was not applicable. It is hoped that more studies will be included in the future to make more accurate pooled estimate values for different populations. Finally, based on limited studies and available data, some essential results were not presented, such as publication bias of included articles, association of IFITM3 rs12252/rs34481144 gene polymorphism with mortality, and other genotypes of IFITM3 (e.g., rs6598045). Considering the limited number and inconsistent results of primary studies on the association between the IFITM3 rs12252/rs34481144 gene polymorphism and COVID-19, our results may provide the strongest evidence to date.

Conclusion

This meta-analysis demonstrated that the IFITM3 rs12252 gene polymorphism had a relationship with COVID-19 susceptibility and that the SNP rs12252-C variant was associated with the severity of COVID-19 infection. The study of genetic polymorphisms in susceptibility to COVID-19 could help vaccine developers better identify clinical trial participants and treatments.

Author contributions

Lanye He and Nanyang Liu are in charge of the conception and design; Yapeng Li and Lanlan Wei extracted the data; Yapeng Li, Nanyang Liu and Jiahui Sun conducted the analysis; and Yapeng Li and Nanyang Liu wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest Statement

The authors have declared that no competing interests exist.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.04.029.

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