Immunologic Parameters in Type 2 Diabetic Patients Infected with Severe Acute Respiratory Syndrome Coronavirus 2

Ghaleb Hussein Obaid Al-Saeedi, Wisam Salih Abood

Department of Medical Microbiology, College of Medicine, Al-Qadisiyah University, Al Diwaniyah, Iraq

Abstract

Background: The complexity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) centers on the unpredictable clinical course of the rapidly progressing disease, which leads to severe and fatal complications. **Objectives:** The objective of this study was to estimate the effect of cytokines (interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF-α], interferon-alpha [IFN-α], and interferon-gamma [IFN-γ]) on the pancreas after infection with SARS-CoV-2. **Materials and Methods:** The study was designed as a serological test to measure the levels of immunological parameters IL-6, TNF-α, IFN-α, and IFN-γ using enzyme-linked immunosorbent assay, and a biochemical test to determine the levels of blood glucose, lipase, and amylase, in addition to measuring hemoglobin A1C (HbA1C) levels for all groups. It was presented to 120 people, who were divided into three groups, whose ages ranged from 18 to 75 years, during the period from January 1, 2022, until the end of April 2022. **Results:** The sensitivity, specificity, positive predictive value, and negative predictive value of diabetic patients with coronavirus disease 2019 (COVID-19) for immunological assays were higher than those in the diabetic group and the control group. Random blood glucose was 335.72 ± 97.56 mg/dL, 328.87 ± 97.2 mg/dL, and 95.8 ± 10.62 mg/dL, respectively, and mean HbA1C levels were 9.46 ± 1.62, 9.62 ± 1.62, and 4.81 ± 0.77, and so on, relative to serum amylase and lipase levels. **Conclusion:** Cytokine disturbances are key drivers of multiple organ failure in many patients with severe COVID-19 complications.

Keywords: Clinical complications, COVID-19, cytokines, immunological biomarkers

Introduction

Coronavirus disease 2019 (COVID-19), initially unknown, was reported in Wuhan, Hubei Province, China, at the end of 2019[1] and caused pneumonia in a group of patients. The etiology was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus was first diagnosed in December 2019 and was initially named the Wuhan virus; its name was changed to 2019-nCoV. On March 11, 2020, the World Health Organization declared the disease a global pandemic.[2] About 5% of COVID-19 patients had severe cases of acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome, and multiple organ impairment or failure, with a high mortality rate.[3]

Encapsulated coronaviruses bear club-shaped or crown-shaped petals giving the appearance of a solar corona, large spherical (120–160 nm), having helical symmetry. Possessing a linear, positive-sense single-stranded RNA ranging in size from 26 to 32 kb, SARS-CoV-2 possesses four important structural proteins: nucleoproteins (N), the membrane (M), the envelope (E), and the spike (S).[4]

The epithelial surface of the oral cavity becomes infected with SARS-CoV-2, which causes the virus to stick to the breathing-related mucosal protein angiotensin-converting enzyme 2 (ACE 2).[5] After entering the host cell, it begins to replicate, preventing the downregulation of ACE 2, which degrades ang-2 into ang (1–7).[6]

Once inside cells, SARS-CoV-2 will present as an antigen to antigen-presenting cells, an important

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Address for correspondence: Dr. Ghaleb Hussein Obaid Al-Saeedi, Department of Medical Microbiology, College of Medicine, Al-Qadisiyah University, Al Diwaniyah, Iraq.
E-mail: ghaleb1974hussein@gmail.com

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part of the body's antiviral immunity, and specialized histocompatibility complex antigenic peptides are displayed on the surface of infected cells, or human leukocyte antigen (HLA), and are then recognized by T lymphocytes by immunostimulation involving CD4, CD8, and cytotoxic factors (CTLs).[7]

Previous studies indicate that several HLA isoforms are associated with susceptibility to SARS-CoV infection, including HLA-Cw*0801 and HLA-DR B.[8] There are two stages of the immune response to the COVID-19 infection: the first is during the incubation stage and the non-severe stages, and the second is the adaptive immune response, which is important to control the spread of the virus, eliminate the disease, and prevent the development of the disease. Enhanced cytokine release syndrome progresses to serious conditions and damages multiple organs.[9]

Studies show that the immune response to a viral infection leads to an increased incidence of cytokine storms. This includes several times the interaction of various interleukins, tumor necrosis factor-alpha (TNF-α), interferon-alpha (IFN-α), and colony-stimulating factors. A cytokine storm is associated with inducing widespread infection or attenuating the severity of infection. Moreover, it is a major cause of multi-organ failure in ARDS and may lead to death in COVID-19 patients.[10]

Interleukin-6 (IL-6) is a protein produced by different cells that helps regulate the immune response. It has a central role in acute inflammatory responses that have both local and systemic effects. The cytokine is important in human metabolism and differentiation of autoimmune cells.[11]

The TNF-α gene, located within the HLA III region of chromosome 6p21, is a pro-inflammatory and important lipid. It is involved in many processes of differentiation, proliferation, and cellular death, in addition to inflammation and immune responses.[12] IFN-α is a glycoprotein produced by a wide variety of cells in response to infection. Upon infection, cellular and viral elusion effects of the host's immune reaction occur, as well as a dysregulated response to IFN by SARS-CoV-2.[13] Interferon-gamma (IFN-γ): An immune protein that is essential for the body's immune response. Interferon interacts with IFN-γ-producing cells, including T cells, macrophages, and dendritic cells, in an inflammatory or tumor microenvironment. IFN-γ stimulates the depolarization of macrophages toward the M1 pro-inflammatory phenotype.[14]

When a cellular storm occurs in the body, the immune system may not be able to kill SARS-CoV-2, which leads to the killing of a large number of normal cells of the organs because of infection. SARS-CoV-2 infection further leads to endothelial inflammation in different organs, directly and indirectly, which explains the impairment of the microcirculation system. About 1%–2% of non-severe cases and 17% of severe cases of COVID-19 patients developed pancreatic damage, a possible injury to the pancreas, such as exacerbation of systemic inflammation or drug-induced pancreatitis, progressing to chronic pancreatitis, which may have a serious effect on health.[15]

Two of the most widely accepted proposed theories describe pancreatic harm because of SARS-CoV-2 infection, either direct or indirect. The direct method explains the high expression of ACE2 and TMPRSS2, receptors that facilitate the entry of SARS-CoV-2 into pancreatic and ductal cells. SARS-CoV-2–induced immune responses result in indirect harm to the pancreas, which in turn leads to infection of endothelial cells as a result of the leakage of these inflammatory substances into various distant tissues. In pancreatitis, activated astrocytes release inflammatory cytokines and chemicals that cause pancreatic fibrosis and downregulate ACE2.[16]

Type 2 diabetes (T2D) was one of the fastest spreading diseases worldwide, along with other types of diabetes. This increased inflammation is accompanied by an increase in the levels of pro-inflammatory cytokines. Also, in patients with COVID-19 who have elevated blood glucose, the cytokine response to the storm alters immune function.[17]

Diabetics were prone to having a cellular storm, and the body was already prone to an inflammatory state; ARDS worsens with the rapid increase in blood sugar, and the COVID-19 patient's state worsens.

Type 2 diabetes mellitus patients have a significantly increased risk of developing SARS-CoV-2. Diabetes is diagnosed by measuring one metabolite, which is glucose. Hyperglycemia can develop if the metabolism that regulates glucose is disrupted (high hemoglobin A1C [HbA1C]), which can vary between individuals (American Diabetes Association, 2021).[18]

The risk is associated with poor glycemic control when infected with COVID-19. T2D increases the risk of other diseases or death in patients with COVID-19.

The use of plasma enzymes as diagnostic tools in diseases: Some enzymes show high activity in one tissue or a number of tissues. The presence of increased levels of these enzymes in the plasma reflects the extent of damage to the corresponding tissues. The diagnostic value determines the location and boundaries of cellular injury. Therefore, isoenzymes present in plasma were a means to determine the site of tissue damage. Among these enzymes are pancreatic amylase and pancreatic lipase secreted by the pancreas.[19]

Materials and Methods

Patients and study design

A case–control study and computed tomography were performed on 120 individuals, and they were divided into three groups: 40 of them were infected with SARS-CoV-2 and were mainly diabetic, the other group included 40 diabetes subjects, and the control group included 40 healthy subjects who were randomly selected as individuals. The ages of the groups ranged between 18 and 75 years. Patients with severe cases were collected from the designated center at Al-Diwaniyah Teaching Hospital during the period from January 1, 2022, to the end of April 2022.

Sample collection

Five milliliters of venous blood samples were collected for each group, including the control group. Following the separation procedure, blood samples were split into two portions for the serum, kept in Eppendorf tubes complemented by three replicates, and then stored at −20°C, one of which was used to determine the levels of IL-6, TNF-α, IFN-α, and IFN-γ by enzyme-linked immunosorbent assay, while the other was used to quantify lipase and amylase levels. The other section (2 mL) of peripheral blood was collected in an anticoagulant tube (K3-ethylenediaminetetraacetic acid) and used to check HbA1C for samples taken directly, and the remaining amount was stored at −20°C.

Statistical analysis

Statistics were examined. The continuous variables' mean values were displayed ± standard deviation. Data with normal distribution were analyzed by one-way analysis of variance. Additionally to the chi-square test, P values were denoted as not significant, $P < 0.05$, and highly significant ($P < 0.001$), along with the receiver operating characteristic (ROC) curve and unpaired two-tailed Student's t-tests.[20]

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with the patient's verbal and analytical approval before a sample was taken. The study protocol, the subject information, and the consent form

Table 1: Levels of some biochemicals (random blood sugar [RBS], hemoglobin A1C [HbA1C], amylase, and lipase) in patients and controls

	Case–control comparison			
	COVID-19 patients with diabetes $n = 40$	**Diabetic patients $n = 40$**	**Control subjects $n = 40$**	**Total P value**
RBS (mg/dL)				
Mean ± SD	335.72 ± 97.56^{A}	328.87 ± 97.2^{A}	95.8 ± 10.62^{C}	<0.001† HS
Range	161.0–577.0	134.0–498.0	76.0–112.0	
Normal, n (%)	0 (0%)	0 (0%)	40 (100.0%)	<0.001¥ HS
High, n (%)	40 (100.0%)	40 (100.0%)	0 (0%)	
HbA1C (%)				
Mean ± SD	9.46 ± 1.62^{A}	9.62 ± 1.62^{A}	4.81 ± 0.77^{C}	<0.001† HS
Range	6.50–12.40	6.90–12.50	3.60–6.30	
Normal, n (%)	0 (0%)	0 (0%)	37 (92.5%)	<0.001¥ HS
High, n (%)	40 (100.0%)	40 (100.0%)	3 (7.50%)	
Amylase (U/L)				
Mean ± SD	168.62 ± 28.5^{A}	142.35 ± 34.4^{B}	84.45 ± 25.34^{C}	<0.001† HS
Range	98.0–243.0	67.0–243.0	25.0–125.0	
Normal, n (%)	3 (7.50%)	18 (45.0%)	40 (100.0%)	<0.001¥ HS
High, n (%)	37 (92.5%)	22 (55.0%)	0 (0%)	
Lipase (U/L)				
Mean ± SD	63.55 ± 21.8^{A}	51.72 ± 25.01^{B}	29.82 ± 9.98^{C}	<0.001† HS
Range	24.0–123.0	18.0–122.0	13.0–42.0	
Normal, n (%)	40 (100.0%)	40 (100.0%)	40 (100.0%)	0.027¥ S
High, n (%)	0 (0%)	0 (0%)	0 (0%)	

n: number of cases, SD: standard deviation, S: significant.

†One-way analysis of variance, ¥Chi-square test, HS: highly significant at $P \leq 0.001$, NS: non-significant at $P \leq 0.05$.

Different letters denote the significant differences at $P < 0.05$

were reviewed and approved by a local ethics committee according to document number 4137 on December 8, 2021.

Results

Levels of biochemical markers (random blood sugar [RBS], HbA1C, amylase, and lipase) in patients and healthy controls: The comparison of biochemical markers between the patient group and the control group was calculated, and the results are shown in Table 1.

Significant levels of RBS were 335.72 ± 97.56 mg/dL, 328.87 ± 97.2 mg/dL, and 95.8 ± 10.62 mg/dL in COVID-19 patients with diabetes compared to patients with diabetes and the healthy control group, respectively; the significant levels were higher in COVID-19 patients with diabetes in comparison with other groups, and the dissimilarity was highly significant ($P < 0.001$). Also, the significant levels of HbA1C were 9.46 ± 1.62, 9.62 ± 1.62, and 4.81 ± 0.77 in COVID-19 patients with diabetes compared to patients with diabetes and the healthy control group, respectively; the significant levels were higher in COVID-19 patients with diabetes in comparison with the other groups.

Amylase levels showed a highly significant increase in serum amylase in COVID-19 patients with diabetes compared to other groups, 168.62 ± 28.5 U/L versus 142.35 ± 34.4 U/L and 84.45 ± 25.34 U/L, respectively ($P < 0.001$).

According to the percentage of serum lipase, this study shows a significant increase in COVID-19 patients with diabetes compared to patients with diabetes and the healthy control group, 63.55 ± 21.8 U/L versus 51.72 ± 25.01 U/L and 29.82 ± 9.98U/L, respectively.

1. Interferon-gamma analysis and levels in COVID-19 patients with diabetes and the control group.

To assess the cutoff value of IFN for the prediction of COVID-19 patients with diabetes as diagnostic or adjunctive tests, ROC analysis was performed and is shown in Figure 1. The IFN cutoff value was >30.46, with sensitivity, specificity, positive prognostic value, negative prognostic value, and area under the curve of 95.0%, 85.0%, 86.4%, 94.4%, and 0.941 (0.879–1.000) [Figure 1].

2. Interferon-gamma levels in patients with diabetes and the control group.

The IFN-γ cutoff value was >20.30, with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve of 92.5%, 80.0%, 82.2%, 91.4%, and 0.885 (0.805–0.966) [Figure 2].

3. Interferon-alpha analysis and levels in COVID-19 patients with diabetes and the control group.

The IFN-α cutoff value was >147.51, with sensitivity, specificity, PPV, NPV, and area under the curve of 97.5%, 97.5%, 97.5%, 97.5%, and 0.999 (0.995–1.000) [Figure 3].

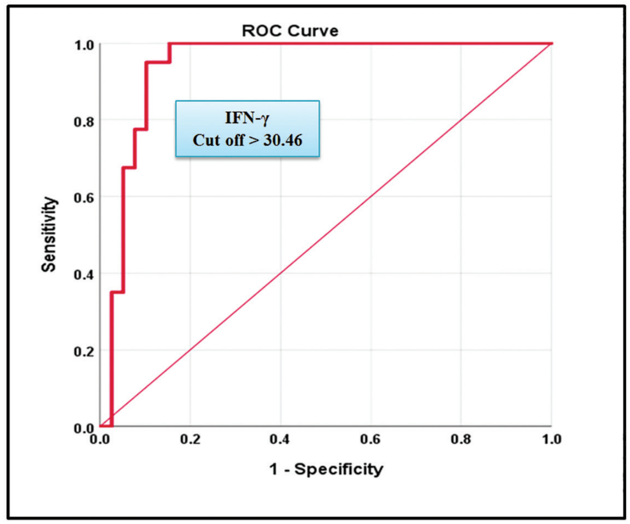

Figure 1: ROC curve for the calculation of interferon-gamma's likely diagnostic cutoff value

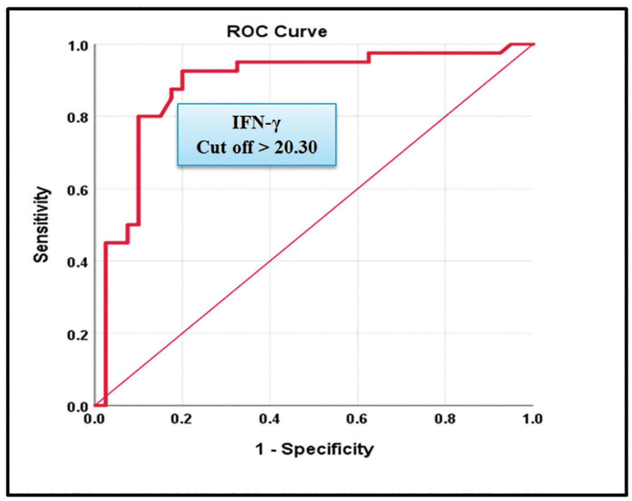

Figure 2: ROC curve for the calculation of interferon-gamma's likely diagnostic cutoff value

4. Interferon-alpha levels in patients with diabetes only and the control group.

The IFN-α cutoff value was >111.52, with sensitivity, specificity, PPV, NPV, and area under the curve of 65.0%, 77.5%, 74.3%, 68.9%, and 0.754 (0.647–0.861) [Figure 4].

5. Human interleukin-6 analysis and levels in COVID-19 patients with diabetes and the control group.

The IL-6 cutoff value was >48.78, with sensitivity, specificity, PPV, NPV, and area under the curve of 97.5%, 92.5%, 92.9%, 97.4%, and 0.988 (0.971–1.000) [Figure 5].

6. Interleukin-6 levels in patients with diabetes and the control group.

The IL-6 cutoff value was >12.63, with sensitivity, specificity, PPV, NPV, and area under the curve of

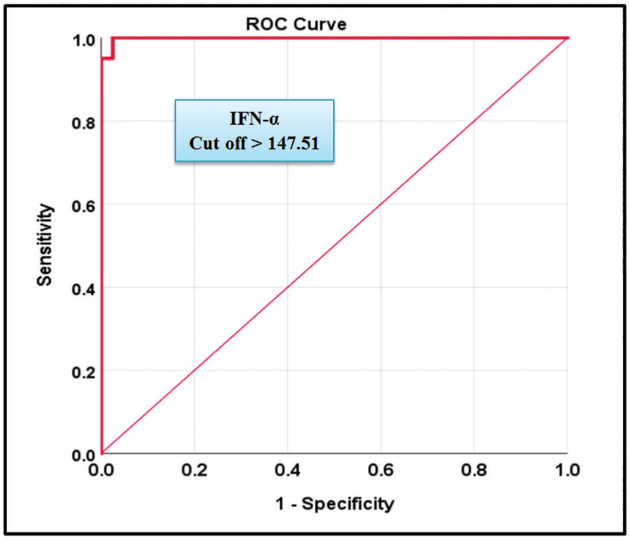

Figure 3: ROC curve for the calculation of interferon-alpha's likely diagnostic cutoff value

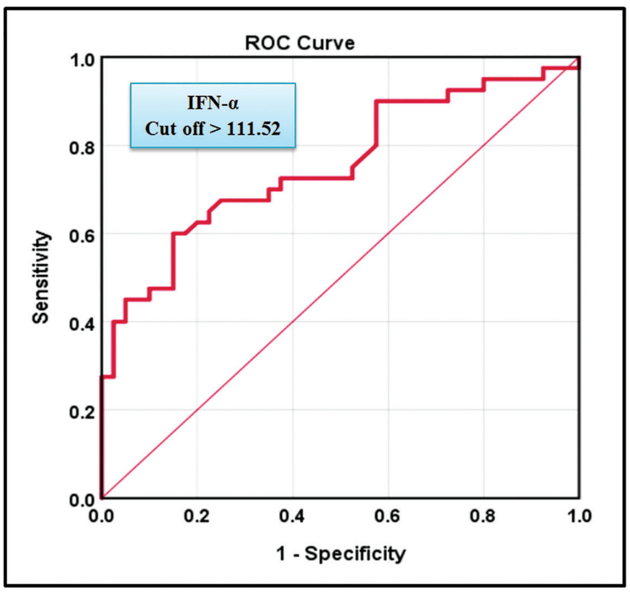

Figure 4: ROC curve for the calculation of interferon-alpha's likely diagnostic cutoff value

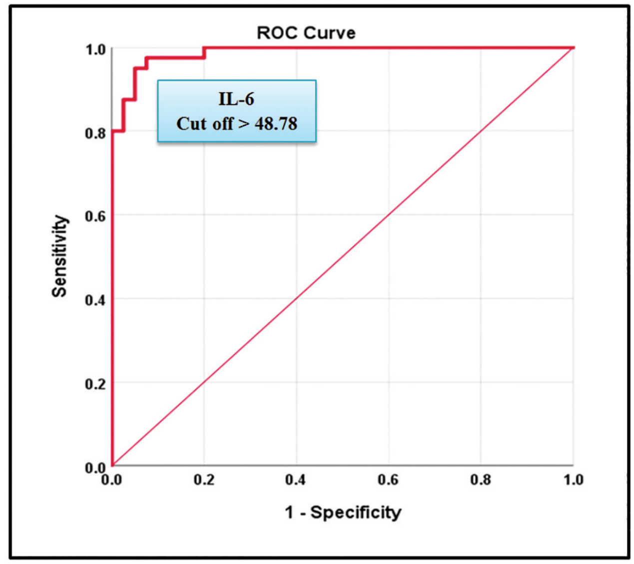

Figure 5: ROC curve for the calculation of interleukin-6's likely diagnostic cutoff value

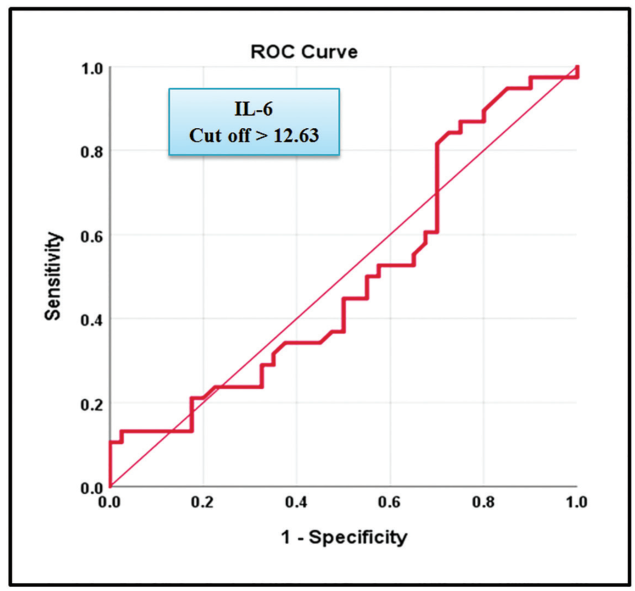

Figure 6: ROC curve for the calculation of interleukin-6's likely diagnostic cutoff value

62.5%, 37.5%, 50.0%, 50.0%, and 0.504 (0.365–0.671) [Figure 6].

7. Tumor necrosis factor-alpha levels in COVID-19 patients with diabetes and the control group.

The TNF cutoff value was >48.78, with sensitivity, specificity, PPV, NPV, and area under the curve of 95.0%, 82.6%, 80.0%, 94.1%, and 0.939 (0.884–0.995) [Figure 7].

8. Tumor necrosis factor-alpha levels in patients with diabetes and the control group.

The TNF-α cutoff value was >64.3, with sensitivity, PPV, NPV, and area under the curve of 62.5%, 60.0%, 61.0%, 61.5%, and 0.600 (0.474–0.726) [Figure 8].

Discussion

Since it was first identified in December 2019 in Wuhan, China, the SARS-CoV-2 pandemic has become a SARS-CoV-2 infection of global health concern. As a representative sample of SARS-CoV-2 patients in Iraq, this investigation was conducted on patients infected with COVID-19 in Diwaniyah governorate who were admitted to the corridors of the private hospital for the purpose of isolating them locally and preventing the deterioration of their health condition, a health measure to prevent the spread of the epidemic.

A complication linked with SARS-CoV-2 infection is the emergence of new cases of diabetes with high prevalence

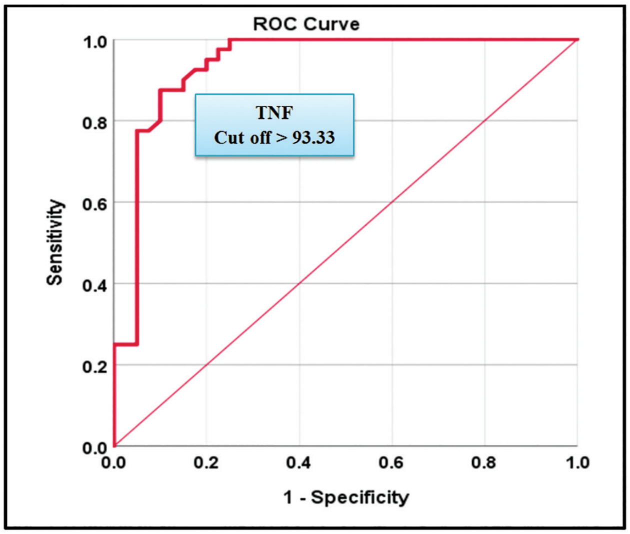

Figure 7: ROC curve for the calculation of tumor necrosis factor-alpha's likely diagnostic cutoff value

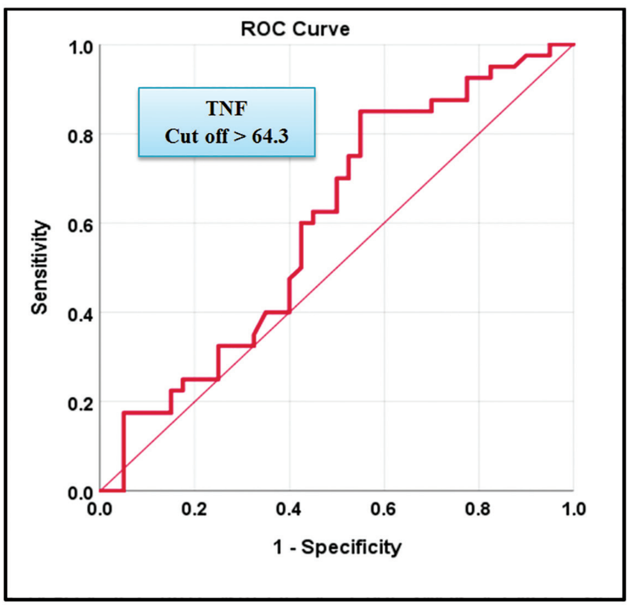

Figure 8: ROC curve for the calculation of tumor necrosis factor-alpha's likely diagnostic cutoff value

among the elderly. A daily follow-up method was used for patients who suffered pancreatic damage during tests to monitor blood sugar in patients with T2D to see if the infection exacerbated their diabetes or disease development. Taking into account an examination to monitor HbA1C on the first day of the patients to isolation lobbies in the hospital, monitoring the extent of damage to the pancreas or the worsening of the health condition of diabetics is associated with a worse outcome due to severe immune reactions leading to the deterioration of human health, mostly due to complete pneumonia, which makes eliminating the virus more difficult. However, even without lung participation, COVID-19 can cause high blood sugar, change the condition, and require admission to the intensive care unit.

COVID-19 can affect individuals of any age, and the study showed that the highest infection rate was between 40 and 49 years, followed by ages between 50 and 59 years. People aged 40 or over, who are at greater risk of contracting COVID-19 than younger age groups, may be due to increased social activity for this age group and turnout for large gatherings or advanced age and physical frailty, which increases the risk of severe pneumonia and deterioration in the health status of developing T2D. Adults may lead to a resurgence of epidemics.

According to gender, through ACE2 receptors, SARS-CoV-2 accesses numerous organs, including endocrine organs, and produces a clinical picture that ranges from moderate to severe and can even be fatal, depending on the individual's immune system, age, gender, and co-occurring disorders. COVID-19 was found in this study to be more prevalent among females than males, as shown in Figure 1. This study agrees with Cromer *et al.*[21] In contrast to the study by Hanan *et al.*,[22] where the incidence of infection in men was higher than that in females, women of working age who are more likely to work in jobs involving health and care are also more likely to have heightened infection rates.

Diabetes mellitus is the highest comorbidity in hospitalized patients with SARS-CoV-2. This indicates the seriousness of infection with this virus and is strong evidence of the susceptibility of SARS-CoV-2 to directly infect the pancreas or through the cytokine storm of the immune system. The results are consistent with Manoj *et al.*,[23] showing that virus-mediated heterologous cell degradation and viral infection of β-cells can bring about cell death, coupled with enhanced proliferation near uninfected cells and reduced insulin synthesis and secretion.

By examining the effect of the immune system reaction and the high sensitivity of the immunoassay results for all immunological study groups, the statistical analysis indicated the role of virus infection in the IFN-γ response. The effect of IFN-γ was evaluated in COVID-19 patients. This study is consistent with these groups in the results, as an elevated level of IFN-γ was observed in SARS-CoV-2 infection.[24]

Statistical analysis of diabetic patients who do not have the virus shows that there is a slight increase when compared with the control group or the healthy ones, and the reason is due to the stimulation of the adaptive immune system for other reasons. Also, this is the case when analyzed with IFN-α; elevated levels of IFN-α showed a highly significant difference for the study groups ($P < 0.001$). In COVID-19 patients with diabetes and the control group, type I has a role in the IFN-α response to COVID-19. These were examined by research groups, and this study is consistent with these groups in the results, where an increased level of IFN was observed in SARS-CoV-2 infection.[25,26]

The mechanism by which these viruses cause pancreatitis is unknown, and each virus might cause pancreatitis by a different mechanism. These mechanisms include viral replication in pancreatic acinar cells and impaired zymogen secretion, resulting in protease leakage and activation. As indicated in the study by Palacios *et al*.,[27] TNF-α and IFN-γ levels can be taken into account to determine the profile in COVID-19 patients and identify the affected pathways.

As COVID-19 patients fail to suppress virus replication in the early stage of infection due to insufficient and delayed IFN-α responses, this exacerbates the production of pro-inflammatory cytokines in the late stage. These were examined by research groups, and this study is consistent with these groups in the results, where increased levels of IFN-α were observed in SARS-CoV-2 infection.[28] Patients with severe cases of COVID-19 have higher serum levels of pro-inflammatory cytokines IFN-α, and this is consistent with a study conducted by Tiwari *et al*.[29]

This indicates that individuals with uncontrolled blood glucose levels are more prone to episodes of cytokine production, which lead to rapid exacerbation of the disease, according to a study by Kandasamy.[30] They also reported that the IFN-γ is the main cytokine acting on inflammation from the pancreas, and these distributions of ACE2 are very likely associated with the characteristics of COVID-19. The results are consistent with what was reported by Pergolizzi *et al*.,[31] showing that hospitalized COVID-19 patients with hyperglycemia have higher levels of IL-6. Excessive inflammation results from an immune system reaction that worsens.

The results showed that high rates in diabetic patients infected with the virus had an imbalance in blood sugar levels, so this cytokine is another clear evidence of the extent of the effect of the reaction of the immune system disciplined when infected with SARS-CoV-2. In the case of SARS infection, monocytes are stimulated, which in turn stimulates the production of cytokines in an uncontrolled inflammatory response, including TNF-α, and thus induces septic shock with irreversible consequences. The results of this study are consistent with what was reported by Liu *et al*.,[32] showing that the levels of TNF-α in the serum of COVID-19 patients reached a peak.

In the diabetes and the control group, the percentage is normal because there is no infection with SARS-CoV-2. To clarify, in the normal body state, when exposed to a pathogen, monocytes are stimulated, which in turn stimulates the production and controlled inflammatory responses of cytokines, including TNF-α, and thus the pathogen is eliminated.

Conclusion

Diabetes and COVID-19 are two types of diseases that have a global impact. Also, infection with COVID-19 exposes diabetics to more severe infections and the lethality of COVID-19. Diabetes should always be considered a major risk factor because of the severity of symptoms associated with COVID-19. The contribution of diabetes in previously infected individuals to the pathophysiology of COVID-19, as a risk factor, along with the complications of chronic diabetes and comorbidities (geriatrics and obesity) and endothelial dysfunction, leads to severe infection with COVID-19, calling to mind changes in endothelial and epithelial cells. The morbidity and mortality of SARS-CoV-2 pneumonia are influenced by the innate immune mechanism. To create medications and vaccines, it is therefore essential to comprehend the structure of novel viruses and their connections with the immune system. Patients with COVID-19 and pre-existing T2D require further treatments (for antibiotics, systemic corticosteroids, inhaled oxygen) in hospital intensive care, and integrated and intensive therapies to manage their COVID-19 symptoms without diabetes. Therefore, even if a patient is admitted for COVID-19 without a history of diabetes, clinicians should monitor their blood glucose levels. COVID-19 should be used to properly monitor all of a diabetic patient's organs, not just the lungs.

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Conflicts of interest

There are no conflicts of interest.

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