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ORIGINAL RESEARCH CORONA EXPERIENCE

The effect of severe COVID-19 infection on biochemical markers (FBS, HbA1C, FA, INS, C-Pep) in diabetic patients

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ABSTRACT

Background & objective: Several studies have been conducted around the world on the impact of COVID-19 on people with diabetes mellitus (DM). Any acute illness can cause stress and increased inflammatory reactions, which increase sympathetic outflow and produce catecholamines, growth hormones, cortisol, and cytokines, all of which raise the risk and severity of complications from diabetes. Diabetes is a significant risk factor for the severity of COVID-19. We conducted this study to identify whether severe COVID-19 infection has any effect on the biomarkers, including fasting blood sugar (FBS), HbA1C, FA, INS, C-Pep, in individuals with DM.

Methodology: This study was simultaneously conducted at Department of Chemistry and Biochemistry, College of Medicine of Al-Nahrain University, and Department of Medicine of Mustansiriyah University College of Medicine, Baghdad, Iraq. During the months of February and March 2022, 50 COVID-19 patients with diabetes and 50 COVID-19 patients without diabetes were included in the study. The control group included 100 healthy, sexually identical people (age 50-80), collected under the supervision of the second supervisor from relatives and students of Mustansiriyah University, College of Medicine. Venous blood samples of 5 mL were taken from all participants and subjected to laboratory tests to detect the levels of the biomarkers.

Results: Average FBS level in DM patients was 304.9 mg/dL, (range 132-545.9 mg/dL), which was remarkably higher than in non-DM patient groups (193.3 mg/dL), range (of 66.2–458). The DM patients' group had a significantly higher concentration of HbA1C (median = 6.70 mg/dL, range 5.2-8.1) than the non-DM patient group (median = 5.8, range 4.2–7.6) with a significant difference. Although The group of DM patients had significantly greater FA concentrations than the group of non-DM patients. In contrast, the median and range for insulin and c-peptide Displays non-significant differences for covid-19 patients (DM and non-DM), but it's significant with a control group.

Conclusion: According to this study, COVID-19 patients with diabetes had greater biochemical indicator levels than non-diabetic people. Pre- and postprandial hyperglycemia and diabetic ketoacidosis were more common in COVID-19 DM patients than in non-infected DM patients. We found that COVID-19 increased the severity risk for T2DM patients and glucose level is raised and progresses in a vicious cycle exacerbated by insulin resistance (IR) and decreased pancreatic b-cell function.

Keywords: COVID-19, Diabetes mellitus, FBS, HbA1C, FA, INS, C-Pep

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1. INTRODUCTION

A global pandemic resulted from coronavirus disease 2019 (COVID-19). a respiratory illness brought on by a new coronavirus 2 that causes severe acute respiratory syndrome (SARS-CoV-2). It is an enclosed virus containing a single-stranded RNA genome. Because of a decreased immune response, people with diabetes are more susceptible to hospital-acquired bacteremia, infectious diseases, and lung infections.[1]

A failure to act or reduced secretion of insulin causes diabetes mellitus (DM), presented by polydipsia, weight loss, polyuria, and hyperglycemia. With concurrent viral infection, DM is frequently associated with microvascular, macrovascular and metabolic issues with increased mortality and diseases.[2]

DM can also exacerbate the effects of other viral infections, including H1N1, and raises the chance of COVID-19 development.[3] Due to comorbidities that are present and a disguised presentation of mild disease, the death rate for COVID-19 patients with DM is approximately 16%.[4.] The relationship between COVID-19 and DM may be bidirectional. Additionally, SARS-CoV-2-induced pancreatic β-cell invasion causes β-cell autoimmunity in vulnerable individuals, leading to type 1 diabetes (T1DM) develop in these individuals.[5]

Angiotensin-I and Angiotensin-II are divided into smaller peptides, respectively, Angiotensin (1-7) and (1-9), by the enzyme ACE2. The lung is protected against ARDS by the ACE2/Ang (1-7) system, which also functions as a major anti-inflammatory and antioxidant. The decreased expression of ACE2 in DM patients may be caused by glycosylation, which could account for the increased risk of severe lung damage and ARDS when COVID-19 is present.[6]

Hyperglycemia brought on by pancreatic injury (PI), a metalloprotease-17 activation (ADAM-17) is caused by SARS-CoV-2 binding ACE2 in the pancreas, which also triggers the ACE2 receptors' losing and the generation of IL-6 and TNF-a. ADAM-17 is activated by hyperglycemia and vice versa. Together, these alterations contribute to the emergence of acute lung injury (ALI) and ARDS, due to diminished antiviral response in DM.[7]

Even in those who don't have diabetes, SARS-CoV-2 can cause pancreatic damage, decreased insulin production, and the development of hyperglycemia, since it enters the body through ACE2 [8,9] (Figure 1). Previous research has demonstrated that the closely related SARS-CoV, which causes SARS-CoV-2, induces transient hyperglycemia and compromises the function of pancreatic β cells during epidemic-derived pneumonia.[10, 11.]

Peripheral insulin resistance (IR) is also brought on by the cytokine storm and inflammation brought on by COVID-19, which are marked by substantial rises in interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-a) levels.[12, 13.] Additionally, the pancreatic β-cells' ability

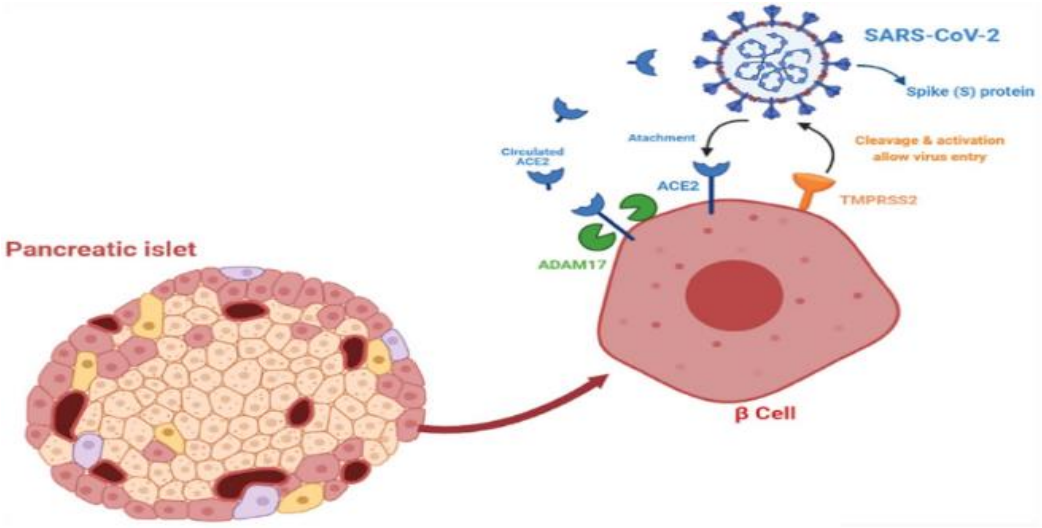

Figure 1: Proposed SARS-Cov-2 interaction/uptake in pancreatic β-cell schematic [16]

to secrete insulin is compromised by the high levels of TNF-a and IL-6 in CS. In COVID-19 patients, glucose elevation develops and progresses in a vicious cycle exacerbated by IR and decreased pancreatic β-cell function.[14.] Both of these are influenced by hyperglycemia, increased oxidative stress, and glucolipotoxicity.[15]

2. METHODOLOGY

This case-control research was conducted from February 3, 2022 to April 4, 2022, at Al-Nahrain University / College of Medicine / Department of Chemistry and Biochemistry. The study protocol was approved by Ethical Committee of Medicine College, Al-Nahrain University.

In this study, 100 Iraqi patients, confirmed to have severe COVID-19 infection and were being treated at Dar Al Salam Field Hospital and Al-Yarmouk Hospital, were included. The consent of all patients was obtained before blood samples were drawn from them, and patient information was noted based on a questionnaire. Tests were conducted at Dar Al Salam Field Hospital and Yarmouk Hospital. `

The patients were randomly split into two groups:

1. First Patient Group: included 50 patients with DM and COVID-19.

2. Second Patient Group: 50 COVID-19 patients without DM.

In these groups, all patients were adults and 50-80 y old. And genders were matched. The severity of the disease noted according to the WHO clinical criteria.

3. Third Control Group included 100 healthy, people ages 50-80 y, enrolled under the supervision of the second supervisor from relatives and students of Mustansiriyah University, College of Medicine.

Subjects who had had organ failure, chemotherapy and malignant carcinoma anywhere, or autoimmune disease, were excluded.

Venous blood samples 5 mL were taken from all participants. The samples were left to clot for 15 min at room temperature; After coagulation, the serum was separated by centrifuge for 10 min at 3000 rpm. The Human serum FA, INS, and C-Pep kits were measured using Elisa Human Reader, purchased from Human Company, Germany. Other tests included FBS done by using appropriate method while HbA1C was measured by adding 2 mL of whole blood to the EDTA tube.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 25.0 was used to analyze the data. The parameters were measured and describe them using statistical information like median and range. Unpaired independent sample t-test between two groups, and to compare groups repeated measures ANOVA was used (evaluating interactions between patient groups). The Spearman correlation coefficient (r) was used to determine the strength of the relationship between continuous variables. Using the Receiver Operating Characteristics (ROC) curve, the cut-off value, sensitivity, and specificity were calculated. When the P values were 1% (P = 0.01) and 5% (P = 0.05), respectively, to illustrate the strength of the evidence indicating significant differences across variables, the results were deemed statistically significant.

3. RESULTS

It was discovered that the levels of INS, C-Pep, and the biochemical parameters were not regularly distributed. Thus, they were expressed as median and range and analyzed with an Unpaired t-test between two groups conducted using an independent sample, repeated-measures ANOVA to examine the interactions between patient groups). The median FBS level of DM patients' groups were significantly higher than non-DM patient groups. Furthermore, the DM patients' group had a significantly higher concentration of HbA1C than the non-DM patient group with a considerable variation. FA concentrations were higher in DM patients than in the

Table 1: The relationship between severe COVID-19 and inflammatory factors in diabetes

Variables	Control (n = 100)	COVID-19 Patients		P-value
		With DM (n = 50)	Without DM (n = 50)	
Sugar (mg/dL)	88 (75-125)	304.9 (132-545.9)	193.3 (66.2-458)	> 0.001**
HbA1C	6 (5.2-6.5)	6.70 (5.2-8.1)	5.8 (4.2-7.6)	
FA (ng/mL)	9.75 (5.4- 13.4)	18.65 (13.78-57.3)	17.10 (10.40-43.72)	
Insulin (µlU/mL)	0.40 (0.25-1.27)	0.77 (0.46 -1.95)	1.18 (0.41-1.90)	
C-pep (ng/mL)	0.74 (0.64-1.13)	1.06 (0.79-2.31)	1.19 (0.76-1.99)	

*Data presented as Median (Range)' .** P ≤ 0.01 = Highly Significant.*

Table 2: Discriminative values of inflammatory marker

Parameters	AUC, 95%	Cut-off value	Sensitivity %	Specificity %	P-value
FBS	0.969	125.5	100	89.28	> 0.001
FA	0.993	13.43	100	97.08	> 0.001
Insulin	0.921	0.53	88.11	88.88	> 0.001
C-peptide	0.951	0.83	85.96	97.67	> 0.001

P < 0.05 considered significant, P < 0.001 considered highly significant

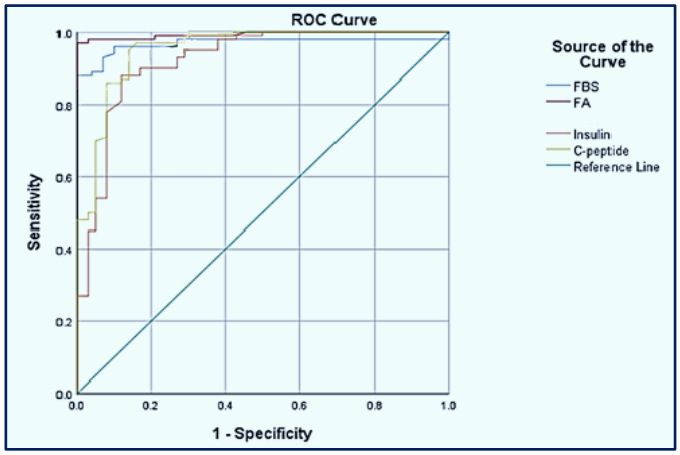

Figure 2: Receiver operating characteristic curve of biochemical markers level in the context of discrimination between patient and control.

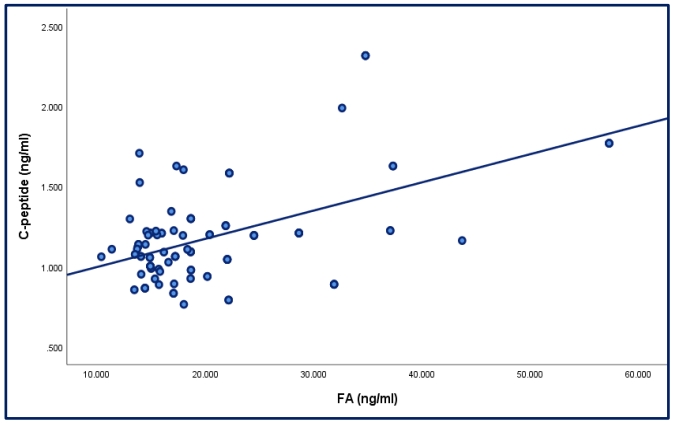

Figure 3: Scatter plot and regression line between FA and C-pep in patients with severe COVID-19

non-DM patient group, but the differences were still noteworthy. Although the INS and C-Pep concentrations in DM patients were lower than in the non-diabetic group, the differences were not statistically significant (Table 1).

3.1. Discriminative values of biochemical marker

The AUC for FBS was 0.969, 95% CI = 0.940-0.997, and P = 0.001. The test's sensitivity and specificity were 100% and 89.28%, respectively, at the FBS cut-off value of 125.5 mg/dL.

Table 3: Spearman correlations of the biochemical marker in severe COVID-19 patients

Variables		FBS	FA	Insulin	C-pep
FBS	r		0.158	0.047	-0.115
	p		0.117	0.643	0.253
FA	r			0.271**	0.322**
	p			0.006	0.001
Insulin	r				0.155
	p				0.123

***Correlation is significant at the 0.01 level (2-tailed).*

AUC = 0.993, 95% CI = 0.983–1.000, P > 0.001 for FA. The test's sensitivity and specificity were 100% and 97.08%, respectively, at the FA = 13.43 ng/mL cut-off value.

The AUC for insulin was 0.921, 95% CI = 0.884-0.959, and P = 0.001. The test's sensitivity and specificity were 88.11% and 88.88%, respectively, at the cut-off value of Insulin = 0.53 Ul/mL.

The AUC for C-pep was 0.951, 95% CI = 0.924-0.979, and P > 0.001. The test's sensitivity and specificity were 85.96% and 97.67%, respectively, at the cut-off value of C-pep = 0.83 ng/mL. (Table 2) (Figure 2).

3.2. Correlation of inflammatory marker with age in severe COVID-19 patients

FA had a significant positive correlation with insulin (r = 0.271, P = 0.006) and C-pep (r = 0.322, P = 0.001). as shown in (Table 3 and Figure 3).

4. DISCUSSION

In this study, the two groups had no significant difference in INS or C-Pep levels. Still, significant differences were in the regular results of the laboratory (FBS, HbA1C, and FA) in people with COVID-19 who were dangerous impacted, whether they have diabetes or

not. This may display utilize a large dose of steroid as a treatment, such as an injection of dexamethasone. Pathological characteristics of COVID-19 include cytokine-associated hyperactivity and inflammation leading to pneumonia, Focuses the light on significance of using corticosteroids in severe patients immediately and appropriately to bypass cytokine storm. This medicament drop insulin levels, inhibits glycolysis, and elevate gluconeogenesis.[17]

These results showed that diabetes individuals on COVID-19 (who had higher fasting blood sugar levels) had more severe infections than non-diabetic patients. subjects with T2DM are repeatedly remedy with ARBs and ACEIs, which may both lead to elevated production in tissues of ACE-2, boost viral assimilation and elevating the risk of severe infection in patients with Type 2 DM. these patients may be correlating with activation the system of renin-angiotensin. [18]

Since stress from an acute illness does not affect HbA1c, it may be used to identify COVID-19 individuals who have recently been diagnosed with diabetes. The impact of newly discovered diabetes (new onset or previously undiscovered) on many COVID-19 patients is now more well-recognized. Furthermore, compared to both those without diabetes and those with known diabetes, COVID-19 patients who have just been diagnosed with the disease appear to be more vulnerable to a bad result.[19]

It is generally known how crucial it is to regularly check a patient's HbA1c level if they have diabetes. However, in some patients, the HbA1c may cause a delay in the initiation of treatment for poorly managed diabetes because it misrepresents glycemic control. We describe a patient whose hemolytic anemia caused by myelodysplastic syndrome caused the HbA1c readings to be artificially low. The patient's blood sugar levels were consistently elevated. Measurement of fructose amine was able to both indicate poorly controlled diabetes and help with diabetic management. Disorders of red blood cells, which have a significant potential impact on HbA1c, do not alter fructose amine.[20]

In COVID-19 patients, the function of C-peptide has yet to be properly studied. When comparing critical cases of COVID-19 patients with the control group, it was found that they had less sensitivity to insulin. However, there was no change in C-peptide or insulin levels between the DM and non-DM groups. However, both groups' C-peptide and insulin levels were found to be above the normal range, which suggests that insulin resistance may be enhanced by COVID-19.[21]

5. CONCLUSIONS

According to the results of the study, diabetic patients with COVID-19 infection—an infection brought on by the virus COVID-19—had greater levels of certain biochemical markers than non-diabetic patients. The renin-angiotensin system's activity may be linked to T2DM. T2DM patients have been routinely prescribed ACEIs and ARBs, which may enhance the production of tissues ACE-2, improve viral absorption, and raise the risk of severe infection. The pathological features of COVID-19 include increased inflammation and cytokine-related lung damage, which serve to prevent a cytokine storm. This type of therapy lowers insulin sensitivity and glycolysis while increasing gluconeogenesis.

6. Data availability

The numerical data generated during this research is available with the authors.

7. Preregistration

The study was registered in the Chemistry and Biochemistry Branch at the College of Medicine/Al-Nahrain University and samples were collected in Dar Al Salam field isolation center for COVID-19 patients and Al-Yarmouk Hospital.

8. Source of Funding

This study was funded personally by the researchers.

9. Conflict of interest

The authors declare that there was no conflict of interest.

10. Authors' contribution

M.S.Y: Conduct of study; literature search; statistical analysis & manuscript editing

E.A.AL: Conduct of study; literature search.

AH.ALQ: Conduct of study; literature search.

Al-Rubaiawi HK: Conduct of study; literature search.

11. REFERENCES

1. Soliman A, Nair AP, Al Masalamani MS, De Sanctis V, Khattab MAA, Alsaud AE, et al. Prevalence, clinical manifestations, and biochemical data of type 2 diabetes mellitus versus nondiabetic symptomatic patients with COVID-19: A comparative study. Acta Biomed. 2020;91(3). [PubMed] DOI: 10.23750/abm.v91i3.10214
2. Meo S, Alhowikan A, Al-Khlaiwi T, Meo I, Halepoto D, Iqbal M, et al. Novel coronavirus 2019-nCoV: prevalence, biological and clinical characteristics comparison with SARS-CoV and MERS-CoV. Eur Rev Med Pharmacol Sci. 2020;24(4):2012-9. [PubMed] DOI: 10.26355/eurrev_202002_20379
3. Ahmed OJ, Al-Wasiti EA, Jamil D, Al-Aubaidy H. Changes in the levels of biochemical markers following coronavirus infection in patients with liver disease, renal disease and diabetes mellitus as compared to control participants: A cross-sectional study. J Pharm Res Int. 2021;33(30B):141-8. DOI: 10.9734/jpri/2021/v33i30B31648

4. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev. 2020;36(7). [PubMed] DOI: 10.1002/dmrr.3321
5. Sathish T, Kapoor N, Cao Y, Tapp RJ, Zimmet P. Proportion of newly diagnosed diabetes in COVID-19 patients: a systematic review and meta-analysis. Diabetes Obes Metab. 2021;23(3):870-4. [PubMed] DOI: 10.1111/dom.14269
6. Chung MK, Karnik S, Saef J, Bergmann C, Barnard J, Lederman MM, et al. SARS-CoV-2 and ACE2: The biology and clinical data settling the ARB and ACEI controversy. EBioMedicine. 2020;58:102907. [PubMed] DOI: 10.1016/j.ebiom.2020.102907
7. Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: the conundrum. Diabetes Res Clin Pract. 2020;162. [PubMed] DOI: 10.1016/j.diabres.2020.108132
8. Michalakis K, Ilias I. SARS-CoV-2 infection and obesity: Common inflammatory and metabolic aspects. Diabetes Metab Syndr. 2020;14(4):469-71. [PubMed] DOI: 10.1016/j.dsx.2020.04.033
9. Liu Z, Xiao X, Wei X, Li J, Yang J, Tan H, et al. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. J Med Virol. 2020;92(6):595-601. [PubMed] DOI: 10.1002/jmv.25726
10. Al-Kuraishy HM, Al-Maiahy TJ, Al-Gareeb AI, Musa RA, Ali ZH. COVID-19 pneumonia in an Iraqi pregnant woman with preterm delivery. Asian Pac J Reprod. 2020;9(3):156. DOI: 10.4103/2305-0500.282984
11. Hadi A, Werge M, Kristiansen KT, Pedersen UG, Karstensen JG, Novovic S, et al. Coronavirus disease-19 (COVID-19) associated with severe acute pancreatitis: case report on three family members. Pancreatology. 2020;20(4):665-7. [PubMed] DOI: 10.1016/j.pan.2020.04.021
12. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4. [PubMed] DOI: 10.1016/S0140-6736(20)30628-0
13. Caruso I, Di Molfetta S, Guarini F, Giordano F, Cignarelli A, Natalicchio A, et al. Reduction of hypoglycaemia, lifestyle modifications and psychological distress during lockdown following SARS-CoV-2 outbreak in type 1 diabetes. Diabetes Metab Res Rev. 2021;37(6). [PubMed] DOI: 10.1002/dmrr.3404
14. Abdul-Hadi MH, Naji MT, Shams HA, Sami OM, Al-Harchan NAA, Al-Kuraishy HM, et al. Oxidative stress injury and glucolipotoxicity in type 2 diabetes mellitus: The potential role of metformin and sitagliptin. Biomed Biotechnol Res J. 2020;4(2):166. DOI: 10.4103/bbrj.bbrj_7_20
15. Albulescu R, Dima SO, Florea IR, Lixandru D, Serban AM, Aspritoiu VM, et al. COVID-19 and diabetes mellitus: Unraveling the hypotheses that worsen the prognosis. Exp Ther Med. 2020;20(6):194. [PubMed] DOI: 10.3892/etm.2020.9324
16. El-Huneidi W, Hamad M, Taneera J. Expression of SARS-CoV-2 receptor "ACE2" in human pancreatic β cells: to be or not to be! Islets. 2021;13(5-6):106-14. [PubMed] DOI: 10.1080/19382014.2021.1954458
17. Zhao R, Li M, Song H, Chen J, Ren W, Feng Y, et al. Early detection of SARS-CoV-2 antibodies in COVID-19 patients as a serologic marker of infection in Patients With Coronavirus Disease 2019. Clin Infect Dis. 2020;71(16):2066-72. [PubMed] DOI: 10.1093/cid/ciaa523
18. Holt A, Mizrak I, Lamberts M, Madsen PL. Influence of inhibitors of the renin-angiotensin system on risk of acute respiratory distress syndrome in Danish hospitalized COVID-19 patients. J Hypertens. 2020;38(8):1612-3. [PubMed] DOI: 10.1097/HJH.0000000000002515
19. Sathish T, Cao Y. What is the role of admission HbA1c in managing COVID-19 patients? J Diabetes. 2021;13(3):273-5. [PubMed] DOI: 10.1111/1753-0407.13140
20. Tavares Ribeiro R, Paula Macedo M, Filipe Raposo J. HbA1c, fructosamine, and glycated albumin in the detection of dysglycaemic conditions. Curr Diabetes Rev. 2016;12(1):14-9. [PubMed] DOI: 10.2174/1573399811666150701143112
21. Robeva R, Petrova D, Elenkova A, Tankova T, Zacharieva S. C-peptide levels and glycemic indices in COVID-19 patients. Biotechnol Biotechnol Equip. 2022;36(1):418-24. DOI: 10.1080/13102818.2022.2090858

