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Effects of poor glycemic control on mortality and severity of COVID-19 disease

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Abstract. – **OBJECTIVE:** **Most patients with a severe COVID-19 infection have underlying diseases such as hypertension, cardiovascular disorders, and diabetes, and the mortality rate in these patients is higher than in other patients. Reasonable glycemic control is a practical approach to prevent the progression of COVID-19 in patients with diabetes. In this study, we aimed at demonstrating that glycemic control status can be used as a biomarker in predicting the severity of the disease in the early period in diabetic patients with COVID-19.**

PATIENTS AND METHODS: **Our retrospective study consisted of 122 patients who referred to Sinop Ayancik State Hospital between April 1, 2020, and April 1, 2021. 40 diabetic patients with poor glycemic control (HbA1C above 7), 40 diabetic patients with reasonable glycemic control (HgA1c below 7), and 42 patients without diabetes were included in the study. The patients' data included in the study were obtained by scanning the retrospective files. These patients' demographic characteristics, clinical features, age, gender, length of stay, hemogram, biochemical, hormonal parameters, HgA1c levels, and atherogenic indexes were calculated and recorded. Study groups were compared in terms of disease severity and mortality.**

RESULTS: **A statistically significant difference was found between mild/severe conditions (*p*-value < 0.001). 72.5% of those with poor glycemic control, 57.5% of those with reasonable glycemic control, and 26.2% without diabetes had severe diseases. Also, a statistically significant difference was found between the distributions of death rate (*p* = 0.008). 17.5% of those with poor glycemic control, 5% of those with reasonable glycemic control, and 0% of patients without diabetes died.**

CONCLUSIONS: **Our results showed that poor glycemic control was an effective indicator of disease severity and mortality in patients with COVID-19 and could predict disease progression and mortality.**

Key Words:
COVID-19, Diabetes, Glycemic control.

Introduction

In December 2019, unexplained cases were reported in Wuhan, China, due to symptoms similar to severe acute respiratory syndrome (SARS), but more aggressive in symptoms and spread. The World Health Organization called the virus the "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which posed significant health threats, especially to people with underlying diseases such as cardiovascular disorders, diabetes, and high blood pressure[1]. According to studies[2,3], most patients with severe diseases have underlying diseases such as hypertension, cardiovascular disorders, and diabetes, and the mortality rate in these patients is higher than in other patients. Studies show[4-6] that the death rate from COVID-19 in people with diabetes is about three times higher than in the average population.

Because cardiovascular diseases, diabetes, and hypertension alone pose a significant challenge to the global health system, and many die each year from these diseases, with the advent of COVID-19 disease, the anxiety between different people with these diseases (which can have adverse effects on a person's health) started to arise. In addition, studies show that psychological factors, especially anxiety, are associated with the pathology of cardiovascular disease. Therefore, the hypersensitivity of the sympathetic nervous system can have adverse effects on glycemic control, which affects the function of the immune system[7,8]. Studies[9,10] have shown that these psychological effects can negatively affect glycemic control in diabetics. Thus, management of diabetes in the face of limited resources has been negatively affected by the COVID-19 pandemic.

Reasonable glycemic control is a practical approach to prevent the progression of COVID-19 in patients with diabetes[4,5]. Furthermore, it is expected that the glycemic control of COVID-19 patients will affect the severity of their disease[6,9].

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Therefore, in this study, we aimed at demonstrating that glycemic control status can be used as a biomarker in predicting the severity of the disease in the early period in diabetic patients with COVID-19.

Patients and Methods

Our retrospective study consisted of patients diagnosed at Sinop Ayancık State Hospital, followed up, and treated there. Patients diagnosed with COVID-19 and hospitalized between April 1, 2020, and September 1, 2021, were included in our study. A total of 122 patients were included in the study. The patients' data included in the study were obtained by scanning the retrospective files. 40 diabetic patients with poor glycemic control (HbA1C above 7), 40 diabetic patients with reasonable glycemic control (HgA1c below 7), and 42 patients without diabetes were included in the study. These patients' demographic characteristics, clinical features, age, gender, length of stay, hemogram, biochemical, hormonal parameters, HgA1c levels, and atherogenic indexes were calculated and recorded. Study groups were compared in terms of disease severity and mortality.

Conformity to normal distribution was evaluated with the Kolmogorov-Smirnov test. The Chi-square test was used to compare categorical variables according to groups. One-way analysis of variance was used to compare normally distributed data according to groups of three or more, and multiple comparisons were performed with Tamhane's T2 and Duncan tests. The Kruskal-Wallis test was used to compare data that were not normally distributed according to groups of three or more. Finally, the Mann-Whitney U test was used to compare the data that were not normally distributed according to the paired groups. Statistics were given as frequency [n (%)] for categorical variables, and mean, standard deviation (mean ± SD), minimum, maximum, and median [Max-Min (M)] for numerical variables. The significance level was taken as p-value < 0.050. Data were analyzed with IBM SPSS V23 (IBM Corp., Armonk, NY, USA).

Results

The study groups consisted of 40 diabetic patients with poor glycemic control (HbA1C above 7), 40 diabetic patients with reasonable glycemic control (HbA1C below 7), and 42 patients without diabetes. According to the groups, a statistically significant difference was found between mild/severe conditions (p-value < 0.001). 72.5% of those with poor glycemic control, 57.5% of those with reasonable glycemic control, and 26.2% without diabetes had severe disease. In addition, a statistically significant difference was found between the distributions of the atherogenic index ($p < 0.001$). A high atherogenic index was found in 72.5% of those with poor glycemic control, 45% of those with reasonable glycemic control, and 26.2% without diabetes ($p < 0.001$). Also, a statistically significant difference was found between the distributions of death rate ($p = 0.008$). 17.5% of those with poor glycemic control, 5% of those with reasonable glycemic control, and 0% of patients without diabetes died. There was no statistically significant difference between the distributions of other variables according to the groups ($p > 0.050$) (Table I).

As Table II shows, a statistically significant difference was found between the mean age values of the patients according to the groups ($p < 0.001$), and the mean age of the healthy patient group was lower than the mean age of the other groups. In addition, a statistically significant difference was found between the median values of ANC ($p = 0.008$), glucose levels ($p < 0.001$), urea ($p < 0.001$), creatine ($p < 0.001$), and GGT ($p < 0.001$). The highest median value for these variables was obtained from the poor glycemic control group, while the lowest median was obtained from the healthy patient group.

A statistically significant difference was found between the median MCV values of the groups ($p = 0.01$), and the median of the poor glycemic control group was lower than the median of the other groups. A statistically significant difference was found for the albumin values ($p = 0.045$), and the median of the healthy patient group was higher than the median of the poor glycemic control group. A statistically significant difference was found between the mean HDL values of the patients according to the groups ($p = 0.005$), and the mean of the healthy patient group was higher than the mean of the poor glycemic control group. A statistically significant difference was found between the median LDL values of the groups ($p = 0.001$), and the median of the poor glycemic control group was lower than the median of the other groups.

A statistically significant difference was found between the median triglyceride values of the

Table I. Comparison of categorical variables by groups.

	Poor glycemic control	Good glycemic control	Without diabetes	Total	Test statistic	*p*-value
Gender						0.798
Female	21 (52.5)	19 (47.5)	23 (54.8)	63 (51.6)	$\chi^2 = 0.450$	
Male	19 (47.5)	21 (52.5)	19 (45.2)	59 (48.4)		
Mild/Severe						< 0.001
Mild	11 (27.5)[a]	17 (42.5)[a]	36 (85.7)[b]	64 (52.5)	$\chi^2 = 30.207$	
Severe	29 (72.5)	23 (57.5)	6 (14.3)	58 (47.5)		
Atherogenic Index						< 0.001
Low	11 (27.5)[a]	22 (55)[b]	31 (73.8)[b]	64 (52.5)	$\chi^2 = 17.772$	
High	29 (72.5)	18 (45)	11 (26.2)	58 (47.5)		
Presence of additional diseases						< 0.001
No	0 (0)[a]	0 (0)[a]	24 (72.7)[b]	24 (22)	$\chi^2 = 70.879$	
Yes	37 (100)	39 (100)	9 (27.3)	85 (78)		
Survival						0.008
Survived	33 (82.5)[a]	38 (95)[ab]	42 (100)[b]	113 (92.6)	$\chi^2 = 9.675$	
Not survived	7 (17.5)	2 (5)	0 (0)	9 (7.4)		
Arrival complaint*						0.594
Cough	17 (42.5)	14 (40)	17 (47.2)	48 (43.2)	$\chi^2 = 27.559$	
Weakness	14 (35)	13 (37.1)	16 (44.4)	43 (38.7)		
Shortness of breath	18 (45)	7 (20)	12 (33.3)	37 (33.3)		
Other	13 (32.5)	12 (34.3)	6 (16.7)	31 (27.9)		
Fever	7 (17.5)	7 (20)	9 (25)	23 (20.7)		
Throat ache	3 (7.5)	8 (22.9)	3 (8.3)	14 (12.6)		
Back pain	5 (12.5)	4 (11.4)	4 (11.1)	13 (11.7)		
Wheezing	5 (12.5)	4 (11.4)	4 (11.1)	13 (11.7)		
Joint pain	5 (12.5)	1 (2.9)	5 (13.9)	11 (9.9)		
Muscle Pain	2 (5)	6 (17.1)	2 (5.6)	10 (9)		
Headache	2 (5)	2 (5.7)	4 (11.1)	8 (7.2)		
Anorexia	3 (7.5)	2 (5.7)	2 (5.6)	7 (6.3)		
Pain	1 (2.5)	4 (11.4)	2 (5.6)	7 (6.3)		
Cold	1 (2.5)	2 (5.7)	2 (5.6)	5 (4,5)		
Diarrhea	1 (2.5)	2 (5.7)	2 (5.6)	5 (4,5)		

χ^2: Chi-square test statistic, [ab]: No difference between groups with the same letter, *Multiple responses.

groups (*p*-value=0.004), and the median of the healthy group was lower than the median of the poor glycemic group. In addition, a statistically significant difference was found between the median values of CRP ($p < 0.001$), Free T4 ($p = 0.017$), and sedimentation ($p < 0.001$) values of the groups. This difference is because the median of the without diabetes group was lower than the median of the other groups. According to the groups, there was no statistically significant difference between the distributions of other quantitative parameters ($p > 0.050$).

Discussion

The present study examined glycemic control data in patients with COVID-19 to investigate the predictive role of glycemic control in disease severity and mortality in COVID-19 patients. Our results showed that poor glycemic control was an effective indicator of disease severity and mortality in patients with COVID-19 and could predict disease progression and mortality. In addition, the atherogenic index was significantly poorer in the poor glycemic control group then in the other two groups. Other findings of our study were significant differences in age, albumin, HDL, CRP, and Free T4 between study groups. These findings are consistent with other COVID-19 diabetic patients studies[11-18]. However, unlike previous ones[11-13], our study did not observe a significant difference in higher disease severity and mortality in male patients.

The study on the correlation between glycemic control and the severity of COVID-19 disease has suggested a link between hospitalization glucose levels and disease severity. In addition, the relationship between poor pre-hospital glycemic control and disease severity has been also report-

Table II. Comparison of quantitative data by groups.

	Poor glycemic control		Good glycemic control		Without diabetes			
	Cover. ± p. Deflection	Cover. (min.-max.)	Cover. ± p. Deflection	Cover. (min.-max.)	Cover. ± p. Deflection	Cover. (min.-max.)	Test statistic	*p*-value
Age	70.43 ± 10.14[a]	70.00 (50.00-90.00)	70.63 ± 11.55[a]	70.00 (46.00-93.00)	58.9 ± 15.18[b]	62.50 (26.00-89.00)	F = 9.625	< 0.001
HbA1C	8.87 ± 1.31	8.40 (7.10-12.30)[a]	6.32 ± 0.45	6.50 (5.30-6.90)[b]	5.68 ± 0.33	5.70 (5.00-6.40)c	χ^2 = 94.753	< 0.001
WBC	5.88 ± 1.85	5.95 (2.80-10.50)	6.4 ± 3.12	5.70 (2.60-17.10)	5.14 ± 2.35	4.50 (2.60-15.70)	χ^2 = 7.294	0.051
HGB	12.6 ± 1.71	12.70 (9.70-17.80)	13.17 ± 2.09	12.90 (8.40-17.30)	12.86 ± 1.57	12.85 (9.40-16.00)	F= 0.992	0.374
Plt	195.65 ± 87.81	185.50 (86.00-644.00)	181.1 ± 66.35	168.50 (83.00-385.00)	172.52 ± 75.13	171.50 (11.00-391.00)	χ^2 = 2.214	0.331
RDW-CV	13.63 ± 1.15	13.35 (11.90-17.00)	14.07 ± 1.75	13.50 (11.90-21.10)	13.58 ± 1.18	13.20 (12.10-17.70)	χ^2 = 4.172	0.124
LYM	1.06 ± 0.48	0.95 (0.40-2.70)	1.05 ± 0.55	0.95 (0.30-2.80)	1.16 ± 0.49	1.05 (0.20-2.60)	χ^2 = 1.941	0.379
ANC	4.47 ± 1.67	4.20 (1.80-8.90)[b]	4.94 ± 2.97	4.15 (1.30-14.70)[b]	3.63 ± 2.09	3.15 (1.40-13.40)[a]	χ^2 = 9.588	0.008
MCV	83.55 ± 5.03	83.60 (70.60-92.50)[a]	85.87 ± 6.07	87.00 (61.10-95.50)[b]	103.84 ± 113.16	86.90 (72.60-819.00)[b]	χ^2= 9.230	0.010
MPV	---	---	10.24 ± 1.04	10.05 (8.20-12.50)	9.88 ± 1.01	9.60 (7.80-12.80)	L = 669.5	0.113
Monocyte/MID	0.29 ± 0.15	0.22 (0.09-0.70)	0.35 ± 0.19	0.31 (0.08-0.80)	0.34 ± 0.21	0.30 (0.10-1.10)	χ^2 = 2.062	0.357
Fasting Glucose	206.2 ± 94.25	177.00 (69.00-525.00)[a]	134.3 ± 32.03	130.50 (88.00-215.00)[b]	106.83 ± 15.2	102.50 (86.00-149.00)c	χ^2 = 51.848	< 0.001
Urea	50 ± 26.01	45.00 (16.10-146.30)[b]	48.82 ± 30.76	40.60 (22.50-202.50)[b]	32.71 ± 14.01	30.15 (12.90-73.60)[a]	χ^2 = 18.603	< 0.001
Creatine	1.22 ± 0.49	1.05 (0.70-2.80)[b]	1.09 ± 0.48	1.00 (0.70-3.30)[b]	0.83 ± 0.18	0.80 (0.60-1.40)[a]	χ^2 = 27.690	< 0.001
ALP	70.55 ± 24.46	66.00 (23.00-137.00)	64.6 ± 13.89	64.50 (43.00-107.00)	64.6 ± 17.16	60.50 (38.00-118.00)	χ^2 = 2.657	0.265
GGT	45.44 ± 30.07	42.00 (14.00-152.00)[b]	31.33 ± 21	24.50 (9.00-120.00)[ab]	24.1 ± 14.99	20.50 (6.00-90.00)[a]	χ^2 = 17.831	< 0.001
LDH	298.55 ± 186.27	255.50 (23.00-1200.00)	300.1 ± 188.87	272.00 (121.00-1137.00)	280.86 ± 94.37	256.50 (148.00-584.00)	χ^2 = 0.236	0.888
AST	45.5 ± 79.29	27.00 (16.00-521.00)	30.9 ± 19.63	26.00 (8.00-125.00)	28.02 ± 9.84	27.50 (14.00-56.00)	χ^2 = 1.723	0.422
ALT	26.23 ± 19.4	21.00 (10.00-115.00)	21.8 ± 13.93	19.00 (6.00-74.00)	20.38 ± 7.72	20.50 (8.00-38.00)	χ^2 = 2.332	0.312
Albumin	40.4 ± 3.95	41.00 (29.00-48.00)[b]	41.65 ± 3.57	42.00 (33.00-48.00)[ab]	42.31 ± 3.73	43.00 (35.00-51.00)[a]	χ^2 = 6.201	0.045
Protein	72.68 ± 7.28	72.50 (56.00-95.00)	73.08 ± 8.92	73.00 (41.00-95.00)	71.9 ± 6.75	73.50 (41.00-81.00)	χ^2 = 0.470	0.791
HDL	32.35 ± 8.62a	30.95 (15.80-50.10)	36.63 ± 10.78ab	36.35 (21.60-77.00)	40.01 ± 11.4b	38.90 (22.60-81.50)	F = 5.563	0.005
LDL	76.35 ± 25.23	72.50 (39.40-148.80)[a]	93.63 ± 34.1	90.60 (18.70-167.10)[b]	98.97 ± 29.57	103.05 (39.70-158.20)[b]	χ^2 = 13.722	0.001

χ^2: Kruskal-Wallis test statistic, F: Analysis of variance test statistic, U: Mann-Whitney U test statistic, ac: No difference between groups with the same letter.

ed in many studies[14-16]. However, strict glycemic control after hospitalization did not significantly improve patient outcomes[17]. These findings mean that glycemic control can be considered a marker for the prognosis of disease severity and poor overall health, not a factor with a causative effect on disease severity.

There was evidence that glycemic control was challenging for diabetic patients in the COVID-19 epidemic. For example, a study[18] found that older people with type 2 diabetes had poorer glycemic control during the COVID-19 pandemic. Another study[19] showed that in the COVID-19 pandemic and during quarantine, glycemic control was poor in patients with type 1 and 2 diabetes. In addition, due to poor glycemic control, patients with diabetes showed a weak immune response to SARS-CoV-2 infection[20]. Components of glycemic control included diet, physical activity, medication use, self-monitoring of blood sugar, healthy coping with complications, foot care, stress management, and preventative strategies to address the challenges of diabetes self-management.

The effects of social distance and staying at home could lead to lifestyle changes and possibly worsening glucose control because. In fact, staying home and keeping social distances limited the physical activities of people with diabetes. Second, limited food resources because of quarantine have forced people with diabetes to change their eating habits. Third, it has been challenging to obtain anti-diabetic medicines, insulin, and glucose strips during persistent constraints. Fourth, people with diabetes could not visit their doctor for routine follow-up. Therefore, it has not been possible to precisely adjust the dose of anti-diabetic medicines. These factors led to fluctuations in blood sugar and poor glycemic control[21].

People with diabetes constantly need essential medicines, equipment, and care. Deficiency or irregularity in the supply of other diabetes medications, equipment, and devices also negatively affects the glycemic control of people with diabetes[22]. If glycemic control is not done correctly and the patient has fluctuating blood sugar, the complications of diabetes and the likelihood of diseases, such as COVID-19 and other infectious diseases, increase because the body's ability to fight infection decreases[20]. On the other hand, infectious diseases such as COVID-19 are more challenging to treat in people with diabetes due to fluctuations in blood glucose and possible complications of diabetes[1,18,21]. Maintaining reasonable glycemic control strengthens the body's natural immune system and helps preventing serious consequences[23-25].

One of the limitations of this study is the small size of the sample and its retrospective nature. Future studies can be performed with larger sample sizes and considering the effect of glycemic control on the need for ICU stay, length of hospital stay, and the need for ventilators.

Conclusions

According to the findings of this study and similar results, with such increasing in the number of patients with diabetes, difficulty in treatment, and increased mortality in patients with diabetes, effective glycemic control in pandemic conditions is very important. Furthermore, it is necessary to use accurate recommendations for prevention and treatment to increase awareness of the disease in the pandemic time and improve the glycemic control results in patients with diabetes.

Conflict of Interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the manuscript's contents, and there is no financial interest to report. We certify that the submission is original work and is not under review for any other publication.

Ethical Approval

This study was conducted under the ethical rules with the approval of the Health Sciences University Samsun Training and Research Hospital Ethics Committee (decision No. 2021/9/6, 05/05/2021).

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