A Systematic Review on Papers That Study on SNPs That Affect SARS-CoV-2 Infection & COVID-19 Severity

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Research Article

Keywords: SARS-CoV-2 infection, COVID-19 severity, SNPs, systematic review, global public health

Posted Date: May 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-470358/v1

Abstract

Background:

COVID-19, caused by SARS-CoV-2 has become the most threatening issue to all populations around the world. It is directly and indirectly affecting all of us and thus, is a emergence topic dealt in global health. In order to avoid the infection, various studies have been done and still ongoing. Now having over 141 million cases of COVID19 and causing over 3 million deaths around the world, the tendency of infection and degree severity of the disease shown in different groups of people came up as an issue. Here, we reviewed 21 papers on SNPs related to SARS-CoV-2 infection severity and analyzed the results of them.

Methods:

The PubMed databases were searched for papers discussing SNPs associated with SARS-CoV-2 infection severity. Clinical studies with human patients and statistically showing relevance of the SNP with virus infection were included. Quality Assessment of all papers were done with Newcastle Ottawa Scale.

Results:

In the analysis, 21 full-text literatures out of 2956 screened titles and abstracts, including 63496 cases, were included. All were human based clinical studies, some based on certain regions gathered patient data and some based on big databases obtained online. ACE2, TMPRSS2, IFITM3 are the genes mentioned most frequently that are related with SARS-CoV-2 infection. 20 out of 21 studies mentioned one of more of those genes. The relevant genes according to SNPs were also analyzed. rs12252-C, rs143936283, rs2285666, rs41303171, and rs35803318 are the SNPs that were mentioned at least twice in two different studies.

Conclusions:

We found that ACE2, TMPRSS2, IFITM3 are the major genes that are involved in SARS-CoV-2 infection. The mentioned SNPs were all related to one or more of the above mentioned genes. There were discussions on certain SNPs that increased the infection severity to certain ethinic groups more than the others. However, as there is limited follow up and data due to shortage of time history of the disease, studies may be limited.

Introduction & Background

In 2020, coronavirus disease 2019 (COVID-19) posed a serious global public health threat. According to JHU Coronavirus Resource Center live update, the total cases of COVID-19 has reached more than 144 million and caused over 3 million deaths over the globe. The COVID-19 pandemic has been studied from diverse perspectives, and health care professionals are trying their best to control the pandemic. As the consequences of COVID-19 are potentially severe, avoiding infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is important. Ethnicity has been found to affect the severity of COVID-19. The virus first emerged in East Asia, but relatively higher rates of morbidity and mortality have been identified in European populations. It is therefore important to determine the mechanism underlying the effect of ethnicity on the severity of COVID-19. With regard to the biochemistry of SARS-CoV-2, the binding of the viral spike (S) protein to cellular receptors and priming of the S protein by host cell proteases are significant factors affecting the entry of SARS-CoV-2 into the host cell.[1, 2] Several studies have found that angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) are involved in this step. ACE2 is the cellular receptor to which SARS-CoV-2 binds, thereby gaining entry into the host cell. ACE2 is involved in regulatory processes in our body. ACE2 is also the functional receptor for severe acute respiratory syndrome coronavirus (SARS-CoV). As the expression levels of ACE2 are high in the heart and lungs, COVID-19 patients can develop heart- and lung-related complications. TMPRSS2 cleaves the spike protein of SARS-CoV-2, leading to the activation of the virus and cellular membrane.[3] Given the involvement of these proteins in the entry of SARS-CoV-2 into host cells, it is possible that the relationship between ethnicity and disease severity is due to single-nucleotide polymorphisms (SNPs) in the corresponding genes. Therefore, in this systematic review, we aimed to discover the related SNPs of SARS-CoV-2 infection by going through all the SNPs mentioned in 21 papers of identical topic. We analyzed 21 papers on SNPs in the genes encoding mainly ACE2 and TMPRSS2 and their connections with COVID-19.

Method

1. Literature search method

PubMed, EMBASE, and Cochrane Library were searched for relevant articles. Going through the selected number of journals related to the topic, keywords were extracted from the journals, and a Medline search expression was created. The main text words were SARS-CoV-2, COVID-19, coronavirus disease, variant genes, whole-exome sequencing, and significant linkage disequilibrium. Then, the MeSH terms were derived from the main text words chosen. Text words were searched as [tiab], and MeSH terms were searched as [MeSH] to indicate the purpose of each word. When linking the keywords, AND and OR was used according to the needs of the selected terms and keywords. The article selection process was

performed by two independent reviewers. The final searching expression used is ((SARS-CoV-2[tiab] OR COVID-19[tiab] OR “Coronavirus disease”[tiab] OR “Severe acute respiratory syndrome coronavirus 2”[tiab] OR coronavirus[tiab]) **OR** (SARS-CoV-2[Mesh] OR “Spike Glycoprotein, Coronavirus”[Mesh] OR COVID-19[Mesh] OR Betacoronavirus[Mesh] OR “Coronavirus Infections”[Mesh])) **AND** ((“Variant gene”[tiab] OR “whole-exome sequencing”[tiab] OR “allele frequency”[tiab] OR mutations[tiab] OR “protein-protein interaction”[tiab] OR “Significant linkage disequilibrium”[tiab] OR LD[tiab] OR PPI[tiab] OR Varients[tiab] OR Coding[tiab] OR Missense[tiab] OR “epigenetic modification”[tiab] OR polymorphism[tiab]) **OR** (“Molecular Docking Simulation”[Mesh] OR “Protein Interaction Domains and Motifs”[Mesh] OR “Virus Internalization”[Mesh] OR “High-Throughput Nucleotide Sequencing”[Mesh] OR “Polymorphism, Single Nucleotide*”[Mesh] OR “Real-Time Polymerase Chain Reaction”[Mesh])).

2. Paper selection

All the papers gained from searching using the Medline expression from above, were taken as initial 2956 papers. Then, the following exclusion criteria were used to exclude the papers inappropriate for inclusion in this systematic review.

The following exclusion criteria were applied:

1. Animal studies and studies with human subjects involving other coronaviruses, such as bovine coronavirus and deltacoronavirus.
2. Editorial letters, case reports, technical notes, meta-analyses, reviews, and systematic reviews.
3. Studies on irrelevant topics, such as porcine diarrhea.
4. Studies on COVID-19 that did not discuss genetics or the cellular infection mechanism.

3. Data extraction

Data extraction was performed by 2 of us independently. Any type of discord on the data selection or extraction were resolved through discussion. Following criteria were considered when extracting the data: type of trial, clinical and study outcomes, study population, statistically powerful results, and topic relevance.

4. Quality Assessment

The Newcastle Ottawa Scale (NOS) was used to assess the quality of the 21 included papers. This quality assessment tool was formed by a collaboration between two universities, the University of Newcastle, Australia, and the University of Ottawa, Canada. The NOS was created for the assessment of the quality of nonrandomized studies, such as case-control and cohort studies. There are 3 domains in the NOS: selection, comparability, and outcome. [4]

Selection considers the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study. For questions 2 and 3 in the outcome section, which ask about follow-up, all papers had to be scored as “yes.” COVID-19 is a recent issue; therefore, the follow-up duration could not be as long as in studies on other topics. The comparability of the duration of follow-up between the included studies and usual studies had to be deemed acceptable. There were 4 assessment questions under the *selection* section. For representativeness of the exposed cohort section, *a) truly representative*, and *b)somewhat representative* were both given one star. For selection of the non-exposed cohort, *a) Drawn from the same community as the exposed cohort* was given one star. For ascertainment of the exposure, both *a)Secure record* and *b)Structured interview* were given a star. Last question under the selection section, demonstrated that outcome of interest was not present at start of study, choice of *a)Yes*, is only given a star. The only criteria to assess the comparability, comparability of the cohorts on the basis of the design or analysis is controlled for cofounders, both choice *a) The study controls for age, sex, and marital status* and *b) Study controls for other factors* were given a star. Under the outcome section, there were three questions to follow in order to assess the corresponding criteria. For assessment of outcome, both choice *a) Independent blind assessment* and *b) Record linkage* were given a star. Second question under outcome section, was follow-up long enough for outcomes to occur, choice *a)Yes* is given a star. Last question for assessing outcome, adequacy of follow-up of cohorts, both answer of *a) Complete follow-up all subject accounted for* and *b) Subjects lost to follow up unlikely to introduce bias-number lost less than or equal to 20% or description of those lost suggested no different from those followed* are the choices given a star. [5]

Results

Out of 2956 papers searched initially, 21 academic papers were selected for the systematic review. (Fig. 1) 21 papers discussing and analyzing genetic factors related to infection with SARS-CoV-2 were reviewed. 18 of them were published in 2020, and 3 were published in 2021. Out of the 21 papers, 5 papers [6–10] recruited patients from specific regions or hospitals. The other 16 papers used large databases, such as the 1000 Genomes Project, gnomAD, National Center for Biotechnology Information (NCBI), Global Initiative on Sharing Avian Flu Data (GISAID) Illumina, and the World Health Organization (WHO) dashboard. All papers reviewed were assessed with Newcastle Ottawa Scale, and scored 8 out of 8 equivalently. In total, the mean ± standard deviation number of patients per paper was 63496 ± 13889.90; the numbers of patients in the

databases mentioned above were not taken into account. The average age of the subjects was 55 years old; however, this value is not accurate because multiple studies did not report age or only recorded the age range and not the average age. The genes investigated in these papers were mainly ACE2 and TMPRSS2. IFITM3, CD147, IFIH1, IL6, LZTFL1, and ACE1 were also mentioned in some papers. (Table 1)

Table 1
Characteristics of the included studies

First author (last name)	publication year	Country	Journal	Database name	number of subjects	mean age (years) mean ± SD	Gene	SNP
Maiti et al. [25]	2020	USA	Immunogenetics	1000 genome project	N/A	N/A	IFIH1	N/A
Torre-Fuentes et al. [6]	2021	Spain	Journal of Medical Virology	MS family cohort	120	N/A	ACE2, TMPRSS2	rs61735794, rs61735792, rs75603675, rs41303171, rs35803318
Gomez et al. [7]	2021	Spain	Cytokine	Hospital Univ. Central Asturias, Spain	311	65.23 ± 15.16	IFITM3	rs12252-C
Zhang et al. [8]	2020	China	The Journal of Infectious Diseases	Patients were recruited from Beijing Youan Hospital, Capital Medical University, Beijing, between January 2020 and February 2020	80	49.5	IFITM3	rs12252-C
Hussain et al. [11]	2020	Pakistan	Journal of Medical Virology	Ensembl, Genome Browser12, gnomAD.	N/A	N/A	ACE2	rs73635825 (S19P), rs143936283 (E329G)
Gomez et al. [9]	2020	Spain	elsvier	Hospital Univ. Central Asturias, Spain	740	67.44	ACE, ACE2	rs2285666(rs879922)
Wang et al. [12]	2020	China	Journal of General Virology	dbSNP, National Genomics Data Center	N/A	N/A	ACE2	rs143936283 rs267606406 rs4646116
Fujikura et al. [15]	2020	Japan	Journal of clinical pathology	1000G, NHLBI, gnomAD, ToMMo, UK10K	669	N/A	ACE2, TMPRSS2	N/A
Yamamoto et al. [16]	2020	Japan	elsvier	high-coverage sequenced data of the phase 3 panel of the international 1000 Genomes Project (1000Genomes) and the Korean Personal Genome Project (KPGP)	N/A	N/A	ACE, ACE2	N/A
Sienko et al. [17]	2020	Poland	Clinical Interventions in Aging	N/A	6272	N/A	ACE2, TMPRSS2, CD147	N/A
Paniri et al. [18]	2021	Iran	Gene Rep	NCBI, UniProtKB, PANTHER	52,456	N/A	ACE2	rs149039346, rs147311723, rs714205, rs1514283, rs4646175, rs3746444, rs113808830, rs3751304
Nguyen et al. [10]	2020	Vietnam	PLoS One	A hospital in Vietnam	44	15–74	hACE2	N/A

First author (last name)	publication year	Country	Journal	Database name	number of subjects	mean age (years) mean ± SD	Gene	SNP
Senapati et al. [19]	2020	India	J Ganet	GTEx, Uniprot	26	60 or more	ACE2, TMPRSS2, CD26	rs112657409, rs11910678, rs77675406 and rs713400, rs13015258
Novelli et al. [20]	2020	Italy	Human Genomics	GnomAD	131	N/A	ACE2	N/A
Vargas-Alarcón et al. [21]	2020	Mexico	ELSEVIER	dbSNPs, Ensembl Genome Browser, and 1000 Genome Project databases	N/A	N/A	ACE2, TMPRSS2, TMPRSS11A, ELANE, CTSL	rs12329760
Benetti et al. [22]	2020	Italy	European Journal of Human Genetics	NIG-db, LOVD, gnomAD,,	389	N/A	ACE2	rs775181355, rs762890235
Strafella et al. [13]	2020	Italy	MDPI	Ensembl, 1000 Genomes, GnomAD	268	46 ± 15	ACE2	rs35803318, rs41303171, rs774469453, rs773676270, rs2285666
Shikov et al. [23]	2020	Russia	Front Genet	gnomAD	58	N/A	ACE2	rs146598386, rs73195521, rs755766792
Srivastava et al. [14]	2020	India	Front. Genet	1,000 genome project	N/A	N/A	ACE2	rs2285666
Yang et al. [26]	2020	Taiwan	PNAS	GISAID Illumi,na	1932	N/A	N/A	N/A
Kim et al. [24]	2020	South Korea	MDPI	World Health Organization (WHO) COVID-19 dashboard	N/A	N/A	IFITM3, ACE2, TMPRSS2, IL6, LZTFL1	rs6598045

Quality assessment

All papers had equal quality assessment scores. (Table 2) The papers varied in terms of the representativeness of the cohort. Specifically, the papers that used databases were categorized as “truly representative.” The remaining papers, which were classified as “somewhat representative,” collected genomic data from patients from a single hospital or region. Since the aim of this systematic review was to identify SNPs associated with infection with SARS-CoV-2 and the severity of COVID-19 regardless of other health factors, papers that were relevant to the purpose of the review were mostly assessed as being appropriate.

Table 2
Newcastle-Ottawa Scale to Assess Quality of Studies involved in Systematic Review

	selection					Outcome			
	representativeness of expressed cohort	selection of non expressed cohort	ascertainment of exposure	outcome not present at the start of the study	Comparability	Assessment of outcomes	Length of follow-up	Adequacy of follow-up	Total score
Maiti et al. [25]	a	a	a	a	a	a	a	a	8
Torre-Fuentes et al. [6]	b	a	a	a	a	a	a	a	8
Gomez et al. [7]	b	a	a	a	a	a	a	a	8
Zhang et al. [8]	b	a	a	a	a	a	a	a	8
Hussain et al. [11]	b	a	a	a	a	a	a	a	8
Gomez et al. [9]	b	a	a	a	a	a	a	a	8
Wang et al. [12]	a	a	a	a	a	a	a	a	8
Fujikura et al. [15]	a	a	a	a	a	a	a	a	8
Yamamoto et al. [16]	b	a	a	a	a	a	a	a	8
Sienko et al. [17]	a	a	a	a	a	a	a	a	8
Paniri et al. [18]	a	a	a	a	a	a	a	a	8
Nguyen et al. [10]	b	a	a	a	a	a	a	a	8
Senapati et al. [19]	b	a	a	a	a	a	a	a	8
Novelli et al. [20]	b	a	a	a	a	a	a	a	8
Vargas-Alarcón et al. [21]	b	a	a	a	a	a	a	a	8
Benetti et al. [22]	b	a	a	a	a	a	a	a	8
Strafella et al. [13]	b	a	a	a	a	a	a	a	8
Shikov et al. [23]	b	a	a	a	a	a	a	a	8
Srivastava et al. [14]	b	a	a	a	a	a	a	a	8
Yang et al. [26]	b	a	a	a	a	a	a	a	8
Kim et al. [24]	a	a	a	a	a	a	a	a	8

Genes and SNPs related

In the 21 included papers, ACE2 was mentioned most frequently, and TMPRSS2 and IFITM3 were also mentioned in some papers. Overall, there were some SNPs reported in multiple studies as being related to infection with SARS-CoV-2 and the severity of COVID-19.

As the study was performed with limited data sources and the diversity of the study populations varied, it was difficult to identify common SNPs. However, several common SNPs were found in the studies, namely rs12252-C [7, 8], rs143936283 [11, 12], rs2285666 [13, 14], rs41303171 [6, 13], and rs35803318 [6, 13]. (Table 3) Two studies mentioned rs12252-C. These studies investigated IFITM3 (transmembrane protein 3), which is known to be associated with the severity of influenza and other viral infections. Gomez et al. 2021 [7] database was on Spanish population and Zhang et al. 2020 [8] study was based on Chinese population. The rs12252 C variant is known to be highly associated with Chinese population's influenza infection. However, as it is commonly found as a risk factor in Spanish database study suggests that rs12252 C affects all population's SARS-CoV-2 infection including European population. The other SNPs that were investigated in multiple studies, namely, rs143936283, rs2285666, rs41303171, and rs35803318 are in ACE2. The papers these SNPs were measured based their study on general databases such as Ensembl, 1000 Genomes, and GnomAD. Therefore, these SNPs can't be specified or analyzed in affecting a certain ethnicity group. Moreover, when looking at the genes and corresponding related SNPs mentioned, ACE2 and TMPRSS2 are often indicated together. Some studies suggest that ACE2 and TMPRSS2 have synergistic effects together, activating the ACE2 as an entry receptor. (Table 1) In detail, TMPRSS2 cleaves the viral spike glycoprotein (S) and leads to viral activation facilitation. [3] Adding on to the above-mentioned SNPs, rs75603675, rs2285666, rs879922, rs73635825, rs143936283, rs143936283 rs267606406 rs4646116, rs149039346, rs147311723, rs714205, rs1514283, rs4646175, rs3746444, rs113808830, rs3751304, rs112657409, rs11910678, rs77675406, rs713400, rs13015258, rs12329760, rs775181355, rs762890235, rs35803318, rs41303171, rs774469453, rs773676270, rs2285666, rs146598386, rs73195521, rs755766792, rs2285666, and rs6598045, in total 34 SNPs, showed relation with ACE2 gene action. 9 SNPs, rs61735794, rs61735792, rs75603675, rs112657409, rs11910678, rs77675406, rs713400, rs13015258, and rs12329760, were the SNPs all showed to have linkage with TMPRSS2. IFITM3 had 2 associated SNPs mentioned out of the studies reviewed, which were rs12252-C and rs6598045. (Table 4) ACE2 had the greatest number of related SNPs and IFITM3, then TMPRSS2.

Table 3
SNPs mentioned twice or more in the reviewed studies

SNP	Gene	Mentioned Paper
rs12252-C	IFITM3	Gomez et al. 2021 [7]
		Zhang et al. 2020 [8]
rs143936283	ACE2	Hussain et al. 2020 [11]
		Wang et al. 2020 [12]
rs2285666	ACE2	Strafella et al. 2020 [13]
		Srivastava et al. 2020 [14]
rs41303171	ACE2	Torre-Fuentes et al. 2020 [6]
		Strafella et al. 2020 [13]
rs35803318	ACE2	Torre-Fuentes et al. 2020 [6]
		Strafella et al. 2020 [13]

Table 4
Genes mentioned twice or more in the reviewed studies and the according related SNPs mentioned

Gene	Related SNPs	Role of the gene
ACE2 (angiotensin I converting enzyme 2)	rs75603675, rs2285666, rs879922, rs73635825, rs143936283, rs143936283 rs267606406 rs4646116, rs149039346, rs147311723, rs714205, rs1514283, rs4646175, rs3746444, rs113808830, rs3751304, rs112657409, rs11910678, rs77675406, rs713400, rs13015258, rs12329760, rs775181355, rs762890235, rs35803318, rs41303171, rs774469453, rs773676270, rs2285666, rs146598386, rs73195521, rs755766792, rs2285666, rs6598045	SARS-CoV-2 spike protein entry receptor [15]
IFITM3 (interferon-induced transmembrane protein 3)	rs12252-C, rs6598045	Gene variants of IFITM3 are related to the infection of influenza and viruses. IFITM3 is significant in taking antiviral actions. It prevents cellular lipid bilayer getting bisected by viruses. [7] Immune effector protein that is significant to restriction of virus is encoded by IFITM3. Also, membrane restriction is done by IFITM3. [8]
TMPRSS2 (transmembrane protease, serine 2)	rs61735794, rs61735792, rs75603675, rs112657409, rs11910678, rs77675406, rs713400, rs13015258, rs12329760	Cleavage of TMPRSS2 activates influenza virus hemagglutinin and the human metapneumovirus F protein [3]

Discussion

This study is started from interest and curiosity on the studies that suggests a certain group of people has greater susceptibility to SARS-CoV-2. Therefore, aim of this study is to find out genes and SNPs that are related to SARS-CoV-2 infection severity. 21 papers are in depth reviewed to analyze the highly associated or frequently mentioned genetic factors. We can conclude that genetic susceptibility to infection with SARS-CoV-2 mainly involves ACE2 and TMPRSS2. Torre-Fuentes et al. [6], Hussain et al. [11], Gomez et al. [9], Wang et al. [12], Fujikura et al. [15], Yamamoto et al. [16], Sienko et al. [17], Paniri et al. [18], Nguyen et al. [10], Senapati et al. [19], Novelli et al. [20], Vargas-Alarcon et al. [21], Benetti et al. [22], Strafella et al. [13], Shikov et al. [23], Srivastava et al. [14], and Kim et al. [24] mention ACE2 as SARS-CoV-2 susceptibility related gene. Fujikura et al. [15], Sienko et al. [17], Senapati et al. [19], Vargas-Alarcon et al. [21], and Kim et al. [24] mention TMPRSS2. Gomez et al. [7], Zhang et al. [8], and Kim et al. [24] discuss IFITM3 as genes that are associated with coronavirus 2019 infection severity.

This study is the first study to gather the genetic studies related to SARS-CoV-2 infection and suggest an analyzed tendency of the data. As COVID-19 is the issue of greatest attention, and there is no determintate cure for the infection of the virus, this study may somehow suggest ways for research in SARS-CoV-2 infection cures. Looking at most of the papers that deal with genetic factors of SARS-CoV-2 infection severity, it clearly tells which factors should be focused and targeted. Also, by further studies of the genes and SNPs mentioned, which biological characteristics of people are comparably more vulnerable to the disease infection. Knowing which group are more vulnerable and what traits makes easier infection or disease development, prevention of epidemics may be improved.

COVID-19 has only been studied for approximately one year; therefore, there are limitations regarding identifying genetic factors related to susceptibility to infection with SARS-CoV-2. First, genetic factors affecting susceptibility to infection and severity of disease have not yet been investigated separately. Some studies have suggested that unlike Asians, Caucasians have SNPs that make them more susceptible to severe COVID-19. The papers did not clearly state which SNPs are involved in infection with SARS-CoV-2 and which are involved in disease progression. It would be useful to investigate these two topics separately in future studies.

Second, the strength of the effects of these SNPs on susceptibility to infection with SARS-CoV-2 should be quantified in future studies. As progression disease is affected by the health status of the individual patient, the strength of the contribution of genetics could be challenging to quantify. However, the genes and SNPs could be ordered in terms of their relative contributions. Third, the SNPs that were mentioned to be related to certain gene's action, (Table 3 & Table 4) do not straight away affect the mechanism. Several SNPs affect the genes' action via indirect path; therefore, it may not always be applicable to all individuals. As they are from all different studies that had different approach, the SNPs collected may not necessarily affect COVID-19 infection. Lastly, as the COVID-19 pandemic developed recently and is ongoing, there were limitations with regard to performing a systematic review. The papers included in this review were mainly published in 2020, with a few published in 2021. As the pandemic started in late 2019, papers on the topic were limited to 2019–2021. This limited the duration of clinical follow-up. Therefore, in the outcome section of the quality assessment of the articles, the second criterion, which pertains to follow-up, had to be marked as "yes." Normally, clinical follow-up of less than one year would not be assessed as "yes." In this case, long-term follow-up was impossible due to the recent cause of the pandemic.

Conclusion

ACE2, TMPRSS2, IFITM3 were found to be the most frequently mentioned genes that are associated with SARS-CoV-2 infection. There were 5 SNPs that were found common in two or more studies (rs12252-C, rs143936283, rs2285666, rs41303171, rs35803318). These SNPs are all related to the genes mentioned above. Although there were some limitations due to lack of data range and follow up time, this study still suggests a general genetic characteristic of vulnerable SARS-CoV-2 infection. Future further research may be done to specify the exact impact of the SNP in terms of severity and degree of impact.

Declarations

Ethics approval, guidelines, and consent to participate:

not needed as the research does not include a direct clinical testing

Consent for publication:

All the authors have approved

Availability of data and materials:

The studies included in the systematic review are all retrieved from PubMed.gov. All studies included can all be found at PubMed.gov.

Competing interests:

Not applicable

Funding:

Not applicable

Author's Contributions:

Siyeon Suh wrote the main manuscript text. Sun Ha Jee helped on choosing the topic and supervised on writing the manuscript. Sol Lee, Ho Gym, Sun Ha Jee, and Sanghyuk Yoon helped to prepare the figures. Seunghwan Park, Jihi Cha, Do-Hyung Kwon, and YunSu Yang have done the administration process to write the article. All authors reviewed the manuscript.

Acknowledgements:

Not applicable

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Figures

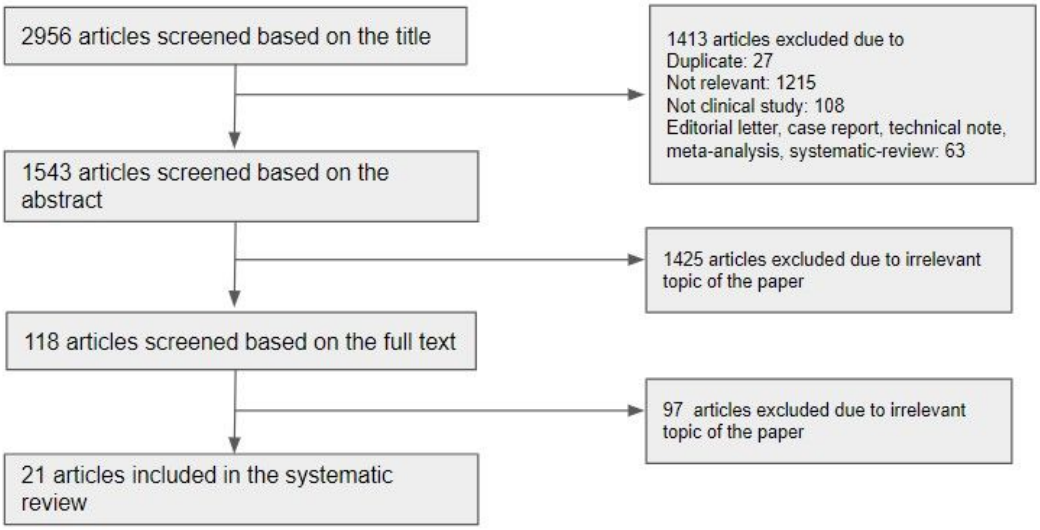

Figure 1

Flow chart depicting literature search and selection process