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## Review

# Genetic polymorphisms as multi-biomarkers in severe acute respiratory syndrome (SARS) by coronavirus infection: A systematic review of candidate gene association studies



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## ABSTRACT

The Severe acute respiratory syndrome may be caused by coronavirus disease which has resulted in a global pandemic. Polymorphisms in the population play a role in susceptibility to severity. We aimed to perform a systematic review related to the effect of single nucleotide polymorphisms in the development of severe acute respiratory syndrome (SARS). Twenty-eight eligible articles published were identified in PubMed, ScienceDirect, Web of Science, PMC Central and Portal BVS and additional records, with 20 studies performed in China. Information on study characteristics, genetic polymorphisms, and comorbidities was extracted. Study quality was assessed by the STrengthening the REporting of Genetic Association (STREGA) guideline. Few studies investigated the presence of polymorphisms in *HLA*, *ACE1*, *OAS-1*, *MxA*, *PKR*, *MBL*, *E-CRI*, *FcγRIIA*, *MBL2*, *L-SIGN* (*CLEC4M*), *IFNG*, *CD14*, *ICAM3*, *RANTES*, *IL-12 RB1*, *TNFA*, *CXCL10/IP-10*, *CD209* (*DC-SIGN*), *AHSG*, *CYP4F3* and *CCL2* with the susceptibility or protection to SARS-Cov. This review provides comprehensive evidence of the association between genetic polymorphisms and susceptibility or protection to severity SARS-CoV. The literature about coronavirus infection, susceptibility to severe acute respiratory syndrome (SARS) and genetic variations is scarce. Further studies are necessary to provide more concrete evidence, mainly related to Covid-19.

## 1. Introduction

Since December 2019, when the first cases of COVID-19 were described in Wuhan (China), the virus has rapidly spread to other parts of the world (Li et al., 2020) and it was considered by the World Health Organization (WHO) as one public health problem (Zheng et al., 2020; Carod Artal, 2020). Coronaviruses (CoVs) consist of an enveloped, positive-sense, single-stranded RNA viruses (genome size - 30 Kb), belonging to the family *Coronaviridae* and subfamily *Coronavirinae* (Fehr and Perlman, 2015) and has been associated with several clinical conditions that involved respiratory, enteric, hepatic, neurological, hypercoagulability and endotheliopathy symptoms and signs (Almqvist et al.,

2020; Benvenuto et al., 2020; Hassan et al., 2020).

Previous outbreaks have reported an association between coronaviruses and severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and the Severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (Rothan and Byrareddy, 2020). Severity ranges from asymptomatic infection or mild disease, characterized by dry cough, fever, dyspnea, and fatigue, to critical illness with respiratory failure, SARS and death (Dahan et al., 2020). In SARS, subjects show clinical inflammation, hemorrhage, alveolar edema, hyaline membrane formation typical of the exudative stage, fluid accumulation with consequent fibrosis pulmonary and lead to respiratory failure (Gralinski and Baric, 2015).

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The pathophysiology of SARS-Cov-2 is related to the mechanism used by the virus to enter into the host cell by binding to the angiotensin-2 converting enzyme (ACE-2) which is expressed in various tissues. The spike protein (localized in virus membrane) is needed to bidding process, and it is also considered as a necessary factor for virulence and to promote specific tissue affinity or tissue tropism and infectivity (Du et al., 2009; Hoffmann et al., 2020; Li, 2016). The protein Spike is cleaved in the S2 domain, which is adjacent to the fusion peptide by the protease TMPRSS2, localized in the host cells, causing a structural modification capable of facilitating the entry of the virus in target cells (Hoffmann et al., 2020).

Single nucleotide polymorphism (SNP) can be localized in coding and non-coding regions and, it may be involved in various phenotypic characteristics including susceptibility, severity, resistance or protection to diseases (Shen et al., 1999). A polymorphism may have functional effects, resulting in modifications of the catalytic function, stability and/or level of expression of the protein (Kelada et al., 2003). Polymorphisms in MHC I and II had influence in the cell entry process by other CoVs (Vera S.F. Chan et al., 2006; Keicho et al., 2009; Wang et al., 2011) (Li et al., 2020, Keicho et al., 2009; Chan et al., 2006; Wang et al., 2011). According to Bender et al. (2020), link between a virus and the Toll-like receptor 7 (TRL7) / Toll-like receptor 8 (TLR8) may activate a pathway that stimulates the production of pro-inflammatory cytokines (Qin et al., 2020). Additionally, the angiotensin I converting enzyme enhances the synthesis of angiotensin II, which induces cell proliferation and enhances proinflammatory cytokines and metalloproteinases matrix (Sprague and Khalil, 2009). These events may be due to the viral and/or host genetic characteristics as described in studies with other coronaviruses (REFERENCIAS). Thus, the aim of this study was to analyze genetics profiles involved in the pathogenesis of the severe acute respiratory syndrome (SARS) in patients with coronavirus disease.

## 2. Material and methods

### 2.1. Design

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (Moher et al., 2009). The systematic review is registered in PROSPERO: CRD42020178334.

### 2.2. Search strategy

The method PICOS (Santos et al., 2007) was used for definition of descriptors for assessing eligibility. In which participants were patients (P) with the severe acute respiratory syndrome and coronavirus; the intervention (I): genetics polymorphisms identification; compared to control groups (C): absence of coronavirus group; outcome (O): the presence or absence of the genetic polymorphism in the group of patients with coronavirus; Study design (S): a genetic association study. The keywords were used as follows: coronavirus, polymorphism genetic and severe acute respiratory syndrome. The databases PubMed, Web of Science, Science direct, PMC central and Virtual Health Library – VHL (Portal BVS - Portal Regional da BVS). To supplement the electronic search, references of all relevant studies were also screened for potential consideration.

### 2.3. Selection criteria

We researched observational studies carried out in humans that evaluated the associations between genetic polymorphisms and susceptibility to severe acute respiratory syndrome and coronavirus. The studies included in the systematic review were (1) articles that investigated genetic polymorphisms about coronavirus associated with severe acute respiratory syndrome, (2) original data, and (3) studies in English or Portuguese language. The exclusion criteria were (1) duplicated

articles; (2) case, review, or articles with only an abstract and (3) articles with in vitro experiments. The full text was read by all authors, because studies could not be decided based only the title and abstract. The selected studies were established by the descriptors eligible for this review. Disagreements regarding to the inclusion of studies were resolved by a consensus (Fig. 1).

### 2.4. Data extraction and quality assessment

The selected articles were analyzed and data were extracted by two independent researchers in regards to the author, year, study design, country, design, sample size, genotyping method, gene, SNPs, outcomes, Hardy-Weinberg equilibrium (HWE) and comorbidities in SARS patients. Four authors (S.P.O.; A.C.M.S.; E.L.M.; L.C.S.) independently extracted data from all eligible studies on the collection forms according to a standard protocol. Two reviewers (BRCS and BBS) independently assessed the study design, methods and results of the genetic association studies. Methodological quality of each study was based on the STrengthening the REporting of Genetic Association (STREGA) guideline and the results were discussed to reach a consensus (Little et al., 2009). STREGA contains five main divisions, including genotyping methods and errors, population stratification, haplotype variation, HWE and replication, with a total of nine items to be evaluated. In all studies, the total score was measured by attributing one point for each item, with a high score indicating studies with better quality (range: 0–9, higher scores indicating higher overall quality).

## 3. Results

### 3.1. Overview of results

In the initial screening, we identified a total of 591 publications and posteriorly we remove the duplicates. A total of 39 papers were eligible and selected for full-text review based on the title and abstract information related with SARS and genetic polymorphism. The primary reasons for exclusion included: no full-text access, duplicates, reviews or meta-analyses and no sufficient information about the theme (Fig. 1).

Finally, 28 eligible studies were included in this review, approaching the following 40 genes: Angiotensin-converting enzyme (ACE) (n = 3) (Chan et al., 2005c; Chiu et al., 2004; Itoyama et al., 2005, Itoyama et al., 2004); Mannose-binding lectin (MBL) (n = 4) (Ip et al., 2005; Tu et al., 2015; Yuan et al., 2005; Zhang et al., 2005); Human leukocyte antigen (HLA) (n = 3) (Keicho et al., 2009; Lin et al., 2003); MX dynamin like GTPase 1 (MxA) (n = 2) (He et al., 2006); Cluster of Differentiation 209 (CD209) (n = 1) (Chan et al., 2010); Tnf alpha (n = 2); Interferon (IFN) (n = 2); liver/lymph node-specific intracellular adhesion molecules-3 grabbing non-integrin (L-SIGN) (n = 2); erythrocyte-complement receptor Type1 (E-CR1) (n = 1) (Wang et al., 2005); 2'-5'-Oligoadenylate Synthetase 1 (OAS1) (n = 1) (He et al., 2006); cluster of differentiation 14 (CD14) (n = 1); toll like receptor 2 (TLR2) (n = 1); toll like receptor 4 (TLR4) (n = 1); Intercellular Adhesion Molecule 3 (ICAM3) (n = 1) (Chan et al., 2007); Fragment of IgE Receptor II (FCER2) (n = 1); C-X-C Motif Chemokine Ligand 10 (CXCL10) (n = 1) (Hsieh et al., 2010); Heme Oxygenase 1 (HMOX1) (n = 1) (Hsieh et al., 2010); Fibrinogen-like protein 2 (FGL2) (n = 1) (Hsieh et al., 2010); alpha 2-HS Glycoprotein (AHSG) (n = 1); Cytochrome P450 Family 3A (CYP4F3A) (n = 1); C-C Motif Chemokine Ligand 2 (CCL2) (n = 1); FcγRIIA (n = 1); Interleukin-10 (n = 1); Interleukin-12 (n = 1); mannose-binding protein-associated serine protease 2 (MASP-2) (n = 1) and Regulated upon Activation Normal T Cell Expressed and Presumably Secreted (RANTES) (n = 1).

Most studies included both male and female participants, however, male sex was more prevalent. Of the 27 articles, 26 were case-control studies and one cohort study. Methods for detecting polymorphisms included PCR-SSP (polymerase chain reaction-sequence specific primers), RFLP for restriction enzyme (Restriction Fragment Length

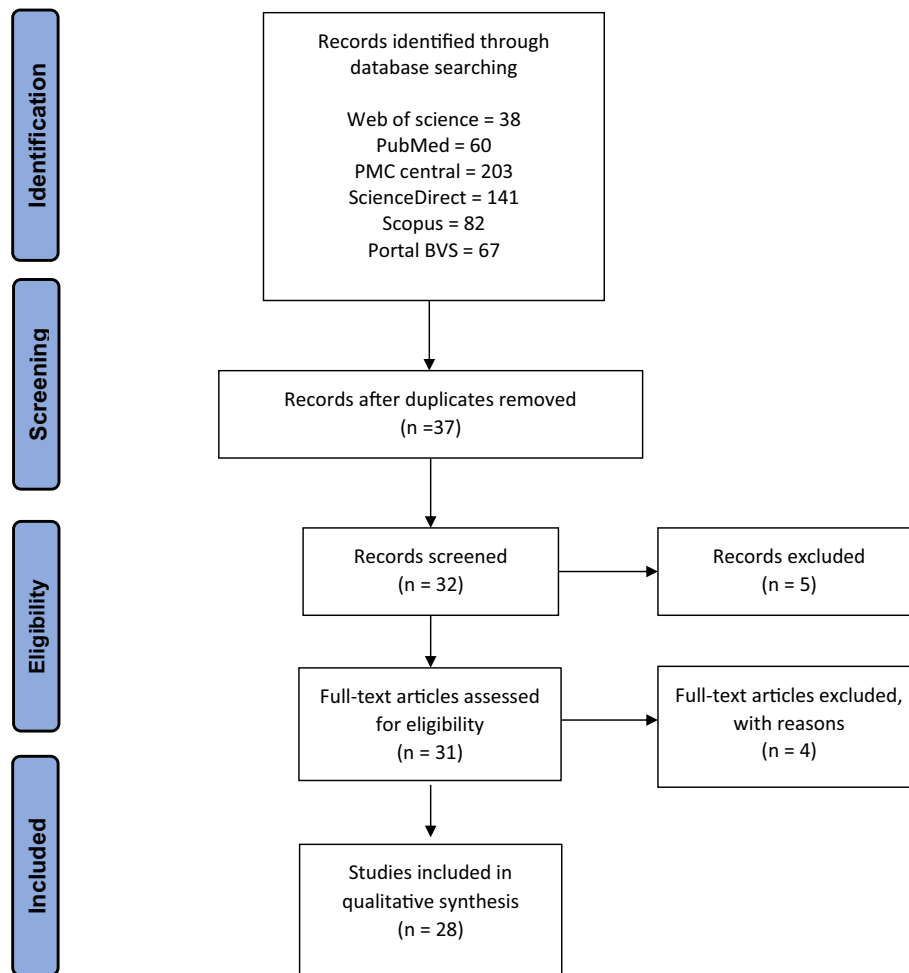


Fig. 1. Flow diagram Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) illustrating the studies' selection process.

Polymorphism), qPCR (real-time PCR), sequencing-based typing (SBT), single specific primer-polymerase chain reaction (PCR-SSP) and sequence-specific oligonucleotides probes (PCR-SSOP) (Table 1). Few studies (Chan et al., 2005c; Itoyama et al., 2004; Lin et al., 2003; Wang et al., 2005; Zhang et al., 2005) reported the presence of SARS-Cov severity associated comorbidities as a chronic obstructive pulmonary disease, flu, coronary artery disease, cerebral vascular disease, cancer, diabetes mellitus, chronic kidney disease, cirrhosis, hepatitis C, Human Immunodeficiency Virus (HIV) and systemic arterial hypertension.

### 3.2. Study quality assessment

Most of the selected studies met four of the nine items in the STREGA guideline. No study reached all nine items. However, one research (Tang et al., 2008) reported seven items, except for descriptions of laboratory/center where the genotyping was done and the statement of whether the study is the first report of a genetic association, a replication effort, or whether the assays were conducted simultaneously or in batch. Only one study (Yuan et al., 2007) described the following items: genotyping methods/platform and the numbers of individuals for whom genotyping was attempted and successful. The majority of the studies reported genotyping methods and platform and Hardy-Weinberg equilibrium (Table 2).

## 4. Discussion

### 4.1. Cytokines

Cytokines play a crucial role in the development of physiological functions, and their dysregulation or activation follows homeostatic changes, triggering the immunopathogenesis of several pathologies. Here, the cytokines interferon gamma (IFN- $\gamma$ ), tumor necrosis factor (TNF- $\alpha$ ) and Interleukin-1 (IL-1) were investigated which were correlated with SARS in patients with covid-19. The interferon gamma (IFN- $\gamma$ ) is important in response immune. It activates monocytes and macrophages, participate in antiviral responses producing free radicals and pro-inflammatory cytokines, such as tumor necrosis factor (TNF- $\alpha$ ) (Biron et al., 1999). Thus, IFN- $\gamma$  and TNF- $\alpha$  play an important role in the antiviral response and the inflammatory process. In a study conducted by Chong and collaborators in 2006, the A allele of the *IFNG* + 874 polymorphism was associated with susceptibility to SARS in population. However, in that same study, no significant correlation was observed in the SNP *TNFA*-308 (Chong et al., 2006).

The mechanism by which the *IFNG* + 874A/T polymorphism influences susceptibility to SARS depends on its role in regulating IFN- $\gamma$  production. It is possible that the high production of IFN- $\gamma$  may impair their antiviral response against SARS-CoV, making these individuals more susceptible to viral infection, where the *IFNG* + 874A allele was significantly associated with a genetic risk factor for SARS (Chong et al., 2006). In another study conducted in the Chinese population, the *IFNG* + 874A allele was associated with susceptibility to SARS (Chong et al., 2006).

**Table 1**  
Characteristics of studies included in this review.

Author, year	Country	Design	Sample size		Genotyping method	Gene	SNPs	Outcomes	HWE (Y/N)	STREGA total score
			Case	Control						
Lin et al., 2003	Taiwan	Case-control	37	190	PCR-SSOP	HLA-class I and II	HLA-A, B and DRB	HLA-B*4601 and risk to SARS	NR	15
Itoyama et al., 2004	Vietnam	Case-control	44	153	Conventional PCR	ACE1	insertion/deletion (I/D)	progression of pneumonia (D allele)	NR	15
Chiu et al., 2004	China	Case-control	168	328	Real-Time PCR	ACE2	rs2285666, rs4646142, rs714205, rs2106809 and rs2074192	No relation	Y	18
Chan et al., 2005a, 2005b, 2005c	China	Case-control	140	326	Conventional PCR	ACE	insertion/deletion (I/D)	No relation	Y	18
Hamano et al., 2005	Vietnam	Case-control	44	103	PCR - RFLP	<i>OAS-1</i>	<i>rs2660 and rs3741981</i>	associated with SARS-CoV infection or development of SARS	N	19
Ip et al., 2005	China	Case-control	569	1189	PCR - RFLP	<i>MxA</i>	-88	susceptibility to SARS	N	20
					PCR - RFLP	<i>PKR</i>	-168		N	
Itoyama et al., 2005	Vietnam	Case-control	44	103	Real-time PCR	<i>MBL</i>	<i>promoter (-221 X/Y) and exon 1 (codon 54 A/B)</i>	No relation	NR	18
					PCR - RFLP	ACE2	rs2285666, rs4646140, rs25082, rs25424, rs4646165, rs2301693, rs2301692, rs30816, rs4646174, rs33121, rs33205, rs36655, rs38926, rs39663, rs39705 and rs39844			
Wang et al., 2005	China	Case-control	54	212	PCR - RFLP	E-CR1	CR1 Hind III	Progression of SARS	Y	18
Yuan et al., 2005	China	Case-control	180	200	PCR- SSP	<i>FcγRIIA</i>	R-H-131	Susceptibility to SARS	NR	18
						<i>MBL2</i>	rs11003125, rs7096206, rs5030737, rs1800450 and rs1800451	Susceptibility to SARS	NR	
Zhang et al., 2005	China	Case-control	352	392	Conventional PCR	<i>MBL</i>	-596, -550, -435, -427, -349, -336, -329 to >324, -221, -70, 4, 223, 230, 239 and 366	B allele had an increased susceptibility to SARS-CoV infection	Y	18
Chan et al., 2006	China	Case-control	285	380	Conventional PCR	L-SIGN (CLEC4M)	CLEC4M 69-nucleotide tandem repeats in exon 4	homozygosity for L-SIGN and protective role	N	15
He et al., 2006	China	Case-control	66	64	Conventional PCR	<i>OAS1</i>	3'UTR 347 locus of the exon 8	susceptibility to SARS	NR	15
Chong et al., 2006	China	Case-control	476	449	PCR - RFLP	<i>MxA</i>	- 88	susceptibility to SARS	NR	15
						<i>IFNG</i>	<i>rs2430561</i>			
Yuan et al., 2007	China	Case-control	152	198	PCR - RFLP	<i>TNF-α</i>	-308	No relation	Y	14
						<i>IL-10</i>	-1082 and -592	No relation	Y	
Chan et al., 2007	China	Case-control	817	906	Real-Time PCR	TLR2 TLR4 ICAM3	2180 and 2408 12,874 and 13,174 rs2304237 (Asp143Gly)	No relation No relation Susceptibility of SARS	NR NR Y	15
					Conventional PCR	<i>FCER2</i>	rs4804773 (Trp62Arg); rs889182; rs1990975; rs2287868 and rs2303112.	No relation	Y	
Ng et al., 2007	China	Case-control	495	578	PCR	<i>RANTES</i>	<i>rs2107538, rs2107538, rs2280789, rs8878, rs4859587 and rs10336</i>	<i>RANTES -28 G</i> allele was associated with SARS susceptibility in Hong Kong Chinese	Y	18
Khoo et al., 2008	China	Case-control	285	380	PCR Multiplex	<i>L-SIGN INF-α, INF-α, INF-β, INF-γ, INF-γ, IL1-α, IL1-α, IL1-β, IL-4, IL-6, iNOS, iNOS</i>	Not described	No relation	NR	18

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Table 1 (continued)

Author, year	Country	Design	Sample size		Genotyping method	Gene	SNPs	Outcomes	HWE (Y/N)	STREGA total score
			Case	Control						
Tang et al., 2008	China	Case-control	115	296	PCR- RFLP	<i>IL-12 RB1</i>	+ 705, + 1158, + 1196 and + 1664	(CT e TT) increased risk of developing SARS	N	20
Wang et al., 2008a, 2008b	China	Case-control	75	92	PCR- SBT	<i>TNF-<math>\alpha</math></i>	-1031, -863, -857, -572, -308, -238, -204, -163	CT genotype protective effect and TT genotype, CT and CC were found associated with a risk effect	NR	16
Xiong et al., 2008	China	Case-control	95	403	PCR- SSP	HLA	HLA-A, HLA-B, HLA-DRB1	No relation	N	18
Keicho et al., 2009	Vietnam	Case-control	62	50	PCR	HLA class I and class II	exons 2 and 3 of HLA -A, -B, and -C exon 2 of HLA-DRB1 and -DQB1	HLA-DRB1*1202 with susceptibility to SARS	Y	15
Wang et al., 2009	China	Case-control	376	523	PCR	MASP2	rs12711521, rs2261695, rs2273346 and rs7548659	No relation	NR	15
Chan et al., 2010	China	Case-control	824	471	Real-Time PCR	CD209 (DC-SIGN)	rs12711521, rs2261695, rs2273346 and rs7548659	No relation	Y	18
						CXCL10/IP-10	-938	Protective	NR	15
						HO-1	-497	No relation	NR	
						Fgl2	+158 (rs2075761)	+158 T/* and Risk	NR	
Hsieh et al., 2010	China	Cohort	824	-	Real-Time PCR	CD209 (DC-SIGN)	-336A (rs4804803)	higher standardized LDH levels	Y	15
Ching et al., 2010	China	Case-control	792	418	PCR	<i>IFN</i>	rs2071430 and rs17000900	-88 T-positive and -123A-positive genotypes were significantly associated with decreased susceptibility to SARS coronavirus infection	Y	16
Zhu et al., 2011	China	Case-control	624	791	PCR-RFLP	AHSG	rs2248690, rs2077119, rs4917, rs2593813 and rs4918	rs2248690 AA and protection	Y	16
						CYP4F3	rs3794987, rs1159776, rs4646519 and rs1290625	rs3794987 GG/AG and increased susceptibility to SARS	Y	
Tu et al., 2015	China	Case-control	932	982	PCR-RFLP	CCL2	rs1024611	risk of SARS-CoV infection	Y	16
						MBL	Codon 54 variant (A > B)	risk of SARS-CoV infection	Y	
Ellinghaus et al., 2020	Italian and Spanish	Case-control	1760	2205	Global Screening Array (GSA)	3p21.31	rs1800450	association signal	NR	20
						9q34.2	rs11385942 (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6 and XCR1)	higher risk in blood group A to SARS-Cov-2	NR	
							rs657152 (ABO blood group locus)			

Type I interferons (alpha and beta), induced by virus infection, has an important role in the first line of defense, inducing intracellular antiviral proteins, such as 2', 5'-oligoadenylate synthetase 1 (OAS-1), and myxovirus resistance-A (MxA) (Samuel, 2001). The 2', 5'-oligoadenylate synthase (OAS) are known to mediate the antiviral response system by activating the RNA cleavage pathway. OAS silencing significantly decreased IL-1 $\beta$ , TNF- $\alpha$  and MCP-1 and had no effect on IL-10 secretion. OAS1, 2 and 3 restrict intracellular mycobacterial replication and increase the secretion of pro-inflammatory cytokines (Leisching, 2019). A case-control study in the Vietnamese population demonstrated that polymorphisms in (rs2660 and rs3741981) *OAS-1* gene was associated with infection/development to SARS-CoV. Additionally, the polymorphism in the -88 position MxA gene was associated with hypoxemic status in the case group (Hamano et al., 2005).

TNF-alpha is a pro-inflammatory cytokine produced mainly by macrophages and lymphocytes (Arslan et al., 2010). The main physiological effect of TNF- $\alpha$  is to promote the immune and inflammatory response, recruiting neutrophils and monocytes (Vitale and de Ribeiro,

2007). TNF- $\alpha$  regulates the expression of neutrophil-endothelial cell adhesion molecules and chemokines, which recruit leukocytes (Makhatadze, 1998). A study relating TNF- $\alpha$  polymorphisms with interstitial pulmonary fibrosis in patients with SARS in China, showed that CT genotype at locus -204 was found associated with a protective effect on SARS compared to the TT genotypes [CI (95% CI) of 0.95 (0.90-0.99)] (Wang et al., 2008a).

In addition, interleukins act as an important component of pro-inflammatory and anti-inflammatory responses, producing and releasing proteins from the acute phase of hepatocytes and inducing symptoms such as fever. IL-12 is responsible for inducing other interleukins and acts in synergy with mainly with TNF- $\alpha$  (Moura et al., 2001). A study in Chinese population found that genetic variants in IL-12 were related to SARS susceptibility to (Tang et al., 2008). Investigations regarding cytokines and the identification of the functioning of the immune response in the face of need to be investigated should become crucial for studies on interventions considering immunotherapy in view of the severity of SARS-CoV infection. Thus, the

**Table 2**  
The quality of reporting using the STrengthening the REporting of Genetic Association (STREGA) guideline.

Author, year	Description of genotyping methods and errors					Description of modeling population stratification	Description of modeling haplotype Variation	Statement of Whether Hardy-Weinberg Equilibrium was considered	Statement of whether the study is the first report of a genetic association, a replication effort, or both	Total score
	Genotyping methods and platforms	Error rates and call rates	Laboratory/center where the genotyping was done	Conducting genotypes simultaneously or in smaller batches	The numbers of individuals for whom genotyping was attempted and successful					
Lin et al., 2003	Y	N	N	N	Y	Y	N	N	N	3
Itoyama et al., 2004	Y	N	N	N	Y	Y	N	N	N	3
Chiu et al., 2004	Y	N	N	N	Y	Y	N	Y	N	4
Chan et al., 2005a, 2005b, 2005c	Y	N	N	N	Y	Y	N	Y	N	4
Hamano et al., 2005	Y	N	N	Y	N	Y	Y	Y	N	5
Ip et al., 2005	Y	N	Y	Y	N	Y	Y	Y	N	6
Itoyama et al., 2005	Y	N	N	Y	Y	Y	N	N	N	4
Wang et al., 2005	Y	N	N	N	Y	Y	N	Y	N	4
Yuan et al., 2005	Y	Y	N	Y	N	N	Y	N	N	4
Zhang et al., 2005	Y	N	N	N	Y	Y	N	Y	N	4
Chan et al., 2006	Y	N	N	N	N	Y	N	Y	N	3
He et al., 2006	Y	N	N	N	Y	Y	N	N	N	3
Chong et al., 2006	Y	N	N	Y	N	N	N	Y	N	3
Yuan et al., 2007	Y	N	N	N	Y	M	N	N	N	2
Chan et al., 2007	Y	N	N	N	Y	Y	N	Y	N	4
Ng et al., 2007	Y	Y	N	Y	N	Y	Y	Y	N	6
Khoo et al., 2008	Y	N	N	Y	Y	N	N	Y	N	4
Tang et al., 2008	Y	Y	N	Y	Y	Y	Y	Y	N	7
Wang et al., 2008a, 2008b	Y	N	N	Y	N	Y	N	Y	N	4
Xiong et al., 2008	Y	N	N	Y	Y	Y	Y	N	N	5
Keicho et al., 2009	Y	N	N	N	Y	M	N	Y	N	3
Wang et al., 2009	Y	N	N	Y	N	N	N	Y	N	3
Chan et al., 2010	Y	N	N	N	Y	Y	N	Y	N	4
Hsieh et al., 2010	Y	N	N	N	N	Y	N	Y	N	3
Ching et al., 2010	Y	Y	N	Y	N	Y	Y	Y	N	6
	Y	N	N	N	Y	Y	N	Y	N	4

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Table 2 (continued)

Author, year	Description of genotyping methods and errors					Description of modeling population stratification	Description of modeling haplotype Variation	Statement of Whether Hardy-Weinberg Equilibrium was considered	Statement of whether the study is the first report of a genetic association, a replication effort, or both	Total score
	Genotyping methods and platforms	Error rates and call rates	Laboratory/center where the genotyping was done	Conducting genotypes simultaneously or in smaller batches	The numbers of individuals for whom genotyping was attempted and successful					
Zhu et al., 2011										
Tu et al., 2015	Y	N	N	N	Y	Y	N	Y	N	4
Ellinghaus et al., 2020	Y	N	Y	Y	Y	Y	N	Y	Y	7

innate and adaptive immune system takes multiple measures to respond to virus infection.

Toll-like receptors (TLRs).

Toll-like receptors (TLRs) have been conserved during evolution of innate immune receptors and expressed in various cells of the mammalian host. TLRs also play roles in the formation of pathogenic specific cellular and humoral immune responses (Kumar et al., 2009). The impairment of Toll-like receptors (TLRs) due to polymorphisms in *TLR* genes may alter immune response to a wide variety of microbial ligands, including virus. Polymorphisms in *TLR2* and *TLR4* have been linked to infectious diseases in human (Yuan et al., 2007). The *TLR-Arg677Trp* polymorphism was reported to be present in a study conducted with Korean lepromatous leprosy patients (Kang and Chae, 2001). This polymorphism has been also associated with tuberculosis in a Tunisian population (Ben-Ali et al., 2004). Yuan et al. (2007) demonstrated a possible link between *CD14*-159 CC genotype and severity of SARS-CoV infection.

#### 4.1.1. Chemokines

Chemokines are proteins involved in immune responses, recruiting leukocytes, and they are divided into two subfamilies: CC and CXC based on the conserved cysteine motifs (Conti and DiGiacchino, 2001; Yadav et al., 2010). The Monocyte Chemoattractant Protein-1 (MCP-1), also known as CCL2, was the first CC chemokine discovered in humans. It is produced by a variety of cells, such as endothelial cells, macrophages, cytokines and growth factors. CCL2 chemokine is expressed in tissue during inflammation and it is important for antiviral response. In the viral infections, CCL2 has been associated with influenza (Lai et al., 2017) and HIV (Ansari et al., 2011).

The main inducers of MCP-1 expression are pro-inflammatory cytokines, such as Interleukin-1, Interleukin-4, Interleukin-6 and tumor necrosis factor alpha. Furthermore, it's can act as a monocytes recruiter during infection and activate T lymphocytes (Bianconi et al., 2018; Deshmane et al., 2009; Gschwandtner et al., 2019; Yadav et al., 2010). Genetic variations in the *CCL2* gene are associated with diseases and its manifestations. A polymorphism in a promoter region of the *CCL2* gene (-2518) was associated with *Mycobacterium tuberculosis* and pulmonary tuberculosis (Singh et al., 2014).

CXCL10, also known as interferon- $\gamma$ -inducible protein 10 (IP-10), is an inflammatory chemokine secreted by monocytes, neutrophils, dendritic cells, lymphocytes and endothelial cells. Th1 cells attract to CXCL10 is categorized as Th1-chemokine (Lee et al., 2009; Oliviero, 2020; Zhao et al., 2018). CXCL10 is located on chromosome 4 in the band q21 (Liu et al., 2011b). CXCL10 has various functions including the

induction of apoptosis, regulation of cell growth and, in the immune response, acts in the recruitment of leukocytes and also induce the production of Interleukin-8 (Lee et al., 2009; Liu et al., 2011a; Ragusa and Fallahi, 2017). In addition, CXCL10 may be highly expressed in various human diseases (Liu et al., 2011a). The GG genotype of the *CXCL10*-135G/A (rs56061981) polymorphism decreased the expression of CXCL10 in T cells, which can alter the recruitment of mononuclear cells, contributing to susceptibility to tuberculosis (Singh et al., 2017).

RANTES (regulated in the activation of normal T cell expressed and secreted), also known as CCL5 is produced by platelets, macrophages, eosinophils, endothelium, and epithelial cells (Appay and Rowland-Jones, 2001; Marques et al., 2013; Trenchevska et al., 2015). RANTES gene is located in chromosome 17q11.2-q12 (An et al., 2002; Lwanira et al., 2015). An increase in the RANTES expression has been associated with several inflammatory processes, including the recruitment of untreated cells (Appay and Rowland-Jones, 2001; Levy, 2009). Also, CCL5 plays a role in the immune response to viral infection, including respiratory tract infections, such as influenza (Chan et al., 2005a, 2005b, 2005c; Marques et al., 2013). Several polymorphisms have been found in the *RANTES* gene such as -403G/A and the -28C/G located in the promoter region, which may alter *RANTES* function or influence its activity (Lwanira et al., 2015; Tahara et al., 2014).

These chemokines are involved in several diseases, including SARS. The involvement of CCL2 was demonstrated in the study of Tu et al., 2015, which showed that individuals who are predisposed to have amounts of CCL2 protein were more susceptible to the development of SARS-CoV infection and a combination of this protein and *MBL* polymorphisms may have a strong correlation with the susceptibility to SARS-CoV infection. Furthermore, the polymorphism in the -28 G allele was associated with the susceptibility to the infection, severe clinical outcomes and death from SARS (Ng et al., 2007). Functional polymorphisms in chemokines can influence its function and may be associated with severe clinical course.

#### 4.1.2. Mannose-binding lectin (MBL)

MBL (mannose-binding lectin) is a component of the innate immune response. MBL is produced by the liver and plays an important role against bacterial and viral infections, activating the lectin pathway in the complement system. In humans, this protein is encoded by the *MBL2* gene and deficiency in MBL serum levels are common, affecting 30% of the population (Heitzeneder et al., 2012). Polymorphisms in the *MBL2* gene that decreased MBL serum levels may be important risk factors for neonatal sepsis and pneumonia (Özkan et al., 2012). Associations with SARS-CoV infection and the codon 54 variant have also been observed



indicating an important role of MBL in the pathogenesis of this disease (Tu et al., 2015; Zhang et al., 2005).

Mannose-binding protein-associated serine protease 2 (MASP-2) is associated with MBL in serum and binds to carbohydrates that initiate the lectin complement pathway which is recognized as the third pathway for complement activation when activated with the MBL-MASP complex (Matsushita, 1996; Stover et al., 2001). This protease is encoded by the *MASP-2* gene, which is located on chromosome 1p36.23–31 (Stover et al., 2001). It has been shown that polymorphism in this gene may affect the levels of MASP-2 in the serum and lead to susceptibility to some diseases such as tuberculosis and leprosy, caused by mycobacteria (Boldt et al., 2013; Chen et al., 2015) and in diseases caused by virus. Polymorphisms in the *MASP-2* gene increased protease levels in a Brazilian population and were associated with susceptibility to HCV infection (Tulio et al., 2011). Another study carried out in Brazil showed an association with HTLV-1 infection (Coelho-dos-Reis et al., 2013). On the other hand, no association was found between coronavirus and *MASP-2* polymorphisms in the infection of SARS-CoV in a Chinese population (Wang et al., 2009).

FcγRs (Fc gamma receptors) are a group of surface glycoproteins belonging to the immunoglobulin (Ig) superfamily that binds to the portion Fc of IgG, these receptors are comprised of two classes: activation and inhibition (Nimmerjahn and Ravetch, 2010). FcγRIIA is expressed in monocytes, macrophages, dendritic cells, eosinophils and neutrophils. This receptor is encoded by the *FCGR2A* gene and polymorphism in that gene can alter the FcγRIIA isoform which can be associated with susceptibility to different infections (Pleass and Woof, 2001). The *FcγRIIA R131H* polymorphism has been evaluated in many diseases (Oliveira et al., 2011). In relation to respiratory diseases, this polymorphism was associated with susceptibility and idiopathic severity of pulmonary fibrosis (Bournazos et al., 2010). In our review, only one study evaluated the *FcγRIIA* polymorphism with SARS-CoV infection, the homozygous RR showed an association with disease severity even when factors such as comorbidities were removed from the analysis, revealing that RR genotype is a risk factor for disease severity (Yuan et al., 2005).

#### 4.1.3. Angiotensin-converting enzymes (ACE)

Angiotensin-converting enzymes are an important component of the Renin-angiotensin-aldosterone system, which plays an important role in SARS-COV and SARS-COV-2 infections (Alexandre et al., 2020). There are two types of this enzyme, Angiotensin-converting enzymes 1 (ACE 1) and Angiotensin-converting enzymes 2 (ACE2). The ACE1 cleaves the angiotensin I into angiotensin (Ang) II that binds to AT1R and promotes vasoconstriction and bronchoconstriction, increases vascular permeability, inflammation and fibrosis, resulting in the development of SARS in individuals infected by SARS-COV and SARS-COV2. ACE2 cleaves angiotensin I to angiotensin and angiotensin II to angiotensin, promoting vasodilation, decreased vascular permeability, inhibition of inflammation and fibrosis formation, blocking the effects of angiotensin II/AT1R and protecting the host against SARS (Alexandre et al., 2020; Rossi et al., 2020). However, the role of ACE2 in SARS-COV (or SARS-COV-2) infection may be more complex because this membrane enzyme acts as a receptor to viral entry into the host cell, causing a detrimental effect on the contamination phase (Wang et al., 2008a, 2008b). Therefore, the expression of ACE 1 and ACE2 plays a fundamental role in COVID-19 infection (Tas et al., 2020). Polymorphisms in these genes may influence the levels of gene expression and the catalytic activity of their enzymes (Rigat et al., 1990). In addition to COVID-19, polymorphisms in the ACE2 gene have been associated with other diseases such as hypertension, stroke recurrence, Type 2 Diabetes Mellitus (Devaux et al., 2020; Wu et al., 2017).

In our review, three studies evaluated the association between polymorphisms in the *ACE1* or *ACE2* genes and susceptibility to SARS (Chan et al., 2005b; Itoyama et al., 2005, 2004). Two studies evaluated the *ACE1* insertion/deletion (I/D) polymorphism and showed

controversial results. Itoyama et al. (2004) showed that the D allele was significantly higher in the hypoxemic group than in the non-hypoxic group. However, Chan et al. (2005a, 2005b, 2005c) found no relationship between the *ACE1* insertion/deletion (I/D) polymorphism and susceptibility to SARS or the need for intensive care in patients with SARS. This inconsistency may be attributed to: (1) differences in the selection of study groups. Itoyama et al. (2004) divided SARS cases into two groups: non-hypoxia or hypoxemia. While Chan et al. (2005a, 2005b, 2005c) categorized subjects with severe disease into patients who developed SARS and patients who required admission to the intensive care unit (ICU); (2) the small sample size in the study conducted in Vietnam. Previous reports have shown that individuals with DD genotype has a two-fold increase in ACE levels when compared to II genotype. Therefore, further studies with this and other polymorphisms in the gene *ACE1* are needed to better understand the susceptibility of SARS in patients with coronavirus.

In Vietnamese Population an association between SNPs in the *ACE2* gene and susceptibility to SARS-COV was observed. This study found 19 SNPs, of these, 13 were new SNPs in the literature. None of these SNPs were associated with susceptibility to SARS-COV. However, the small sample size may have influenced the result (Itoyama et al., 2005). The lack of studies involving polymorphisms in the *ACE2* gene in susceptibility to SARS-COV is evident. Therefore, it is necessary to conduct further studies on this topic.

#### 4.1.4. Human leukocyte antigen system (HLA)

The HLA exhibits more than 27,258 known alleles (Institute, M.E.B, n.d.) and molecules resulting from the expression of these genes are also known as MHC (Major Histocompatibility Complex). The HLA gene is found on chromosome 6, in the short arm, and for educational purposes, these genes are grouped into 3 groups, I, II and III genes (Dausset, 1984; Goldberg and Rizzo, 2015).

Class I is located in the most distant region, encoding histocompatibility molecules, classic heavy chains, such as HLA-A, B and C molecules, having an excellent polymorphic characteristic. Class II is located in the most centromeric portion of the MHC region and encodes two chains that form the functional heterodimers: HLA-DR, HLA-DQ, HLA-DP, HLA-DM and HLA-DO, being recognized for its influence on the control immune response. Expression in class II is more restricted when compared to class I, and expression in antigen-presenting cells, such as macrophages and Langerhans cells is predominant. Class III genes are located between class I and I and, even included in the MHC complex, they do not encode histocompatibility molecules and encode other molecules that may or may not be part of the immune system (Goldberg and Rizzo, 2015; Nepom and Erlich, 1991).

In the immune aspect, the action of HLA depends directly on cellular configuration to develop its activity of presenting antigens. Class I cells have extracellular domains, in their heavy chain, that contain amino acid residues, forming peptides that will later be presented to the CD4 T lymphocyte. These molecules are expressed on the surfaces of the nucleated cells. The class II molecules present on the surfaces of some types of cells, such as macrophages and dendritic cells, have 2 domains with amino acid residues that after being processed, join the binding grooves, stabilizing and presenting them to the CD4 T lymphocytes. The variation of amino acids in the regions of the HLA molecules binds and presents different peptides, being recognized by different T lymphocytes. Evidences suggest that this variation is due to the different responses of subjects when they come into contact with foreign antigens (Fernandes et al., 2003).

Each HLA molecule is able to bind widely to various types of peptides (Colten, 1985). The association between HLA class I and the severity of SARS was evidenced by an important increase in the odds ratio of *HLA-B\* 4601* in the group of SARS patients who died or were intubated compared to other groups (Lin et al., 2003). In this study, HLA-class I and II alleles were typed by PCR-SSOP and included 37 cases of probable SARS, 28 patients with fever later excluded as probable SARS and 101

uninfected health professionals who were exposed or possibly exposed to the coronavirus SARS. A set of 190 healthy unrelated normal Taiwanese was used as a control group.

On the other hand, in the study by Keicho et al. (2009) between HLA class II genes, *HLA-DRB1\*12* there was a positive association and *HLA-DRB1\*13* showed a negative association when the SARS group was compared with the contacts. When patients contact and non-contacts were compared together as a single control group, *HLA-DRB1\*1202* showed a significant association, under the dominant model, it was the most strongly associated with SARS. The study population was composed by unrelated Vietnamese patients: 44 SARS patients, 103 staff members from the same hospital who had contact with patients, and 50 healthy individuals with no history of contact with SARS patients.

A study conducted in Chinese population, included 95 individuals recovered from SARS (Xiong et al., 2008), found no association between the HLA -A,-B and -DRB1 alleles with the development of SARS. The authors suggest that other factors such as relative population density, frequency and extent of travel by affected individuals and the rapid introduction and adoption of protective measures may have influenced the restricted spread of SARS.

#### 4.1.5. Cluster of differentiation

Immune responses to pathogens are identified by Pattern recognition receptors (PRRs) (Amarante-Mendes et al., 2018; Lee and Kim, 2007). Polymorphisms in this gene may consecutively affect the immunity of the host, entry and replication of the virus (Geijtenbeek et al., 2009). In this review we identified that polymorphisms in cluster of differentiation 209 (*CD209/DC-SIGN*), cluster of differentiation 14 (*CD14*), liver/lymph node-specific intracellular adhesion molecules-3 grabbing non-integrin (*L-SIGN*), cell-specific intercellular adhesion molecule and dendrites (*ICAM-3*) and fibrinogen-like protein 2 (*FGL2*) have been associated with SARS in patients with coronavirus.

The *CD209* gene is located on chromosome 19p13.2-3 and the polymorphism of *DC-SIGN* (*CD209* 9) in promoter region -336A>G (rs4804803) affects Sp1 transcription factor and was reported influencing in the transcription activity of *CD209* in vitro (Liu et al., 2003). It was investigated in study included, and this molecule is relevant in the early interaction of some pathogens with dendritic cells specially viruses (Sakuntabhai et al., 2005). This polymorphism was not related with susceptibility to SARS (Chan et al., 2010). However, the A/A genotype of this variant was related to increase serum levels of lactate dehydrogenase (LDH). This enzyme is released into the extracellular environment during cellular damage and it was associated with inflammation in infections (Glick, 1969).

*ICAM-3* (cell-specific intercellular adhesion molecule and dendrites) is a linked to mannose expressed on the surface of dendritic cells and is a molecule relevant for initiating the immune responses measured by T cells (Fawcett et al., 1992; Montoya et al., 2002). *L-SIGN* is homolog to *DC-SIGN* (*CD209*) belongs to calcium-dependent lectin and expression is restricted to lymph node endothelial cells, sinusoidal endothelial cells of the placenta and liver (Braet and Wisse, 2002). In a research conducted in a Chinese population, the homozygosity for *L-SIGN* was linked to a protective role to SARS susceptibility (Chan et al., 2006). A correlation between homozygous *ICAM3* Gly143 (rs2304237) polymorphism and higher LDH levels and lower total white blood cell counts in SARS Chinese patients (Chan et al., 2007).

LDH is an enzyme that catalyzes the conversion of pyruvate to lactate with subsequent conversion to NADH and NAD<sup>+</sup> (Hsu and Sabatini, 2008). Increased levels can lead to injury and organ failure, influencing the clinical outcomes of patients with COVID-19 (Henry et al., 2020). Investigations into the role of LDH levels in COVID-19 infection concluded that there was a significant increase in patients with disease severity and pneumonia (Henry et al., 2020; Hsu and Sabatini, 2008), contributing to the dynamics of mortality. In addition, the decrease in blood components can culminate in hypoxic conditions in critically ill patients.

The differentiation antigen cluster 14 (*CD14*) is a receptor with multiple inflammatory functions and it is located on the surface of macrophages and monocytes (Mendel et al., 2014). *CD14* associated with lipopolysaccharide (LPS) receptor pathway through the TLR4, culminate in the release of proinflammatory cytokines (Fernández-Real et al., 2003), triggering inflammation reaction which causing the endothelial damage, disturbance of immunologic function and vascular smooth muscle cells proliferation (De Tena et al., 2005). In Chinese population with coronavirus and SARS, the C/C genotype of -159 C>T SNP (rs2569190) in *CD14* gene was more frequent in patients with SARS, suggesting that enhanced viral toxicity due to decreased antiviral response leading to disease severity (Yuan et al., 2007).

Fibrinogen-like protein-2 (*FGL2*) is regulated by CD4<sup>+</sup> T cells and has immunosuppressive and inflammatory properties (Lin et al., 2017). This protein was investigated as a candidate biomarker to predict the severity of the disease in viral infections (Luft et al., 2018; Zhu et al., 2005). In patients with SARS due to coronavirus infection, the +158 T/\* (rs2075761) polymorphism was described as a risk of disease severity (Hsieh et al., 2010). Studies have previously shown that *Fgl2* influences the inhibition of dendritic cells maturation and progression of B cells apoptosis and macrophages (Joller et al., 2014; Liu et al., 2010).

#### 4.2. Others polymorphisms

Other polymorphisms were identified in order to trace knowledge about the genetic background of patients with SARS-COV infection: Alpha 2-HS Glycoprotein (*AHSG*); Cytochrome P450 Family 3A (*CYP4F3A*) and protein kinase R (*PKR*). Alpha 2-HS Glycoprotein (*AHSG*) and Cytochrome P450 Family 3A (*CYP4F3A*) have been studied in the Chinese population with SARS-CoV during 2003 epidemic. The authors concluded that AA genotype of the SNP rs2248690 of the *AHSG* gene was correlated with protection for SARS, which is related to the elevation of serum levels of this liver glycoprotein. This is vital for the deactivation of macrophages in view of the immune response, which suggests that polymorphisms in this gene are relevant to determine a possible role for resistance to SARS-CoV infection (Zhu et al., 2011).

A recent study conducted in the Spanish and Italian population carried out a study of genomic association in the Spanish population in order to be able to track SNPs related to the severity of the disease and consecutively with respiratory failure. It was concluded that in locus 3p21.31, the genes *SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6* and *XCR1* were related to SARS-CoV-2. The 9q34.2 locus present in the ABO blood group, demonstrated that people with blood group A are 1.45 times more likely to develop severe SARS-CoV-2 when compared to blood group O (Ellinghaus et al., 2020).

## 5. Conclusion

In conclusion, our systematic review emphasized the association of polymorphisms with susceptibility or protection to SARS-COV infection. The study of genetic polymorphisms related to SARS-COV has been explored in the literature. Therefore, new studies with this proposal may contribute to a better understanding of the disease susceptibility, mainly of COVID-19 (SARS-COV-2) which has been current focus on global health, considering clinical syndromes associated: mild disease, uncomplicated pneumonia, severe pneumonia, SARS, sepsis and septic shock. Additional studies, including best study designs, implications polymorphisms on the profile clinic (presence of comorbidities) and severity (including asymptomatic population; classification of patient severity), laboratorial parameters (blood count, coagulation profile, including renal and liver function, creatine kinase, lactate dehydrogenase, electrolytes, myocardial enzymes, cytokines, serum ferritin and procalcitonin), genetic polymorphism and prolonged mechanical ventilation and genic expression are needed to enhance the prediction of these results leading to a better understanding of the interaction between genes and outcome of clinic SARS-COV.

## Declaration of competing interest

1. All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.
2. This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue.
3. The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript
4. The following authors have affiliations with organizations with direct or indirect financial interest in the subject matter discussed in the manuscript.

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