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## **Immunological parameters in hyperglycemic COVID19 patients of wasit-Iraq**

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**Abstract**---Background: A number of studies have also reported that preexisting diabetes as well as newly diagnosed diabetes with a first glucose measurement on hospital admission are both associated with an increased risk of all-cause mortality. This study aimed to investigate the immunological characteristics of patients with severe COVID-19 with diabetes mellitus. Methods: This study was carried out in a period between November 2021 and March 2022 in Iraq. A total of samples were subjected to laboratory examinations including Human Glutamic acid decarboxylase (GAD) ELISA Kit, Tumor necrosis factor  $\alpha$  using specific kit ELISA Kit, Human Islet cell antibody (ICA)ELISA Kit and Human C-Peptide ELISA Kit using specific ELISA Kit. Results: Regarding mean difference of variables among diabetic and non-diabetic COVID-19 patients all the investigated parameters has been showed significant differences between diabetic and non-diabetic patients with a P-value less than 0.001 except for CRP, correlation between age and COVID-19 patients immunological parameters showed that there was no significant correlation between age and the studied variables, mean differences of COVID-19 patients between males and females did not revealed a significant differences, mean differences of COVID-19 patients correlated to steroid therapy showed that there was non-significant differences were recorded between COVID-19 patients and steroid treatment related to the studied variables.

**Keywords**---Hyperglycemia, COVID-19, Immunological Characteristics.

## 1 Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that results in the clinical disease coronavirus disease 2019 (COVID-19) was first reported in December 2019 in Wuhan, China, and has claimed over 2 million lives globally (1). Certain chronic comorbidities, such as hypertension, cardiovascular disease, obesity, diabetes, and kidney disease, are highly prevalent in people with COVID-19. While these comorbidities do not appear to increase the risk of developing COVID-19, they are associated with an increased risk of a more severe case of the condition as well as mortality (2). Severe hyperglycemia is common in critically ill patients and is often seen as a marker of disease severity (3). Several studies over the course of the pandemic have reported that COVID-19 is associated with hyperglycemia in people with and without known diabetes (4). One study from Wuhan of hospitalized, mainly elderly COVID-19 patients reported that 21.6% had a history of diabetes, and, based on the first glucose measurement upon admission, 20.8% were newly diagnosed with diabetes (fasting admission glucose  $\geq 7.0$  mmol/L and/or HbA1c  $\geq 6.5\%$ ), and 28.4% were diagnosed with dysglycemia (fasting glucose 5.6–6.9 mmol/L and/or HbA1c 5.7–6.4%) (5).

A number of studies have reported new-onset diabetes (that phenotypically could be classified as either type 1 diabetes [T1D] or type 2 diabetes [T2D]) as being associated with the presence of COVID-19, a study from London, U.K., reported 30 children aged 23 months to 16.8 years with new-onset T1D. Of these, 70% presented with diabetic ketoacidosis (DKA), 52% with severe DKA, and 15% with a positive COVID-19 test. The authors concluded that this represented an 80% increase in new-onset T1D during the pandemic compared with previous years (6). Further, it would also appear that the severity of presentation of youth with T1D is increased (7, 8). Conflicting results have also been reported, however, with data from 216 pediatric diabetes centers in Germany showing no increase in the number of children diagnosed with T1D during the early months of the pandemic (8). However, the same centers reported data on 532 children and adolescents with newly diagnosed T1D and found significant increases in DKA and severe ketoacidosis at diagnosis during the same time period (9). Clinical and laboratory investigations show that lymphocytopenia, an abnormally low level of lymphocytes in the blood and a marker of severe prognosis, is significantly associated with the severity of COVID-19. Absolute numbers of T lymphocytes, CD4+ T cells, and CD8+ T cells are all greatly decreased in nearly all COVID-19 severe patients compared with non-severe cases (10).

## 2 Materials and Methods

### Samples collection

Blood samples were taken from eighty patients with covid19 with hyperglycemic or uncontrolled blood sugar level. Study was carried out in Wasit-Iraq in virology and immunity laboratories. A total of samples were subjected to laboratory examinations including Human Glutamic acid decarboxylase(GAD)ELISA Kit, Tumor necrosis factor  $\alpha$  using specific kit ELISA Kit, Human Islet cell antibody(ICA)ELISA Kit and Human C-Peptide ELISA Kit (11). This case control (cross sectional) study was carried out in Al-Zahraa teaching hospital in Al-Iraq

in period between November 2021 and February 2022. This study followed the cross sectional design. The populations of our study included 80 samples with covid19 aged between (25-90) 38 male and 42 female in addition to 20 subjects as a control. The objectives and methodology of this study were explained to all participants in the current study to gain their consent.

### Principle of ELISA test

ELISA works on the principle that specific antibodies bind the target antigen and detect the presence and quantity of antigens binding. In order to increase the sensitivity and precision of the assay, the plate must be coated with antibodies with high affinity. ELISA can provide a useful measurement of antigen-antibody concentration (12).

### Procedure of ELISA Kit

Dilution of standard solutions in this kit has a standard of original concentration, which was diluted in small tubes by user independently the company instructions, as well as the same for procedure followed company instructions.

### Calculation of results for all markers used in current study

Known concentrations of each marker standard and its corresponding reading optical density (OD) was plotted on the log scale (x-axis) and the log scale (y-axis) respectively. The concentration of each marker in sample was determined by plotting the sample's O.D. on the Y-axis. The original concentration is calculated by multiplying the dilution factor (13).

## 3 Results and Discussions

Mean difference of variables among diabetic and non-diabetic COVID-19 patients All the investigation listed in the table below showed significant differences between diabetic and non-diabetic patients with a P-value less than 0.001 for all of them. Only the CRP had non-significant differences in the mean between the two groups, table (1).

Table 1  
Mean difference in continues variables among diabetic and non-diabetic participant COVID-19 patients

Variables	Diabetes status		P-value (independent sample t-test)
	Yes	No	
Mean± standard deviation			
Age (years)	55.83±17.81	40.90±11.95	<0.001
HbA1c* (%)	5.30±0.63	4.79±0.39	<0.001
R.B. S ** (mg/dl)	207.08±62.77	117.01±7.32	<0.001
F.B. S*** (mg/dl)	142.31±11.48	77.75±3.41	<0.001
SPO2**** (%)	89.38±3.66	92.25±1.51	<0.001
C.R. P***** (mg/L)	84.58±17.20	80.35±9.12	0.165

\*HbA1c: Hemoglobin A1c.

\*\*RBS: Random Blood Sugar.

\*\*\*FBS: Fasting Blood Sugar.

\*\*\*\*SPO<sub>2</sub>: Saturation of Peripheral Oxygen.

\*\*\*\*\*CRP:C-Reactive Protein.

### Correlation between age and COVID-19 patients parameters

In present study table (2) showed that there was no significant correlation between age and the studied variables.

Table (2)  
Correlation between age and the selected four parameters among COVID-19 patients.

Parameters	Correlation Coefficient (R)	P-value
C. peptide	0.045	0.691
Anti-GAD	0.044	0.700
ICA	0.041	0.715
TNF	0.133	0.238

Mean differences of COVID-19 patients and studied parameters

In present study table (3) showed that there was no significant differences between COVID-19 patients and the studied variables.

Table (3)  
Mean differences in the four studied parameter (G.A.D ,I.C.A, T.N.F, C. peptide) among studied population between males and females.

Studied parameter	Sex		P-value (Independent sample t-test)
	Male	Female	
C. peptide*	0.48±0.49	1.86±4.62	0.063
G.A. D**	16.68±22.11	18.19±28.15	0.792
I.CA***	4.17±7.19	4.65±11.15	0.820
T.N. F****	21.11±27.34	18.11±27.87	0.629

\* Connecting peptide.

\*\* Anti Glutamic Acid Decarboxylase antibody.

\*\*\* Islet Cell Antibody.

\*\*\*\* Tumor Necrosis Factor- $\alpha$ .

Mean differences of COVID-19 patients correlated to steroid therapy

In present study table (4) showed that there was non-significant differences were recorded between COVID-19 patients and steroid treatment related to the studied variables.

Table (4)  
Treatment protocol (steroid) impact on the studied parameters among COVID-19 patients

Parameters	Steroid treatment	No steroid	P-value (independent sample t-test)
	Mean $\pm$ standard deviation		
C. peptide*	1.17 $\pm$ 3.83	1.27 $\pm$ 2.40	0.908
G.A. D**	15.00 $\pm$ 24.96	22.61 $\pm$ 25.76	0.210
I.CA***	3.98 $\pm$ 9.85	5.34 $\pm$ 8.58	0.528
T.N. F****	16.85 $\pm$ 24.06	25.11 $\pm$ 33.35	0.266

\* Connecting peptide.

\*\* Anti Glutamic Acid Decarboxylase antibody.

\*\*\* Islet Cell Antibody.

\*\*\*\* Tumor Necrosis Factor- $\alpha$ .

#### 4 Conclusion

Diabetes Mellitus was also found to be a common comorbidity with COVID-19. Previous reports have shown that 19–30% of COVID-19 patients have DM (14). Furthermore, a growing body of evidence supports the susceptibility to severe COVID-19 in diabetic and non-diabetic patients. In a study of 500 patients from Wuhan city, a severe disease was found in 19% of diabetic patients. This was also illustrated in a study of 85 fatal cases where it was found that 22% of patients had DM or newly diagnosed as hyperglycemic (15).

There is a two-way relationship between COVID-19 and DM. In the first way, diabetes is associated with a poor COVID-19 prognosis (16). In the other way, new-onset DM and severe complications of pre-existing DM, including diabetic ketoacidosis (DKA) hyperosmolarity, have been reported in patients with COVID-19. Severe acute respiratory syndrome coronavirus 2 may enter the pancreatic beta cells through the expression of angiotensin-converting enzyme 2 (ACE2) receptors, impairing insulin production, and consequently, either worsening DM or developing new-onset DM. Insulin resistance due to higher levels of interleukin-6 and tumor necrosis factor-alpha in patients with severe COVID-19 could be another probable explanation for developing DM (17). Despite this, many recently published data entailed the effect of previously diagnosed DM on the clinical course and outcome of COVID-19. Only a few data are available regarding the new-onset of DM among COVID-19 patients, its different types, its clinical course, and its outcome after the recovery from COVID-19. The purpose of this work was to determine the frequency of newly diagnosed DM and its different types among COVID-19 patients, and to assess the infection outcome and glycemic control during the study (18).

Mean of age in diabetes diabetes status was higher, while lower in non-diabetes in present study, in addition HbA1c, random blood sugar (RBS), fasting blood sugar (FBS), and C-reactive protein (CRP) has been showed the same results, except for saturation of peripheral oxygen (SPO2) was higher in non-diabetic patients, current data were compatible with Farag et al. (2021) in study comprised 570 confirmed COVID-19 patients. The mean age of the study population was 47.9  $\pm$  10.9 years, and 317 patients (55.5%) were males. Diabetes was newly defined in 77 (13.5%) patients. Our results showed that there were significant differences

between newly diagnosed diabetic patients and non-diabetic patients regarding body mass index (BMI) and family history of DM ( $p < 0.001$ , for both). Fasting blood glucose ( $208.3 \pm 109.9$ ) and glycated hemoglobin ( $5.7 \pm 0.8$ ) were found to be significantly higher in the newly diagnosed diabetic patients ( $p < 0.001$ ). In terms of onset symptoms in the newly diagnosed diabetic patients, 70 (90.9%) patients exhibited symptoms of fever; the other common symptoms were cough in 70 (90.9%), dyspnea in 66 (85.7%), and diarrhea in 11 (14.3%) patients. There were several differences in laboratory findings between newly diagnosed diabetic patients and non-diabetic patients, including higher levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and D-dimer in newly diagnosed DM ( $p < 0.001$ , for all). The study enrolled 297 severe COVID-19 cases (52.1%) and 273 mild/moderate cases (47.9%). Out of all cases of newly diagnosed DM, 89.6% had a severe infection (69/77), which was significantly higher than that among non-diabetic patients ( $p < 0.001$ ). A total number of 62 patients died during the study (10.9%) from COVID-19 sequelae. Mortality was significantly higher among diabetic subjects (18.2%) than non-diabetic subjects (9.7%) ( $p < 0.001$ ). Out of 77 diabetic patients, newly discovered pre-existing DM was defined in 12 (2.1%) patients, new-onset type 1 DM developed in seven (1.2%) patients, and 58 (10.2%) patients had new-onset type 2 DM. HbA1C level was significantly elevated in group IIA ( $7.2 \pm 0.4$ ), compared with group IIB ( $5.3 \pm 0.5$ ) and group IIC ( $5.4 \pm 0.5$ ) ( $p < 0.001$ ). However, fasting insulin and C-peptide levels were much lower in group IIB ( $3.6 \pm 1.3$ ,  $0.3 \pm 0.1$ ) compared with group IIA ( $33.4 \pm 9.2$ ,  $3.5 \pm 1$ ) and group IIC ( $38.1 \pm 9.1$ ,  $3.6 \pm 0.8$ ) ( $p < 0.001$ ). including higher levels of CRP predicting ( $p < 0.001$ , for each) (19). Li et al., (2020) who reported that COVID-19 patients with newly diagnosed DM and hyperglycemia were slightly older and obese (5).

In the current work, patients presented with diabetic on admission. This was in agreement with Reddy et al., (2020) who stated that COVID-19 may accelerate DM in those with new-onset or pre-existing DM (20). Our study also revealed that patients with newly diagnosed DM had more severe infection symptoms such as elevated levels of inflammatory markers such as CRP than non-diabetic patients. Our results were in concordance with Li et al., (2020) who stated that patients with newly diagnosed diabetes and hyperglycemia often had more severe symptoms as well as higher levels of inflammatory markers . Infection with COVID-19 decreases ACE2 expression, resulting in hyperinflammation, cellular damage, and respiratory failure (21).

The biochemical and immunological profile of patients in relation to age may play an important component in estimating the severity and prognosis of the disease. Several studies have focused on various biochemical markers such as urea, alanine aminotransferases (ALT), aspartate aminotransferases (AST), and sodium levels in COVID-19 infections, while other tested the correlation with TNF and other investigation. These parameters have not only been associated with the age of COVID-19 patients but also with the worst outcomes in terms of in-hospital mortality (22).

Our data were agreed with Karki R et al. (2021), who concluded that treatment of COVID 19 infected with the anti-TNF- $\alpha$  increased surviving rate (23) and study Nguyen et al. (2022) and study of Liu Y et al. (2021), whose results shows that

hyperglycemia correlated with the increased mortality rate in aged diabetics patients with COVID-19 infection, showed that over time, the survival rate of aged patients was decreases with a high concentration of (HbA1c, fasting blood glucose and TNF-alpha) compared with a mean of low concentration (24, 25).

While these information were non-compatible with Sadiq, Khurram et al. (2021) (26) study aimed to identify at admission biochemical and immunological parameters that can discriminate between patients with mild to moderate (non-severe), severe, critical disease in confirmed COVID-19 infection cases in relation to their age and showed positive correlation. In the elderly, weaker immunity and decreased tolerance and response to infections can lead to increased severity and worst prognosis. Liu et al. noted that as the age of the COVID-19 patients increases, the severity of the disease also increases (27). In a study by Yang et al., (2020) age and comorbidities were associated with increased mortality in relation to biochemical and immunological profile of patients (28).

Regarding C peptide, GAD, ICA and TNF antibodies our information were compatible with Li et al. (2021) whom found that the increased risk of diabetes by these antibodies positivity is only limited in male adults. This result implicated that there might be a different mechanism of GADA promoting diabetes in male adults but possible explanation of this difference needs further researches (29). On the other hand our data were disagreed to other mentioned that 81% of the epidemiology investigations about type 1 diabetes reported that the incidence in male adults was larger than that in female adults (male-to-female ratio 1.47), even in low-incidence countries such as China (30, 31). However the frequency of GADA did not vary between genders, either in our study or previous studies (32). The hallmark of pulmonary pathology in COVID-19 disease is diffuse alveolar damage, often associated with thickening of alveolar walls with infiltration by inflammatory cells dominated by macrophages and mononuclear cells, it has been also observed that COVID-19 patients develop significant pulmonary vascular endothelial cell injury and endothelialitis, which is associated with intravascular thrombosis and microangiopathy (33). Corticosteroids therapy (CST) has been used extensively in acute respiratory conditions, which share similar pathological features with COVID-19 disease like SARS-CoV, MERS-CoV and H1N1 influenza, as well as in community acquired pneumonia (CAP), and ARDS. However, their effectiveness in reducing mortality and improving other outcomes in these conditions remain controversial, recent attempts to interpret these data led to more controversy regarding the therapeutic potential of CST in severe COVID-19 disease where some authors support and others recommend against their use in this disease (34). Our outcomes were in consistence to Bai et al. (2020) an Ruan, Yang et al. (2020) as non-survivors showed markedly reduced immunological test, suggesting the existence of immune deficiency against viral infection in COVID-19, these outcomes were not correlated to patients outcomes (35) (36).

While our outcomes were non similar to Russell, Millar et al. (2020) (34) revealed that out of 1067 citations screened for eligibility, one RCT and 19 cohort studies were included (16,977 hospitalized patients). Ten studies (1 RCT and 9 cohorts) with 10,278 patients examined the effect of CST on patients immunological investigations. The pooled adjusted RR was 0.92 (95% CI 0.69–1.22, I<sup>2</sup> = 81.94%).

This effect was observed across all stages of disease severity. Four cohort studies examined the effect of CST on composite outcome of death, ICU admission and mechanical ventilation need. The pooled adjusted RR was 0.41(0.23–0.73, I<sup>2</sup> = 78.69%). Six cohort studies examined the effect of CST on delayed viral clearance. The pooled adjusted RR was 1.47(95% CI 1.11–1.93, I<sup>2</sup> = 43.38%). The immune alterations reverted after the corticosteroid treatment and were maintained during the 4-month follow-up, and their normalization correlated with clinical amelioration. The current work highlights an immunopathogenic basis together with a possible role for steroids in the treatment for long-COVID (37).

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