Ассоциация полиморфного варианта гена интерферон-индуцируемого трансмембранного белка-3 (rs12252) с COVID-19: мета-анализ

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Аннотация

В настоящее время точная связь между полиморфизмами гена *IFITM3* и восприимчивостью к COVID-19 до конца не изучена. Кроме того, результаты многочисленных исследований противоречивы, поэтому мы провели мета-анализ и обобщили имеющиеся данные. Наши результаты не подтвердили связь полиморфизма rs12252 гена *IFITM3* с тяжестью COVID-19.

Ключевые слова: коронавирусная инфекция; COVID-19; SARS-CoV-2; полиморфизм; ген интерферон-индуцируемого трансмембранного белка-3; *IFITM3*; rs12252.

Association between the interferon-induced transmembrane protein 3 gene (IFITM3) rs12252 and COVID-19

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that first appeared in Wuhan City, Hubei Province, China in December 2019 and has rapidly spread around the world. It is currently required to understand why a significant number of people develop a critical illness, ending in death (Zhang Y. et al., 2020). New research shows that differences in genotypes between individuals and host genetic factors may also contribute to differences in COVID-19 phenotypes (Alghamdi J. et al., 2021).

The interferon-induced membrane protein family (IFITM 1-5) plays a critical role in protecting adaptive and innate immunity against microbial infection. The interferon-induced IFITM3 gene is a strong candidate gene for preventing multiple influenza viruses. IFITM3 protein inhibits hemifusion of the viral membrane between the host and the cytoplasm of the viral cell. It can block the formation of fusion pores between the virus and host membranes, preventing the virus from penetrating the cell membrane (Schönfelder K. et al.. 2021).

Various studies have established that single nucleotide polymorphisms (SNPs) in the IFITM3 gene are associated with differences in expression, susceptibility, and severity of influenza or other viral infections (Cuesta-Llavona E. et al. , 2021). A genetic variant of the interferon-induced transmembrane protein 3 (IFITM3) gene has been associated with the severity of COVID-19, in particular with the single nucleotide polymorphism rs12252.(Zhang Y. et al.,2020). It is mechanistically predicted that the rs12252 SNP alters the splicing acceptor site resulting in a truncated and mislocalized IFITM3 protein that lacks the first 21 N-terminal amino acids (Δ21IFITM3) (Schönfelder K. et al.. 2021).
Various studies have established that single nucleotide polymorphisms (SNPs) in the IFITM3 gene are associated with differences in expression, susceptibility, and severity of influenza or other viral infections. SNP rs12252 T/C has been associated with avian influenza virus severity (Pan Y. et al., 2017; Martins J. S. C. et al., 2020). Some authors have shown that the genetic variant of the interferon-induced transmembrane protein 3 (IFITM3) gene was associated with the severity of COVID-19, in particular, with the single nucleotide polymorphism rs12252. Variant C of the rs12252 allele of the IFITM3 gene is recognized as a risk factor for hospitalization with COVID-19 (but not in the intensive care unit) (Gómez J. et al., 2021). Also, some authors have found that this allele may contribute to the severity of COVID-19 in a population infected with SARS-CoV-2 and covering all COVID-19 phenotypes (Alghamdi J. et al., 2021). Thus, the difference in the clinical manifestations of COVID-19 may be associated with gene variants that control the host's defense mechanisms against the virus.

At this moment, the exact association between IFITM3 gene polymorphisms and susceptibility to COVID-19 has not been established. Numerous studies show conflicting results, so we decided to conduct a systematic review and summarize the available data.

Methods

Literature search method

We performed a bioinformatic search of literature related to the rs12252 polymorphism of the IFITM3 gene in the Web of science, Science Direct, NCBI Pubmed, SNP, Frontiers databases. The main text words were SARS-CoV-2, COVID-19, coronavirus disease, variant genes, COVID-19 IFITM3 rs 12252, COVID-19 IFITM3, rs 12252.

Paper selection

All selected 62 articles were original and taken from the search retrieved from the search. The following exclusion criteria were then used for papers not eligible for inclusion in this meta-analysis.

Inclusion Criteria:

1. Research based on human infection with the coronavirus.
2. Studies on SARS-CoV-2 discussing the association of this disease with the IFITM3 gene and the mechanism of cellular infection.
3. Studies including case-control.
4. Studies with direct mention of rs-12252 and the IFITM3 gene.
5. Studies reporting an association between IFITM3 rs12252 gene polymorphisms and susceptibility to COVID-19
6. Studies reporting an association between IFITM3 gene polymorphisms and COVID-19 severity

Exclusion Criteria:

1. Human studies with other viruses such as Middle East Respiratory Syndrome and influenza virus
2. Editorial letters, feature reports, technical notes, meta-analyses, reviews and systematic reviews.
3. Studies on COVID-19 that did not discuss the association of this disease with the IFITM3 gene and the mechanism of cellular infection.
4. Studies without allele and genotype frequencies
5. Studies with division into groups according to the severity of the disease

Determining the severity of the disease

Due to differences in the classification of COVID-19 disease severity among the included studies, we adopted all patient classifications defined by individual studies, and groups in our work were formed according to the WHO COVID-19 severity classification of all patients into two groups: mild and severe cases.

Mild type: outpatients, mild clinical symptoms, COVID-19 with fever, respiratory symptoms, and pneumonia on imaging.

Severe type: symptoms of acute respiratory distress syndrome (ARDS), septic shock, oxygen saturation <93%, mechanically ventilated respiratory failure, shock, or other organ failure (Zhang Y. et al., 2020).

Study selection and review process

The study selection and review process were carried out by both of us independently. When selecting and reviewing studies for meta-analysis, the following criteria were taken into account:

study type, clinical results and study results, study population, statistically significant results, relevance of the topic, allele and genotype frequencies. Clinical and research results refer to the IFITM3 gene and rs-12252, which is associated with susceptibility to SARS-CoV-19. The relevance of the topic was assessed primarily according to the above inclusion and exclusion criteria. Articles were then further screened by determining whether the article directly mentioned the IFITM3 gene of interest associated with COVID-19 infection or rs-12252.

Statistical analysis

All statistical analyzes were performed using the RevMan 5.4 software. All publications included in the meta-analysis had controls in Hardy-Weinberg equilibrium and were assessed using the $\chi 2$ test.

We calculated the aggregate odds ratio (OR) and a 95% confidence interval (95% CI) to estimate association strength using fixed and random effects models. A chi-square test was then applied to evaluate Hardy-Weinberg equilibrium (HWE) for genotype frequencies, and a P value of less than 0.05 to determine significance. The effects of the rs12252 polymorphism of the IFITM3 gene were studied in accordance with the following five genetic models: dominant inheritance model (CC+TC vs TT genotype), recessive inheritance model (CC vs TC+TT), allelic model (C vs T), homozygous model (CC vs TT), heterozygous model (TC vs TT). Literature review identified other IFITM3 gene polymorphisms associated with COVID-19 severity, but there was not enough input data to include them in the meta-analysis. Data from each model were calculated as a measure of odds ratio (OR) and 95% confidence interval (CI).

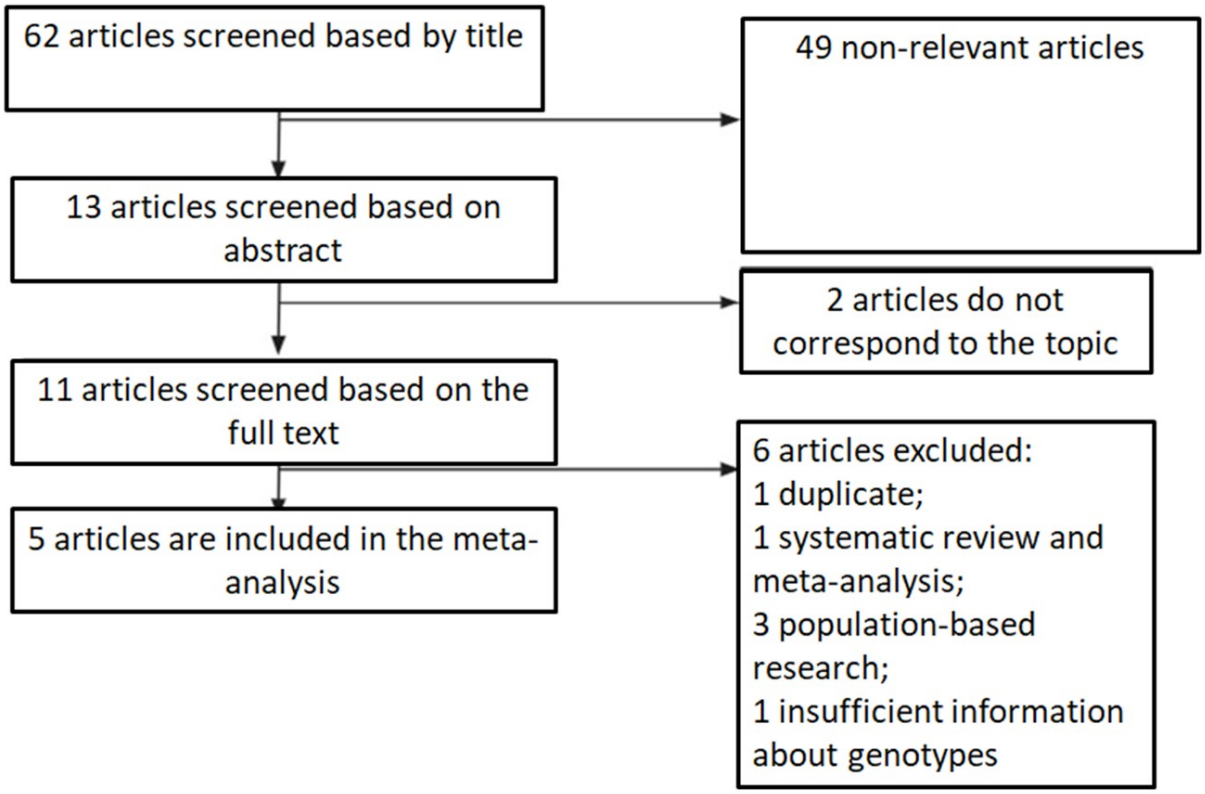
The heterogeneity of the studies was assessed using the $\chi 2$ and I2 criteria in the Revman 5.4 program. The value of $I2<25\%$ - low level of heterogeneity, I2 in the range from 25 to 50% was considered an indicator of moderate heterogeneity, and $I2>50\%$ meant high heterogeneity. With high heterogeneity of the results, the OR was calculated by the method of inverse dispersion with non-fixed outcomes according to the OR with CI 95%. We used a Z test to conduct pooled ORs and considered a P value of less than 0.05 to indicate statistical significance.

The bias associated with the preferred publication of positive study results (publication bias) was not assessed due to the number of studies less than ten.

Results

The search resulted in 62 articles screened based by title. 49 articles non-relevant articles (Fig. 1). 13 articles screened based on abstract. 2 articles do not correspond to the topic. 11 articles screened based on the full text. We removed 6 articles from these articles. The one article was a duplicate of another from different databases. One article was a systematic review and

meta-analysis. Three more articles were not eligible due to the fact that the study was conducted at the population level with the participation of different ethnic groups, and also combined other SNPs without specifying genotypes. Allele frequencies were given in different populations without specifying the number of individuals studied. Finally, one more article was rejected by us, as it did not have enough data to be included in the meta-analysis, only generalized results were given without specific numbers. We received 5 articles for further analysis.



Flow chart depicting literature search and selection process

The study characteristics are presented in Table 1. A total of 1975 patients were registered. Of these, 736 patients (37.3% of the total cases) were classified as severe as they required intensive care and intensive care units as they had significant mechanically ventilated respiratory failure and oxygen saturation <93%. In Table 2, we plot genotype frequencies according to “mild and severe” COVID-19, respectively.

Table 1

Author	Year	Author	Sample size		Age, y		Sex, Male (%)		Genotyping methods
			Mild	Severe	Mild	Severe	Mild	Severe	
Alghamdi	2021	Saudi Arabia	457	404	29.9 ± 10.5	54.1 ± 16.2	288 (64.1%)	161 (35.9%)	RT-PCR
Cuesta-Llavona	2021	Northern Spain	332	152	64 ± 16	67 ± 16	198 (59%)	113 (74%)	PCR
Juan Gómez	2021	Northern Spain	230	81	43.5 (34–56.5)	67.5 (57.75–74.25)	24 (42.86%)	9 (37.5%)	PCR
Schönfelder	2021	Germany	164	75	57.0 (18–94)	64 (26–99)	86 (52.4%)	55 (73.3%)	RT-PCR
Zhang	2020	China	56	24	66.33 ± 10.34	64.85 ± 16.53	114 (50%)	60(74%)	RT-PCR

Table 2

		Mild						**Severe**					
Athour, year	**country**	**total**	**TT**	**TC**	**CC**	**T**	**C**	**total**	**TT**	**TC**	**CC**	**T**	**C**
Alghamdi,2021	Saudi Arabia	457	372	82	3	826	88	404	330	73	1	733	75
Cuesta-Llavona, 2021	Northern Spain	332	300	30	2	630	34	152	133	17	2	283	21
JuanGómez,2021	Northern Spain	230	297	22	1	616	24	81	69	10	2	148	14
Schönfelder,2021	Germany	164	147	15	2	309	19	75	68	7	0	143	7
Zhang, 2020	China	56	10	30	16	50	62	24	5	7	12	17	31

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

For the association between the IFITM3 rs12252 gene polymorphism and susceptibility to COVID-19, a fixed effects model was adopted to get the results of the RR, since the heterogeneity of all gene models was less than 25%.

The overall result in all models did not show a statistically significant relationship between the rs12252 polymorphism of the IFITM3 gene and the severity of COVID-19, since the statistical values were as follows: for the dominant model - OR = 0.93, 95% CI: 0.71–1.20, p = 0.72, for recessive model - OR = 0.56, 95% CI: 0.28-1.15, p = 0.40, for allelic model - OR = 0.89, 95% CI: 0.71-1.12, p = 0.40, for homozygous model - OR = 0 .73, 95% CI: 0.32–1.65, p = 0.37, for heterozygous - OR = 0.92, 95% CI: 0.70–1.20, p = 0.39. Forest plots for a meta-analysis of COVID-19 patients stratified by severity (mild and severe) are presented in Fig. 2.

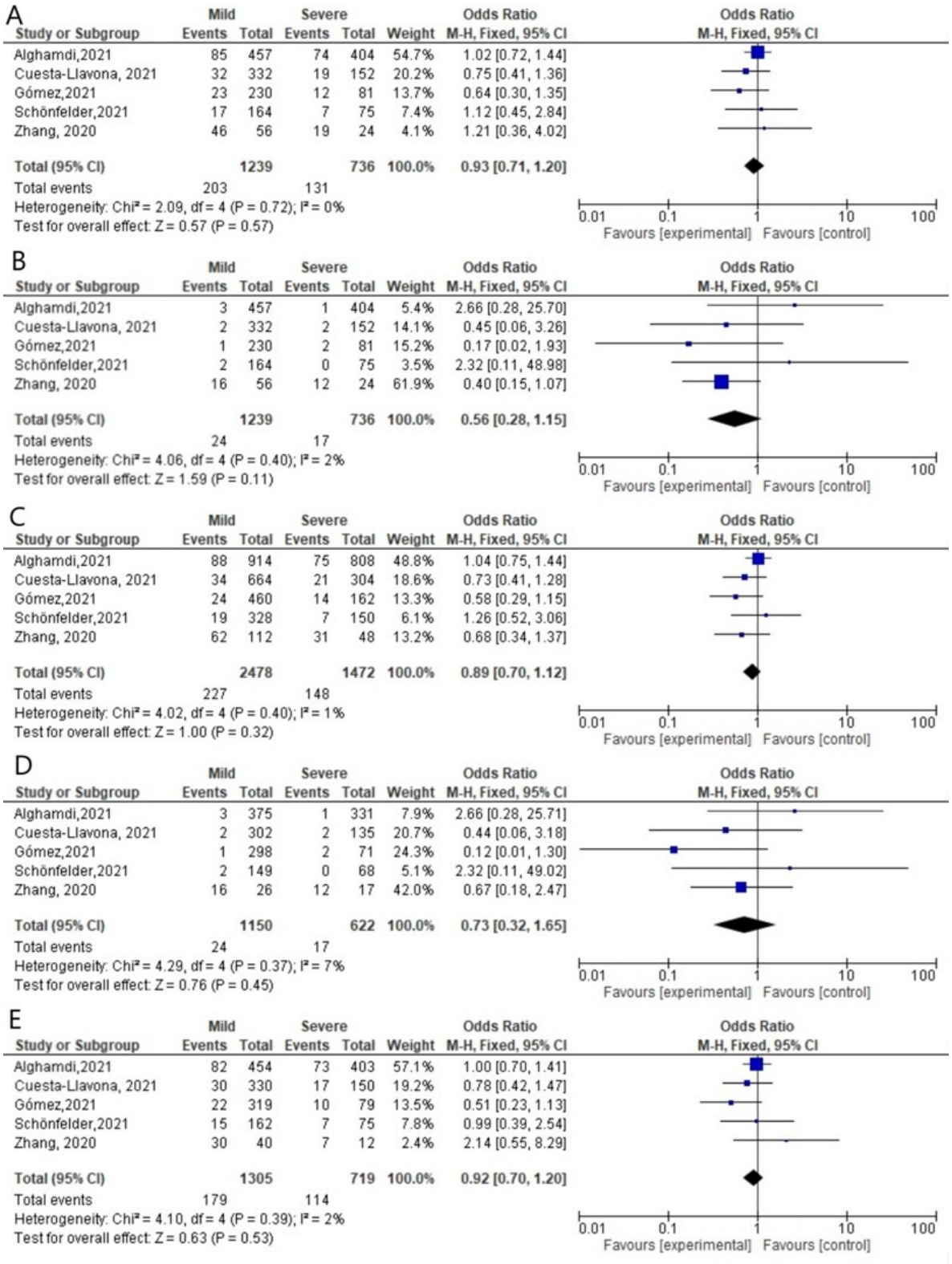


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Figure 2. Forest section of the IFITM3 rs12252 gene between mild and severe: A: dominant inheritance model (CC+TC vs TT); B:), recessive inheritance model (CC vs TC+TT); C: allelic model (C vs T); D: homozygous model (CC vs TT); E: heterozygous model (TC vs TT).

Discussion

Our results did not confirm an association between the IFITM3 rs12252 gene polymorphism and COVID-19 severity.

With regard to SARS-CoV-2 infection and COVID-19 severity, to our knowledge, only a few studies have examined the association of disease severity with the IFITM3 SNP. Zhang et al. compared 56 mild and 24 severe COVID-19 patients and found a higher incidence of GG homozygotes among severe cases (Zhanget al., 2020).Schönfelder et al. also, no association was found between rs12252 or rs34481144 and SARS-CoV-2 infection risk or COVID-19 severity in the German cohort (239 patients and 253 controls).

But on the other hand Cuesta-Llavona E. et al. (2021) found a significantly higher frequency of rs12252-C among COVID-19 patients who required hospitalization (n = 288) during the first pandemic wave (March–May 2020) in Spain compared to an age- and sex-matched controll population (n = 440). In a study of 880 Saudi patients, Alghamdi et al. found that rs12252-C was associated with hospitalization (OR = 1.65; 95% CI = 1.01–2.70) and mortality (OR = 2.2; 95% CI = 1.16–4.20) (Alghamdi et al., 2021). The minor allele frequency of the C allele is significantly higher in East Asians, and the effects may be more pronounced. Zhang et al. observed an up to 6.37-fold increase in the risk of developing severe COVID-19 in carriers of the C allele (MAF 0.30 vs 0.50, P = 0.0093) in their preliminary study with Chinese patients (Zhao T., 2020).

Therefore, the effect of rs12252 on the severity of COVID-19 needs to be tested in larger cohorts and different ethnic groups, as the results of different studies differ from each other. Further research is needed to confirm this genetic link to COVID-19 severity.

References

1. Zhao T. Interferon-induced transmembrane protein 3 related to coronavirus disease 2019 //The Journal of Infectious Diseases. – 2020. – Т. 222. – №. 8. – С. 1413-1413.
2. Zhang Y. et al. Interferon-induced transmembrane protein 3 genetic variant rs12252-C associated with disease severity in coronavirus disease 2019 //The Journal of infectious diseases. – 2020. – Т. 222. – №. 1. – С. 34-37.
3. Alghamdi J. et al. Interferon-induced transmembrane protein-3 genetic variant rs12252 is associated with COVID-19 mortality //Genomics. – 2021. – Т. 113. – №. 4. – С. 1733-1741.
4. Cuesta-Llavona E. et al. Association between the interferon-induced transmembrane protein 3 gene (IFITM3) rs34481144/rs12252 haplotypes and COVID-19 //Current Research in Virological Science. – 2021. – Т. 2. – С. 100016.
5. Schönfelder K. et al. The influence of IFITM3 polymorphisms on susceptibility to SARS-CoV-2 infection and severity of COVID-19 //Cytokine. – 2021. – Т. 142. – С. 155492.
6. Gómez J. et al. The Interferon-induced transmembrane protein 3 gene (IFITM3) rs12252 C variant is associated with COVID-19 //Cytokine. – 2021. – Т. 137. – С. 155354.
7. Pan Y. et al. IFITM3 Rs12252-C variant increases potential risk for severe influenza virus infection in Chinese population //Frontiers in cellular and infection microbiology. – 2017. – Т. 7. – С. 294.
8. Martins J. S. C. et al. Investigation of human IFITM3 polymorphisms rs34481144A and rs12252C and risk for influenza A (H1N1) pdm09 severity in a Brazilian cohort //Frontiers in cellular and infection microbiology. – 2020. – С. 352.

Сергеева А. Д., Ворошилова Д. А., Тальнишних Е. Р., Деревянчук Е. Г., Association between the interferon-induced transmembrane protein 3 gene (IFITM3) rs12252 and COVID-19 // «Живые и биокосные системы». – 2023. – № 44; URL: https://jbks.ru/archive/issue-44/article-1/. DOI: 10.18522/2308-9709-2023-44-1