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BIOMEDICAL SCIENCES

IFITM3 rs12252 polymorphism association with COVID-19 severity and mortality in a Brazilian sample: an update and a meta-analysis

JOÃO L.F. DE ARAÚJO, VICTÓRIA F. BONIFÁCIO, LORENA M. BATISTA, RENATA ELIANE DE ÁVILA, RENATO S. AGUIAR, LUCIANA BASTOS-RODRIGUES & RENAN P. DE SOUZA

Abstract: This study investigated the association between the *IFITM3* rs12252 polymorphism and the severity and mortality of COVID-19 in hospitalized Brazilian patients. A total of 102 COVID-19 patients were included, and the outcomes of interest were defined as death and the need for mechanical ventilation. Genotypes were assessed using Taqman probes. No significant associations were found between the rs12252 polymorphism and COVID-19 outcomes in the original sample, both for death and the need for mechanical ventilation. A meta-analysis, incorporating previous studies that used death as a severity indicator, revealed no association in the allelic and C-recessive models. However, due to the rarity of the T allele and its absence in the sample, further replication studies in larger and more diverse populations are needed to clarify the role of rs12252 in COVID-19 prognosis.

Key words: interferon, COVID-19 prognosis, SNP, polymorphisms, genetic association.

INTRODUCTION

COVID-19 can manifest with diverse symptoms, and these symptoms may differ between infections caused by various variants, particularly those categorized as variants of concern. The prognosis can vary significantly, with patients either remaining asymptomatic or experiencing symptoms that span from mild to severe, potentially leading to fatal outcomes in extreme cases. Several factors, including environmental, social, and genetic elements, contribute to the variability in clinical outcomes (Wiersinga et al. 2020).

Previous reports have suggested a role for the interferon-induced transmembrane protein 3 (*IFITM3*) gene. The encoded transmembrane protein plays a key role in restricting the cellular entry of pathogens, including influenza and Ebola viroses (Harmand et al. 2017, Prabhu et al. 2018). Susceptibility to SARS-CoV-2 infection may also be influenced by genetic variability in *IFITM3* (Xu et al. 2022). The *IFITM3* rs12252 polymorphism was the first to be investigated in a candidate gene association study with COVID-19 outcomes. In a sample of 80 hospitalized Chinese patients, individuals carrying the CC genotype were 5.37 times more likely than those with CT or TT genotypes to develop severe COVID-19, as defined by respiratory or other organ failures (Zhang et al. 2020). A recent meta-analysis revealed no association between the rs12252 polymorphism and ICU admission (Araújo et al. 2022). Herein, we conducted an association study of *IFITM3* rs12252 with severity and mortality in hospitalized Brazilian patients.

MATERIALS AND METHODS

One hundred and two COVID-19 patients, who were hospitalized at Hospital Eduardo de Menezes between August and October 2020, were enrolled in the study. The molecular diagnosis of COVID-19 was performed using RT-qPCR. The project received approval from the UFMG Human Research Ethics Committee (number 31095820.4.0000.5149).

Genotyping of the rs12252 polymorphism was conducted using TaqMan probes (Thermo Fisher Scientific, C_175677529_10) with the Bio-Rad CFX Opus 96 system. The genotyping process was carried out independently of clinical data and repeated in 10% of the samples as a quality control measure, showing a 100% agreement rate.

Statistical analyses were performed using R version 4.0.2, with a significance level of 0.05. Associations were assessed using Pearson's Chi-squared test or Fisher's exact test. Median age and days of hospitalization were compared using Wilcoxon tests. To evaluate the association of rs12252 with death, we updated the search described in a previous systematic review (Araújo et al. 2022) using the PubMed database. A meta-analysis, combining odds ratios, was conducted using the metabin function of the meta package.

RESULTS

No significant differences or associations were found between outcomes and clinical variables, as presented in Table I. The Hardy-Weinberg equilibrium was observed in all groups, and no association between *IFITM3* rs12252 and severity or mortality was identified. The updated search for the systematic review did not yield any additional studies exploring the same outcome. Consequently, we combined our findings with three previous studies.(Alghamdi et al. 2021, Cuesta-Llavona et al. 2021). No association was observed for the allelic model (OR: 1.43, 95% CI: 0.99-2.07) (Figure 1a) and the C-recessive model

Table I. Evaluation of factors associated with severity and mortality outcomes. No significant effects were observed.

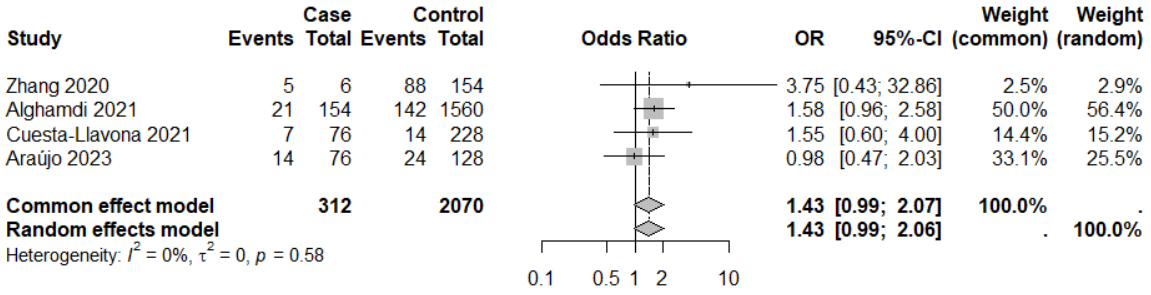
Phenotype	Mechanical ventilation		p-value	Death		p-value
	No, n = 83	Yes, n = 19		No, n = 64	Yes, n = 38	
Age (years)	60 (52,68)	65 (48,68)	0.997	60 (52, 67)	66 (51,70)	0.545
Hospitalization (days)	18 (9,35)	32 (10,60)	0.125	19 (9,41)	20 (10,35)	0.890
Sex female	40 (48%)	6 (32%)	0.189	33 (52%)	13 (34%)	0.089
Sex male	43 (52%)	13 (68%)		31 (48%)	25 (66%)	
Systemic arterial hypertension	46 (55%)	11 (58%)	0.845	37 (58%)	20 (53%)	0.610
Neurological diseases	17 (20%)	4 (21%)	>0.999	14 (22%)	7 (18%)	0.677
Hypothyroidism	9 (11%)	3 (16%)	0.692	7 (11%)	5 (13%)	0.758
Cancer	3 (3.6%)	0 (0%)	>0.999	1 (1.6%)	2 (5.3%)	0.554
Asthma	2 (2.4%)	2 (11%)	0.157	2 (3.1%)	2 (5.3%)	0.627
HIV infection	6 (7.2%)	1 (5.3%)	>0.999	5 (7.8%)	2 (5.3%)	>0.999
Alcoholism	4 (4.8%)	1 (5.3%)	>0.999	3 (4.7%)	2 (5.3%)	>0.999
Smoker	4 (4.8%)	1 (5.3%)	>0.999	4 (6.2%)	1 (2.6%)	0.648
rs12252 T/T	53 (64%)	11 (58%)	0.628	40 (62%)	24 (63%)	0.947
rs12252 T/C	30 (36%)	8 (42%)		24 (38%)	14 (37%)	

(OR: 2.54, 95% CI: 0.59-10.91) (Figure 1b). However, the T-recessive model showed significance (OR: 0.65, 95% CI: 0.43-0.98), assuming non-heterogeneity across the included studies (p = 0.60) (Figure 1c).

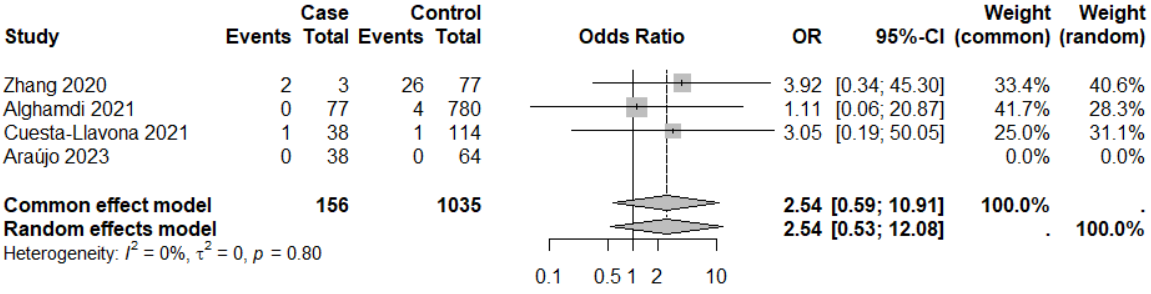
DISCUSSION

The association results of the rs12252 polymorphism with COVID-19 outcomes have shown heterogeneity. While the initial report by Zhang et al. found significance (Zhang et al. 2020), Gomez and collaborators (Gómez et al. 2021), along with two others (Cuesta-Llavona et al. 2021, Schönfelder et al. 2021), did not identify increased odds of requiring intensive care unit treatment in CC carriers. However, the additive model revealed significance for the likelihood of hospitalization in Alghamdi and collaborators (Alghamdi et al. 2021) (OR: 1.65,

a



b



c

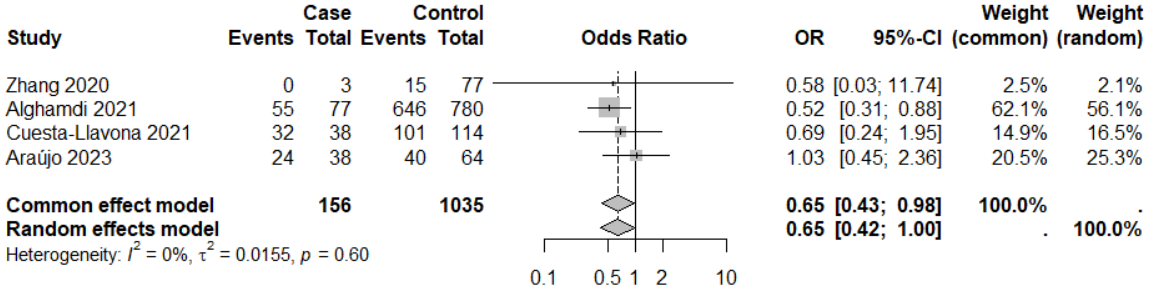


Figure 1. ***IFITM3*** **rs12252 association with mortality under the (a) C-allele model. (b) T-recessive model. (c) C-recessive model. The T-recessive model was significant.**

95% CI: 1.01-2.70, p=0.04). While our original finding supports the lack of association, we observed reduced odds of death in TT carriers compared to CC and CT subjects using meta-analysis. It is crucial to note that the T allele is rare, and its homozygosity was not found in our sample. Three meta-analyses explore the rs12252 polymorphism in susceptibility to SARS-CoV-2 infection, indicating the C allele as associated with an increased likelihood of infection (Gupta et al. 2022, Li et al. 2022, Pecoraro et al. 2023). Furthermore, in Pecoraro et al. a meta-analysis addressing death was conducted, observing no significance (Pecoraro et al. 2023). Consideration of the differences in the composition of compared groups in these studies is essential. The experimental design involves non-survivors versus survivors, and variations are observed within these groups. In our sample, all patients were hospitalized, whereas in Alghamdi et al, for instance, the survivor group included patients with mild to severe symptoms (Alghamdi et al. 2021). Two additional studies explored the likelihood of death in COVID-19 positive patients. Cuesta-Llavona and collaborators (Cuesta-Llavona et al. 2021) did not observe an association of the rs12252 polymorphism with the likelihood of death, while Alghamdi and collaborators (Alghamdi et al. 2021) reported significance in both the dominant model (OR: 1.76, 95% CI: 1.03-2.99, p = 0.04) and additive model (OR: 2.20, 95% CI: 1.16-4.20, p = 0.01). Replications in larger and ethnically diverse samples are warranted to further understand the role of *IFITM3* rs12252 in COVID-19 prognosis.

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JOÃO L.F. DE ARAÚJO[1]
https://orcid.org/0000-0001-9469-9673

VICTÓRIA F. BONIFÁCIO[2]
https://orcid.org/0009-0002-0882-3354

LORENA M. BATISTA[2]
https://orcid.org/0000-0003-0439-4660

RENATA ELIANE DE ÁVILA[3]
https://orcid.org/0000-0003-4025-3558

RENATO S. AGUIAR[1,4]
https://orcid.org/0000-0001-5180-3717

LUCIANA BASTOS-RODRIGUES[2]
https://orcid.org/0000-0002-9053-7201

RENAN P. DE SOUZA[1]
https://orcid.org/0000-0002-9479-4432

[1]Universidade Federal de Minas Gerais, Departamento de Genética, Ecologia e Evolução, Instituto de Ciências Biológicas, Laboratório de Biologia Integrativa, Grupo de Pesquisa em Bioestatística e Epidemiologia Molecular, Av. Presidente Antônio Carlos, 6627, Pampulha, 31270-901 Belo Horizonte, MG, Brazil

[2]Universidade Federal de Minas Gerais, Departamento de Nutrição, Escola de Enfermagem, Av. Alfredo Balena, 190, Santa Efigência, 30130-100 Belo Horizonte, MG, Brazil

[3]Hospital Eduardo de Menezes, Rua Doutor Cristiano Resende, 2213, Bonsucesso, 30622-020 Belo Horizonte, MG, Brazil

[4]Instituto D'OR de Pesquisa e Ensino, Rua Diniz Cordeiro, 30, Botafogo, 22281-100 Rio de Janeiro, RJ, Brazil

Correspondence to: **Renan Pedra de Souza**
E-mail: renanpedra@gmail.com

Author contributions

All authors contributed to the study's conception. JLFA: conducted data curation, visualization, investigation, analysis, and original draft writing. VFB: conducted data curation, visualization, investigation, and analysis. LMB and REA: conducted data curation. RSA and LBR: Conceptualized the experimental design, provided supervision, obtained funding, and reviewed the manuscript. RPS: Conceptualized the experimental design, provided primary supervision, obtained funding, reviewed, and edited the manuscript. All authors read and approved the final manuscript.