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Research Article

Incidence of New-Onset Diabetes and Hyperglycemia in COVID-19 Patients: A Family History-Based Study

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ABSTRACT

Aim: To investigate the association between COVID-19 and the onset of diabetes in patients with and without a family history of the disease. **Methods:** Blood glucose tests were performed on patients who had close contact with COVID-19 and had infected individuals admitted to the hospital. Patients were categorized into five groups based on their diabetes status: (1) diagnosed with diabetes before COVID-19, (2) diagnosed with diabetes after COVID-19, (3) hyperglycemia after COVID-19, (4) pre-existing diabetes before COVID-19, and (5) without diabetes. **Results:** Among the COVID-19 positive patients, 34.69% had a family history of diabetes. Regardless of familial history, COVID-19 patients showed a predisposition to diabetes. However, individuals with a family history of diabetes were found to be more susceptible to developing the condition. **Conclusions:** This study highlights the increased risk of developing diabetes in COVID-19 patients, regardless of a family history of the disease. However, individuals with a family history of diabetes should be particularly vigilant. Early identification and management of COVID-19-associated diabetes, especially in high-risk populations, such as those with a family history of diabetes, are essential.

Keywords: COVID-19, diabetes, random blood sugar, fasting blood sugar, RT-PCR

INTRODUCTION

The COVID-19 pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a critical health concern. The virus was first identified in December 2019 in Wuhan, China. Coronaviruses (CoV) are enveloped single-stranded positive-sense RNA viruses that cause respiratory infections in humans. These infections are associated with high mortality and morbidity rates, with older individuals being more severely affected [1- 3]. As per the Coronavirus statistics released by Johns Hopkins University, the number of reported deaths due to the Coronavirus disease (COVID-19) has surpassed 8.43 million in the United States and 5.5 million worldwide as of January 2022. These staggering numbers highlight the

severe impact of the virus on a global scale. Efforts must continue to curb the spread of the virus and ensure that appropriate measures are taken to mitigate the risk of further fatalities [4]. In addition, emerging evidence suggests that COVID-19 exacerbates the symptoms and severity of pre-existing medical conditions such as pulmonary and renal infections, notably diabetes [5, 6]. A meta-analytical observational study has revealed a significant correlation between diabetes and the exacerbation of COVID-19 severity, eventually leading to in-hospital mortality of patients with COVID-19 [7]. Currently, there is limited knowledge regarding the potential association between COVID-19 infection and the likelihood of developing diabetes in patients with and without a family history of the disease.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been found to worsen the symptoms and severity of pre-existing conditions, including respiratory and renal infections, and increase the risk of developing diabetes [8]. The pathogenesis of COVID-19 infection might involve organ failure as a predisposing factor. Studies have shown that 2019-nCov/SARS-CoV-2 and SARS-CoV share a common HKU9-1 progenitor from the bat coronavirus family. Additionally, the protein spikes of SARS-CoV-2 exhibit a high affinity for angiotensin-converting enzyme 2 (ACE2) [9]. ACE2 receptors on various target cells render them highly susceptible to internalization of SARS-CoV-2 and subsequent pathogenesis. Of note, type II alveolar cells in the lungs have the highest expression levels of ACE2, rendering the lungs a primary target for coronavirus pathogenesis [10]. Certainly, several studies have demonstrated that the presence of ACE2 receptors on various target cells, such as lung cells, cardiac cells, gastrointestinal cells, and renal cells, renders these organs susceptible to SARS-CoV infection and subsequent failure [11- 16].

Furthermore, the literature has reported that COVID-19 infection leads to an upregulation of ACE2 expression in the pancreas, which can potentially damage the pancreatic cells [17]. The ACE2 receptor, which COVID-19 targets, disrupts the pancreas and ultimately leads to the dysregulation of insulin-related proteins involved in glucose metabolism, resulting in the development of diabetes. The disruption of the pancreatic cells due to increased ACE2 expression after COVID-19 infection is well-documented in the literature. The resulting damage to the pancreas leads to the deregulation of insulin-related proteins and the eventual development of diabetes [18, 19].

Several studies have demonstrated that pre-existing diabetes mellitus is a significant comorbidity factor in COVID-19-infected patients. However, the precise underlying mechanism remains unclear, though researchers have suggested several potential pathways to explain the susceptibility of diabetic patients to COVID-19 pathogenesis. These pathways include efficient viral binding to the cells, the low potential of cells to clear the virus, ease of viral entry into cells, heightened susceptibility to cytokine storm and inflammation, and decreased T-cell function. The exact mechanism underlying the vulnerability of diabetic patients to COVID-19 requires further investigation [20, 21]. Several studies have suggested that diabetes is a significant risk factor for SARS-CoV-2 infection. However, it has been observed that some individuals who have contracted COVID-19 may develop diabetes, indicating a possible bidirectional relationship between the two diseases. The occurrence of newly diagnosed diabetes after COVID-19 infection can be explained by several possibilities. Firstly, the individual may have been affected by diabetes but remained undiagnosed. Secondly, the individual may have had pre-diabetes, which predisposes one to diabetes. Lastly, it is plausible that the individual may have been genetically predisposed to diabetes, and the COVID-19 infection accelerated the onset of the disease, which may become permanent in the long-term follow-up of COVID-19 patients [22, 23].

In this study, we investigated the occurrence of hyperglycemia and diabetes in COVID-19 patients. We revealed that diabetes might transpire in individuals with both diabetic and

non-diabetic family histories. This may be due to pancreatic cell receptor malfunction or damage to the organ cells caused by COVID-19 infection. The findings of this study contribute to a better understanding of the underlying mechanisms of COVID-19-induced diabetes and may aid in developing appropriate management strategies.

MATERIALS AND METHODS

Study setting and design

The present study utilized a cross-sectional analytical design and public data to investigate the occurrence of hyperglycemia and diabetes among individuals diagnosed with COVID-19 from October 2020 to October 2021 at a tertiary care hospital in Mardan (Mardan Medical Complex, MMC). Ethical approval was obtained from the Ethical Committee of MMC before conducting the study and informed consent was taken from all participants. Blood samples were collected from individuals in close contact (people in regular care and within 6 feet of distance with a patient) with admitted COVID-19 patients and kept under follow-up to undergo COVID-19 testing. If an individual becomes positive, follow-up testing is made for each individual.

Sample collection and preparation

The blood samples for Random blood sugar (RBS) and Fasting blood sugar (FBS) estimation were collected in gel tubes and centrifuged at 4000 RPM for 10 minutes. After centrifugation, the serum was separated and analyzed using the Architect ci4100 chemistry analyzer (Abbott, USA). Additionally, nasopharyngeal swabs were taken from the patients and collected in VTM to detect SARS-CoV-2.

RT- PCR

The COVID tests were performed using the RT-PCR method. RNA extraction (Catalogue no. 92114002) was performed using an auto nucleic acid extractor (NE 48, Genrui Biotech Inc, China), and amplification was done using a master mix kit (Catalogue no. 92115009, Genrui Biotech Inc, China) which detects N, S and ORF1ab genes. The RT-PCR was run on a thermocycler (Singu 9600, Singuway Biotech Inc, China). Both positive and negative controls were run along with the samples.

Inclusion and exclusion criteria

To identify potential participants for the study, a set of criteria was established. Specifically, individuals who tested positive for COVID-19 and had a family history of diabetes were considered, as were those who tested positive for COVID-19 but had no family history of diabetes. Exclusion criteria included suspected contacts under the age of 25 and pregnant women. There were no limitations on upper age, and the study included both genders. The patients belonging to both categories, i.e., diabetic family history and non-diabetic family history, were segregated into five groups for analysis purposes: (A) individuals diagnosed with diabetes for the first time prior to contracting COVID-19, (B) individuals diagnosed with diabetes for the first time after COVID-19 infection, (C) patients exhibiting hyperglycemia (transient high blood sugar levels after COVID-19 infection), (D) individuals who were already prediabetic, and (E) non-diabetic patients following COVID-19 infection. Patients' blood glucose levels were evaluated before, during, and after 15 days of being diagnosed with COVID-19. Patients who had raised sugar levels after 15 days were retested after 2 weeks to confirm the diagnosis of diabetes. The reference ranges for patients diagnosed with high sugar levels for a longer period, hyperglycemia (high sugar levels for a short period), and non-diabetic patients were set at RBS 80-160 mg/dL and FBS 70-126 mg/dL. For patients already diagnosed with diabetes, the reference range was considered as RBS 70-180 mg/dL; we have not collected the FBS samples for diagnosed diabetic patients.

Statistical analysis

The obtained experimental data were subjected to thorough statistical analysis using the Statistical Package for Social Sciences (SPSS) version 20. The continuous data were calculated for their standard deviation (±SD) and mean. All experiments were performed in triplicate to ensure the reliability and consistency of the results. The data were then subjected to further statistical analysis to draw meaningful conclusions. The entire analysis was carried out using rigorous scientific methods to ensure the accuracy and validity of the results.

RESULTS

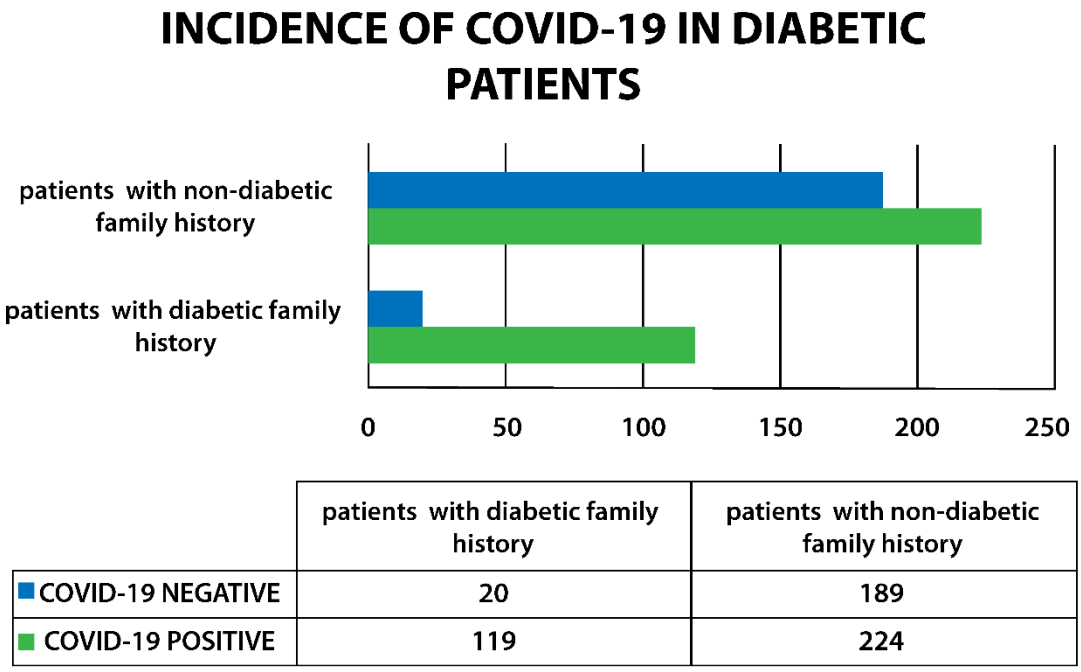
COVID-19 onset is preferentially high in diabetic patients:

The study included a total of 183 COVID-19 positive patients who were admitted to the hospital. Blood samples were also collected from individuals in close contact with the admitted patients, with 597 samples collected. Of these, 343 (57.45%) were infected with COVID-19 and 254 (42.54%) were non-infected. Among the COVID-19 positive patients, 139 had a diabetic family history which, 119 (34.69%) became positive, and n=20 remained negative during our study, while the remaining 224 (65.30%) positive had a non-diabetic family history, with 234 having no COVID-19 infection. The distribution of patients from both categories is presented below in Table I (Fig. I).

Table 1: Summary of Study Patients and Diabetes Status in Relation to COVID-19

Variables	**n (%)**	**RBS expression range**	**Rbs Ref range mg/dL**
Admitted patients	183	-	-
Close contact people with admitted patients	597	-	-
Positive COVID patients	343 (57.45)	-	-
Negative patients	254 (42.54)	-	-
Positive COVID patients with diabetic family history	**119 (34.69)**	-	-
Women	46 (38.65)	-	-
Men	73 (61.34)	-	-
Age range (years)	29-82	-	-
Below 40 years	18 (15.12)	-	-
Above 40 years	101 (84.87)	-	-
Mean age	56.95±13.524	-	-
Diabetes before COVID-19	4 (3.36)	180-310	80-160
Diabetes after COVID-19	37 (31.09)	185-320	80-160
Hyperglycemia	45 (37.81)	166-275	80-160
Diabetic before and after COVID-19	17 (14.28)	140-460	70-180
Non diabetic	20 (16.80)	75-98	80-160
Positive COVID patients with non-diabetic family history	**224 (65.30)**	**-**	**-**
Women	85 (37.94)	-	-
Men	139 (62.05)	-	-

Age range (years)	20-82	-	-
Below 40 years	67 (29.91)	-	-
Above 40 years	157 (70.08)	-	-
Mean age	52.89±18.39	-	-
Diabetes before COVID-19	2 (0.8)	180-310	80-160
Diabetes after COVID-19	5 (2.232)	185-320	80-160
Hyperglycemia	17 (7.58)	166-275	80-160
Diabetic before and after COVID-19	13 (5.803)	140-460	70-180
Non diabetic	189 (84.37)	75-98	80-160



	patients with diabetic family history	patients with non-diabetic family history
COVID-19 NEGATIVE	20	189
COVID-19 POSITIVE	119	224

Figure 1: COVID-19 incidence in patients with diabetic and non-diabetic family history

Exploring the Relationship between COVID-19 and Diabetes Mellitus

This study evaluated a cohort of 119 COVID-19-positive diabetic patients, consisting of n= 46 (38.65%) women and n= 73 (61.34%) men, with a mean age of 56.95±13.524 (Range 29-82 years). The patients were divided into two age groups: those below 40 years (n=18; 15.12%) and those above 40 years (n=101; 84.87%). Among the positive COVID-19 patients with a diabetic family history, n=4 (3.36%) were diagnosed with diabetes for the first time before COVID-19 infection, n=37 (31.09%) patients had diabetes diagnosed for the first time after COVID-19, and n= 45 (37.81%) patients had hyperglycemia after COVID infection. In addition, n=17 (14.28%) patients already had diabetes before COVID-19 infection, and n=16 (13.44%) patients did not show any change in sugar level after COVID-19 infection (refer to Fig II). The findings suggest that COVID-19 infection may increase the risk of diabetes in patients with diabetic family history. The current study findings suggest that diabetes in COVID-19 infection is more prevalent among patients with a family history of diabetes. This could be attributed to the susceptibility of pancreatic cells to the SARS-CoV-2 virus, as ACE2 receptors present on various target cells, including the pancreas, render these cells highly

susceptible to viral internalization and subsequent pathogenesis. Based on these findings, it is recommended that diabetic patients adopt mandatory prophylactic measures and standard operating procedures (SOPs), including the use of face masks, social distancing, and prompt vaccination, to prevent disease severity (Fig.2).

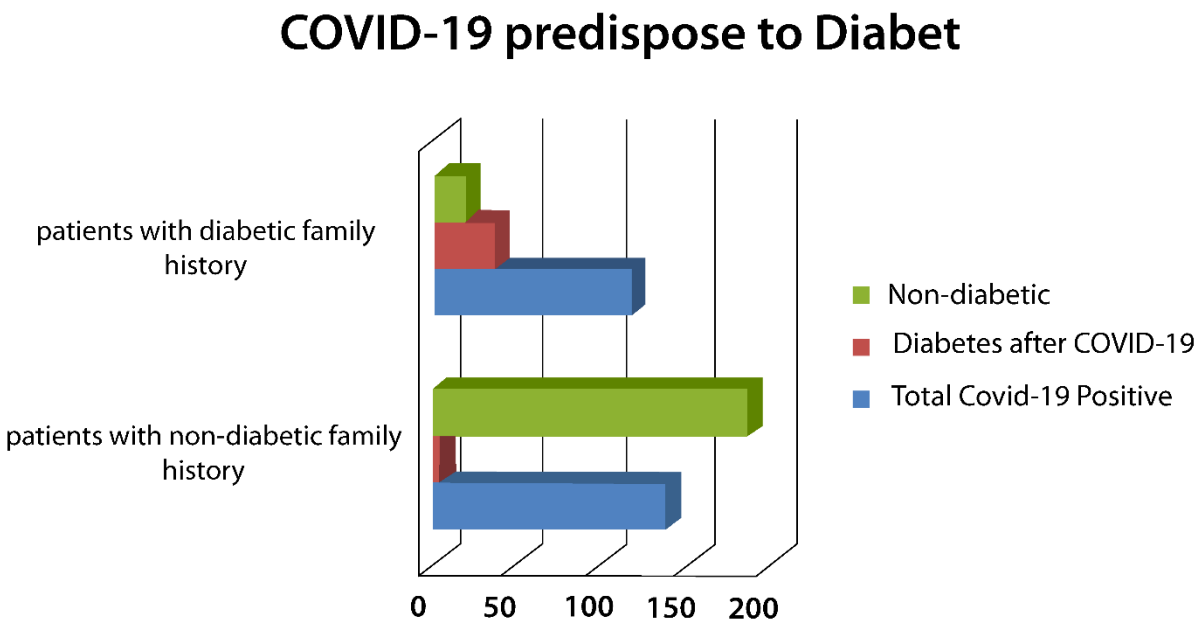


Figure 2: Prevalence of diabetes is higher among COVID-19 positive patients with both diabetic and non-diabetic family history, suggesting that COVID-19 may be a predisposing factor for diabetes

COVID-19 infection significantly alters blood parameters.

In the cohort of 343 COVID-19-positive patients, 175 individuals (51.02%) exhibited high total leukocyte count (TLC), while 14 patients (4.08%) demonstrated low TLC levels, with the remaining 154 (44.89%) showed normal TLC levels. Differential leukocyte count analysis revealed that 197 patients (48.41%) had high neutrophil counts, 47 patients (11.49%) had low neutrophil counts, and the remaining 99 (40.09%) demonstrated normal neutrophil levels. Furthermore, 169 patients (41.56%) exhibited low lymphocyte counts, 58 (14.18%) patients had high lymphocyte counts, and 116 (44.25%) patients had normal lymphocyte levels. Additionally, high Monocyte levels were observed in 57 patients (13.93%), while 286 patients (86.06%) showed normal levels. Finally, 166 patients (40.83%) exhibited low platelet levels, and 177 (59.16%) had normal platelet levels (S.1. Table).

Furthermore, the results indicate that among the COVID-19-positive patients, 78.48% (n=301) showed high levels of LDH, while 21.51% (n=42) exhibited normal levels. Similarly, 323 patients (100%) had high d-Dimmer levels, whereas 20 (100%) displayed normal levels. Additionally, 88.75% (n=314) of patients had high CRP values, and 11.24% (n=29) showed normal values. Among the patients, 45.47% (n=186) had high Ferritin levels, while 54.52% (n=157) had normal levels. In terms of liver function tests (LFTs), only 4.40% (n=18) of patients had high ALT levels, whereas 95.59% (n=325) had normal levels. Similarly, only 3.66% (n=17) of patients had high Bilirubin levels, while 96.33% (n=326) had normal levels. Regarding renal function tests (RFTs), only 4.40% (n=11) of patients showed high urea levels, while 95.59% (n=332) had normal levels. Furthermore, only 1.22% (n=5) of patients had high Creatinine levels, while 98.77% (n=338) had normal levels. Moreover, 9 patients had high

TROP 1, and 334 had normal Trop I. Notably, patients with abnormal LFTs and RFTs due to other diseases were excluded from the study (S.1. Table).

DISCUSSION

The COVID-19 pandemic is an urgent global public health crisis that demands immediate attention. The acceleration of trials for multiple potent therapeutic drugs is of utmost importance in evaluating their efficacy in combating this pandemic. Researchers are under immense pressure to develop promising COVID-19 therapeutic drugs. Potential therapeutic drugs include bioengineered vector-based antibodies and cytokines, which have the potential to halt viral gene expression and aid in vaccine development. While multiple vaccines are currently available, no drugs have been found to treat or prevent COVID-19 infection effectively.

Previous studies have revealed that COVID-19 infection may predispose to multiple organ disruption, particularly in organs such as the cardiac, renal, lungs, and pancreas. This can be attributed to the presence of ACE2 receptors on the surface cells of these organs, which facilitate the internalization of viral particles into the cells and subsequently cause organ damage [24- 27]. The current understanding regarding the potential of COVID-19 infection to cause diabetes is limited, and thus, this area of investigation warrants further exploration. Therefore, this study aims to investigate the potential link between COVID-19 infection and the onset of diabetes in patients without a pre-existing diabetic family history. Building on previous studies, we postulate that COVID-19 infection may serve as a predisposing factor for the development of diabetes. In this regard, our study aims to analyze the association between the onset of diabetes and glucose levels in post-COVID-19 patients with both diabetic and non-diabetic family histories. Our goal is to establish the potential relationship between COVID-19 infection and diabetes and shed light on the underlying mechanisms involved.

The present study included a sample size of n=119 COVID-19-positive patients with a diabetic family history, comprising 46 (38.65%) women and 73 (61.34%) men with a mean age of 56.95±13.524 (Range 29-82 years) and n=224 positive COVID-19 patients with non-diabetic family history, including 85 (37.94%) women and 139 (62.05%) men. The fasting and random glucose levels were measured before and after the COVID-19 infection to detect hyperglycemia in the selected patients. However, fasting and random glucose estimation alone were not considered sufficient to confirm diabetes status in the patients. Therefore, post-COVID-19 hyperglycemic patients were further subjected to the Oral Glucose Tolerance Test (OGTT) to confirm the diagnosis of diabetes. In the group of COVID-19-positive patients with a diabetic family history (n=119), n=4 individuals (3.36%) were found to have newly developed diabetes after COVID-19 infection.

Conversely, in the group of COVID-19-positive patients with a non-diabetic family history (n=224), n=37 individuals (31.09%) were diagnosed with diabetes for the first time after COVID-19 infection. In comparison, n=45 (37.81%) and n=17 (14.28%) individuals exhibited hyperglycemia after COVID-19 infection and prior hyperglycemia, respectively. In the present study, 224 positive COVID-19 patients with non-diabetic family history were evaluated, comprising 85 (37.94%) women and 139 (62.05%) men. Among these patients, n=2 (0.8%) were diagnosed with diabetes prior to COVID-19 infection, while n=5 (2.23%) were diagnosed with diabetes for the first time following COVID-19 infection. Furthermore, n=17 (7.58%) patients exhibited hyperglycemia after COVID-19 infection. It is important to note that the diagnosis of diabetes was made based on a confirmatory oral glucose tolerance test (OGTT) rather than solely relying on fasting and random glucose estimations. The present findings provide valuable insights into the potential association between COVID-19 infection

and the development of diabetes, particularly in patients with no prior family history of diabetes.

The findings of this study provide supportive evidence for our hypothesis that COVID-19 infection is associated with diabetes onset and might act as a predisposing factor. It is plausible that COVID-19 infection affects the cellular architecture of pancreatic beta cells through the viral entry into the pancreas via the ACE2 receptor present in the pancreas. This may lead to alterations in insulin secretion or disruption of its function, ultimately resulting in diabetes [28, 29]. Further investigation is needed to identify the underlying mechanisms of COVID-19-induced diabetes. Studies should be conducted to determine the extent of damage to pancreatic beta cells and whether the damage is reversible. The effect of COVID-19 infection on insulin resistance and its relationship with diabetes onset should also be explored. Researchers indicated a higher risk of developing diabetes in post-COVID-19 infection, which suggests a possible linkage between COVID-19 and dysregulation of glucose metabolism [30, 31].

Additionally, the role of inflammatory cytokines in developing diabetes after COVID-19 infection needs to be investigated. Further studies on the long-term effects of COVID-19 on glucose metabolism in patients with and without pre-existing diabetes should also be conducted. Understanding the mechanism behind the association between COVID-19 and diabetes can help develop effective preventive and therapeutic strategies for this emerging public health challenge.

The findings of our study suggest that COVID-19 infection may be linked to the onset of diabetes, and this association may not be limited to patients with a diabetic family history. Our results also indicate that COVID-19 can induce hyperglycemic conditions in patients with normal glucose levels. Furthermore, our study highlights that COVID-19 infection can significantly impact various blood parameters, such as differential leukocyte count, liver function enzymes, CRP, D-dimmer, and muscle enzyme Lactate dehydrogenase (LDH).

However, further research is required to fully understand the underlying mechanisms by which COVID-19 may contribute to the development of diabetes and the alteration of blood parameters. It is necessary to investigate the possible impact of COVID-19 infection on the pancreatic beta cells, insulin secretion and function, and other related mechanisms to determine the potential predisposing factors of COVID-19-associated diabetes. Future studies should also explore the long-term effects of COVID-19 infection on glucose metabolism and blood parameters to evaluate the risk of diabetes and other related health issues. Further investigations must be carried out to unravel the potential mechanisms through which COVID-19 infection affects pancreatic cell receptors and their role in the onset of diabetes. Elucidating the intricate interplay between the virus and pancreatic cell receptors could shed light on the underlying molecular mechanisms and identify potential targets for therapeutic intervention. Additionally, studies on the long-term effects of COVID-19 infection on pancreatic function and glucose regulation in patients with and without pre-existing diabetes are warranted. These studies would aid in better understanding the pathophysiology of COVID-19-induced diabetes and help develop effective management strategies.

CONCLUSION

Our findings suggest that COVID-19 infection may be a predisposing factor for diabetes development, particularly in patients with a diabetic family history. We also demonstrated that COVID-19 infection could induce hyperglycemia in patients with normal glucose levels prior to infection. However, additional studies are needed to unravel the underlying mechanisms and further investigate the effects of COVID-19 on pancreatic cell receptors and the association of drugs used during the infection.

Data Availability Statement
All relevant data are within the paper and its Supporting Information files.

Conflict of interest/ Competing interests
The authors declare that they have no conflict of interest. The authors have no relevant financial or non-financial interests to disclose. The authors have no competing interests to declare that are relevant to the content of this article.

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Ethics approval
The study was approved by the ethical committee and institutional research board (IRB), Mardan Medical Complex.

Author contributions
Wasim Iqbal and Uroosa Irum: Conceived the idea and wrote the initial draft of the manuscript. Wasim Iqbal, Kalim Ullah: Carried out the investigations. Yasir Ali and Fazal Jalil: Proofreading and overall supervision for this study.

Consent to participate
All participant of the study were willing to participate in the study and confirmation was taken via written consent form.

Consent for publication
A written informed consent was taken from all the participant of the study and all shows willingness for publication of their data.

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