IFITM3 rs12252 polymorphism and coronavirus disease 2019 severity: A meta-analysis

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Abstract. Interferon-induced transmembrane protein 3 (IFITM3) serves a critical role in the immune defense against viral infection, including that of severe acute respiratory syndrome coronavirus 2. To the best of our knowledge, the association between *IFITM3* rs12252 polymorphism and coronavirus disease 2019 (COVID-19) severity has not been determined. In the present study, a meta-analysis of published case-control studies assessing the association between the *IFITM3* rs12252 polymorphism and COVID-19 severity was performed. PubMed, EMBASE, China National Knowledge Infrastructure, Wanfang and preprint servers were searched up to March 30, 2022. A fixed-effect model was used to calculate odds ratio (OR) and 95% confidence interval (95% CI). Analyses were conducted for additive, dominant and recessive genetic models. A total of five studies were identified, with 1,443 mild-to-moderate cases and 667 severe cases, including 121 deaths. Overall, the CC genotype of *IFITM3* rs12252 was associated with increased risk of severe COVID-19 (OR=1.97, 95% CI, 1.06-3.69) and mortality (OR=4.61, 95% CI, 1.44-14.75) compared with the CT/TT genotypes. Stratified analysis by ethnicity revealed that this association was strong in Chinese individuals (severity, OR=2.84, 95% CI, 1.34-6.04; mortality, OR=7.91, 95% CI, 1.29-48.44), but not notable in Caucasians (severity, OR=0.79, 95% CI, 0.23-2.80; mortality, OR=2.16, 95% CI, 0.37-12.55). A significant association with mortality was observed in Caucasians when comparing patients with the C allele of *IFITM3* rs12252 and those without (CC/CT vs. TT: OR=1.73, 95% CI, 1.09-2.75). The results suggested that the *IFTM3*-rs12252 CC genotype is associated with severe COVID-19 and mortality in Chinese individuals and the *IFTM3*-rs12252 C allele may be associated with COVID-19 mortality in Caucasians. Large-scale studies are needed to confirm the association in different global populations.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a major health threat all over the world. As of 8 April 2022, a cumulative total of 494,587,638 COVID-19 cases were reported globally, including 6,170,283 deaths, according to the World Health Organization (1).

The spectrum of SARS-CoV-2 infection ranges from asymptomatic to clinical symptoms, including fever, dry cough, dyspnea, fatigue, muscle pain, headache, diarrhea, loss of taste and/or smell, nasal obstruction and runny nose (2). The majority of patients with COVID-19 have a mild or moderate form. However, infection in certain patients becomes severe, presenting with respiratory failure. In the most severe cases, acute respiratory distress and multiple organ dysfunction syndrome, coagulation abnormalities and shock have been observed (2).

Older age (>60 years), unvaccinated, associated comorbidities (such as cardiovascular disease, hypertension, chronic pulmonary disease, diabetes, chronic liver and kidney disease and malignancy), immunodeficiency, obesity and heavy smoking are key host risk factors for severe COVID-19 (2). Apart from these factors, studies have shown that host genetics may also be key in the development of severe COVID-19 and should be considered in COVID-19 prognosis (3,4).

Interferon-induced transmembrane proteins (IFITM1, 2 and 3) are stimulated by interferon and serve a critical role in the immune defense against viral infection (5-7). Among them, IFITM3 has the strongest antiviral effect. It blocks fusion with the host cellular membranes in a broad spectrum of enveloped viruses, such as SARS-CoV, influenza, human immunodeficiency virus (HIV), Ebola and Zika (5-7). The human *IFITM3*,

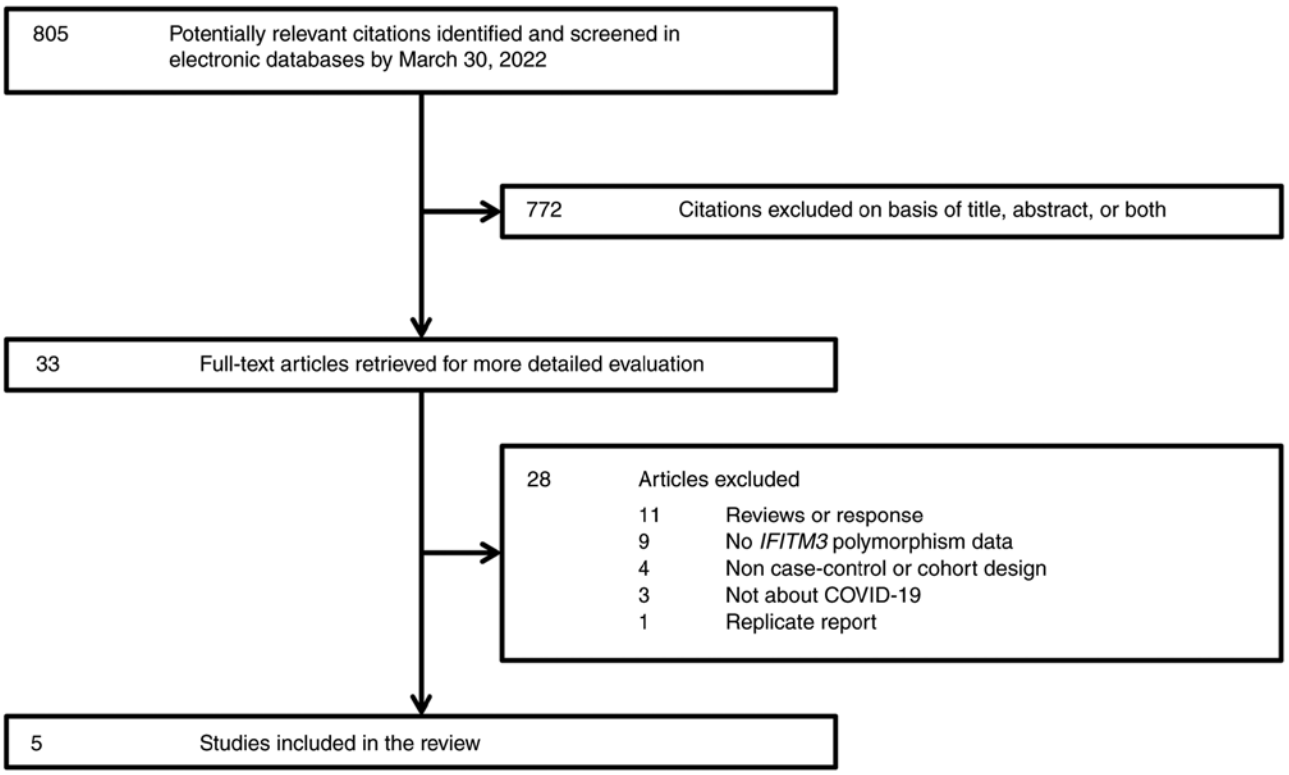

Figure 1. Flow diagram of the study selection process. *IFITM3*, interferon-induced transmembrane protein 3; COVID-19, coronavirus disease 2019.

located on chromosome 11p15.5, is composed of two exons and one intron. The single nucleotide polymorphism (SNP) rs12252-C allele of *IFITM3* truncates the protein, leading to decreased restriction of virus replication *in vitro* (8). A meta-analysis indicated that this SNP may be associated with severe influenza infection (9).

Recently, studies have investigated the association of the *IFITM3* rs12252 polymorphism with COVID-19 severity (10-14). However, the findings are inconsistent. Such inconsistency may be due partly to population differences in genotype distribution, insufficient power, a small effect of the *IFITM3* rs12252 polymorphism on COVID-19 severity and false-positive results. Therefore, a meta-analysis of published studies was performed to investigate whether the *IFITM3* rs12252 polymorphism is associated with COVID-19 severity.

Materials and methods

Searching. Major databases and preprint servers, including PubMed (pubmed.ncbi.nlm.nih.gov), EMBASE (https://www.embase.com), China National Knowledge Infrastructure (https://www.cnki.net), Wanfang (https://www.wanfangdata.com.cn), MedRxiv (https://www.medrxiv.org) and BioRxiv (https://www.biorxiv.org), were searched for studies concerning *IFITM3* and COVID-19. The last search update was performed on March 30, 2022. The search strategy is supplied in Appendix S1. No language restrictions were applied. Manual searching was conducted for references of relevant reviews and included articles.

Study selection. Studies that were included met the following criteria: i) Evaluated the association between *IFITM3* rs12252 polymorphism and COVID-19 severity; ii) cohort or case-control study; iii) contained sufficient data to calculate odds ratio (OR) and iv) COVID-19 infection was clearly defined. COVID-19 was diagnosed based on symptoms and laboratory tests. Laboratory confirmation was defined as a positive result using reverse transcription PCR, serological tests (anti-SARS-CoV-2 IgM) or both. Studies were excluded when they were: i) Review articles, comments, responses or case reports; ii) not associated with *IFITM3* rs12252 polymorphism and COVID-19 severity or iii) non-human studies. When there were multiple studies involving the same or overlapping population, only the most recent study with the largest sample size was included. A total of two authors (KY and JW) assessed each study independently. The titles and abstracts of all citations were screened. Then, full texts of relevant citations were examined for inclusion. Disagreements between reviewers were resolved through discussion with a third author (WW). Fig. 1 outlines the study selection process that led to the final five studies in the present meta-analysis.

Data extraction and quality assessment. A total of two authors (KY and JW) independently extracted the following information from each included study: Study design, ethnicity, definition and number of mild-to-moderate and severe cases, age, sex, confounding factors by matching or adjustment, genotyping method, frequency of genotype and consistency of genotype frequencies with Hardy-Weinberg equilibrium (HWE) in control subjects without COVID-19 or mild-to-moderate COVID-19 cases.

A total of two authors (KY and JW) independently assessed the methodological quality of each included case-control study using the Newcastle Ottawa Scale (NOS) for selection,

comparability and exposure. The NOS scores ranged from 0 to 9 and a score ≥7 indicated high quality (15). Disagreements were resolved as aforementioned.

Statistical analysis. ORs with their corresponding 95% confidence intervals (CIs) were calculated to assess the strength of the association between the *IFITM3* rs12252 polymorphism and COVID-19 severity. When mortality data was available, the association between *IFITM3* rs12252 polymorphism and COVID-19 mortality was also assessed. The associations were examined under three genetic models: Additive (CC vs. TT), dominant (CC/CT vs. TT) and recessive (CC vs. CT/TT). HWE was evaluated using χ^2 test and P<0.05 was considered to indicate a statistically significant difference. Sensitivity analysis was performed using the one-study remove approach to assess the impact of each study on the combined effect.

Between-study heterogeneity was evaluated using Cochran's Q test and I^2 statistic. If the P-value for the Q test was <0.10 or if the I^2 statistic was ≥50%, significant heterogeneity was considered and the random-effect model was used. Otherwise, the fixed-effect model was used. Egger's test and Begg's funnel plot were not used to provide a diagnosis of the potential publication bias as there were only five studies included in the meta-analysis (16). All statistical analyses were performed with Stata 15.0 (StataCorp LP). A two-sided P<0.05 was considered to indicate a statistically significant difference. The performance and reporting of the present meta-analysis complied with the Meta-analyses Of Observational Studies in Epidemiology statement (Appendix S2) (17).

Results

Characteristics of included studies. A total of five independent studies were identified regarding *IFITM3* rs12252 polymorphism and COVID-19 severity (Fig. 1). These five studies were published from 2020 to 2021, with four in the English language and one in Chinese. A total of two studies were conducted in the Chinese population (10,11), one in the Saudi population (12), one in the Spanish population (13) and one in the German population (14). In total, 2,110 patients with COVID-19 were included. Of these, 1,443 were mild-to-moderate cases and 667 were severe cases, including 121 deaths. The definition of severity was not identical across studies (Appendix S3). All studies but one showed that patients with severe cases had older ages compared with mild-to-moderate cases (14). A total of three studies genotyped healthy controls or controls without COVID-19 (11,13,14). The *IFITM3* rs12252 C allele frequency was higher in the Chinese population compared with Caucasian population (49.2-55.4% vs. 2.8-9.6%, respectively; Table I). All studies were consistent with HWE. Detailed characteristics of the five studies are described in Table I. NOS scores of all included studies ranged from 8 to 9, which indicated good quality (Appendix S4).

Association between IFITM3 rs12252 polymorphism and COVID-19 severity. Under each genetic model, no significant heterogeneity was detected by the Q test and I^2 statistic (Fig. 2A-C). Thus, in the meta-analysis, the fixed-effect model was used for each genetic model. Only under the

Table I. Characteristics of studies included in the meta-analysis.

			Mild-to-moderate			Severe						
Study	Population	Genotype method	Male, %	Age, years	CC/CT/TT	Male (%)	Age, years	CC/CT/TT	Died CC/CT/TT	Control CC/CT/TT	Factors adjusted	C allele, %	HWE P-value
Zhang *et al*, 2020 (10)	Chinese	Sequencing	42.9	43.5 (34.0-56.5)	16/30/10	37.5%	67.5 (57.8-74.3)	12/7/5	2/1/0	NA	Age	55.4	>0.5
Pan *et al*, 2021 (11)	Chinese	Sequencing	54.2	39.5	126/203/105	50.0%	51.8	7/2/3	3/0/0	15/34/16	Age	49.2	>0.7
Alghamdi *et al*, 2021[a] (12)	Saudi	Taqman	64.0	30.0	3/82/372	56.0%	59.0	1/73/330	0/21/56	NA	Age, sex	9.6	>0.5
Cuesta-Llavona *et al*, 2021 (13)	Spanish	Taqman	59.0	64.0±16.0	2/30/300	74.0%	67.0±16.0	2/17/133	1/5/32	0/10/172	Age, sex	2.8	>0.7
Schönfelder *et al*, 2021 (14)	German	Sequencing	52.4	57.0 (18.0-94.0)	2/15/147	73.3%	64.0 (26.0-99.0)	0/7/68	NA	0/19/234	Age, sex	3.8	>0.5

Age is presented as median (interquartile range) for Zhang *et al* (10), mean for Pan *et al* (11) and Alghamdi *et al* (12), mean ± standard deviation for Cuesta-Llavona *et al* (13) and median (range) for Schönfelder *et al* (14). [a]Age and sex were estimated based on baseline information. C allele frequency of the *IFITM3* rs12252 polymorphism and HWE were calculated in controls without COVID-19 or else in mild-to-moderate cases. HWE, Hardy-Weinberg equilibrium; NA, not available.

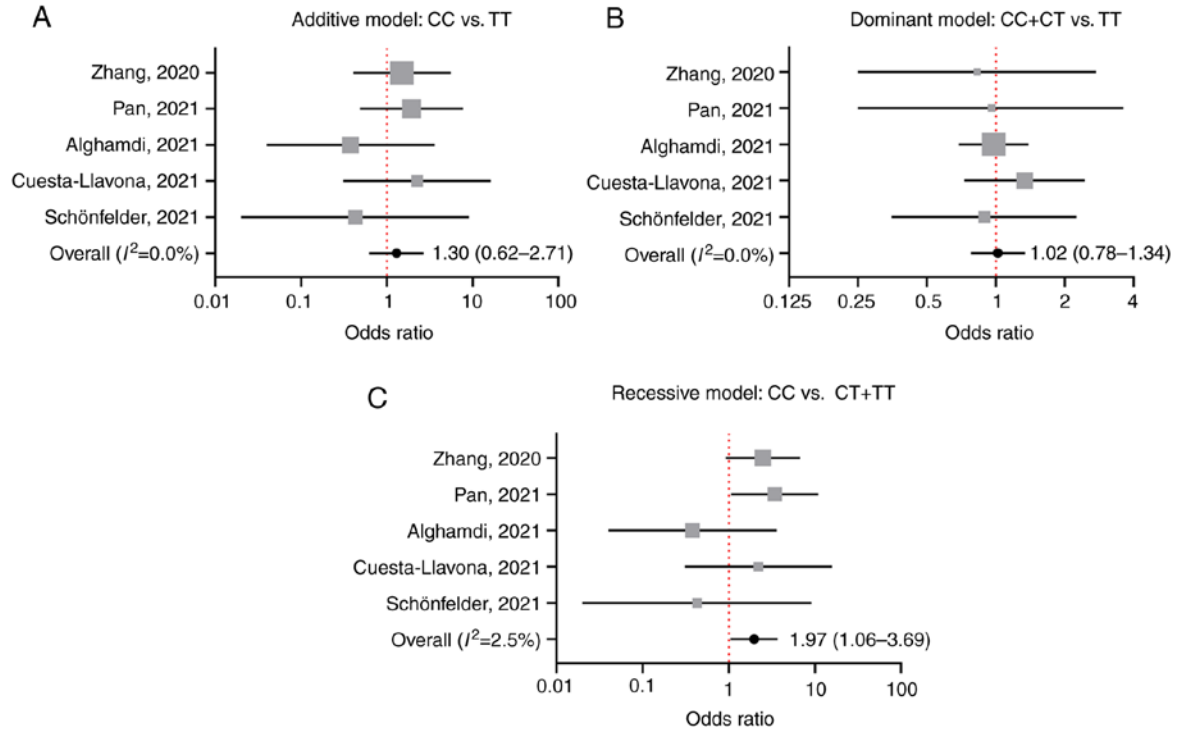

Figure 2. Forest plots for interferon-induced transmembrane protein 3 rs12252 polymorphism and coronavirus disease 2019 severity using (A) additive, (B) dominant and (C) recessive model. The overall odds ratios (with 95% confidence intervals) are labeled.

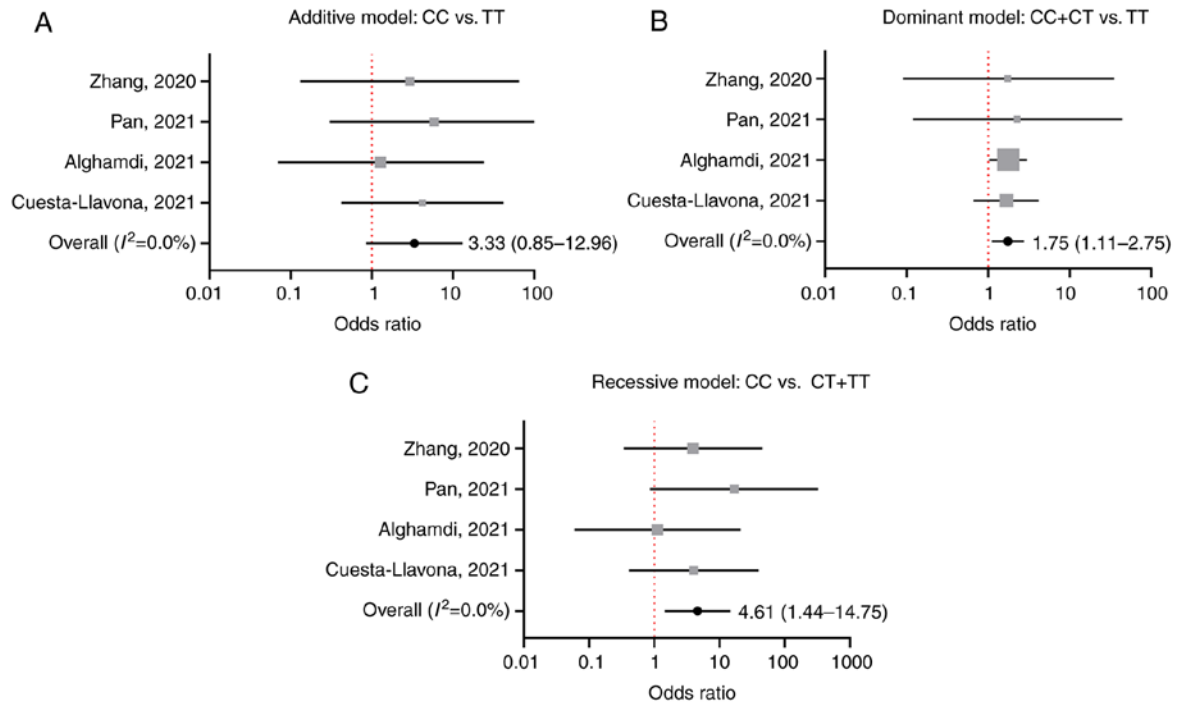

Figure 3. Forest plots for interferon-induced transmembrane protein 3 rs12252 polymorphism and coronavirus disease 2019 mortality using (A) additive, (B) dominant and (C) recessive model. The overall odds ratios (with 95% confidence intervals) are labeled.

recessive model (CC vs. CT/TT) was a significant association between the *IFITM3* rs12252 polymorphism and COVID-19 severity observed. Overall, the OR of developing severe COVID-19 was 1.97 (95% CI, 1.06-3.69) in patients carrying the CC genotype compared with those with other genotypes (CT/TT; Fig. 2C). The association was not observed under the additive (CC vs. TT) or the dominant model (CC/CT vs. TT; Fig. 2A and B).

The Chinese population had a significantly higher frequency of *IFITM3* rs12252 C allele compared with the Caucasian population. Stratified analysis by ethnicity showed that only in the Chinese population was the CC genotype

Table II. Meta-analysis of studies on associations of the *IFITM3* rs12252 polymorphism with COVID-19 severity and mortality.

Overall/stratified analysis	No. of studies	No. of patients	Additive model (CC vs. TT)			Dominant model (CC/CT vs. TT)			Recessive model (CC vs. CT/TT)		
			OR (95% CI)	Z-value	P-value	OR (95% CI)	Z-value	P-value	OR (95% CI)	Z-value	P-value
Severity (severe vs. mild/moderate)											
Overall	5	2,110	1.30 (0.62-2.71)	0.70	0.487	1.02 (0.78-1.34)	0.17	0.862	1.97 (1.06-3.69)	2.13	0.033
Chinese population	2	526	1.70 (0.66-4.39)	1.10	0.270	0.88 (0.36-2.14)	0.27	0.784	2.84 (1.34-6.04)	2.72	0.007
Caucasian population	3	1,584	0.80 (0.23-2.83)	0.35	0.730	1.04 (0.78-1.38)	0.27	0.788	0.79 (0.23-2.80)	0.36	0.720
Mortality (died vs. survived)											
Overall	4	1,871	3.33 (0.85-12.96)	1.73	0.083	1.75 (1.11-2.75)	2.43	0.015	4.61 (1.44-14.75)	2.58	0.010
Chinese population	2	526	4.31 (0.51-36.34)	1.34	0.180	2.00 (0.24-16.55)	0.64	0.521	7.91 (1.29-48.44)	2.24	0.025
Caucasian population	2	1,345	2.37 (0.41-13.87)	0.96	0.337	1.73 (1.09-2.75)	2.33	0.020	2.16 (0.37-12.55)	0.86	0.391

OR, odds ratio; CI, confidence interval; *IFITM3*, interferon-induced transmembrane protein 3.

associated with severe COVID-19 (CC vs. CT/TT; OR=2.84; 95% CI, 1.34-6.04). This association was not observed in the Caucasian population (Table II).

Association between IFITM3 rs12252 polymorphism and COVID-19 mortality. A total of four studies included *IFITM3* rs12252 polymorphism data for patients who died with COVID-19. In total, 121 patients who died and 1,989 who survived were included to assess its association with COVID-19 mortality. Under each genetic model, no significant heterogeneity was detected and the fixed model was used (Fig. 3A-C). Overall, the CC genotype of *IFITM3* rs12252 was strongly associated with increased COVID-19 mortality risk compared with the CT/TT genotype [recessive model (CC vs. CT/TT); OR=4.61; 95% CI, 1.44-14.75; Fig. 3C]. Compared with the TT genotype, the CC/CT genotype was associated with increased COVID-19 mortality risk [dominant model (CC/CT vs. TT); OR=1.75; 95% CI, 1.11-2.75; Fig. 3B]. This trend was observed when comparing the CC and TT genotype but it was not statistically significant [the additive model (CC vs. TT); OR=3.33; 95% CI, 0.85-12.96; Fig. 3A].

Stratified analysis by ethnicity showed that in the Chinese population the CC genotype of *IFITM3* rs12252 was strongly associated with increased COVID-19 mortality risk compared with the CT/TT genotype (CC vs. CT/TT; OR=7.91; 95% CI, 1.29-48.44). In the Caucasian population, the CC/CT genotype was associated with increased COVID-19 mortality risk compared with the TT genotype (CC/CT vs. TT; OR=1.73; 95% CI, 1.09-2.75; Table II). Using other genetic models, the association between *IFITM3* rs12252 polymorphism and COVID-19 mortality was not observed in either the Chinese or Caucasian population (Table II).

Sensitivity analysis. Sensitivity analysis was performed to assess the impact of each study on the pooled results by omitting individual studies in turn (Table III). The pooled OR of developing severe COVID-19 was sensitive to the two Chinese studies (10,11) and for COVID-19 mortality was sensitive to Pan *et al* (11) and Alghamdi *et al* (12).

Discussion

Recently, the association between the *IFITM3* rs12252 polymorphism and COVID-19 severity has been investigated in several studies but the results were inconsistent (10-14). To the best of our knowledge, the present study is the first meta-analysis conducted on the aforementioned association. The current meta-analysis, which pooled five studies with 2,110 patients, showed that the CC genotype of *IFITM3* rs12252 was associated with increased risk of severe COVID-19 and mortality. Subgroup analyses revealed that this association was strong in the Chinese population. Larger-scale studies are required to determine whether genotyping for rs12252 SNP of *IFITM3* in Chinese and other Asian patients infected with SARS-Cov-2 predicts those who might progress to severe disease. Useful tools combining this SNP with other risk factors may be developed to improve prognosis of the patients by early targeted intervention.

Notably, the CC genotype of *IFITM3* rs12252 is rare in Europeans (0.3%) and common in Asians (25-44%) (8,18).

Table III. Sensitivity analysis using the one-study remove approach.

	Additive model (CC vs. TT)			Dominant model (CC/CT vs. TT)			Recessive model (CC vs. CT/TT)		
Study omitted	OR (95% CI)	Z-value	P-value	OR (95% CI)	Z-value	P-value	OR (95% CI)	Z-value	P-value
Severity									
Overall (5 studies)	1.30 (0.62-2.71)	0.70	0.487	1.02 (0.78-1.34)	0.17	0.862	1.97 (1.06-3.69)	2.13	0.033
Zhang *et al*, 2020 (10)	1.21 (0.50-2.96)	0.42	0.673	1.04 (0.78-1.37)	0.25	0.803	1.67 (0.74-3.79)	1.24	0.217
Pan *et al*, 2021 (11)	1.08 (0.44-2.63)	0.17	0.865	1.03 (0.78-1.36)	0.19	0.849	1.58 (0.75-3.35)	1.19	0.233
Alghamdi *et al*, 2021 (12)	1.57 (0.70-3.49)	1.10	0.272	1.10 (0.71-1.71)	0.42	0.674	2.40 (1.23-4.69)	2.57	0.010
Cuesta-Llavona *et al*, 2021 (13)	1.19 (0.54-2.64)	0.44	0.660	0.96 (0.71-1.30)	0.27	0.788	1.95 (1.01-3.78)	1.98	0.048
Schönfelder *et al*, 2021 (14)	1.42 (0.66-3.08)	0.90	0.371	1.04 (0.78-1.38)	0.26	0.795	2.18 (1.14-4.19)	2.34	0.019
Mortality									
Overall (4 studies)	3.33 (0.85-12.96)	1.73	0.083	1.75 (1.11-2.75)	2.43	0.015	4.61 (1.44-14.75)	2.58	0.010
Zhang *et al*, 2020 (10)	3.47 (0.79-15.28)	1.64	0.101	1.75 (1.11-2.77)	2.40	0.016	4.90 (1.34-17.96)	2.40	0.017
Pan *et al*, 2021 (11)	2.56 (0.54-12.21)	1.18	0.238	1.73 (1.10-2.74)	2.36	0.018	2.76 (0.68-11.11)	1.43	0.154
Alghamdi *et al*, 2021 (12)	4.27 (0.81-22.55)	1.71	0.087	1.74 (0.74-4.06)	1.28	0.202	6.63 (1.61-27.38)	2.61	0.009
Cuesta-Llavona *et al*, 2021 (13)	3.12 (0.63-15.48)	1.39	0.163	1.77 (1.06-2.98)	2.17	0.030	4.77 (1.25-18.21)	2.29	0.022

OR, odds ratio; CI, confidence interval.

Thus, it is possible that the power of the present meta-analysis may have been insufficient to detect an effect of the CC genotype in the Caucasian population. This was indicated by a lower but statistically significant OR regarding COVID-19 mortality when patients with CC/CT and TT genotypes were compared in the Caucasian population (OR=1.73; 95% CI, 1.09-2.75). Similar results have been reported for Caucasian patients with influenza, in which studies found no or weak association between *IFITM3* rs12252 polymorphism and disease severity (19,20).

IFITM3 is a virus restriction factor mediating cellular resistance to multiple classes of enveloped viral pathogens that enter cells via the acidic endosome (7). IFITM3 inhibits human coronaviruses, including SARS-CoV-1 and Middle East respiratory syndrome coronavirus, as well as SARS-CoV-2 (21,22). Previous studies showed an increased homozygosity of the minor C allele of SNP rs12252 in *IFITM3* in patients with severe viral infection, such as influenza (18), cytomegalovirus (23), enterovirus (24), Hantaan virus (25) and HIV (26). SNP rs12252-C allele encodes a splice acceptor site of the human *IFITM3* gene. Everitt *et al* (8) found that the rs12252-C allele may be associated with a truncated protein with an N-terminal 21 amino acid deletion, which may lead to decreased restriction of virus replication *in vitro*. However, other evidence does not support the hypothesis that CC genotype carriers express truncated *IFITM3* (27); full-length transcript/protein is dominant in all rs12252 genotypes (27). It is hypothesized that rs12252 may be in linkage disequilibrium with a causative SNP near the *IFITM3* locus.

The primary limitation of the present meta-analysis is that it only included five studies with a relatively small size. Thus, the findings in the current meta-analysis are not robust. Sensitivity analysis in the present study also indicated this. Larger cohort studies are needed to confirm the genetic association with COVID-19 severity. As with most meta-analyses, another limitation of the present study is that it is based on unadjusted estimates. Individual information was not available to adjust for confounding factors, such as age, sex and underlying diseases. Finally, all patients included in the present meta-analysis were infected with early strains of SARS-CoV-2 and vaccination coverage was relatively low at that time. Whether and to what extent *IFITM3* rs12252 polymorphism has an effect on COVID-19 needs to be investigated as the virus mutates and herd immunity develops (28-30).

In conclusion, the present meta-analysis suggested that *IFTM3*-rs12252 CC genotype was significantly associated with increased risks of severe COVID-19 and mortality in the Chinese population and that the *IFTM3*-rs12252 C allele may be associated with increased risk of COVID-19 mortality in the Caucasian population. Large-scale studies are needed to confirm the genetic association with COVID-19 severity in different global populations.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

KY, JW, HL and WW conceived and designed the study, collected, analyzed and interpretated data and wrote and revised the manuscript. KY and WW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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