CROSS-SECTIONAL STUDY

# The Pathological Basis for Severe Corona Virus Disease-19 in Diabetic Patients

Esraah Alharris*, Dina Saleh

*Department of Pathology and Forensic Medicine, College of Medicine, University of Al-Qadisiyah, Al Diwaniyah, Iraq.*

***Received: 12th February, 2022; Revised: 19th April, 2022; Accepted: 16th May, 2022; Available Online: 25th June, 2022***

## ABSTRACT

**Background:** It has been documented that the mortality rate in diabetic persons can reach 10%. In addition, it has been shown that the rate of mortality and the need for respiratory support are higher among newly diagnosed cases of diabetes mellitus compared with patients known to have diabetes mellitus for a relatively long duration. In the setting of the pandemic of COVID-19, glycemic control for the patients admitted to hospitals is critical, as is diabetes screening to uncover undiagnosed cases.

**Aim of the study:** To explore the possible link between diabetes mellitus and COVID-19 in Iraq

**Patients and methods:** The current research was carried out in Al-Diwaniyah Province, Iraq, in Al-Diwaniyah Teaching Hospital, including the word of medicine, respiratory unit, and intensive care unit. The study started on Sept 15, 2021 and ended on Apr 15, 2022. The study was cross-sectional and included 100 patients with a diagnosis of COVID-19 evidenced by polymerase chain reaction (PCR) test and CT-scan "computed tomography scan of the chest. Those patients were chosen randomly from the pool of patients visiting the teaching hospital. The age range of patients was between 18 and 94 years, with 45 males and 55 females. Laboratory investigation results were retrieved from patients' records and included random blood sugar, lactate dehydrogenase, d-dimer, HbA1c%, and "C-reactive protein (CRP)."

**Results:** The mean values of age, random blood sugar (RBS), lactate dehydrogenase (LDH), d-dimer, HbA1c, and HS-CRP were comparable between males and females ($p > 0.05$). Patients with high HbA1c levels (HbA1c $\geq$ 6.5%) were older and had significantly higher levels of random blood sugar and d-dimer than patients with HbA1c < 6.5%**.** The d-dimer level showed a significant positive correlation to RBS, LDH, HbA1c, and HS-CRP ($p < 0.05$).

**Conclusion:** Higher levels of markers of inflammation were associated with HbA1c levels in the diabetic range, indicating a bi-directional relation between diabetes mellitus and the severity of COVID-19.

**Keywords:** COVID-19, Diabetes mellitus, Iraq.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.2.74

**How to cite this article:** Alharris E, Saleh D. The Pathological Basis for Severe Corona Virus Disease-19 in Diabetic Patients. International Journal of Drug Delivery Technology. 2022;12(2):873-877.

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

Late in 2019, an infectious disease related to coronaviruses was discovered in China, Hubei, City of Wuhan.[1,2] The outbreak later became a pandemic because of the extremely rapid spread of the virus all over the world.[3,4] The novel virus that resulted in such pandemic was identified as the "2019 novel coronavirus",[5] but later one was renamed by World Health Organization (WHO) as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)".[6] Initially, the virus was thought to be acquired from exposure to Huanan Seafood Market based on some epidemiological data.[3] However, the virus was shown later to have the ability to spread by direct contact from person to person via respiratory droplets, and that was a great challenge to public health.[7] From a clinical perspective, the disease may cause cough, myalgias, fever, chest pain, sore throat, sputum production, shortness of breath, hemoptysis, vomiting, nausea, rhinorrhea, diarrhea, headache, anosmia, and others.[8,9] In most the cases, spontaneous recovery is the rule (3); nevertheless, it has been realized that patients with already existing comorbidity are at higher risk of morbidity and mortality, such as those with diabetes mellitus (DM), and hypertension, chronic lung disorders, and malignant disease.[10,11]

It has been documented that the mortality rate form diabetic patients with COVID can reach 10%.[12] In addition, it has been shown that the rate of mortality and the need for respiratory support are higher among newly diagnosed cases of diabetes mellitus in comparison with patients known to have diabetes mellitus for a relatively long duration.[12] In the pandemic of COVID-19, glycemic control in patients admitted to hospitals is critical, as is diabetes screening to uncover undiagnosed cases.[12]

**Author for Correspondence: esraah.alharris@qu.edu.iq*

In a cohort study that is population-based from England, diabetic people ( whether type I or type II DM) who have HbA 1c >10% carry a greater risk of death from SARS-CoV2 than those with HbA 1c of 6.5%.[13] Diabetic individuals having COVID-19 showed a greater hypertension incidence (56.9%), disease of the heart and blood vessels (20.9%), and CVA (7.8%) than patients with no DM (28.8, 11.1, and 1.3%, respectively) according to a retrospective Chinese study.[14] A meta-analysis in China dealing with COVID-19 patients found that diabetes prevalence of 9.7%,[15] which is in line with the prevalence of DM in China. In a study from the UK, inpatient death was reported in 23,804 patients with COVID-19, of whom 32% had type II diabetes mellitus (T2DM) and 1.5% had type I DM (T1DM), with a 2.03 and 3.5 times potential of hospital death, respectively, compared to patients with no DM.[16]

Based on these reports and due to the poverty of Iraqi literature dealing with the association between COVID-19 and diabetes mellitus, the planning of the current study was justified, and it has been conducted in Iraq in Al-Diwaniyah province to figure out this issue.

## PATIENTS AND METHODS

The current analysis was held in Al-Diwaniyah Province, Iraq, in Al-Diwaniyah Teaching Hospital, including the word of medicine, respiratory unit, and intensive care unit. The study started on Sept 15, 2021 and ended on Apr 15, 2022. The study was cross-sectional and included 100 patients with a diagnosis of COVID-19 documented by PCR test and CT scan of the chest. Those patients were chosen in a random way from the pool of patients visiting the teaching hospital. The age range of patients was between 18 and 94 years, and they were 45 males and 55 females. Laboratory investigation results were retrieved from patients' records, including random blood sugar, lactate dehydrogenase, d-dimer, HbA1c%, and "highly sensitive C-reactive protein (HS-CRP)."

The research was approved by the College of Medicine, University of Al-Qadisiyah by its ethical approval committee. Every patient or his care giver gave a verbal consent after a full illustration of the goals and the procedures of the study. A formal agreement was issued by the directorate of health in the province.

Data were analyzed and described using the "statistical package for social sciences (SPSS for Windows, Version 16.0. Chicago, SPSS Inc.)". Quantitative variables were outlined as mean, range, and standard deviation (SD). Comparison of mean of numeric variables was made using independent samples student *t*-test. Pearson correlation test was used to study correlation among variables. The cutoff of a significant level was based on or at $p \leq 0.01$ (**) or $p \leq 0.05$ (*).

## RESULTS

The general characteristics of COVID-19 individuals enrolled in the present study are outlined in Table 1. The average age of all participants was 49.00 ± 16.71, and there was no significant variation in the average age between males and females ($p$ = 0.858). The mean random blood sugar (RBS) of all patients was 183.30 ± 69.83, and there was no significant variation in its average between males and females ($p$ = 0.294). The mean

**Table 1:** General characteristics of subjects with COVID-19 enrolled in the present study

| *Characteristic* | *Total* *n = 100* | *Male* *n = 45* | *Female* *n = 55* | *p* |
|---|---|---|---|---|
| Age (years) | | | | |
| Mean ±SD | 49.00 ± 16.71 | 48.67 ± 17.74 | 49.27 ± 15.98 | 0.858 I |
| Range | 18-94 | 18-94 | 18-94 | NS |
| RBS (mg/dL) | | | | |
| Mean ± SD | 183.30 ± 69.83 | 175.16 ± 75.50 | 189.96 ± 64.77 | 0.294 I |
| Range | 90-365 | 91-365 | 90-365 | NS |
| LDH (mg/dL) | | | | |
| Mean ± SD | 360.63 ± 152.29 | 332.55 ± 134.88 | 383.61 ± 162.79 | 0.095 I |
| Range | 70-865 | 70-641 | 92-865 | NS |
| D-Dimer (µg/mL) | | | | |
| Mean ± SD | 0.76 ± 0.40 | 0.72 ± 0.32 | 0.79 ± 0.46 | 0.373 I |
| Range | 0.19-2.6 | 0.28-1.6 | 0.19-2.6 | NS |
| HbA1c % | | | | |
| Mean ± SD | 6.44 ± 0.90 | 6.35 ± 1.08 | 6.52 ± 0.73 | 0.354 I |
| Range | 4.1-8.9 | 4.1-8.9 | 4.9-8.9 | NS |
| HS-CRP (mg/L) | | | | |
| Mean ± SD | 80.03 ± 38.49 | 83.58 ± 37.05 | 77.12 ± 39.74 | 0.406 I |
| Range | 9.8-200 | 9.8-200 | 18.4-169.8 | NS |

**SD**: standard deviation**; *n***: number of cases; **RBS**: random blood sugar; **LDH**: low-density lipoprotein; **HbA1c**: glycated Hb; HS-CRP: highly sensitive C-reactive protein; **NS**: not significant at $p$ >0.05; **I**: independent samples *t*-test

**Table 2:** Comparison of patients' characteristics with respect to the glycated hemoglobin level

| *Characteristic* | *HbA1c ≥6.5 %* *n = 50* | *HbA1c <6.5 %* *n = 50* | *p* |
|---|---|---|---|
| Age (years) | 52.60 ±15.68 | 45.40 ±17.09 | 0.031 I*<br>NS |
| RBS (mg/dl) | 223.30 ±64.66 | 143.30 ±49.05 | < 0.001 I* |
| LDH (mg/dl) | 375.95 ±152.93 | 345.32 ±151.62 | 0.317 I<br>NS |
| D-Dimer ug/mL | 0.86 ± 0.44 | 0.65 ± 0.33 | 0.010 I ** |
| HS-CRP (mg/L) | 83.06 ± 44.52 | 76.99 ± 31.52 | 0.433 I<br>NS |

Data were presented as mean ±standard deviation; **RBS**: random blood sugar; **LDH**: low density lipoprotein; **HbA1c**: glycated Hb; HS-CRP: highly sensitive C-reactive protein; **: significant at $p \leq 0.01$; **NS**: not significant at $p > 0.05$; *: significant at $p \leq 0.05$;

**Table 3:** Correlations of d-dimer titer with other variables

| | *D-Dimer µg/mL* | |
|---|---|---|
| *Characteristic* | *r* | *p* |
| Age (years) | 0.058 | 0.563 |
| RBS (mg/dL) | 0.241 | 0.016 * |
| LDH (mg/dL) | 0.438 | < 0.001** |
| HbA1c % | 0.222 | 0.027* |
| HS-CRP (mg/L) | 0.108 | 0.287 |

**RBS**: random blood sugar; **LDH**: low density lipoprotein; **HbA1c**: glycated Hb; HS-CRP: highly sensitive C-reactive protein; **: significant at $p \leq 0.01$; *: significant at $p \leq 0.05$;

level of lactate dehydrogenase (LDH) of all patients was 360.63 ±152.29 mg/dL, and there was no substantial variation in average LDH between males and females ($p = 0.095$). The mean d-dimmer level of all patients was 0.76 ±0.40 µg/mL, and there was no substantial variation in the mean d-dimer level between males and females ($p = 0.373$).

The mean HbA1c of all patients was 80.03 ± 38.49 %, and there was no substantial variation in mean HbA1c between males and females ($p = 0.406$). Correlations of d-dimer titer with other variables are shown in Table 2. It showed a significant positive correlation to RBS, LDH, and HbA1c ($p < 0.05$).

A comparison of patients' characteristics with respect to the level of glycated hemoglobin is presented in Table 2. The average age of persons with high HbA1c was significantly higher than that of subjects with HbA1c < 6.5% ($p = 0.031$). Meet random blood sugar and mean d-dimer level were also substantially more significant than that of patients with HbA1c < 6.5% ($p \leq 0.01$), but there was no significant variation in mean LDH and mean HS-CRP with respect to HbA1c level ($p > 0.05$).

Correlations of d-dimer titer with other variables are shown in Table 3. The d-dimer level showed a significant positive correlation to RBS, LDH, HbA1c, and HS-CRP ($p < 0.05$), but it showed no significant correlation to the age of patients ($p = 0.563$).

## DISCUSSION

In our study, it has been found that the mean values of age, RBS, LDH, d-dimer, HbA1c, and HS-CRP were comparable between females and males ($p > 0.05$). In addition, mean age was also comparable between females and males. Previously, comparable mean age between males and females with COVID-19 has been described by researchers; but they described the more severe disease and higher mortality in association with male gender.[17] In our study, however, the lack of significant variation in inflammatory markers may contradict the previous findings.

Gender and sex have been found to be additive risk variables for COVID-19 outcomes.[18] Indeed, sex bias in the case of COVID-19 mortality has been documented in various investigations. Men are found to have a larger probability of having a severe pattern of the illness than females, emphasizing the need of gender-disaggregated COVID-19 case data.[19] Primary data from China, followed by statistics from numerous European nations, revealed that males and women have the same number of confirmed cases.[20,21]

The unavailability of data concerning hospitalization duration, rate of complications needed for respiratory support, and mortality rate in our study has compromised our conclusion about the clinical severity of the disease contrasted between males and females, and this was the major limitation of the current study.

In addition, in our study, we found that patients with high HbA1c levels (HbA1c ≥ 6.5%) were older and had significantly higher levels of random blood sugar and d-dimer than patients with HbA1c < 6.5% and that the d-dimer level showed a significant positive correlation to RBS, LDH, HbA1c and HS-CRP ($p < 0.05$). As a cross-sectional study, it is not easy to make a causal relationship between diabetes mellitus and predisposition to COVID-19 or its severity.

However, a bi-directional relation between COVID-19 severity and diabetes mellitus can be inferred from our result in that higher HbA1c levels (in the diabetic range) were correlated to greater levels of inflammatory markers, namely d-dimer and LDH. Therefore, the prior affection by DM may alter the immune response and result in a more severe inflammatory response, or that more severe inflammatory response might alter blood sugar levels. However, it should be kept in mind that higher levels of HbA1c need a relatively long time to happen. Thus, we prefer to say that the already existing diabetic or pre-diabetic state is the cause behind higher levels of inflammatory markers and not vice versa.

Certain molecular pathways have been proposed to investigate the probable causative relationship between prolonged untreated raised blood glucose and greater rates of death in COVID-19 subjects. In COVID-19 individuals with diabetes, an insufficient immune reaction to infection with the virus is the leading cause of death.[22] Increased blood sugar levels are likely to have a significant impact on the bacterial intracellular breakdown, neutrophil phagocytosis and chemotaxis, and boosting affinity of viral binding and entrance while lowering virus clearance.[23] Furthermore, it has a major impact on proteins by inducing glycosylation and changing complement composition,[24,25] and glycosylation makes cells more vulnerable to viral inflammation and damage.[26,27] Furthermore, endotheliitis could be a trigger for organ malfunction that leads to critical COVID-19 disease, which is exacerbated by endothelial dysfunction combined with chronic hyperglycemia.[28]

Diabetes is linked to the severity of infection by a number of factors. Hyperglycemia can initiate, intensify, or extend the acute inflammatory response.[29] It also causes a fibrinolysis and coagulation mismatch, leading to increased factors of coagulation and relative inhibition of the system of fibrinolysis, promoting a state of pro-coagulation.[30] Furthermore, SARS-CoV-2 is thought to use ACE2 as an entrance receptor on the islets of Langerhans. This can cause these cells to dawn in a moderate to the severe manner, resulting in mild hyperglycemia and life-threatening diabetic ketoacidosis.[27]

## CONCLUSION

Higher levels of markers of inflammation were associated with HbA1c levels in the diabetic range, indicating a bi-directional relation between diabetes mellitus and severity of COVID-19.

## REFERENCES


1. Pekar J, Worobey M, Moshiri N, Scheffler K, Wertheim JO. Timing the SARS-CoV-2 Index Case in Hubei Province. bioRxiv. 2020.
2. Wang F, Cao J, Yu Y, Ding J, Eshak ES, Liu K, et al. Epidemiological characteristics of patients with severe COVID-19 infection in Wuhan, China: evidence from a retrospective observational study. Int J Epidemiol. 2021;49(6):1940-50.
3. Krishnan A, Hamilton JP, Alqahtani SA, Woreta TA. COVID-19: An overview and a clinical update. World J Clin Cases. 2021;9(1):8-23.
4. Baloch S, Baloch MA, Zheng T, Pei X. The Coronavirus Disease 2019 (COVID-19) Pandemic. Tohoku J Exp Med. 2020;250(4):271-8.
5. Wang M, Zhang N. Focus on the 2019 novel coronavirus (SARS-CoV-2). Future Microbiol. 2020;15:905-18.
6. Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5(4):536-44.
7. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;382(13):1199-207.
8. Esakandari H, Nabi-Afjadi M, Fakkari-Afjadi J, Farahmandian N, Miresmaeili SM, Bahreini E. A comprehensive review of COVID-19 characteristics. Biol Proced Online. 2020;22:19.
9. da Rosa Mesquita R, Francelino Silva Junior LC, Santos Santana FM, Farias de Oliveira T, Campos Alcantara R, Monteiro Arnozo G, et al. Clinical manifestations of COVID-19 in the general population: systematic review. Wien Klin Wochenschr. 2021;133(7-8):377-82.
10. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its Impact on Patients with COVID-19. SN Compr Clin Med. 2020;2(8):1069-76.
11. Sharif N, Opu RR, Ahmed SN, Sarkar MK, Jaheen R, Daullah MU, et al. Prevalence and impact of comorbidities on disease prognosis among patients with COVID-19 in Bangladesh: A nationwide study amid the second wave. Diabetes Metab Syndr. 2021;15(4):102148.
12. Dubai diabetes and endocrinology journal. Basel, Switzerland: S. Karger AG; 2020.
13. Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol. 2020;8(10):823-33.
14. Shi Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, et al. Clinical Characteristics and Risk Factors for Mortality of COVID-19 Patients With Diabetes in Wuhan, China: A Two-Center, Retrospective Study. Diabetes Care. 2020;43(7):1382-91.
15. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109(5):531-8.
16. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol. 2020;8(10):813-22.
17. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Front Public Health. 2020;8:152.
18. Falahi S, Kenarkoohi A. Sex and gender differences in the outcome of patients with COVID-19. J Med Virol. 2021;93(1):151-2.
19. Maleki Dana P, Sadoughi F, Hallajzadeh J, Asemi Z, Mansournia MA, Yousefi B, et al. An Insight into the Sex Differences in COVID-19 Patients: What are the Possible Causes? Prehosp Disaster Med. 2020;35(4):438-41.
20. Chen J, Bai H, Liu J, Chen G, Liao Q, Yang J, et al. Distinct Clinical Characteristics and Risk Factors for Mortality in Female Inpatients With Coronavirus Disease 2019 (COVID-19): A Sex-stratified, Large-scale Cohort Study in Wuhan, China. Clin Infect Dis. 2020;71(12):3188-95.
21. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ. 2020;11(1):29.
22. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. Diabetes Care. 2018;41(10):2127-35.
23. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020;318(5):E736-E41.
24. Jafar N, Edriss H, Nugent K. The Effect of Short-Term Hyperglycemia on the Innate Immune System. Am J Med Sci. 2016;351(2):201-11.
25. Wang Q, Fang P, He R, Li M, Yu H, Zhou L, et al. O-GlcNAc transferase promotes influenza A virus-induced cytokine

storm by targeting interferon regulatory factor-5. Sci Adv. 2020;6(16):eaaz7086.
26. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol. 2020;8(6):546-50.
27. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010;47(3):193-9.
28. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417-8.
29. Moutschen MP, Scheen AJ, Lefebvre PJ. Impaired immune responses in diabetes mellitus: analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. Diabete Metab. 1992;18(3):187-201.
30. Schuetz P, Castro P, Shapiro NI. Diabetes and sepsis: preclinical findings and clinical relevance. Diabetes Care. 2011;34(3): 771-8.