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A Comprehensive Examination of the Association Between the ACE2 Gene with the Susceptibility to COVID-19 and the Occurrence of Diabetes Mellitus

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دراسة شاملة حول العلاقة بين جين ACE2 وقابلية الإصابة بكوفيد-19 والإصابة بمرض السكري

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ABSTRACT

Background:
The rate of transmission, as well as the risk of death associated with COVID-19, is significantly higher than that of previous epidemics. Among the underlying health conditions frequently observed in affected populations, diabetes stands out as one of the most prevalent. Individuals with diabetes who contract Covid-19 face a heightened risk of disease progression compared to those with other conditions.

Materials and Methods:
A case-control study was implemented to assess biomarkers using classical lab work procedures and genetic markers using congenital PCR, then the association between ACE2 gene, COVID-19 and Diabetes Mellitus were implemented.

Results:
The analysis of the ACE2 (ID; DD) group revealed statistically significant differences between the groups. However, the II as well as I groups did not demonstrate any notable differences. The chi-square method employed, with a p-value set at < 0.05, indicating statistical significance. Among the manage organization, those with covid-19 , and humans with diabetes plus covid19, the ACE2 D genotype was the most common genotype, accounting for 72.6%, 85%, and 54% of the full population, respectively. After this, the DD, ID, and I genotypes have been applied to the samples.

Conclusions:
The ACE2 D genotype showed significant prevalence in COVID-19 and diabetes populations, while the II and I genotypes showed no notable differences, highlighting ACE2 D's potential importance

Key words: COVID-19; ACE2 gene; Cytokine Strom; pandemics; Diabetes Mellitus

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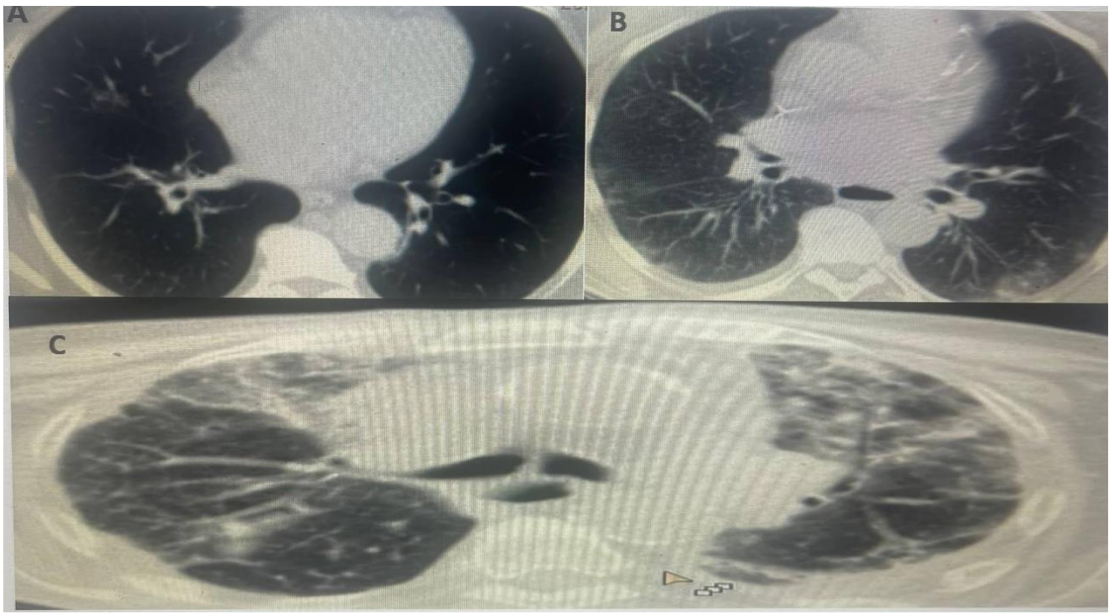
INTRODUCTION

An RNA genome this is single-stranded and encased in a lipid bilayer this is blanketed with proteins that makes up the structure of the SARS-CoV-2 virus. There is a pandemic referred to as SARS-CoV this is capable of inflicting an excessive illness known as SARS [1]. This virus is able to impact the respiratory gadget. The shape of the nucleocapsid (N) glycoprotein is made out of multiple one of a kind auxiliary protein, as well as the the membrane (M) glycoprotein, the nucleocapsid (N) glycoprotein, CoV2 spike (S) glycoprotein, as well as the small envelope (E) glycoprotein [2]. One of the components of SARS-CoV.2 is viral protein. The spike protein, additionally referred to as the S glycoprotein, is an essential trans membrane protein observed at the floor of the virus. This protein has a molecular weight of approximately one hundred fifty kilo Daltons and is organized into homotrimers that challenge from the viral envelope. These spike protein homotrimers facilitate the virus's capability to connect to host cells by way of interacting with angiotensin-changing enzyme 2 (ACE2), that's expressed on the cells lining the decrease respiratory tract.The spike protein undergoes a crucial cleavage process done by way of a host mobile enzyme known as a furin-like protease. This cleavage separates the spike protein into subunits, S1 and S2. The S1 subunit contains the receptor-binding domain, that's important for figuring out the variety of host cells that the virus can infect. The S2 subunit, however, is involved inside the fusion of the viral envelope with the host cell membrane, facilitating the access of the virus into the cell. This fusion system is critical for the virus's potential to set up a contamination [3]. Severe instances of COVID-19 can be development to acute respiratory distress syndrome (ARDS), which generally manifests around eight to nine days after the initial onset of symptoms [4]. ARDS is characterized with the aid of signs such as pneumonia, pulmonary edema, a decrease in oxygen saturation levels (SpO2) to about 93%, breathing failure requiring invasive air flow, and the need for admission to an intensive care unit. Additional signs and symptoms that can become glaring include cytokine typhoon, viremia, multi-organ damage as well as coagulopathy, and lymphopenia, [5, 6]. Diagnosing excessive COVID-19 involves a comprehensive set of bodily examinations and laboratory assessments. These assessments include measuring SpO2 levels, evaluating D-dimer tiers to assess fibrinolysis, monitoring inflammatory markers, counting leucocytes, and acting computed tomography (CT) scans Figure 1 illustrates the results of those diagnostic exams [7]. Pulmonary edema, one of the vital complications, is characterized by means of fluid accumulation in the lungs, which disrupts the gas alternate process. This fluid leakage from the blood vessels impairs the change of oxygen and carbon dioxide, ensuing in decreased SpO2 tiers, breathing failure, and an extended want for extensive care. Coagulopathy in COVID-19 sufferers may additionally found in unique bureaucracy, consisting of micro vascular thrombosis and diffuse intravascular coagulopathy (DIC) [8]. Micro vascular thrombosis is a more common form of coagulopathy. It is possible that a catastrophic state is present in instances of lymphopenia that are severe. A pandemic caused by COVID-19, one of the most common hyper-inflammatory indications seen in people who have survived severe illnesses is scarring and fibrosis of the lungs. These findings are indicative of tissue damage that is produced by inflammation that is not well managed [9]. Furthermore, examining of the lungs of persons who have passed away

as well, it has been shown via research that there is a correlation between Neutrophophil Extracellular Traps (NETs) and the development of lung damage in COVID-19 patients. This damage may be linked to inflammation, thrombosis, and fibrosis[10].



Figures (1). The levels of intensity can be categorized as mild, moderate, or severe, Presenting a visual comparison of three cases.

Concerns have been raised about the impact that COVID-19 has on people who have diabetes mellitus since these individuals have a greater likelihood of being infected with the virus to begin with. There is a substantial correlation between COVID-19 [11] and admission to the intensive care unit, invasive ventilation, and death. Type 2 diabetes mellitus (T2DM) may be a major factor in predicting adverse outcomes, despite the fact that there is no apparent differential in COVID-19 [12]. In an effort to provide an explanation for the correlation among the severity of diabetic mellitus (DM) as well as COVID-19, scientists proposed by a number of hypotheses. Individuals with poorly managed diabetes experience compromised innate immune system[13], that is the body's primary defense mechanism versus infections such as SARS-CoV-2 Diabetes mellitus is often associated with an imbalanced and excessive inflammatory response. Research has shown that diabetic sufferers exhibit extensively improved stages of inflammatory markers, together with C-reactive protein, interleukin-6 (IL-6), as well as ferritin, compared to non-diabetic people. This indicates that human beings with diabetes are greater at risk of an excessive inflammatory response, commonly referred to as a cytokine typhoon. Such a response can result in extreme headaches, which includes acute respiratory misery syndrome (ARDS), shock, and rapid development of COVID-19.

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Moreover, preceding research [14] had indicated that people with diabetes who participated in COVID-19 trials had better concentrations of D-dimer, a marker of blood clot formation, compared to non-diabetic individuals. This can be attributed to an over activation of the hemostatic system, exacerbated by using diabetes mellitus, which already predisposes individuals to a hypercoagulable and seasoned-thrombotic country. In the context of COVID-19, the coagulation cascade from excessive activation can lead to intense thromboembolic occasions as well as, in excessive cases, bring about dying.[15]

Furthermore, studies have recognized a correlation between diabetes and reduced ranges of angiotensin-converting enzyme 2 (ACE2), an enzyme found in numerous organs such as the lungs, kidneys, belly, and vascular endothelium. ACE2 performs a critical role in degrading angiotensin II, as well as converting angiotensin I into smaller peptides like angiotensin (1-7) and angiotensin (1-9). Studies [16] have proven that the ACE2/Ang(1-7) pathway has anti inflammatory and antioxidant consequences. The decrease expression of ACE2 in diabetic people may additionally assist provide an explanation for the accelerated prevalence of extreme lung damage and ARDS related to COVID-19[17] .

The ACE2/angiotensin 1-7/mas receptor axis is thought to counterbalance the ACE/angiotensin II/AT1R axis. This involved in various conditions such as high blood pressure, heart failure, as well as cardiac hypertrophy, other cardiovascular sicknesses [18]. Turner and associates [19] have cited that the SARS-CoV-S protein binds to ACE2, facilitating the infection technique. The next priming of the SARS-CoV-S protein via mobile proteases surface, together with the serine protease TMPRSS2, permits the fusion of viral and cellular membranes, leading to viral entry and replication in goal cells. Lower stages of ACE2 had been associated with decreased viral contamination and replication. It is extensively general that the binding of the SARS-CoV-S protein to ACE2 is a crucial thing for the SARS-CoV infection technique [20]. When inspecting the interplay among angiotensin-receptor blockers (ARB), as well as angiotensin-changing enzyme inhibitors (ACEi) it is important to recognize their ability implications. Both ACE inhibitors and ARBs are normally prescribed medicines used in the main for coping with excessive blood strain and safeguarding kidney feature in diabetic people. These tablets affect the renin-angiotensin-aldosterone machine (RAAS) by means of counteracting accelerated degrees of angiotensin-II, which, in flip, ends in an improved expression of ACE2, an enzyme worried in high blood pressure law. Unfortunately, SARS-CoV-2, the virus accountable for COVID-19, relies on ACE2 as a receptor to go into and infect the host's lung cells, referred to as pneumocystis. Consequently, expanded ACE2 stages may also facilitate less difficult viral access and replication in the respiration system. Moreover, as the virus utilizes ACE2 to advantage access into host tissues, it outcomes in down regulation of this enzyme, leaving the lungs less blanketed and more susceptible to damage[21] .

Furthermore, COVID-19 has the potential to get worse the condition of patients with type 2 diabetes, particularly folks that are insulin resistant. This effect is notably severe in individuals

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who are obese and have significant insulin resistance. Even with relatively low levels of COVID-19, there is an increase in inflammatory markers such as IL-6, IL-1, monocyte chemo attractant protein-1 (MCP-1), tumor necrosis factor (TNF),as well as inducible protein-10. These elevated levels can adversely affect insulin sensitivity. Research has demonstrated that obesity, often associated with type 2 diabetes, exacerbates the body's cytokine response, causing heightened insulin resistance[22] .

Additionally, SARS-CoV has been shown to elevate blood levels of fetuin-A, a glycoprotein linked to impaired insulin sensitivity [23]. It is important to investigate whether SARS-CoV-2 might also increase fetuin-A levels. Finally, a connection exists between COVID-19 and hypokalemia, characterized by reduced pulmonary ACE2 levels, increased angiotensin-II levels, and elevated aldosterone production. In individuals with type 2 diabetes, low potassium levels may further complicate blood sugar control, potentially worsening glycemic management[24] .

MATERIALS AND METHODS

During the month of October in the year 2023, the sample was comprised of a broad gathering of persons, which included both males as well as females. The Marjan Teaching Hospital as well as Al-Turki Hospital were the locations from where the samples were taken. The severity of the injuries varied, ranging from light to moderate to severe, and some of them required treatment in intensive care units (ICUs). The proportions of injuries were serious varied. The research comprised a total of 31 patients, 31 of which had both COVID and diabetes, while the other 30 participants just had COVID. The participants made up the total number of participants. For the purpose of DNA extraction, about 2 milliliters of blood were obtained from each participant and placed in an EDTA tube. After the DNA was extracted, it was placed in a deep freeze and kept at a temperature of -20 degrees Celsius. Consent was obtained from each and every participant before they were allowed to take part in research.

Designing primers and determining optimal amplification conditions: In accordance with the stringent necessities of ISO 9001:2000, the primer become made by using Bioneer in a sterile environment. This became achieved to make sure that there was no presence of DNase or RNase and that the environment turned into without DNA. Lyophilized primers had been the most normal shape that Bioneer® primers were offered in. Several Pico moles containing a massive amount of lyophilized primer devices have been made to be had. To construct an inventory of primers, you must first prepare the primer through reassembling it in a sterile answer of 1X TE (1 mM Tris, zero.1 mM EDTA, pH of 8), nuclease-free water. This will set up a stock of primers. A practise manual was given via the manufacturer that certain the process of generating a grasp stock of primers via which include a positive quantity of sterile, nuclease-unfastened water or TE. After that, this grasp stock is probably used in the production of working inventory.

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STATISTICAL ANALYSIS

To have a look at differences in frequency distributions, the chi-square check became applied. This statistical check helps to decide whether located variations throughout distinct organizations are vast or if they might have occurred by means of hazard. The importance of the consequences became assessed using a p-value threshold of zero.05 or lower, which shows the probability of the findings being because of random version as opposed to a true impact. For estimating the percentages ratio (OR), a computer software program called SPSS version 23 changed into employed. SPSS, which stands for Statistical Package for the Social Sciences, is broadly used for performing complicated statistical analyses. By the usage of this software, accurate calculations of the odds ratio have been made to assess the power of the association among the variables.

RESULTS AND DISCUSSION

DNA Extraction

Blood samples have been obtained from 3 organizations: wholesome manipulate individuals, patients recognized with COVID-19, and those with diabetes who were also inflamed with COVID-19. To extract and purify the genomic DNA from these samples, a specialized DNA extraction kit produced with the aid of Fibrogene, a business enterprise based totally within the United States, was hired. This package facilitated the efficient extraction and purification of DNA from the accumulated blood samples. Subsequently, the extracted DNA samples underwent evaluation through agarose gel electrophoresis. This step served as an initial verification approach to affirm the presence and integrity of the DNA. The electrophoresis results, as illustrated in Figure 2, displayed the DNA bands corresponding to the three groups under investigation. This visual representation allowed for the assessment of the DNA quality and confirmed that the samples from all groups were suitable for further genetic analysis.

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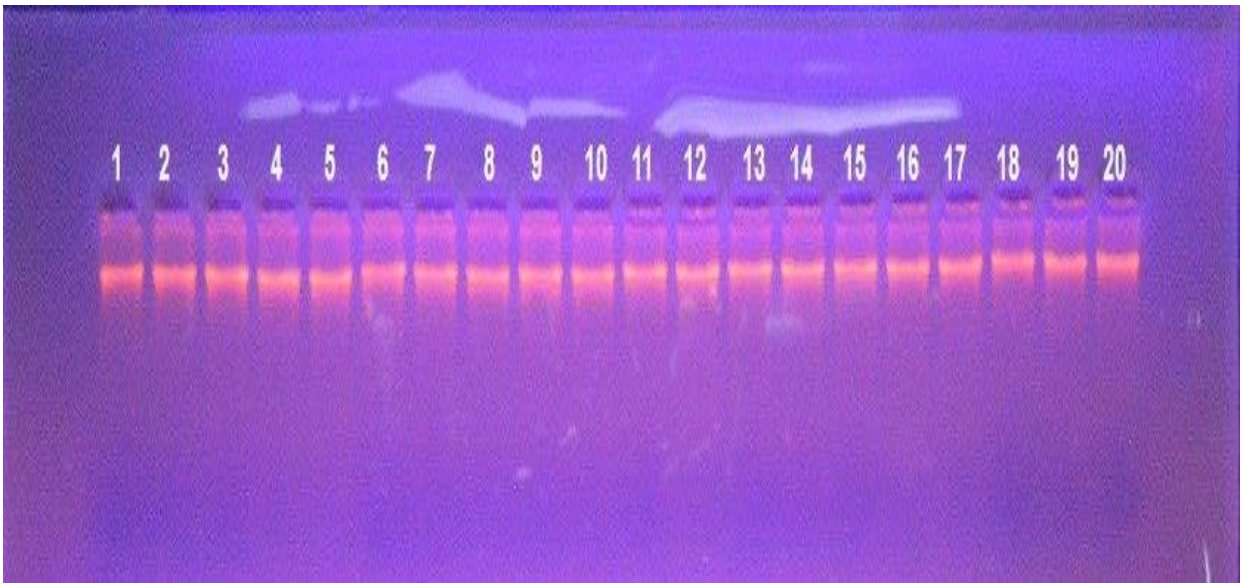

Figure2: The process involves extracting DNA from a blood sample, followed by electrophoresis on a 1% agarose gel using TBE1X buffer at 75 volts and 20 mA for a duration of one hour (with 10 µl in each well). Lanes 1 through 6 include DNA samples for the purpose of control, lanes 7 through 13 contain DNA from COVID-19 patients, and lanes 14 through 20 contain DNA from COVID-19 patients who have diabetes mellitus.

Genotyping for ACE2

The ACE2 I/D polymorphism genomic DNA subjected to amplification employing polymerase chain reaction (PCR) with specific primers. The sequences for these primers are as follows: ACE-F 5'-CTGGAGACCACTCCCATCCTTTCT-3' and ACE-R 5'-GATGTGGCCATCACATTCGTCAGAT-3'. During the PCR process, each reaction utilized 7 milliliters of the reaction mixture. Following amplification, the PCR products were analyzed through electrophoresis on a 1% agarose gel. The electrophoresis was conducted after an initial denaturation step at 94°C. The gel was run in a 0.5X TBE buffer solution. The amplification process consisted of cycling through 15 seconds at 94°C for denaturation, 1 minute at 57°C for annealing, and 30 seconds at 75°C for extension. The electrophoresis was carried out at 75 volts for a total duration of 45 minutes. This electrophoretic analysis allowed for the identification of the allele sizes: 490 base pairs (representing the I allele) and 190 base pairs (representing the D allele), as depicted in Figure 3.

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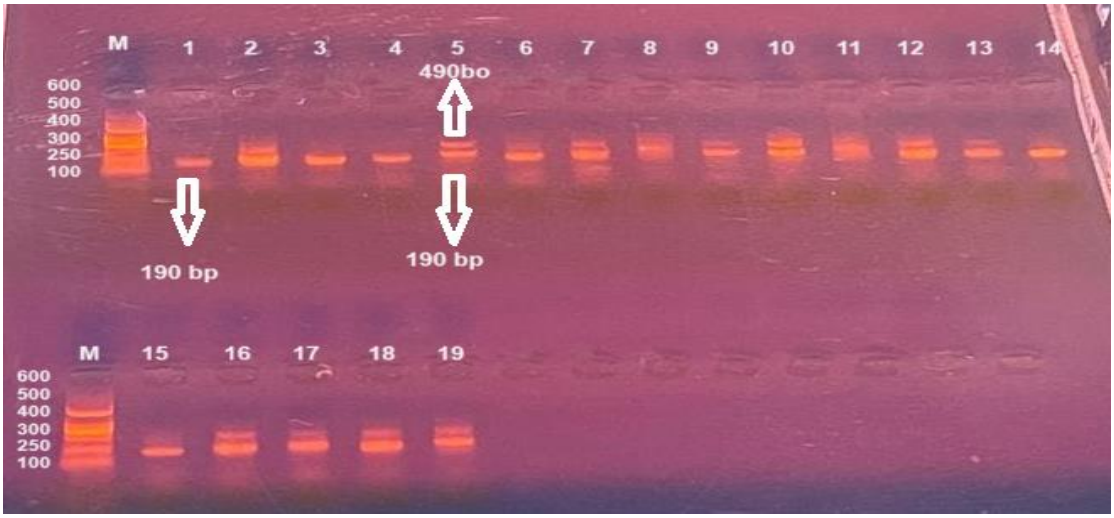

Figure 3: The electrophoresis analysis of the PCR products used for ACE2 I/D genotyping reveals two distinct bands with sizes of 490 base pairs (bp) and 190 bp. This banding pattern was consistently observed across samples from all three groups: the control group, patients with diabetes mellitus who were infected with COVID-19, and individuals solely infected with COVID-19. The electrophoresis was conducted under standardized conditions using a 1% agarose gel. The annealing temperature was set at 57°C, and the electrophoresis was carried out at 75 volts and 20 milliamperes for a duration of one hour.In the electrophoresis setup, Line- M features the Promega molecular weight ladder, which serves as a reference for the sizes of the PCR products. Lanes 1 through 6 display the PCR products obtained from the control group samples. Lanes 7 through 13 show the PCR products from individuals diagnosed with COVID-19, while lanes 14 through 19 are designated for the PCR products from patients with both COVID-19 and diabetes mellitus (DM). This systematic approach allows for clear differentiation and analysis of the ACE2 I/D genotyping patterns across different sample groups.

Examining the genotype distribution of the ACE2 gene polymorphism in both patients as well as controls

The distribution of the ACE2 gene was shown in table (1) among control participants, patients with diabetes mellitus who were infected with covid-19, and patients who were infected with covid-19.At a p-value of 0.04, the ID; DD group demonstrated statistically significant differences for the purpose of the research. On the other hand, statistically significant differences were not found between the II and I groups. An application of the chi-square test with a significance level of 0.05 was used in the statistical analysis that was carried out.

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Table (1): Genotype distribution of the ACE2 gene polymorphism among patients as well as the control

ACE2 Genotype	Control	Covid-19	Covid and DM	Chi-squared	Sig.
II	0	0	0		
ID	17(54.8%)	9(30.0%)	8(25.8%)	6.53	0.04*
DD	14(45.2%)	21(70.00%)	23(74.2%)		
I	17(27.4)	9(15.0)	8(12.9)	5.05	0.8
D	45(72.6)	51(85.0)	54(87.1)		

***Significant at (P≤ 0.05)**

This research examines the ACE2 genotyping distribution across three distinct groups: a control group, individuals infected with COVID-19, and patients with diabetes who are also infected with COVID-19. Our study reveals that the ACE D genotype is the most prevalent among these groups, with frequencies of 72.6% in the control group, 85% in those infected with COVID-19, and 54% in diabetic patients via COVID-19. Following this, the genotypes DD, ID, and I were analyzed within the sample populations. The outcomes of this study align with previous research that explored the ACE I/D genotype in a cohort of 26 COVID-19 patients. That study revealed a significantly higher prevalence of the ACE DD genotype, which observed in 73.0% of the participants [25]. Furthermore, a study conducted by Karagiannidis and colleagues in 2020 demonstrated a link between ACE2 genotypes and susceptibility to SARS-CoV-2 infection [26]. Earlier research has also suggested that genetic variations in angiotensin receptors, particularly ACE2, could potentially increase individuals' susceptibility to repeated infections. This current study corroborates those earlier findings and extends the understanding of how genetic polymorphisms might affect infection risk. Additionally, numerous studies have proposed that mutations in genes responsible for key components of the angiotensin system, like ACE or ACE2, could potentially alter the risk of infection due to various underlying mechanisms [27]. Using a significance threshold of 0.04, we found that there were significant differences between the groups that were assigned the ID and DD designations and those who were assigned the I and D designations. It is possible that specific genotypes are related with greater blood levels of ACE2 or with enhanced expression of ACE2 in cells, as shown by this data [28]

The polymorphisms present in the coding region of the ACE2 gene appear to play a significant role in determining the severity of infections. However, their exact utility and implications are still under investigation [29]. As detailed in Table 1, there are distinct differences in the distribution of ACE2 genotypes among individuals with diabetes mellitus infected by COVID-19, those who are infected but do not have diabetes, and the control subjects. Beyond the well-documented risk

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factors such as male gender and chronic health conditions, an analysis using the Qi square method has identified the DD-allele as a risk factor for contracting COVID-19. This adds a new dimension to the already recognized risk factors. Recent studies suggest that genetic variations in ACE2 could substantially affect the outcome of COVID-19 [30].

In the control groups, individuals infected with COVID-19, as well as diabetic patients with COVID-19, the proportion of individuals carrying the D allele was found to be significantly higher, as indicated by the study's results. This increase was notably larger in comparison with alleles (DD, ID, and I), that were less prevalent. The statistical analysis also revealed the presence of SCA (specific cellular analysis) among these groups. It has been found that individuals with the D-allele might produce higher amounts of ACE2 in their systems compared to those with DD or ID genotypes. Consequently, those carrying the D-allele may be at an increased risk for COVID-19 infection due to elevated ACE2 levels in their bodies. This heightened vulnerability could lead to more severe infections, affecting vital organs such as the heart, lungs, and pancreas [31].

CONCLUSIONS

Significant Differences in ACE2 Genotypes: The ACE2 D genotype exhibited significant differences across the three groups (control, COVID-19, and diabetes with COVID-19), indicating that this genotype may play a role in differentiating these conditions.

Lack of Significance in Other Genotypes: The II and I genotypes did not show any significant differences across the groups, implying that they may not have a major impact on the conditions being studied or may be less prevalent.

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Conflict of interests.

There are non-conflicts of interests

References

1. I-Y., Chen; M., Moriyama; C., Ming-Fu; and I., Takeshi. "Severe Acute Respiratory Syndrome Coronavirus Viroporin 3a Activates the NLRP3 Inflammasome", *Frontiers in Microbiology*, vol. 10, no.2, pp.50, Jan. 2019.
2. S., Jiang; C. Hillyer, and L. Du, "Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses", *Trends in Immunology* , vol. 41, no. 5, pp. 355-59, May. 2019.

3. C., Walls, Alexandra; Young-Jun Park, M. Alejandra Tortorici, Abigail Wall, Andrew T. McGuire, and David Veesler, "Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein", *Cell*, vol. 181, no. 2, pp. 281-92 , Apr. 2020.
4. Y., Michael Zhipeng; M., Yang; and Ch.-L., Lai. "Post-COVID-19 syndrome comprehensive assessment: from clinical diagnosis to imaging and biochemical-guided diagnosis and management", *Viruses*, vol. 15, no. 2, pp 533, Feb. 2023.
5. H., Ben; H., Guo; P., Zhou; and Z.-Li Shi, "Characteristics of SARS-CoV-2 and COVID-19", *Nature reviews microbiology*, vol. 19, no. 3, pp141-154, Mar. 2021.
6. I., Ryota; K., Hanari; K., Shimada; M., Iwagami; A., Sakamoto; Y., Sun; T., Mayers; T., Sugiyama and N., Tamiya. "Barriers to and facilitators of advance care planning implementation for medical staff after the COVID-19 pandemic: an overview of reviews", *BMJ open*, vol. 13, no. 10 , pp. e075969, Oct. 2023.
7. I., Arevalo-Rodriguez; D., Buitrago-Garcia; D., Simancas-Racines; Zambrano-Achig; R., Del Campo; A., Ciapponi; O., Sued; L., Martinez-Garcia; A.W., Rutjes; N.Low and P.M., Bossuyt. "False-negative results of initial RT-PCR assays for COVID-19: a systematic review", *PloS one* , vol.15, no. 12, pp. e0242958, Dec. 2020.
8. J.M., Connors; and J.H., Levy "COVID-19 and Its Implications for Thrombosis and Anticoagulation ", *Blood* , vol. 135, no. 23, pp. 2033-2040, Jun. 2020.
9. T., Soheil; T., Rakhshandehroo; E.X., Wei and M., Rashidian. "Lymphopenia During the COVID-19 Infection: What It Shows and What Can Be Learned ", *Immunology Letters* , vol. 225, pp. 31, Sep. 2020.
10. J.M., Dan; J., Mateus; Y., Kato; K.M., Hastie; E.D.,Yu,; C.E., Faliti; A., Grifoni; S.I., Ramirez; S., Haupt; A., Frazier, and C, Nakao. " Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection", *Science*, vol.371. no. 6529 , pp. eabf4063, Feb. 2021.
11. H.K., Sun; S.I.A., Daniel; C.H., William; K.E., LeBlanc; E., Mylonakis; R., Pratley; and A.G., Pittas. "New-onset diabetes after COVID-19", *The Journal of Clinical Endocrinology & Metabolism*, vol. 108, no.11, pp. e1164-e1174, Nov. 2023.
12. N.S., Murthy; G., Suryanarayana; G.B., Kumar; G., Anudeep; and G., Vinay Sa. "A Comprehensive Survey on Diabetes Type-2 (T2D) Forecast Using Machine Learning ", *Archives of Computational Methods in Engineering*, vol. 31, no. 5, pp. 1-19, Feb.2024.
13. M.T., Yordanos; P.M., Cuccaro; K.S., Elliott; J., Xie; J., Martinez; M., Owens; C.R., Alvarado; and J.M., Yamal."Vaccine Uptake and Intentions: Insights from a Texas Survey on Factors Influencing COVID-19 Vaccination Decisions", *Vaccines* , vol. 12, no. 6 , pp. 601, May. 2024.
14. A.S., Naidu; C.K., Wang; P., Rao; F., Mancini; R.A., Clemens; A., Wirakartakusumah; H.F., Chiu; C.H., Yen; S., Porretta; I., Mathai and S.A., Naidu "Precision nutrition to reset virus-induced human metabolic reprogramming and dysregulation (HMRD) in long-COVID", *npj Science of Food*, vol. 8, no. 1, pp. 19, Mar. 2024.
15. H., Akhtar; B.,t Bhowmik; and N.C., do Vale Moreira, "COVID-19 and diabetes: Knowledge in progress", *Diabetes research and clinical practice*, vol. 162, pp.108142, Apr.2020.
16. J.TY., Huang; H., Sun; and L., Yang. "Research progress of post-acute sequelae after SARS-CoV-2 infection", *Cell Death & Disease ,* vol.15, no. 4, pp. 257, Apr.2024.

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17. S., Tianyuan; T., Zhang; Q., Cai; Y., Yi Ding; and Gu, Zhenyu. "A novel angiotensin I-converting enzyme inhibitory peptide APPLRP from Grifola frondosa ameliorated the Ang II-induced vascular modeling in zebrafish model by mediating smooth muscle cells ", *International Journal of Biological Macromolecules*, vol.278, pp.134998, Oct.2024.
18. R.A.S., Santos; W.O., Sampaio; A.C., Alzamora; D., Motta-Santos; N., Alenina; M., Bader and M.J,Campagnole-Santos "The ACE2/Angiotensin-(1-7)/MAS Axis of the Renin-Angiotensin System: Focus on Angiotensin-(1-7)" , *Physiological reviews*, vol. 98, no.1, pp. 505-553, Jan. 2018.
19. Nishiga, M., Wang, D.W., Han, Y., Lewis, D.B. and Wu, J.C., "COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives ", *Nature Reviews Cardiology*, vol. 17, no. 9, pp. 543-558, Sep. 2020.
20. M., Riou; F., Coste; A., Meyer; I., Enache; S., Talha; A., Charloux; C. Reboul and B.,Geny. "Mechanisms of Pulmonary Vasculopathy in Acute and Long-Term COVID-19: A Review", *International Journal of Molecular Sciences* , vol. 25, no. 9, pp. 4941, Apr. 2024.
21. W., Samy; O.A., Gaber; R.M., Amer; N.A., El-Deeb; A.A., Abdelmoaty; A.L., Sharaf; A.M., El-Gebaly; R., Mosbah; M.E., Alsadik; A. Fawzy; and A.A., Ahmed "Role of ACE2 and TMPRSS2 polymorphisms in clinical severity and outcomes of COVID-19 in Egypt", *African Journal of Laboratory Medicine*, vol.13, no.1, pp.1-8, Aug. 2024.
22. R., Kassir. "Risk of COVID-19 for Patients with Obesity", *Obesity Reviews*, vol. 21, no. 6, Jun. 2020.
23. S.S., Sakat; V., Kuvar; A., Kharche; M., Sagar; P.K., Pandey; O., Bagade; R. Bendgude; and R., Bendgude. "Diabetes mellitus manifestations and challenges in post-COVID-19 syndrome: A critical review", *Journal of Applied Pharmaceutical Science*, vol. 14, no.7, pp. 22-28, May. 2024.
24. M., Lotfy; J., Adeghate; H., Kalasz; J.Singh; and E.,Adeghate. "Chronic complications of diabetes mellitus: a mini review ", *Current diabetes reviews* , vol. 13, no.1 , pp. 3-10, Feb. 2017.
25. A., Anna; A., Coppola; M., Lanza,; F., Simioli; P., Imitazione; N., Pepe; V., Maddaloni; L., Atripaldi; and G., Fiorentino. "ACE DD polymorphism in severe COVID-19", *J. Transl. Sci*, vol. 7, no. 1, pp. 10-15761, Apr. 2020.
26. C., Karagiannidis; F., Krause; C., Bentlage; J., Wolff; T., Bein; W., Windisch; and R., Busse. "In-hospital mortality, comorbidities, and costs of one million mechanically ventilated patients in Germany: a nationwide observational study before, during, and after the COVID-19 pandemic" ,*The Lancet regional health. Europe*, vol. 42 , pp.100954, Jun. 2024.
27. A., Novelli; M., Biancolella; P., Borgiani; D., Cocciadiferro; V.L., Colona; M.R., D'Apice; P., Rogliani; S., Zaffina; F.,Leonardis; A.Campana and M., Raponi. "Analysis of ACE2 Genetic Variants in 131 Italian SARS-CoV-2-Positive Patients ", *Human Genomics* , vol. 14, pp. 1-6, Dec. 2020.
28. E., Tug; I., Fidan; G., Bozdayi; F., Yildirim; O.G., Tunccan; Z., Lale; and D.,Akdogan. " The relationship between the clinical course of SARS-CoV-2 infections and ACE2 and TMPRSS2 expression and polymorphisms", *Advances in Clinical and Experimental Medicine*, vol. 33, no. 1, pp.39-51, Jan. 2024.
29. K., Gao; R., Wang; J., Chen; L., Cheng; J., Frishcosy; Y., Huzumi; Y., Qiu; T., Schluckbier; X., Wei and G.W., Wei "Methodology-centered review of molecular modeling, simulation, and prediction of SARS-CoV-2", *Chemical Reviews*, vol. 122, no.13, pp. 11287-11368, May. 2022.

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30. D., Alwazeer; F.F.C., Liu; X.Y. Wu and T.W.,LeBaron "Combating oxidative stress and inflammation in COVID-19 by molecular hydrogen therapy: mechanisms and perspectives", *Oxidative Medicine and Cellular Longevity*, vol. 2021, no. 1, pp. 5513868, Oct. 2021.
31. N., Etebar; S., Naderpour; S., Akbari; A., Zali; M., Akhlaghdoust; S.M., Daghighi; M., Baghani; S.H. Hamidi and M., Rahimzadegan. "Impacts of SARS-CoV-2 on brain renin angiotensin system related signaling and its subsequent complications on brain: a theoretical perspective ", *Journal of Chemical* Neuroanatomy, vol. 138, pp.102423, May. 2024.

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الخلاصة

المقدمة:

معدل انتقال العدوى، وكذلك خطر الوفيات المرتبطة بفيروس كوفيد-19، يفوق بشكل كبير معدل انتقال الأوبئة السابقة. ومن بين الحالات الصحية الأساسية التي تُلاحظ بشكل متكرر في السكان المتأثرين، يبرز مرض السكري كواحد من أكثر الأمراض انتشارًا. يواجه الأفراد المصابون بمرض السكري الذين يصابون بكوفيد-19 خطرًا متزايدًا لتطور المرض مقارنة بأولئك الذين يعانون من حالات أخرى.

طرق العمل:

تم تنفيذ دراسة الحالات المرضية والكونترول لتقييم العلامات الجينية باستخدام تفاعل البوليميراز المتسلسل الخلقي، ثم تم تنفيذ الارتباط بين الجين ومرض السكري وكوفد-19

الاستنتاجات:

أظهر النمط الجيني أظهر النمط الجيني "دي" انتشارًا كبيرًا في مجموعات مرضى كوفيد-19 والسكري , في حين لم يظهر النمط الجيني الاول والثاني أي اختلافات ملحوظة، مما يسلط الضوء على الأهمية المحتملة لـ ACE2 D

الكلمات المفتاحية:

كوفيد- 19 , ACEجين ,,الأوبئة , السكري سايتوكاينين ستروم