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Impacts of SARS-CoV-2 on diabetes mellitus: A pre and post pandemic evaluation

Nabi AHMN *et al*. SARS-CoV-2 and diabetes mellitus

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic caused by the novel beta coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) crippled the whole world and has resulted in large number of morbidity and mortality. The origin of the SARS-CoV-2 is still disputed. The risk of infection with SARS-CoV-2 is dependent on several risk factors as observed in many studies. The severity of the disease depends on many factors including the viral strain, host immunogenetics, environmental factors, host genetics, host nutritional status and presence of comorbidities like hypertension, diabetes, Chronic Obstructive Pulmonary Disease, cardiovascular disease, renal impairment. Diabetes is a metabolic disorder mainly characterized by hyperglycemia. Diabetic individuals are intrinsically prone to infections. SARS-CoV-2 infection in patients with diabetes result in β-cell damage and cytokine storm. Damage to the cells impairs the equilibrium of glucose, leading to hyperglycemia. The ensuing cytokine storm causes insulin resistance, especially in the muscles and liver, which also causes a hyperglycemic state. All of these increase the severity of COVID-19. Genetics also play pivotal role in disease pathogenesis. This review article focuses from the probable sources of coronaviruses and SARS-CoV-2 to its impacts on individuals with diabetes and host genetics in pre- and post-pandemic era.

Core Tip: The coronavirus disease 2019 (COVID-19) pandemic caused by the novel beta coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) crippled the whole world and has resulted in large number of morbidity and mortality. The origin of the SARS-CoV-2 is still disputed. The risk of infection with SARS-CoV-2 is dependent on several risk factors as observed in many studies. The severity of the disease depends on many factors including the viral strain, host immunogenetics, environmental factors, host genetics, host nutritional status and presence of comorbidities like hypertension, diabetes, Chronic Obstructive Pulmonary Disease, cardiovascular disease, renal impairment. Diabetes is a metabolic disorder mainly characterized by hyperglycemia. Diabetic individuals are intrinsically prone to infections. SARS-CoV-2 infection in patients with diabetes result in β-cell damage and cytokine storm. Damage to the cells impairs the equilibrium of glucose, leading to hyperglycemia. The ensuing cytokine storm causes insulin resistance, especially in the muscles and liver, which also causes a hyperglycemic state. All of these increase the severity of COVID-19. Genetics also play pivotal role in disease pathogenesis. This review article focuses from the probable sources of coronaviruses and SARS-CoV-2 to its impacts on individuals with diabetes and host genetics in pre- and post-pandemic era.

INTRODUCTION
Diabetes and pre pandemic era

The term "diabetes" first appeared in a medical text book around 1425 and was first suggested by a Greek scientist, Araetus of Cappodocia (81-133AD)[1]. Thomas Willis added the word "mellitus" (meaning "sweet taste of urine") to the word diabetes in 1675. Diabetes was referred to as Madhumeha in ancient Indian medicine[1,2]. In 1776, a British physician named Matthew Dobson identified excess sugar in urine and blood as the cause of their sweet taste, and glucose was identified as the responsible sugar[1,2]. The experimental creation of diabetes in 1889 in experimentally pancreatectomized dogs eventually confirmed that the pancreas is the causative organ of the disease followed by the isolation of insulin in 1922, which finally established that diabetes is an endocrine disorder due to deficiency of insulin[2-4].

Diabetes mellitus has been recognized as one of the major health concerns and is considered a global epidemic affecting 382 million people worldwide. According to the prediction of the World Health Organization, diabetes will be the seventh leading cause of death by 2030[5]. Diabetes is a metabolic disorder caused by hyperglycemia and characterized by polyuria, polyphagia, polydipsia, and weight loss. Diabetes mellitus causes macrovascular and microvascular complications. Macrovascular complications include coronary heart disease, cardiomyopathy, arrhythmias and sudden death, cerebrovascular disease and peripheral artery disease. Myocardial infarction, stroke, and peripheral artery disease are more prevalent in individuals with diabetes mellitus. Microvascular complications include retinopathy, nephropathy, and neuropathy. These complications are the major contributing factors to the increasing mortality rate in patients with diabetes and an estimated 4 million individuals are dying each year due to diabetes related complications.

American Diabetes Association classified diabetes into four categories: Type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and diabetes induced by or related to particular specific illnesses, pathologies, and/or syndromes are the four primary forms or categories of diabetes, respectively. T1DM, often referred to as type 1A diabetes mellitus (DM), insulin-dependent diabetes mellitus (IDDM), or juvenile-onset diabetes, accounts for around

5%-10% of all diabetes cases. It is an autoimmune condition marked by the T-cell-mediated apoptosis of pancreatic beta-cells, which causes an insulin shortage and ultimately leads to hyperglycemia. T2DM, also known as non-insulin-dependent diabetes mellitus accounts for 90%-95% of all cases of diabetes. This kind of diabetes is characterized by two main insulin-related abnormalities: insulin resistance and β-cell dysfunction. Any degree of glucose intolerance or diabetes, typically discovered in the second or third trimester of pregnancy, is referred to as GDM. Other than T1DM, T2DM, and GDM, other types of diabetes although in smaller percentages relative to the overall diabetic incidence scenario, has been found to be linked to a number of other illnesses, including several pathologies[6].

Endocrinopathies, exocrine pancreatic diseases, diabetes caused by monogenic deficiencies in β-cell function, and diabetes caused by genetic abnormalities in insulin action are the most common types of diabetes. Type 1 diabetes is a chronic autoimmune disease that has both hereditary and environmental causes. In those who have a genetic predisposition to developing autoimmunity, viruses may affect the susceptibility of the infectious disease and trigger it. The most frequently studied viruses in relation to type 1 diabetes are enteroviruses. Pancreatic islet autoimmunity and the onset of type 1 diabetes clinical symptoms have also been linked to respiratory viral infections. In animal models, the influenza virus can infect human pancreatic cell lines and result in pancreatitis and hyperglycemia. In case-report studies, influenza A virus infection has also been linked to acute pancreatitis and type 1 diabetes. There may be a connection between pandemic influenza and type 1 diabetes, according to two small retrospective investigations. These revealed a parallel rise in type 1 diabetes among kids throughout the pandemic influenza timeframe. It normally takes several years from the induction of islet autoimmunity to the clinical presentation of type 1 diabetes, hence studies with longer follow-up following influenza are necessary to clarify how pandemic influenza contributes to the development of diabetes.

Diabetes patients are up to six times more likely than healthy people to require hospitalization for influenza virus or flu-like infections, and they are also more likely to

experience infection related complications. Diabetic individuals, especially those with uncontrolled diabetes, are more prone to fungal infections[7]. Community-based pneumonia was more frequent in those diagnosed with diabetes mellitus[8]. Increased mortality risk from cardiovascular disease, chronic lower respiratory illnesses, influenza and pneumonia, and kidney disease is linked to baseline diagnosed diabetes[9]. A regulated immune response that leads to more severe and prolonged lung pathology is most likely the cause of the higher disease severity seen in mice with REMS and co morbid type 2 diabetes[10]. According to a systematic analysis of 637 Middle East respiratory syndrome (MERS)-CoV cases, 50% of the patients had both diabetes and hypertension. Obesity was prevalent in 16% of cases, while cardiac problems were present in 30%[11].

SARS coronavirus and the pre- pandemic era

There are similarities between many epidemics and industrial revolutions that have occurred throughout history. No other virus, bacteria, or germ has ever produced as many pandemics and as many deaths on Earth in as little time as plagues and flu. Plague is a disease caused by a bacterium called Yersinia pestis, which is mainly transmitted by rats and one type of fly. History shows that the first plague occurred between 165 and 180 AD (also known as the Antonine Plague that brought the Roman Empire to the brink of destruction) and caused the deaths of 500000 people. Plague outbreaks followed in 541-542 AD, 1347-1351 AD, 1665 AD and 1629-1631 AD. At this time, the word "industrial" revolution did not appear in the world. But history tells us that the plague that occurred in 1885 between the first and second industrial revolutions caused the death of more than a million people in China and India alone. During the Second Industrial Revolution in 1889-1890 and 1918-1919, respectively, the Russian flu and the Spanish flu struck, which took the lives of about 60 million people in the world. During the Third Industrial Revolution, Asian flu (1957-1958), Hong Kong flu (1968-1970), and AIDS (still ongoing since 1981) killed over 40 million people. Among these, flu-like diseases are caused by different types of influenza viruses that belong to the

same genus but differ in the structure of their genetic material. The genetic material of the influenza, swine flu viruses is formed by ribonucleic acid, or RNA.

Different types of wildlife frequently carry diseases or disease agents that are harmful, and in some cases fatal, to humans. Recent studies have shown that 60% of the infectious diseases that are currently occurring are zoonotic, that is, the bacteria responsible for these diseases spread from animals to humans. Although these bacteria are common in animals, they can also infect humans. Also 70% of infectious diseases originate from wildlife[12]

The study of Corman *et al*[13] revealed that bats are the natural host of the coronavirus. Even the age of corona virus found in bats is much longer than that of coronavirus found in other animals. This suggests that the virus has overcome the barriers that normally exist to spread from one species to another and has now adopted humans as its home[14]. Bats are also thought to be the source of two other strains HCoV-NL63 and HCoV-HKU1[15]. Every organism has a natural reservoir. The more we disturb nature, the more likely it is to deplete natural resources. As a result, the microbes are in crisis of existence and to adapt to the changing environment, they cause rapid change or mutation. The significant natural reservoirs of the coronavirus are bats, camels and palm civets. Because of its crown like shape, it is called the "coronavirus". Before making devastating impacts, the human race has always received signs of warnings for larger damage. For example, SARS (Severe Acute Respiratory Syndrome, SARS) in 2002-2003, swine flu (2009-2010) in 2009-2010 and MERS (Middle East Respiratory Syndrome, MERS from 2015 to the present.

Coronavirus can be generally divided into four genera - alphacoronavirus, beta coronavirus, gamma and delta. Among these, the beta group is further divided into four groups – A, B, C and D. Human strains of coronaviruses include HCoV 229E (HCoV 229E) and HCoV NL63 of the alpha genus, and HCoV OC43 and HKU1 of the beta genus. SARS-CoV and MERS-CoV are also members of the beta genus. A study in 2003 found that the genome of SARS-CoV-1 in humans was 99.8% identical to that of SARS-CoV in palm civets. Later, the genome of human SARS-CoV-1 was found to be

approximately 87%-92% similar to that of SARS-CoV recovered from Chinese bats. From this, it is assumed that the natural source of this virus is the Chinese bat. The virus is transmitted to humans using the palm civet as an intermediate vector.

Since the outbreak of MERS-CoV, scientists have begun more research on bat-borne coronaviruses. In line with this, a study in Saudi Arabia found that the genome sequence of human MERS-CoV is nearly 100% identical to a virus found in bats called Taphozous perforates. In addition, some preliminary studies have found viruses similar to this virus in several species of bats. The scientists then sequenced the replication gene of MERS-CoV and found that the virus resembled the HKU4 coronavirus of Tylonycteris bats. However, a 2013 study found that MERS-CoV is actually a member of the beta-coronavirus family and that camels are intermediate carriers of the virus.

Novel coronavirus or SARS-CoV-2

The Coronaviruses are enveloped virus. It is a positive sense, single-stranded RNA composed of about 29000 nucleotides. 229E (HCoV-229E) virus is a close relative of the currently prevalent CoV virus in humans due to several conformations. Their habitat was also known to be in the hipposideridae family of African bats. It is hypothesized that they may have used dromedaries as intermediate habitats between bats and humans[16].

The HCoV virus has also been found to be related to viruses in other animals. For example, HCV-OC43 has been shown to be highly homologous to mouse hepatitis virus and bovine respiratory coronavirus[13]. The habitats of these two viruses are rats and cows respectively. An enzyme called hemagglutinin esterase is found in all of them.

Pangolin is also another natural reservoir of coronavirus. Analysis of the Genome Sequence of the currently alarming virus has shown that some parts of the RNA of Novel Coronavirus 2019 or COVID-19 came from bats and some parts came from Pangolin, and this recombination process took place in a third animal. We are destroying these animals for food and medicine.

The genome of SARS-CoV-2 is similar to that of other beta coronaviruses. Most of the proteins that SARS-CoV-2 encodes are similar in length to those that SARS-CoV encodes[17]. From 5′ to 3′, the genomic structure contains leader sequence, ORF1/ab, Spike (S), ORF3a, Envelope (E), Membrane (M), ORF6a, ORF7a, ORF7b, ORF8, Nucleocapsid (N), ORF10 and lacks the hemagglutinin-esterase gene which is found in some β-CoVs. ORF1a/b is made up of 16 non-structural proteins (nsp1–16) and accounts for almost two-thirds of SARS-CoV-2 RNA. The replicase gene encodes a large polyprotein (pp1ab), which is involved in transcription and virus replication. It is fragmented by proteolysis into 16 non-structural proteins. The remaining one-third of the genome, at the 3′-terminus, contains ORFs that code for structural and auxiliary proteins of SARS-CoV-2[18]. With the exception of the S protein, which is different, the structural proteins (E, M, and N) of SARS-CoV-2 share around 90% of their amino acid composition[19,20]. The majority of SARS-CoV-2 non-structural proteins share more than 85% of their amino acid sequences with SARS-CoV[17].

Zoonosis of coronaviruses

Endemic coronaviruses have animal origins: HCoV-NL63 and HCoV-229E are speculated to have originate in bats whereas; HCoV-OC43 and HKU1 are likely to have originated in rodents[21,22]. Bats are also considered as the natural reservoir of SARS-CoV, MERS-CoV and SARS-CoV-2[16,20,23]. Masked palm civet and dromedary camel are the intermediate hosts of SARS-CoV and MERS-CoV, respectively[23]. However, the intermediate host of SARS-CoV-2 is not clear till date. Pangolin, snakes, minks, turtles, ferret and companion animals are possible candidates for the intermediate hosts of SARS-CoV-2[24] (Figure 1).

Cohorts from The United States, Germany, Netherlands, Singapore and the United Kingdom that 20% to 50% individuals not exposed to SARS-CoV-2 previously had T cell activity against peptides that match the sequences of the SARS-CoV-2[25-29]. The T cell activity was mostly due to CD4+ T cells. This might be due to the presence of

preexisting memory against endemic coronaviruses which share sequence homology with SARS-CoV-2.

Comorbidities and COVID-19

Despite the fact that risks are generally higher in men and rise with age, there is now compelling evidence that those who have a number of medical conditions—including chronic kidney disease, diabetes, lung and liver disease, cardiovascular disease, obesity, immunodeficiency, certain disabilities, and mental health conditions—are also at higher risk[30].

People with complex diabetes, obesity, and psychological disorders are at the highest risk (relative risk of about 1.3 compared to those without these illnesses), whereas those with cardiovascular disease are at a lower risk (relative risk roughly 1.1)[31]. The evidence is inconclusive for asthma, hypertension, and viral hepatitis, while it is scarcer for other illnesses like obesity, sickle cell disease, and substance use disorders. Inflammatory and hormonal routes, as well as social factors like being in a crowded or institutionalized environment, are proposed as possible disease susceptibility and severity processes, albeit the precise mechanisms remain unknown[32,33].

Based on the frequency of chronic diseases, it is projected that one in five people globally are at an increased risk of negative COVID-19 outcomes. Along with age, the risk rises when there are more underlying conditions[34]. Ages 50 to 64 have a fourfold rise in mortality risk compared to those under 40, and 85 and older see a more than tenfold increase[35]. Similar to this, those with one comorbidity or more than 10 comorbidities had a 1.5- and 3.8-times higher risk of dying than those without any underlying diseases[31]. To assist clinical judgments, a number of risk score calculators have been developed using these data[36,37]. Previous research has shown that individuals with H7N9 infection have a 3.4-fold higher chance of having acute respiratory distress syndrome when any comorbidity is present. Similar to the influenza virus, the coronavirus causing severe acute respiratory syndrome (SARS-CoV) and the

MERS-CoV, Covid-19 more easily predisposes susceptible patients to respiratory failure and mortality[38].

A report consisting of 72314 cases in China, case fatality rate was observed to be increase in individuals with preexisting comorbidities like cardiovascular disease (10.5%), diabetes (7.3%), chronic respiratory disease (6.3%), hypertension (6.0%) and cancer (5.6%)[39]. In a study, 399 instances (25.1%) out of the 1590 reported having at least one comorbidity. The prevalence of specific comorbidities included hepatitis B infections (28; 1.8%), chronic obstructive pulmonary disease (24; 1.5%), chronic kidney disease (21; 1.3%), malignancy (18; 1.1%), and immunodeficiency (3; 0.2%). Hypertension (269; 16.9%), other cardiovascular diseases (53.7%), cerebrovascular diseases (30; 1.9%), diabetes (130; 8.2%), and diabetes-related complications were also common. None of the cases had asthma diagnosed by a doctor. In severe instances *vs* non-severe cases, at least one comorbidity was more frequently observed (32.8% *vs* 10.3%). Patients with at least one comorbidity tended to be older (mean: 60.8 *vs* 44.8 years), more likely to experience shortness of breath (41.4% *vs* 17.8%), nausea, or vomiting (10.4% against 4.3%), and to present abnormally on chest X-rays (29.2% *vs* 15.1%)[38].

Diabetes and COVID-19

The world has experienced the devastating impact of infectious organism novel coronavirus or SARS-CoV-2 since it's inception in December 2019. Physicians faced enormous challenges to battle against the COVID-19 related complications especially determining or selecting the way of managing the disease *i.e.*, which group of individuals are at higher risk of worst severity[40]. Epidemiological evidences supported that comorbidities have added extra burden to the miseries of pandemic. Among the comorbidities, diabetes took the lead. Further, individuals with diabetes had greater risk of sufferings from the complications caused by this virus. The ongoing COVID-19 pandemic has once again emphasized the importance of preventing and managing type

2 diabetes. Complications even worsen in individuals with both heart disease and diabetes or macrovascular complications due to chronic diabetes.

Diabetic individuals are more prone to both primary and secondary infections caused by bacteria, viruses, fungus and as disease progresses, severity of the disease intensifies compared to their nondiabetic counterparts[10,41]. Obesity and poor control of blood glucose has been found to be directly linked to the clinical outcomes of COVID-19 and poor prognosis followed by increased mortality[42-45]. Zhu et al[45] in a cohort study comprised of 7337 confirmed COVID-19 cases demonstrated that the occurrence of ARDS (16.9% vs 7.2%), acute heart injury (7.3% vs 3.0%), acute kidney injury (3.9% vs 0.8%), septic shock (3.8% vs 1.0%), and DIC (0.5% vs 0.2%) were in individuals with T2D compared to the non-diabetic group. SARS-CoV-2 infects multiorgan system and pancreas is no exception as this organ also expresses angiotensin converting enzyme 2[46]. Previous findings reported presence of ACE2 receptor in the pancreatic beta cells for SARS-CoV-1 virus that acts as the viral entry point leading to the destruction of β-cells and insulin insufficiency causes hyperglycemia[47]. Studies reported morphological, translational and functional modification of pancreas followed by impaired insulin secretion as SARS-CoV-2 is able to successfully infect different cell types of both exocrine and endocrine system which include pancreas[48,49]. SARS-CoV-2 infected patients with poor control of blood sugar had high mortality rate compared to those with well controlled blood glucose. Further investigation revealed that even individuals suffering from COVID-19 disease with a glucose range of 3.9 to 10.0 mmol/L had a lower mortality rate than that of their counterparts with blood glucose levels above 10.0 mmol/L[44]. Moreover, COVID-19 patients with poorly controlled blood glucose had to extend their hospital stay[44]. Thus, better management of blood glucose results in improved outcome in patients with multiple organ damage and reduced the mortality rate in COVID-19 patients[45,50].

In an investigation of two major health-care datasets, US CDC researchers discovered that COVID-19 was associated with a higher risk of diabetes than pre-pandemic acute respiratory infections and that non-SARS-CoV-2 respiratory infections

were not. In the post-acute phase of COVID-19, those under the age of 18 who had SARS-CoV-2 infection had a higher probability of being diagnosed with diabetes than non-infected controls. Despite this, the study was unable to differentiate between type 1 and type 2 diabetes[51].

A Scottish study of individuals under the age of 35 found an overall 20% rise in the incidence of type 1 diabetes during the pandemic and an elevated risk of the disease within the first 30 days following SARS-CoV-2 infection, but not afterward[52]. Another study of 428650 individuals with COVID-19 and 428650 matched controls revealed a net increase in the incidence of diabetes in the first four weeks following COVID-19. This increase persisted from five to twelve weeks but not from thirteen to fifty-two weeks. The participants in this study had a median age of 35[53].

Cytokine storm, COVID-19 and Diabetes or Diabetes, COVID-19 and inflammation
Several advances have been made in understanding the pathophysiology of type 2 diabetes. Inflammation plays an important role in the pathogenesis of type 2 diabetes as it mediates hypoxia and cell death of adipose tissue, activation of important factors in signal transduction *i.e.,* nuclear factor-κB (NF-κB) and JUN N-terminal kinase, interleukin-1β and recruitment of immune cells. Factors associated with innate immune response are found to be in the circulation, insulin-sensitive tissues and pancreatic islets in type 2 diabetes. Obesity, one of the major causes of developing insulin resistance followed by type 2 diabetes, leads to elevated levels of C-reactive proteins, haptoglobin, fibrinogen, plasminogen activator inhibitor and serum amyloid A and sialic acid, as well as cytokines and chemokines.

Exaggerated immune response is responsible for the most of the fatalities in case of coronavirus infection. Release of inflammatory cytokines is contributing to the severity of the disease. The inflammatory cytokine release is primary thought to be due to macrophages[54-56]. Infection by the highly pathogenic respiratory viruses such as SARS-CoV-1, Middle East respiratory syndrome (MERS)-CoV, influenza, and respiratory syncytial virus results in the release of substantial amount of cytokine and chemokine

by provoking a prolonged inflammatory macrophage phenotype, allowing for direct viral infection of infiltrating cells. This causes massive cell death and damage of alveolar lung tissue, increasing morbidity for the patient[57]. Coronaviruses also induce macrophage mediated cytokine storm in patients with type 2 diabetes[58]. Coronavirus infection causes decrease expression of histone methyltransferase, SETDB2 that results in decrease of the repressive trimethylation of histone 3 Lysine 9 (H3K9me3) at NF-κB binding sites on inflammatory gene promoters of inflammatory genes which in turn effectively increases inflammation[58].

Diabetes is linked to a proinflammatory condition, which may increase the chance of developing severe COVID-19and a higher chance of suffering a cytokine storm. As part of the low-grade chronic inflammation, the proinflammatory cytokines and hazardous metabolites that are present in a cytokine storm are already chronically increased in people with diabetes[59-61]. One of the most significant pathophysiological mechanisms that contribute to higher risk in diabetic patients is believed to involve the proinflammatory NF-kappa-B pathway, which is chronically activated in patients with diabetes[59,62]. Although the underlying pathogenesis of low-grade inflammation leading to a more rapid progression of COVID-19 and the associated cytokine storm is unclear, it is thought to be one of the most important pathophysiological mechanisms. Interleukin-6, interleukin-8, and tumor necrosis factor- may have the worst prognosis or may be fatal for diabetes individuals among the cytokines that have been studied in research. Increased cytokines are linked to risk factors and comorbidities such hypertension and cardiovascular disease and are associated with greater mortality. In diabetic individuals with COVID-19 who had at least one prior comorbidity, especially hypertension and CVD, management of diabetes by insulin treatment may reduce the rate of mortality among diabetic patients, but it may also be contraindicate[63]. The interplay between SARS-CoV-2 infection and diabetes is shown in Figure 2.

Genetics of diabetes

Diabetes, an endocrine system disease marked by exceptionally high blood glucose levels, is one of the most common diseases in the world. Vascular problems of both the macrovascular system (cardiovascular disease, or CVD) and the microvascular system are the main causes of morbidity and mortality in patients with diabetes (diabetic kidney disease, diabetic retinopathy, and neuropathy)[64]. Despite the complexity and lack of complete knowledge of the precise mechanisms underlying hyperglycemia-induced vascular damage, increased intracellular glucose are thought to result in increased reactive oxygen species production, altering a number of significant downstream pathways, including the flux of the polyol pathway, the formation and activation of advanced glycation end products, the activation of protein kinase C, and the flux of the hexosamine pathway[65].

The HLA has received the majority of attention. in genetic studies of the diabetes, despite the fact that genome-wide association study (GWAS) have so far identified more than 50 Loci that affect Type I Diabetes (T1D) risk[66-69]. PTPN22 possesses a cluster of unusual variants that disrupt mRNA splicing, according to targeted sequencing of known locus, even though no large-scale sequencing projects have been successfully completed in T1D patients[70]. The largest GWAS on T2D to date is a meta-analysis of 32 European cohorts with roughly 74000 cases and nearly 824000 controls. 243 Loci reached genome-wide significance. Together, these top GWAS signals account for more than 17% of the variation in T2D phenotypes, and 73 signals supporting a single causative variable were discovered by thorough fine-mapping research on these loci[71]. People with polygenic scores in the top 2.5% do have a lower probability of getting the condition, despite the fact that these scores, which combine the genetic risk for T2D across numerous genetic loci, are not any more reliable than clinical markers for T2D prediction[72].

The Diabetic Nephropathy Collaborative Research Initiative, led by the GENIE collaboration, published the largest GWAS on diabetic kidney disease (DKD) to date in 2019[73]. The sample size was increased by three times for European Americans with T1D compared to the prior study, and 16 additional significant genome-wide loci

connected to multiple illness definitions were found[73]. The missense variant SNP rs55703767 of the type IV collagen alpha 3 chain gene (COL4A3frequent), whose minor allele (T) guards against DKD and numerous other albuminuria-related symptoms, was the one with the highest correlation. Notably, Alport syndrome is caused by loss-of-function mutations in COL4A3[74]. The mutation was also associated with a reduction in glomerular basement membrane (GBM) thickness in a normoalbuminuric cohort for whom ultrastructural data were available for analysis. The SNP rs55703767 had a significantly greater impact in women. In addition, the protective association in an observational study and in those randomly assigned to a conventional *vs* intensive glycemic control in the Diabetes Control and Complications Trial was most pronounced in people with higher hemoglobin A1c (HbA1c) levels, which is noteworthy and might be expected for genetic effects expressed in the context of diabetes[73]. In dissected human glomerulus samples from Pima Indians with DKD and glomerulosclerosis, COL4A3 expression levels were discovered to be negatively correlated with GBM surface density. Furthermore, this study project identified three additional genetic loci that exceeded a strict threshold after controlling multiple correction testing (rs144434404 in intron 1 of BMP7, rs142823282 near TAMM41 and rs145681168 in intron 3 of HAND2-AS1)[73]. The SNP rs144434404 in intron 1 of BMP7, a gene involved in renal morphogenesis that is almost exclusively expressed in mouse podocytes, was found to be associated with microalbuminuria. The SNPs rs142823282 and rs145681168, which are located close to TAMM41, as well as rs145681168, which is located in intron 3 of HAND2-AS1, were both substantially linked to microalbuminuria across the entire study. The expression of the neighboring gene PPARG (an expression quantitative trait locus), which is a known T2D GWAS gene but has not been previously studied, was also connected to the TAMM41 signal[74].

With respect to diabetic retinopathy, significant result was found by only one study[75] at the discovery and replication meta-analysis stages by merging two T2D cohorts, one T1D cohort of European ancestry, and one T2D Indian cohort. The genotypes linked to sight-threatening diabetic retinopathy were significantly correlated

with genotypes at SNP rs9896052, a variant 17 kb upstream of the *GRB2* gene. This gene encodes an epidermal growth factor receptor-binding protein that is expressed in healthy human retina and is elevated in the retina of a transgenic mice model of retinal stress[76]. Since then, there have been two further comprehensive GWAS of diabetic retinopathy, but at the meta-analysis stage, they have not yet been able to provide definitive proof of a genetic relationship. The genome-wide significant intronic variant SNP rs3913535, which affects NOX4, was discovered by the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) discovery cohort.

Regarding diabetic neuropathy, the two main GWAS carried out in the GoDARTS project discovered three signals nominally associated with diabetic nerve pain (rs71647933 in ZSCAN20 in female cases and sex-combined analyses only, rs6986153 at chr8q23 in male cases only, and rs17428041)[77,78]. The presence of foot ulcers in people with diabetic neuropathy was compared to two different groups of control people with diabetes and without foot ulcers in a third GWAS using the same GoDARTS dataset. Comparing cases and controls with diabetic neuropathy, the authors discovered the intronic SNP rs80028505 in MAPK14 related with foot ulcers. These studies are from a single cohort, which is significant.

Genetics of COVID-19 disease

The COVID-19 is caused by the novel SARS-CoV-2 and was first reported in Wuhan, China. The clinical manifestation of this disease ranges from an asymptomatic to severe disease outcome. Considering the broad spectrum of COVID-19 disease severity, risk factors that predict the disease severity might play a crucial in improving the clinical outcome of COVID-19 patients. Older age, male gender, increased BMI, pre-existing comorbidities and ethnicity are some of the risk factors that are relevant in the context of COVID-19 disease severity and susceptibility. The host genetic predisposition has also been recognized as the crucial risk factor for COVID-19 which is evident by the large number of genome wide association studies, Whole exome sequencing and candidate gene studies conducted by different consortia (COVID-19 Host Genetics

Initiative (HGI), Genetics of Mortality In Critical Care (GenOMICC), COVID human genetic effort, independent academic working groups, and commercial genomics service providers such as 23 and Me and Ancestry DNA) regarding the COVID-19 disease to decipher the disease susceptibility and severity[79].

Human Leukocyte Antigen (HLA) are encoded by the most polymorphic MHC genes. Several HLA alleles have been found to be associated with COVID-19 severity and susceptibility. In a study comprising of 82 Chinese individuals, HLA- C*07:29 and B*15:27 were significantly higher in COVID-19 patients compared to control population after correcting the P value[80]. HLA- DRB1*15:01, - DQB1*06:02 and HLA- B*27:07 were significantly higher in 99 severe or critical COVID-19 patients compared to 1017 reference individuals previously analyzed by the research team after applying Bonferroni's multiple test correction[81]. HLA-DRB1*08 was found to be significantly higher in COVID-19 positive individuals and it was also correlated with mortality[82]. HLA-A*11:01, B*51:01, and C*14:02 alleles were found to be significantly associated with worst COVID-19 outcome[83]. In a study comprising of 619 healthy Sardinian controls and 182 SARS-CoV-2 patients, the haplotype HLA-A*02:05, B*58:01, C*07:01, DRB1*03:01 was absent in the patients. The HLA allele HLA-C*04:01 allele and the three-loci haplotype HLA-A*30:02, B*14:02, C*08:02 were significantly more frequently in COVID-19 patients[84].

The cytokine storm has been implicated in severe COVID-19. Seven IL-6 (rs140764737, rs142164099, rs2069849, rs142759801, rs190436077, rs148171375, rs13306435) variants and five IL-6R variants (rs2228144, rs2229237, rs2228145, rs28730735, rs143810642) can be implicated in the pathogenesis and severity of COVID-19[85]. Patients with no previous history of severe infection may develop life-threatening COVID-19 pneumonia due to inborn defects of type I IFN immunity that are TLR3- and IRF7-dependent[86]. None of the asymptomatic patients and 2.1% of severely affected males had the TLR7 deleterious variants[87]. Interferon-alpha and -beta receptor subunit 2 (IFNAR2) variant rs2236757 was associated with critical COVID-19[88].

The ACE2 gene is located at position Xp22.2. The S1 subunit of the spike protein (S) of SARS-CoV-2 binds with the Angiotensin Converting Enzyme 2 (ACE2) on the surface of the host cell. The entry into the host cell requires the cleavage at the S1/S2 site by a cellular serine protease, TMPRSS2[89]. The TMPRSS2 variants rs12329760 was found to have deleterious effect on the protease activity and protective role in COVID-19 patients[90]. The T allele of rs2285666 of ACE2 gene was found to be a risk factor for critical COVID-19 especially for men[91]. The splice site variant rs2285666 was also found to be overrepresented in SARS-CoV-2 positive individuals compared to the 100K genome project controls and in hospitalized European patients compared to outpatients. This variant increases the expression of ACE2. The eQTL rs12006793 was found to be more prevalent in patients in this study[92]. The ACE2 variant (rs190509934:C; a rare X-linked variant) was found to reduce the risk of COVID-19 but not the risk according to a meta-analysis[79].

Ellinghaus et al[93] found the 3p21.31 Locus (rs11385942) was associated with severe COVID-19 and respiratory failure in a GWAS study. 3p21.31 spans the gene cluster containing the genes sodium-amino acid transporter 1 (SLC6A20), human leucine zipper transcription factor like 1, CC motif chemokine receptor 9, FYVE and coiled-coil domain-containing protein 1, C-X motif chemokine receptor 6, and X-C motif chemokine receptor 1 genes. A second locus 9q34.2 (rs657152) overlapping with the ABO locus was also found to be significantly associated with severe COVID-19[93]. The GenOMICC (Genetics of Mortality In Critical Care) genome-wide association study involving 2244 critically ill COVID-19 patients from 208 United Kingdom intensive care units, identified significant associations on chromosome 12q24.13 (rs10735079), chromosome 19p13.2 (rs74956615), chromosome (rs2109069) and on chromosome 21q22.1 (rs2236757)[88].

The rs35705950 of the MUC5B was found to be associated with hospitalization in COVID-19. rs35705950 is a promoter specific mutation (https://www.covid19hg.org/results/r6/). The association of rs1886814 in the transcription factor FOXP4 was found to be associated with hospitalization by HGI[94].

Independent of pre-existing dementia, cardiovascular illness, or type 2 diabetes, the ApoE e4e4 homozygous genotype was observed to increase the risk of severe COVID-19[95].

Long-term effects of COVID-19 disease

It has been demonstrated that COVID-19's clinical presentation varies greatly, frequently exhibiting substantial respiratory problems. A number of patients with SARS-CoV-2 have gone on to experience long-term problems from the virus, making it notable. Long-haul COVID-19 has evolved to represent a wide range of problems and sequelae of symptoms that may occur, beyond the original reports of individuals feeling weary for months following initial infection[96]. Lung fibrosis, venous thromboembolism (VTE), arterial thromboses, heart thrombosis and inflammation, stroke, "brain fog," dermatological issues, and general mood dysfunctions are some of the potential late consequences that could result from COVID-19 infection, according to prior investigations[97]. Despite the wide range of these long-term problems, certain patient characteristics have been proven to predict which symptoms they would experience and for how long[98].

COVID-19 is mostly a respiratory disease, despite the fact that SARS-CoV-2 can have widespread effects throughout the body. Following COVID-19 infection, numerous long-term pulmonary problems have been reported. Dyspnea, ventilator dependency, oxygen dependence, pulmonary function test (PFT) abnormalities, and fibrotic lung disease are only a few of them. Dyspnea is the most frequent pulmonary symptom associated with COVID-19, and it might last for two months in 22.9% to 53.3% of patients[99-101]. Infection with SARS-CoV-2 can lead to verifiable long-term alterations in pulmonary physiology in addition to subjective symptoms. Up to 6.6% of survivors who make it to hospital discharge have been found to be oxygen dependent[101]. Long-term weaning from ventilator use is not frequently successful in patients with respiratory insufficiency necessitating a tracheostomy. Only 48% of patients in Spain's 1890 tracheostomy patients were successful in weaning off artificial breathing at the 1-

month follow-up[102]. Previous studies have also discussed abnormalities in lung function as determined by PFT. In a study of 55 non-critically ill COVID-19 patients in China, PFT evaluation over a three-month follow-up period indicated abnormalities in 25% of patients, with a decrease in DLCO being the most prevalent (16%)[103]. Salem *et al*[104] made similar observations with elevated incidence of restrictive lung findings when compared with matched controls.

After being released from the hospital following COVID-19, cardiac problems are a frequent complaint. As many as 21% of patients had chest pain 60 days after leaving the hospital, according to Carfì *et al*[99]. Palpitations have also been reported to occur often in as many as 9% of patients at the 60-day follow-up. Aside from the subjective cardiac symptoms listed among the long-term effects of SARS-CoV-2 infection, there have also been a number of quantifiable results. Investigation into the precise prevalence of postural tachycardia syndrome, which has been associated with SARS-CoV-2 infection, is still ongoing[105].

Acute COVID-19 has been linked to a higher risk of thrombotic events, particularly in patients who are severely sick[106,107]. The causes of this coagulopathy are multifaceted and include hypoxia's impact on the activation of hypoxia-inducible transcription factors, microvascular dysfunction, and enhanced expression of tissue factors in response to inflammatory cytokines[108,109]. The regular administration of intermediate-dose anticoagulation (enoxaparin 1 mg/kg) is recommended due to the elevated risk of thrombosis found in this patient population. Recently, a comparison of typical preventive anticoagulation (enoxaparin 40 mg daily) and severely ill individuals with a randomized controlled method in the INSPIRATION trial, COVID-19. Treatment with intermediate-dose anticoagulation did not appear to lower the composite endpoint of arterial or venous thrombosis. ECMO, or death at 30 days as compared to prophylactic anticoagulation at a standard dose[110]. Even though bleeding incidents do occur, most patients benefit more from inpatient VTE prevention than they risk due to the minimal risk of significant bleeding[111,112].

With SARS-CoV-2 infection came a number of long-term neurological and behavioral problems. Two months after the acute infection, patients continued to experience neurological symptoms as fatigue, muscle weakness, difficulty sleeping, myalgia, and headaches, according to long-term symptom data from numerous sources[99,113]. These signs and symptoms have come to represent the long COVID syndrome. In contrast to other viral infections, SARS-CoV-2 infection has also been associated with loss of taste and smell. At a 2-month follow-up, 11% to 13.1% of patients still had chronic loss of taste and smell[100,113]. Due to the considerable burden of severe, life-threatening illness and acute respiratory distress syndrome (ARDS) associated with COVID-19, cognitive disturbances comparable to those shown in ARDS patients in previous studies should be anticipated. At one year of follow-up, ARDS survivors from other causes have reported memory problems (13%), verbal fluency problems (16%), and executive function problems (49%)[114].

A review of the literature found that of the reported cutaneous manifestations of COVID-19 infection, the most prevalent cutaneous manifestation was maculopapular exanthem (morbilliform), which was reported by 36.1% of 72 documented patients in 18 studies. Other cutaneous manifestations included papulovesicular rash (34.7%), urticaria (9.7%), painful red acral purple papules (15.3%), and urticaria, with 19.4% of these manifestations[115]. Another international study of 2560 patients reported that the most prevalent cutaneous manifestation (51.5%) was pernio-like lesions, and that children had a 1.5-day latency period between upper-respiratory infections and cutaneous findings compared to adults, who had a 7.9-day latency period[116]. Only 47 of 1655 hospitalized patients in the Chinese post-acute COVID-19 study (3%) reported skin rashes six months after the infection started[113]; hair loss, on the other hand, was a symptom that was much more frequently reported for patients' months after the COVID-19 infection and was reported in 24 of 120 patients (20.0%) as a post-discharge symptom 110 days after hospital discharge. However, other, more uncommon presentations have been described in case reports, indicating that, although having the same virus in their bodies, the symptoms in various patients may change[117]. Vesicular

rashes may be diagnostic of an initial diagnosis of COVID 19 and may be predictive of disease prognosis, although the particular use of these symptoms in this manner has not yet been proven and should be the subject of future prospective research[118].

Children often experience a milder disease during the acute phase of COVID-19 and receive diagnoses at a lesser rate than adults[119]. Multisystem inflammatory syndrome in children (MIS-C), which is characterized by fever and multiorgan dysfunction in the weeks following SARS-CoV-2 infection[120,121], is one of the consequences and sequelae of infection. 316 cases per 1000000 infections are reported for MIS-C, which primarily affects youngsters from racial/ethnic minority backgrounds[122,123]. Nearly 75% of MIS-C patients require ICU admission, and the condition shares characteristics with both severe acute COVID-19 and Kawasaki illness[120-122]. The most typical symptoms include gastrointestinal issues, cardiovascular issues, respiratory issues, mucocutaneous issues, and neurological issues[122-124].

Poorer COVID-19 outcomes have been linked to pre-existing diabetic mellitus. Meanwhile, COVID-19 has been linked to both type 1 and type 2 diabetes patients' new-onset hyperglycemia and rapid decompensation of diabetes, including diabetic ketoacidosis[125]. In addition to iatrogenic hyperglycemia caused by steroid usage, other suggested mechanisms for hyperglycemia after infection include insulin resistance brought on by the inflammatory state and insulin secretory deficiencies from defective beta cells—caused either directly or indirectly by viral damage[125,126]. Unknown numbers of people with newly discovered diabetes following COVID-19 may have already had undiagnosed diabetes prior to infection, which was merely concealed or made worse by the infection. It's also not certain whether diabetes that develops after being hospitalized for COVID-19 is a lifelong condition. In order to better understand the relationship between COVID-19 and diabetes and to better define the length of post-COVID-19 diabetes, the global CoviDiab Registry was established[127].

Acute COVID-19 patients frequently experience acute kidney injury (AKI), and 5% of all hospitalized patients need inpatient renal replacement treatment[128]. The causes of AKI are multifactorial, and they include aberrant coagulation, systemic hypoxia,

inflammatory cytokine effects, and direct virus harm[129]. The most frequent histological finding is acute tubular necrosis, however glomerulopathy[130] and microvascular thrombi[131] can also occur[132-136]. AKI is linked to an increase in hospital mortality, and those who make it out of the hospital[128].

Shared variants responsible for diabetes and severity of COVID-19 disease
Frequencies of variations in human ACE2 receptor gene is not uniform rather varied considerably from population to populations. Mutations emerging within the SARS-CoV-2 genome and natural polymorphisms harbored within the ACE2 receptor gene are crucial for the binding of receptor binding domain of spike protein of SARS-CoV-2 followed by the entry and transmission of the virus[137]. Several studies have been conducted to evaluate the binding affinity of the novel SARS-CoV-2 variants to hACE2[138-140] and association of population specific ACE2 variants with disease susceptibility as well as severity has been reported[141-143]. Presence of ACE2 receptor polymorphisms can alter binding interaction with SARS-CoV-2 followed by COVID-19 disease susceptibility[144] on one hand while on the other side different mutations in SARS-CoV-2 revealed varied binding pattern to its host receptor, ACE2[145].

Studies on different population revealed linkage between the single nucleotide polymorphisms within the angiotensin converting enzyme 2 receptor gene and hypertension, diabetes, cardiovascular diseases[146,147]. The ACE2 variants rs2285666, rs879922, rs4646188, rs2106809, rs4240157, rs4830542, rs2158083, rs879922, rs1514283, rs2074192, rs4646155, rs4646176, rs4646174 and rs233575 have been reported to be associated with primary hypertension while rs2106809, rs2074192, rs4646156, rs879922, rs4240157 and rs233575 were found to be linked with left ventricular hypertrophy[148]. Incompatible results have been reported regarding association of *ACE2* gene variants with the risk as well as severity of COVID-19 disease. Studies conducted on Turkish, Italian and Spanish populations reported that *ACE2 receptor* gene rs2106809, and rs2285666 polymorphisms were not associated with the severity of COVID-19 infection[148-151] while ACE2 rs2285666 (AA allele) and ACE2 rs2074192 (TT allele), and

for ACE2 rs4646174 (GG allele), ACE2 rs4646156 (TT allele) and ACE2 rs2158083 (TT allele) the most significant correlation with COVID-19 in Polish population[152]. On the other hand, in another study Cafiero *et al*[153] reported SNPs within the members of renin angiotensin system such as rs2074192 within ACE2, rs1799752 within ACE1 and rs699 within angiotensinogen, SNPs could potentially be a valuable tool for predicting the clinical outcome of SARS-CoV-2 infected patients.

Intronic variant rs228666 (located in intron 3) can cause change in mRNA splicing followed by altered ACE2 expression which ultimately results in higher binding affinity to novel coronavirus[152] and similar characteristics in case of rs2158083 was observed in patients with arterial hypertension[138]. Another intronic variant rs2074192 has been demonstrated to dysregulate SARS-CoV-2 binding to its host receptor by mediating imbalance in ACE2 transcription/translation through inducing changes in secondary structure of RNA[138,152]. Sienko *et al*[152] demonstrated significant correlation of the *ACE2 receptor* gene rs2074192, rs2158083, rs2285666, rs4646156, rs4646174 polymorphisms with the severity of COVID-19 in adult patients. Strong correlation of T allele and TT genotype with respect to of rs2074192 within *ACE2 receptor* gene has been shown with disease severity caused by SARS-CoV-2[151,152] and in French-Canadian and British patients (n = 1644) with COVID-19 disease in obese smoking males[154]. Recent research has demonstrated that persons with type 2 diabetes (T2D) experience COVID-19 with greater severity and mortality as compared to healthy individuals. Patients with T2D who are infected with SARS-CoV-2 are more prone to experience severe cytokine storm consequences and need to be hospitalized to high-dependency or intensive care facilities. Due to the severe activation of inflammatory cascades, some COVID-19 individuals are known to experience different types of acute respiratory distress syndrome and have a greater mortality risk.

Recently, Wu *et al*[155] tried to find the common genetic determinants between T2D and COVID-19. They analyzed the key pathways that were shared between T2D and COVID-19 in order to identify the common pathways between the two diseases. Using iGSEA4GWAS, they discovered chemokine binding, G-protein coupled chemoattractant

receptor activity pathways (CCR2 and CCR3), TFAP2 family pathway (TFAP2B), and ventricular cardiac muscle cells differentiation (RARB and PROX1) pathways shared by T2D and COVID-19. Immunological cell recruitment to infection sites is aided by the chemokine binding pathway, and leukocyte chemotaxis and innate and adaptive host immune responses are mediated by the G-protein coupled chemoattractant receptor. Additionally, using PASCAL, 15 pathways that were common between T2D and COVID-19 were discovered. These pathways were linked to a number of biological functions and organs, including the heart, axons, and calcium channels. However, no shared pathways between the four pathway-based analytic programs were discovered. 394 genes were associated with T2D according to PASCAL analysis, while 58 genes were associated with COVID-19. Five were discovered to be common between T2D and COVID-19 after comparing the important genes in T2D and COVID-19: PTPRD, CSMD1, MAGI1, ASIC2, and DAB1.

Significantly positive genetic correlations between T2D and COVID-19 were found in genome-wide linkage disequilibrium score regression studies (R for genetic = 0.15, P value = 0.01). There is a slight polygenic overlap between COVID-19 and T2D, as evidenced by the enrichment of associations with COVID-19 across different degrees of association with T2D[22]. Wu *et al*[155] further revealed two loci shared between COVID-19 and T2D: ABO (rs505922, intronic) and NUS1 (rs3924604, intronic) based on a threshold of conjFDR<0.05. Both of these independent loci were displaying a consistent direction when the effect directions of the shared independent loci were compared (conjFDR<0.05). One locus (rs505922) has shown a favorable effect, whilst the other (rs3924604) demonstrated a detrimental effect. SNPnexus was used to identify these two genes from two separate SNPs. In the genes closest to the identified loci shared between COVID-19 and T2D, eight pathways were found to be significantly overrepresented, with the faulty DHDDs causing retinitis pigmentosa 59 pathway being the most significant (P value = 1.88×10^{-4}).

CONCLUSION

The world has overcome the devastating impact of COVID-19 by undergoing massive vaccination program against SARS-CoV-2. The pandemic has also showed us weaknesses of the health care system of both the developed and underdeveloped world. Also, we should think about preserving our forests, water reservoirs *i.e.*, the natural habitats of all living beings. To do so, we need to revisit the actions of climate change. Moreover, the world researchers, policy makers, health care providers should also consider the probable impacts of long COVID on human health. Understanding the genetics of hosts and disease pathophysiology could be one of the many steps towards better human health and well-being.

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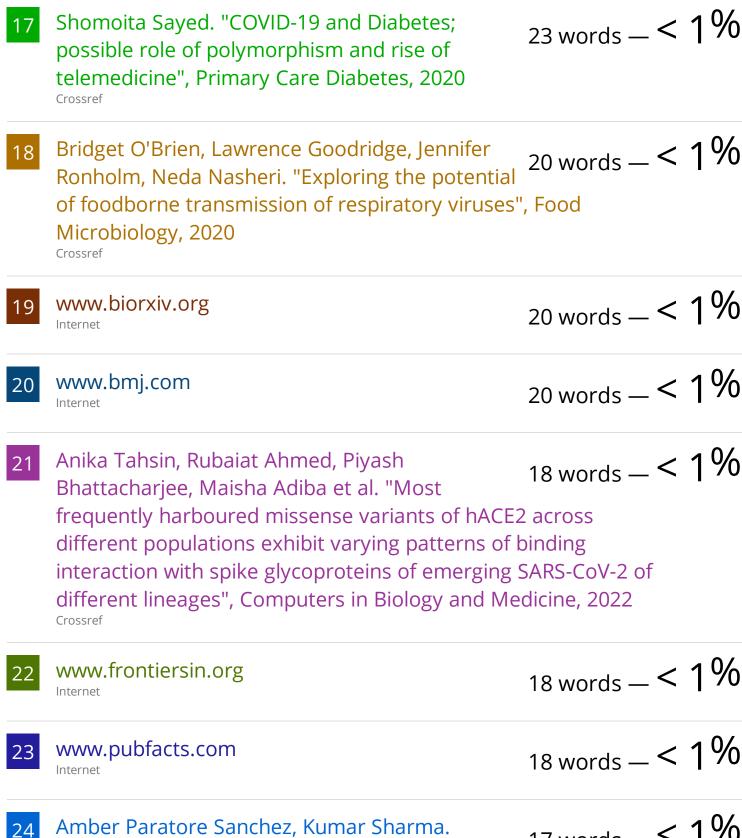
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