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*Review Article*

# Angiotensin-Converting Enzyme 2 (ACE2) Polymorphism Underlies Greater Genetic Association with COVID-19: A Systematic Review

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**Keywords:** Angiotensin converting enzyme 2, Single nucleotide polymorphism, SARS-COV-2, COVID-19

## Abstract

**Introduction:** Susceptibility to SARS-COV-2 has been associated with genetic variants in different Cohort and genome wide association studies. SARS-COV-2 is a deadliest virus that has so far leads to millions of deaths around the globe. Different risk factors have been determined for COVID-19 infection including older age, gender and associated comorbidities i.e. cardiovascular disease, diabetes and obesity. Recent developments have shown that certain genes can augment or reduce the infection process. This study was mainly focused to investigate the genetic association of ACE2 polymorphism with COVID-19.

**Methods**: Current study includes systematic review of ACE2 gene and different polymorphism involvement in susceptibility to COVID-19. Data was extracted from all the selected papers. Original articles and papers written in English language were retrieved from Dec 2019 to March 2022. A total of 32 articles were selected for this review.

**Results:** Reports confirmed that SARS-COV-2 uses ACE2 as a receptor to enter into the cell. Analysis showed that females are less prone to be infected compared to males. One study confirmed that the variant (rs190509934) having allelic frequency 0.2-2% downregulate the expression of ACE2 by 37% thus lowering the infection risk of SARS-COV-2 by 40% confirming that there is strong association of ACE2 polymorphism with COVID-19. Besides, several studies showed that presence of certain variants exhibits a protective effect by decreasing the binding affinity of ACE2 to spike protein. One study suggested that individuals having HLA-B 15:03 allele may have immunity against infection.

**Conclusion:** Different genetic variants play crucial role in the outcome of the disease. An association was found between genetic polymorphism and susceptibility to COVID-19. The fact that ACE2 gene polymorphism is associated with various diseases can become an important marker for identifying the susceptibility and resistance against SARS-COV-2 infection.

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## Introduction

Coronavirus that causes COVID-19 disease first surfaced in Wuhan city, China, on December 8, 2019. In March 2020 World Health Organization (WHO) declared it pandemic and classified virus as SARS-COV-2 (previously known as n-CoV) according to international virus classification commission [1]. COVID-19 which is caused by severe acute respiratory syndrome Corona-Virus 2 (SARS-COV-2) infected over 410 million people in 181 countries leading to about 5.8 million deaths to date.

Coronaviruses belong to single positive-stranded RNA viruses class that has the largest genome of all RNA viruses, can cause Cardiovascular, Respiratory and Enteric diseases in humans and animals [2]. Transmitted mainly to lung epithelial cells through aerosols, certain immune cells also in response to SARS-COV-2 can augment the process of infection like peripheral neutrophilia and lymphocytopenia. At the same time sudden upsurge in Pro-inflammatory cytokine can also have serious repercussion making it a good marker for understanding COVID-19 pathophysiology [3]. Elderly people with comorbidities such as Diabetes, Cardiac disease, pulmonary disease, kidney disease, and hypertension are at the risk to develop more severe symptoms and high mortality count rate [4]. Angiotensin converting enzyme 2 (ACE2) is one of the key receptors to which SARS-COV-2 spike protein binds and with the aid of TMPRSS2 (Transmembrane serine protease 2) it gains entry into the cell [5, 6]. ACE2 is a zinc metalloproteinase, act as a monocarboxy-peptidase which dissociates AngI to generate nonapeptide 1-9 and AngII to generate heptapeptide Ang 1-7. ACE2 and TMPRSS2 is involved in the entry of SARS-COV-2 to the cell.

Depending upon the presence and expression of ACE2 receptor SARS-COV-2 mainly infects the lungs, heart, liver, kidney, small intestine, and testes therefore, genetic differences in ACE2 and TMPRSS2 could be playing an important role in outcome of COVID [7]. ACE2 has multiple roles that includes, functional receptor for SARS-COV-2 [8], catalytic activities with different substrates [9], Cardiovascular homeostasis, Cardiac physiology, negative regulator of activated Renin-aldosterone system in Diabetic Cardiomyopathy, regulation of cardiac function and an amino acid transporter [10]. Initially ACE2 was considered to be only expressed in heart, kidney, testes but later reports identified its expression in various other organ system including cardiovascular system (Cardiac fibroblast, Cardiomyocytes and coronary vascular endothelium), brain lungs and kidney [11]. Few studies also mentioned that not only genetic difference contribute to why certain population are more affected by SARS-COV-2 but gender-based-differences also play crucial role in susceptibility and severity of COVID-19. For instance, elevated level of testosterone increase the level of TMPRSS2 (transmembrane serine protease 2) causing male gender to be more susceptible to COVID-19 [12].Polymorphism in ACE2 gene is linked to various diseases therefore studying and analyzing those genetic variants and their expression can provide detailed information about these variants and can help in finding certain markers that cabe used for identifying susceptibility or resistance against SARS-COV-2 infection [13]. Numerous genetic factors include viral entry and immune response can augment the severity and susceptibility to SARS-COV-2. This systematic review aims to discover the genetic association of ACE2 polymorphism with COVID-19 disease severity and susceptibility by studying the published literature to identify the risk indicators and their consequences.

## Materials and Methods

### Study Design

A systematic review of literature was carried out using PRSIMA guidelines and articles were selected according to our relevant study. Reviews were available on ACE2 gene, its variants, polymorphism and association with diseases (diabetes, cardiovascular disease, and hypertension).

### Search strategy

PubMed and Google Scholar search databases was used for this review. The literature was searched and filters were applied for the last two years. Different combinations of searching terms were used for search strategy like; COVID-19, ACE2 gene, ACE2 gene polymorphism, Variation in variants and ACE2 gene variants susceptibility to COVID-19. Primary screening was done only by reviewing titles and abstracts; those that were related to our study were then accessed for full text.

### Study Selection

All type of studies showing significance and pertinent to our study were included (Randomized controlled trials, Cohort, case control, Cross sectional studies and metanalyses).

### Article type

Original peer reviewed, published in English language and relevant to our study showing the association of ACE2 polymorphism with COVID-19 were retrieved.

### Exclusion criteria

A. Editorials, opinions and pre-printed articles that was not peer reviewed were not considered.
B. Non-human studies and papers not mentioning the keywords of this paper
C. Papers having inaccessible full text
D. Results suspicious of duplication in any other database

**Data Extraction**

After selection of studies, information related to article type, author, country of origin, date of publication, age, gender and genetic susceptibility were extracted from the articles and organized it in tabulated form.

## Results

A total of 417 results were retrieved after searching literature (filter applied from 2019-2022). After reading and reviewing their title only 50 full articles were accessed out, of which 18 were excluded and 32 were selected to be included in analysis based on being research articles and relevancy to our study as per study flow chart given in Figure 1.

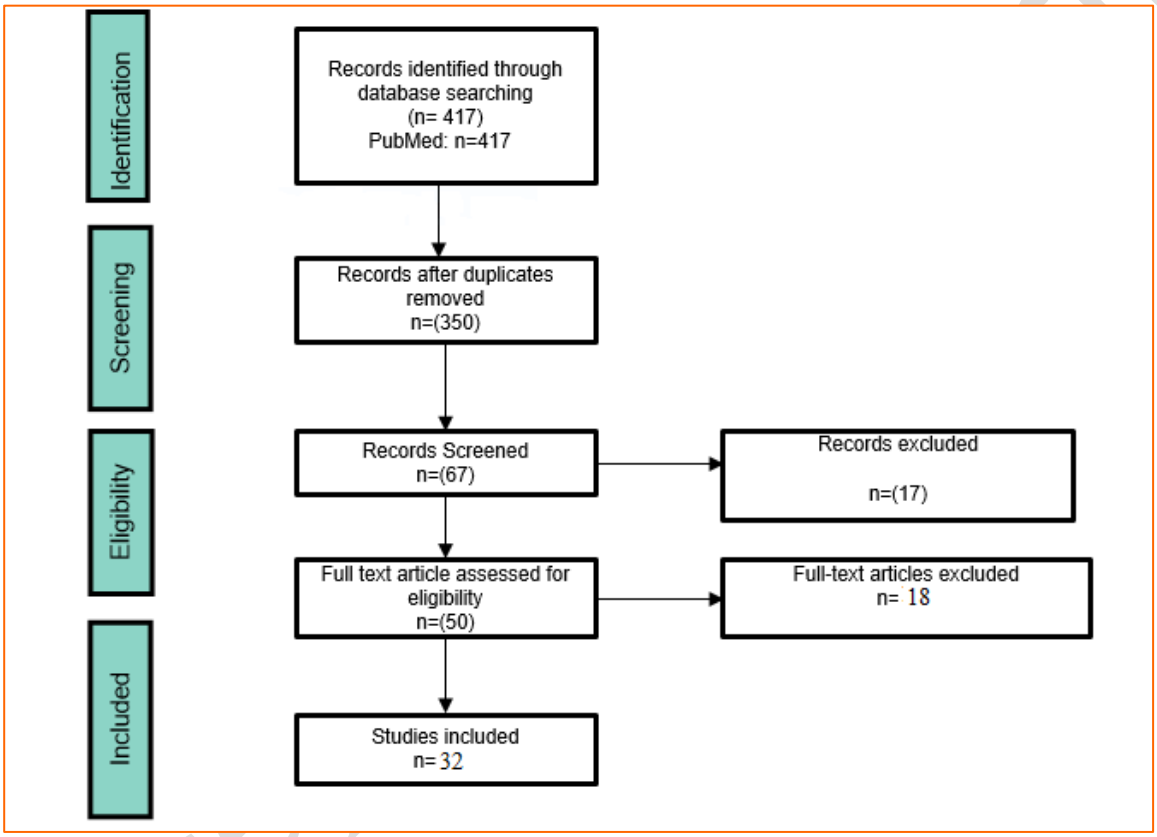


**Figure 1:** Flow Chart of Systematic Review

Findings revealed that SARS-COV-2 use ACE2 as a receptor to gain entry to the cell. Reviewed article showed certain polymorphism in ACE2 and TMPRSS2 makes individual susceptible or resistive to COVID-19. Few studies reported that some variants in ACE2 are associated with essential hypertension. One study reported substantial correlation of ACE2 variant (rs2285666) with low infection and case-fatality rate. One study suggested that males have more tendency hence, high susceptibility to SARS-COV-2 infection than females, with males more likely about 65% to die from COVID-19 infection (Table 1).

**Table 1:** Selected studies for identification of genetic susceptibility with COVID-19

| S.No | Reference | Study type | Country | Study subject | Risk Indicator | Result |
|---|---|---|---|---|---|---|
| 1 | Hou et al. [14] | Correspondence | USA | COVID-19 patients | P.Arg514Gly in African/African American population was found to be highly associated with Cardiovascular and pulmonary condition by playing a role in Aginotensinogen-ACE2 interaction. Expression quantitative trait locus (rs12329760) in Transmembrane serine protease (TMPRSS2) could be considered as a marker to answer the differential genetic susceptibility to COVID-19. Predominantly 4 deleterious variants in East Asian, South Asian and Finnish population while 6 germline variants in TMPRSS2 were found in coding region( Val160Met, Gly181Arg, Arg240Cys, Gly259ser, pro335Leu and Gly432Ala). | TMPRSS2 being present on 21q22.3 could be conjectured that people with Down syndrome are at greater risk of COVID-19 infection thus suggesting that age might have an association with TMPRSS2 polymorphism and calls for further investigation. Val160Met was found to have highest allelic frequency (25%) in all population while p.Asp435Tyr was suggested to have allelic frequency predominantly present in European population only. |
| 2 | Luo et al. [15] | Research | China | Patients with Essential hypertension from China | Variant (rs2074192) was highly associated with Essential hypertension while variants like (rs4830542, rs4646155 and rs4240157) showed stronger correlation with Essential hypertension and hypertension related Artrial Fibrillation in Chinese population | They showed high risk of Essential hypertension in the presence of rs4646188 variant. |

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| 3 | Kachuri et al. [16] | Research | USA | COVID-19 patients | ACE2 gene | ACE2 is the functional receptor that SARS-COV-2 uses enter into the cell. |
| 4 | Gomez et al. [17] | Research | Spain | COVID-19 Patients | rs2285666 showed significant correlation with severe COVID-19 in hypertensive patient | Study showed that male gender experienced severe outcomes in association with comorbidities like hypertension and hypercholesterolemia. Study concluded that it is highly unlikely that ACE2 coding variants can have substantial effect on susceptibility to SARS-COV-2 infection. |
| 5 | Srivastava et al. [18] | Original research article | India | ACE2, COVID-19 | For the first time it has been showed that the presence of this variant rs2285666 (G8790A) soared the expression of this gene up to 50%, thus playing an important role in susceptibility to SARS-COV-2. | Substantial correlation was found out in the presence of rs2285666 with low infection and case-fatality rate. Susceptibility to SARS-COV-2 is associated with genomic variants in ACE2 gene. |
| | Gemmati and Tisato [19] | Hypothesis | Italy | ACE1, ACE2, ABO locus | COVID-19 patients | Males have more tendency and susceptibility to become infected with SARS-COV-2 infection than females, with males more likely about 65% to die from COVID-19 infection |
| 7 | Asselta et al. [20] | Research paper | Italy | ACE2, COVID-19 | rs2285666 (G8790A) a single nucleotide polymorphism having an allelic frequency of 0.2 in Italian and European populations and 0.55 in East Asian population has found to be a potential risk factor for people with comorbidities such as Coronary Artery disease, type 2 diabetes and hypertension suggesting a | Study concluded that sex difference in disease severity cannot be explained through sex difference in ACE2 expression level. However, it is yet to be evaluated whether there is any correlation of ACE2 expression level in lungs with disease severity and susceptibility. This study further confirmed the results of Srivastava et al (presence of rs2285666 variant A/A genotype increase the |

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| | | | | | possible predisposing factor in COVID-19 patients. | expression of ACE2 up to 50%) by analysing rs2285666 variant concluded that substitution of G with A increase the strength of splice site by about 9.2% in serum with high level of ACE2 protein. |
| 8 | Devaux et al. [21] | Mini review | Chinese and Indian | ACE2 | Three variants of ACE2 (rs4240157, rs4646155, and rs4830542) were documented to have an association with hypertension in Chinese population.<br>Similarly a cohort study of 264 hypertensive and 274 normotensive Indian patients indicated an association of hypertension with a mutation (rs21068809) in ACE2 gene. | Study showed that mutation in ACE2 gene, variation in mRNA expression at transcriptional level, post-transcriptional modification and putative ACE2 protein mutation might be playing an important role in COVID-19 outcome (blood pressure) by affecting the RAAS pathway. |
| 9 | Beyerstedt et al. [22] | Review | General population | COVID-19, ACE2 | Study concluded that two variants (K26R and I468W) can influence the attachement of spike protein to ACE2 and hACE2 receptor. | ACE2 is the functional receptor for SARS-COV-2 and key regulator in Renin-Angiotensin system. SARS-COV-2 cause the disruption and imbalance activation of RAAS system leading to COVID-19, particularly in patients having comorbidities like Cardiovascular disease, diabetes mellitus and hypertension. |
| 10 | Hamet et al. [23] | Original article | French Canadian | SARS-COV-2, ACE2 | T allele (rs2074192) of ACE2 gene was found to be considered as risk factor for developing hypertension in obese and smoker males. | For the first time this study documented the association of ACE2 variants with severe hypertension and earlier penetrance along with more severe covid-19 outcome in obese and smoking males. |

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| 11 | Möhlendicka [24] | Original article | Germany | ACE2, COVID-19 | Two to three-fold increase in SARS-COV-2 infection or even COVID-19 fatality was associated with GG genotype of rs2285666. | In contrast to the result of Gomez et two-to-three-fold increased risk of COVID-19 infection was found in association with G genotype of ACE2 variant rs2285666. Similarly another contrasting result to Gomez et al was negligible or no effect of ACE variant rs179952 D/I on natural course of COVID-19. This paper did not mention any specific reason for this discrepancy. |
| 12 | Yamamoto et al. [25] | Review | NA | ACE2 gene, SARS-COV-2, RAAS system | COVID-19 patients | Renin-Angiotensin system play a vital role in SARS-COV-2 infection thus polymorphism in these genes that control the enzymatic activities involves in this system can be an indicator for elucidating the pathogenicity of COVID-19 |
| 13 | Akbari et al. [26] | Research | IRAN | ACE1, ACE2 | rs4359 polymorphism in ACE1 showed a significant protective effect in over dominant model for COVID-19. | ACE1 polymorphism can play a potential role and can be considered as a risk factor for COVID-19 and expression of ACE transcripts. RBC, HCT and HB level was positively correlated with expression of ACE2 level in COVID-19 patients. |
| 14 | Pouladi and Abdullah [27] | Original article | NA | ACE2, COVID-19 | 3 variants (rs233574, rs2074192, and rs4646188) have considerable effect on secondary structure of RNA of ACE2. | The study revealed that some variants has the potential to bring about changes in stability of ACE2 that can ultimately lead to different COVID-19 susceptibility. |
| 15 | Akin et al. [28] | Original article | Netherland | ACE2, COVID-19, aldosterone/Renin ration | COVID-19 patients | This study defined different factor that can play an important role in COVID-19 disease severity such as low aldosterone-Renin ratio and |

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| | | | | | | presence of TMPRSS2 rs2070788 non-AA genotype |
| 16 | Iphigenia gintoni et al. [29] | Review | NA | ACE, ACE2 | COVID-19 patients | The presence of D variant of ACE I/D is positively correlated with chronic obstructive pulmonary disease progression and the multiple studies have quoted that the presence of this variant whether in homozygous (DD) or heterozygous (ID) form has the capability to predispose Asian population to COPD. |
| 17 | Qian et al. [30] | Hypothesis | NA | CAT, ACE2 | COVID-19 patients | This study hypothesized that another gene CAT located in cell membrane and extracellular area shows a significant positive correlation to ACE2 in the lungs could be considered as intermediator in binding of ACE2 to spike protein of SARS-COV-2 thus playing an important role in susceptibility of COVID-19. |
| 18 | Pandey et al. [31] | Research article | NA | TMPRSS2, ACE2 | COVID-19 patients | For the first time a positive correlation was found between case fatality rate and genetic variant rs2070788 in Indian population that can act as biomarker to predict the population susceptible to COVID-19. |
| 19 | Paniri et al. [32] | Research article | NA | ACE2 | COVID-19 patients | Bioinformatics analysis showed that about 60 intronic region ad 4 missense single nucleotide polymorphism exhibited different frequencies across different populations. In particular two missense SNPs have been considered to play an important role in function and stability of ACE2. |

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| 20 | Molina et al. [33] | Research article | NA | ACE, ACE2, AGTR1 | For the first time this study quoted that the presence of the variant (rs2074192) G/A genotype in females provide a protective factor for those patients who have not associated comorbidities. rs5183 genotype A/A was associated with higher risk of hospitalization in patients with no associated comorbidities. | Study concluded that variation in ACE2 gene is positively correlated with severity of disease. In particular two SNPs rs2106809, rs2285666 were specifically concerned with higher risk of being hospitalized and disease severity. Similarly other factors like associated comorbidity, male gender and older age also contribute to an increase risk of being severely infected from COVID-19. |
| 21 | Benetti [34] | Article | Italy | ACE2, COVID-19 | Three variants were found to be playing crucial role in interfering with spike protein and structure stabilization and de-stabilization. | Whole- exome sequencing data of 131 patients suggested that genetic background can contribute to inter-individual variation of ACE2 gene associated with COVID-19. Not only genetic background but epigenetic factor can also play an important role in susceptibility and resistance to SARS-COV-2 and outcomes of disease. |
| 22 | Lanjanian et al. [35] | Article | | ACE2 | COVID-19 patients | Study of whole genome sequencing of 1200 individuals revealed 570 different genetic variation like single nucleotide polymorphism and insertion deletion (INDEL), of which two missense variants namely (S331F, K26R) showed promising results in reducing the binding of receptor to spike protein. |
| 23 | Singh et al. [13] | Review | NA | ACE2, TMPRSS2 | COVID-19 patients | Study documented that single nucleotide polymorphism in ACE2 gene like rs879922, rs2285666, rs4646176, rs4646155, and |

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| | | | | | | rs1514283 had been associated with essential hypertension in Chines Han population. |
| 24 | Hussain et al. [36] | Article | NA | ACE2, SARS-COV-2 | COVID-19 patients | This computational analysis suggested that most of Single nucleotide polymorphisms have no observable and functional effect on binding to SARS-COV-2 spike protein but their study also suggested that some variants like rs2285666, S19P and E329G showed greater variation in their binding to coronavirus spike protein. |
| 25 | Othman et al. [37] | Article | NA | ACE2 | COVID-19 patients | They studied 8 different variants resides at ACE2 interaction point with spike protein of SARS-COV-2 suggested that out of these 8 variants not even a single one was able to cause Disruption at the interaction point of ACE2 with spike protein of SARS-COV-2. |
| 26 | Mahmood et al. [38] | Article | Iran | ACE,ACE2 | COVID-19 patients | Study concluded different factors that could contribute to COVID-19 disease severity and susceptibility includes, C-reactive protein, neutrophil-to-lymphocyte ratio and SARS-COV-2 RT-PCR cycle threshold value. Two variants of ACE and ACE2 (rs4646994 and rs2285666) were found not to have any role in developing COVID-19. |
| 27 | Suryamohan et al. [39] | Article | NA | ACE2, SARS-COV-2 | COVID-19 patients | Analysis of more than 29000 samples from more than 400 population groups revealed certain variants ( S19P, I21V, |

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| | | | | | | E23K, K26R, T27A, N64K, T92I, Q102P and H378R) that increase the risk of susceptibility to COVID-19 while some variants ( were found to have protective effect by decreasing the binding affinity of K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L and D509Y) spike protein to ACE2 receptor. Biochemical assays further corroborated the results by showing that 2 variants (K31R and E37K) had decreased binding affinity while two variants (K26R and T92I) have increased binding affinity to spike protein. |
| 28 | Saih et al. [40] | Research article | NA | ACE2, SARS-COV-2 | COVID-19 patients | Using different bioinformatics software to find out the effect of missense variants on structure and stability of ACE2 protein, the study documented six high risk pathogenic variants (D427Y, R514G, R708W, R710C, R716C, and R768W) that could be playing an important role in effecting the binding, function and structure of protein. |
| 29 | Fagyas [41] | Article | NA | ACE2 | COVID-19 patients | Study conducted on 176 patients (including 101 critically ill and 66 severely ill) revealed that serum ACE2 level is positively correlated with COVID-19 severity and mortality regardless of any comorbidity. |

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| 30 | Breemen et al. [42] | Article | NA | ACE2, SARS-COV-2 | COVID-19 patients | cannabigerolic acid and cannabidiolic acid was found to prevent infection of epithelial cells by intercepting the entry of live SARS-COV-2 into the cell. Study also confirmed that both these acids were also active against both the alpha and beta variant of SARS-COV-2 suggesting that these acids have the capability to prevent and treat infection of SARS-COV-2. |
| 31 | Godri et al. [43] | Review | USA | ACE2, HLA-B | COVID-19 patients | Study suggested that individuals expressing HLA-B*15:03 might have immunity to COVID-19. |
| 32 | Horowitz et al. [44] | Article | USA | ACE2,IFNAR2,DPP9,MHC,L2TFL1 | COVID-19 patients | Genome wide association study showed that variant (rs190509934) having allelic frequency 0.2-2% downregulate the expression of ACE2 by 37% thus lowering the infection risk of SARS-COV-2 by 40% confirming that there is strong association of ACE2 polymorphism with COVID-19. Study also confirmed the association of previous reported 6 risk variants, of which four were further confirmed to be responsible for severe outcomes in the infected individuals located in/near IFNAR2, DPP9, MHC, and L2TFL1. |

## Discussion

ACE2 is a zinc metalloproteinase, composed of 18 exons, found on X chromosome (Xp22) that act as a monocarboxy-peptidase and play an important role in RENIN-ANGIOTENSIN pathway.it is the homologue of ACE that serves different functions ranging from regulation of blood pressure, maintaining heart activities, osmotic pressure, catalytic activities with different substrates, cardiac physiology, negative regulator of activated Renin-aldosterone system in Diabetic Cardiomyopathy to functional receptor for SARS-COV-2 [5, 7-10].

Our findings showed several factors contribute to genetic susceptibility of COVID-19 includes: low aldosterone-renin ration, RBC, HCT, HB levels, ACE2, TMPRSS2, ACE, C-reactive protein, neutrophil-to-lymphocyte ratio, SARS-COV-2 RT-PCR cycle threshold value, S19P, I21V, E23K, K26R, T27A, N64K, T92I, Q102P, H378R, cytokine storm, Basigin, K26R, IFNAR2,DPP9,MHC,L2TFL1 and I468W [14, 22, 24, 26, 28, 35, 38, 39, 44, 45].Our review showed that variation and genetic risk factors can play vital role in severity, transmissibility and susceptibility to SARS-COV-2.

SARS-CoV-2 transmissibility, severity and susceptibility not only depend on environmental factors i.e., (Climate, Social, Cultural, economic inequalities, pollution, health care system organization) and comorbidities (hypertension, Dyslipidemias, Cardiovascular disease, Diabetes, respiratory conditions, Cancer, or compromised immune system) but also depends on inter-individual difference and inter-populational differences along with inflammatory and immune response. Certain factors like age, lifestyle status, ethnicity, genetic polymorphism from host while type of mutation in virus, viability of virus, stability of viral strain in an environment and viral load from virus contribute to progression and development of COVID-19 disease [13].

ACE2 not only expressed in heart, kidney, and testes but in various other organs also includes cardiovascular system (cardiac fibroblast, cardio myocytes, and coronary vascular endothelium) brain, lungs and kidneys [46-48]. Several studies have suggested that polymorphism in ACE2 gene plays a potential role in determining whether the disease will be more transmissible and severe. Severity, transmissibility and susceptibility have been shown to be associated with difference in gender and age group, with older age group having comorbidity are considered as more vulnerable group [49]. Different studies have suggested that its prevalence is high in males then females showing that males are at higher risk [14, 19].

Receptor binding domain of spike protein of SARS-COV-2 facilitates binding to ACE2 [19]. Studies have found certain variants (S19P, E23K, I21V, T27A, N64K, T92I, K26R, Q102P and H378R) that increase the risk of susceptibility to COVID-19 while some variants (K31R, N33I, E35K, F72V, E37K, D355N, D38V, Y50F, N51S, M62V, K68E, H34R, Y83H, G326E, G352V, Q388L and D509Y) were found to have protective effect by decreasing the attachment capacity of spike protein to ACE2 receptor [39]. Genome wide analysis study of about 52,630 COVID-19 individuals and 704,016 individual having no record of SARS-COV-2 aggregated from four studies showed that there is a strong genetic association of ACE2 polymorphism with COVID-19.

The study showed that variant (rs190509934) having allelic frequency 0.2-2% downregulate the expression of ACE2 by 37% thus lowering the infection risk of SARS-COV-2 by 40% confirming that there is strong association of ACE2 polymorphism with COVID-19 [44].Study also confirmed the association of previous reported 6 risk variants, of which four were further confirmed to be responsible for severe outcomes in the infected individuals located in/near IFNAR2, DPP9, MHC, and L2TFL1 [44]. Computational analysis suggested six missense pathogenic variants (rs2285666, S19P and E329G) that play a vital role effecting the binding affinity and structure of protein [36].

Certain studies also indicated the association of ACE2 polymorphism with cardiovascular disease by modifying the Angiotensinogen-ACE2 interaction, P.Arg514Gly in African/African American population and this variant was predominantly present in East Asian/South Asian and Finish population [14]. Similarly another Single nucleotide polymorphism (rs2285666) that has so far extensively been studied having an allelic frequency of 0.2 in Italian and European population and 0.55 in East Asian population was found to be a potential risk factor for individuals with comorbidities like Coronary artery disease and diabetes and for the first time this variant was found to increase the expression of ACE2 by 50% [20, 24, 33]. One study reported that presence of this variant (rs2285666) is positively correlated with low infection and case-fatality rate [18]. Lastly some evidence indicates that SARS-COV-2 entry to the cell is also

mediated by the polymorphism of cellular protease in the presence of furin [43].Furin assist TMPRSS2 in cleaving spike protein which in turn results in the entry of SARS-COV-2 into the cell thus showing an association with SARS-COV-2 [50].

## Conclusion

In conclusion our systematic review showed detailed analysis of the polymorphism in ACE2 gene and how these polymorphism effect the severity, transmissibility and susceptibility to COVID-19. An association was found between ACE2 polymorphism and susceptibility to SARS-COV-2. SARS-COV-2 uses ACE2 as a receptor to gain entry into the cell. Genome wide analysis studies showed that there is strong association between ACE2 polymorphism and COVID-19. Extensive Genome wide analysis is important for the better comprehension of polymorphism involved in susceptibility and resistivity to SARS-COV-2.

### Abbreviations

TMPRSS2: Transmembrane serine protease 2 WHO: World Health Organization, PRISMA: Preferred reporting items for systematic reviews and meta-analyses.

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### Author Contributions

The concept of the study was designed by: BB, AH.BA Acquisition of the data: WI, UB. Analysis and interpretation: WI, AM. Drafting the article: BB, WI, and UB. Revising it critically: WI, AH, UB. Final approval AM, BB, UB, AH, WI.

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This research did not receive funding grants from any institution.

### Availability of data materials

The author stated that all the information could be shared.

### Declaration

Ethical approval and consent to participate

As the present study was extracted from already published articles therefore, no consent and ethical approval is required.

### Consent for publication

Not Applicable

### Competing Interest

The authors declare that there are no competing interest regarding publication of this manuscript.

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